

Access to Indoles via Diels-Alder Reactions of Vinylpyrroles

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BY

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Professor Wayland E. Noland

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Dedication

This dissertation is dedicated to my family, without whose support and encouragement this project would not have been possible.

Abstract

The indole moiety is extremely common in biologically active natural and un-natural products. Exploration and discovery of methodologies generating the indole nucleus provides new and potentially more efficient options for synthetic approaches to indole-containing compounds. Vinylpyrroles have electron-rich pi systems and perform well as dienes in normal electron-demand Diels-Alder reactions with sufficiently electron-deficient dienophiles. The resulting substituted dihydro- or tetrahydroindoles are dehydrogenated to the corresponding indoles. *N*-Tosylation of pyrrole promotes Friedel-Crafts acylation at the difficult-to-access 3-position, which after reduction and dehydration gives 3-vinylpyrroles. These partially deactivated stable crystalline pyrroles have sufficient electron density to provide a novel and advantageous [4+2] cycloaddition route to indoles. Due to the high reactivity and consequent tendency of pyrroles to undergo undesired side-reactions, protecting groups are often desirable in pyrrole chemistry. However, the requirement for a sufficiently electron-rich diene, along with the sensitive nature of pyrroles, restricts the use of traditional blocking groups. Methylthio-protected 2-vinylpyrroles are shown to act as effective dienes in Diels-Alder reactions, demonstrating new blocking group techniques for chemistry involving sensitive pyrroles.

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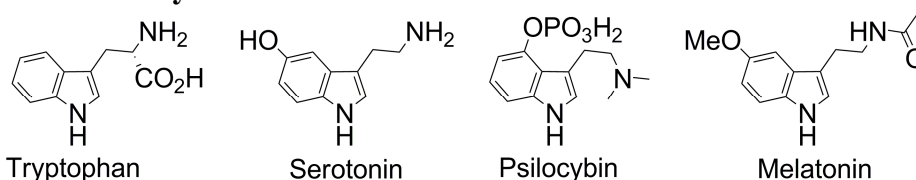
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Background

Synthesis of the indole nucleus continues to receive much attention¹ due to its common presence in the molecules of living systems as well as the biological activity exhibited in both natural^{2,3} and synthetic⁴ indole-containing products. Some of the simplest and best-known bioactive indoles, such as the amino-acid tryptophan, the neurotransmitter serotonin, the psychoactive substance psilocybin, and the hormone melatonin (Figure 1), highlight indole's ubiquity in nature. Wipf et al. recently determined:

“Interestingly, a relatively uniform fraction of ~4% of all pharmaceuticals, high-throughput screening samples, as well as natural products, contain an aromatic or partially saturated indole core.”^{1c}

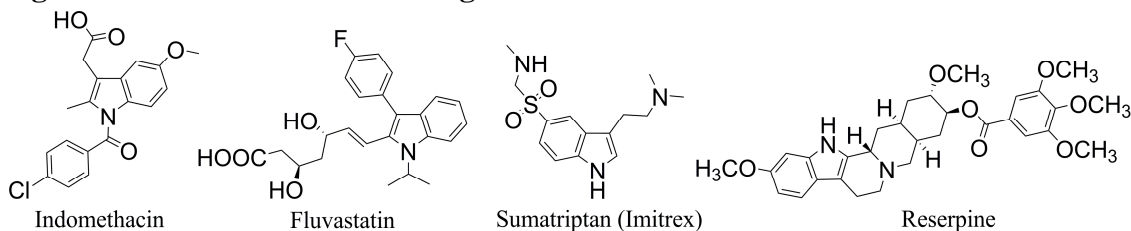
Figure 1. Commonly Known Bioactive Indoles



Examples of indole-containing pharmaceuticals include Indomethacin, an anti-inflammatory, Fluvastatin, which lowers cholesterol, Sumatriptan (Imitrex), used for migraine therapy, and Reserpine, an antipsychotic and antihypertensive medication (Figure 2). Indole-containing natural products are common in plants and animals, and as a class, indole alkaloids represent the largest number and are the most complicated of the marine alkaloids.⁵ Marine sources of indole alkaloids include sponges, tunicates, red alga, acorn worms, and symbiotic bacteria,⁵ with pharmacological activities

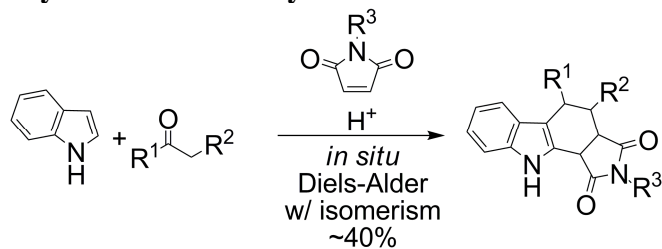
including cytotoxic, antiviral, antimicrobial, antiparasitic, anti-inflammatory, Ca^{2+} releasing, calmodulin-antagonistic, and antitopomerase-I activities.²

Figure 2. Some Indole-Containing Pharmaceuticals

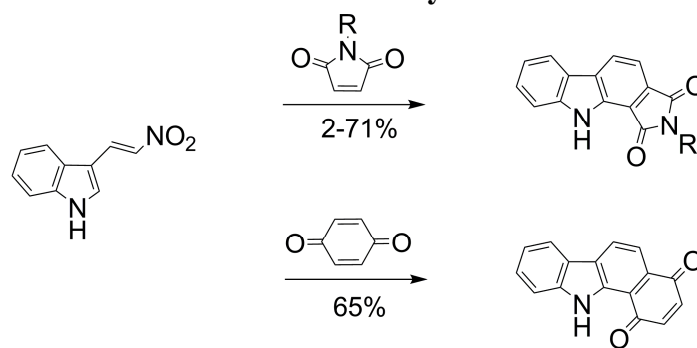


The Noland group has reported 3-vinylindoles are generated from condensation of indole and ketones, which then undergo an *in situ* Diels-Alder reaction with maleimides to form tetrahydrocarbazoles (Scheme 1).⁶ Additionally, the Noland group has reported 3-nitrovinylindoles react as dienes in Diels-Alder reactions with maleimides and *p*-benzoquinone to form carbazoles (Scheme 2).⁷ To expand upon this general methodology, in a desire to find improved synthetic methods towards indole and to generate novel indoles for biological testing, it was chosen to study the use of vinylpyrroles as the diene in Diels-Alder reactions to make tetrahydroindoles, which could then be aromatized to form the corresponding indoles (Scheme 3).

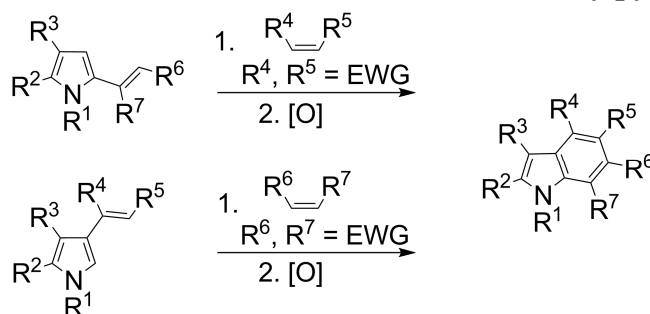
Scheme 1. *In Situ* Synthesis of Tetrahydrocarbazoles from Ketones



Scheme 2. Diels-Alder Reactions of 3-Nitrovinylindole

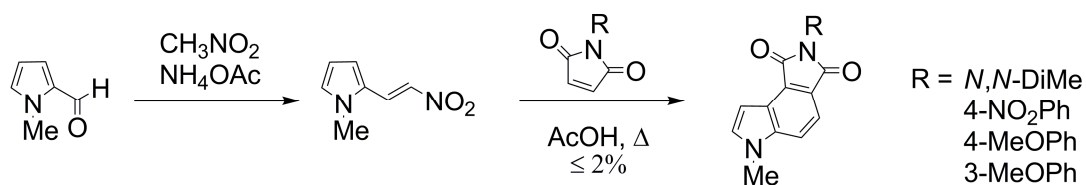


Scheme 3. Access to Indoles via Diels-Alder reactions of Vinylpyrroles



As a first attempt towards the vast array of possible products indicated by Scheme 3, and as an analog to the indole work depicted in Scheme 2, in research towards a plan B Master's degree, defended August 2002, the author studied the use of nitrovinylpyrroles as dienes in Diels-Alder reactions with maleimides (Scheme 4). Four novel products were generated in extremely poor yields, with the highest at less than 2%. Inspired by the analogous work done with vinylindoles by the Noland group,⁷ and by others,⁸ it was hoped that with extrusion of nitrous acid and dehydrogenation of the adduct occurring *in situ*, the indoles would be conveniently accessible. Unfortunately, with much of the resulting product being dark insoluble solids or sticky tars, the strong oxidizing properties of the nitro group likely prevented the desired product from being isolated in practical yield. The analogous experiments using *p*-benzoquinone as the dienophile performed by the Noland group,⁹ and by others,¹⁰ parallel these results.

Scheme 4. Master's Research



Part I of this project describes the pyrrole-analog of the indole work depicted in Scheme 1, in which 2-vinylpyrroles are generated from condensation of 2-alkylpyrroles and cyclic ketones, which then undergo an *in situ* Diels-Alder reaction with maleimides to form tetrahydroindoles.¹¹ In Part II, Diels-Alder reactions of 2-vinylpyrrole with maleimides and quinones are detailed, with subsequent oxidation to the corresponding indoles.¹² Part III focuses on Diels-Alder reactions of *N*-tosyl-3-vinylpyrroles, with aromatization and subsequent detosylation to give *N*-H indoles.¹³ Part IV describes Diels-Alder reactions of 2-methylthio-5-vinylpyrroles, with aromatization of the adduct and, lastly, demethylthioation.¹⁴

Compound Attribution

The author had assistance in synthesizing some of the compounds described in this project. Unless specifically attributed in this section, the author performed all synthesis and characterization. All NMR analysis, writing, reviews of the literature, and ideas presented in this project are the product of the author.

In Part I, the compounds were synthesized by Elena P. Sizova (compounds **5-14**, **44-54**, and **67-71**), Lakshmanan Venkatraman (compounds **15**, **16**, **20**, **22**, **24**, **32**, **34**, **36**, **72-87**, **89**, **90**, **92**, **100-106**, **108**, **109**, and **111**), and Oleg V. Afanasyev (compounds **17-43**, **55-66**, **84**, **88**, **89**, **91**, **93-99**, **103**, **107**, **108**, **110**, and **112**), some compounds were duplicated. The author conducted all NMR analysis, COSY, and NOE experiments. All high-resolution mass spectrometry and elemental analysis of O.V.A's compounds were taken by the author, as were many other pieces of data reported in the Experimental section. The explanation for, and the discovery and characterization of the multiple isomers present in the products of Part I was by the author.

In Part II, the compounds were synthesized by L.V. (compounds **122**, **124**, **127**, **129-140**, **150-162**, **171**, **173**, **176**, **178-189**, and **196-208**), Nicholas F. Anderson under the author's guidance (compounds **141**, **143-146**, **149**, **190**, **193**, and **194**), and by the author (compounds **123**, **125**, **126**, **128**, **142**, **147**, **148**, **163-170**, **172**, **174**, **175**, **177**, **191**, **192**, and **195**). Glen C. Gullickson took the X-ray spectra of compound **119**. The author conducted all NMR analysis, COSY, and NOE experiments. The author discovered, isolated, and proposed a mechanism for the formation of the double-

addition products **163-170**. The author synthesized and characterized all 2-vinylpyrrole starting materials.

In Part III, all compounds were synthesized and characterized by the author.

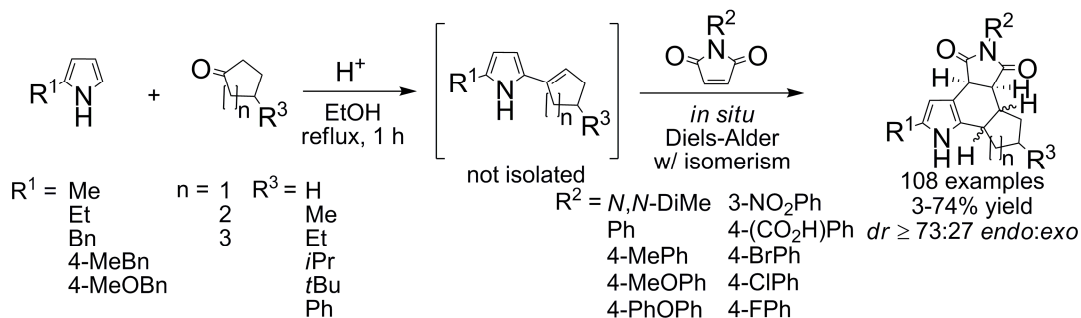
In Part IV, all the compounds were synthesized and characterized by the author, with the exception of compound **245**. Rozalin Dickson, under the author's guidance, helped to establish that **240** and **241** could be vacuum distilled, and isolated dimethyl 2-methylthiomaleate **245**, which was identified by the author. Huy Nguyen, under the author's guidance, discovered that compounds **240** and *N*-methyl-2-methylthio-pyrrole-2-carboxaldehyde could be cleanly separated via trituration with hexanes.

Part I. *In Situ* Vinylpyrrole Synthesis. Diels-Alder Reactions with Maleimides to Give Tetrahydroindoles.¹¹

1.1 Introduction

Pyrrole preferentially undergoes electrophilic attack at its 2-position since the most stable resonance structure of the reactive species has its greatest electron density α to the iminium nitrogen. For indole, dearomatization of the fused benzene ring inhibits a similar adjacent placement of charge. Instead, the highest electron-density occurs at the 3-position; thus, indole has favored electrophilic substitution at the 3-position in spite of greater charge separation. Correspondingly, the Noland group's previous work involved the trapping of 3-vinylindoles produced from condensation of indole with ketones (Scheme 1), whereas in this work the trapped intermediates are 2-vinylpyrroles (Scheme 5). This has bearing on the topology; the products of this work are *e*-side maleimide-fused tetrahydroindoles, whereas the tetrahydroindole component of the products of the vinylindole work are maleimide-fused at the *g*-side.

Scheme 5. *In Situ* Diels-Alder Reactions of 2-Vinylpyrrole



There are several known examples of 2-vinylpyrroles participating in Diels-Alder reactions,¹⁵ including employing as the dienophiles carboxyl-substituted acetylenes,^{16,17}

several acyclic electron-deficient alkenes,^{17,18} maleic anhydride and/or *N*-phenylmaleimide with *N*-benzenesulfonyl-2-vinylpyrrole^{18,19} and methyl 3-nitroacrylate with *N-p*-toluenesulfonyl-2-vinylpyrroles²⁰, tetrachloro- or tetrabromocyclopropene with *N-p*-toluenesulfonyl-2-vinylpyrrole²¹, *N*-phenylmaleimide with *N*-methyl- and *N*-propanoyloxy-2-vinylpyrrole,¹⁸ *N*-H-maleimide with 3-(*N*-alkyl-2-pyrrolyl)acrylates²² and *N*-alkyl-2-styrylpyrroles,^{22,23} and one example using various maleimides with both *N*-H and *N*-alkyl-2-vinylpyrroles.²⁴ Several of these studies report biological activity from this class of compounds, particularly anti-cancer activity.^{22,23,24} No prior demonstration of 2-vinylpyrrole formation accompanied by *in situ* trapping with a dienophile has been found to exist, a route which avoids the multiple steps involved in synthesizing the vinylpyrrole before the Diels-Alder reaction, affording considerable efficiency over the alternative procedures available for tetrahydroindole formation.

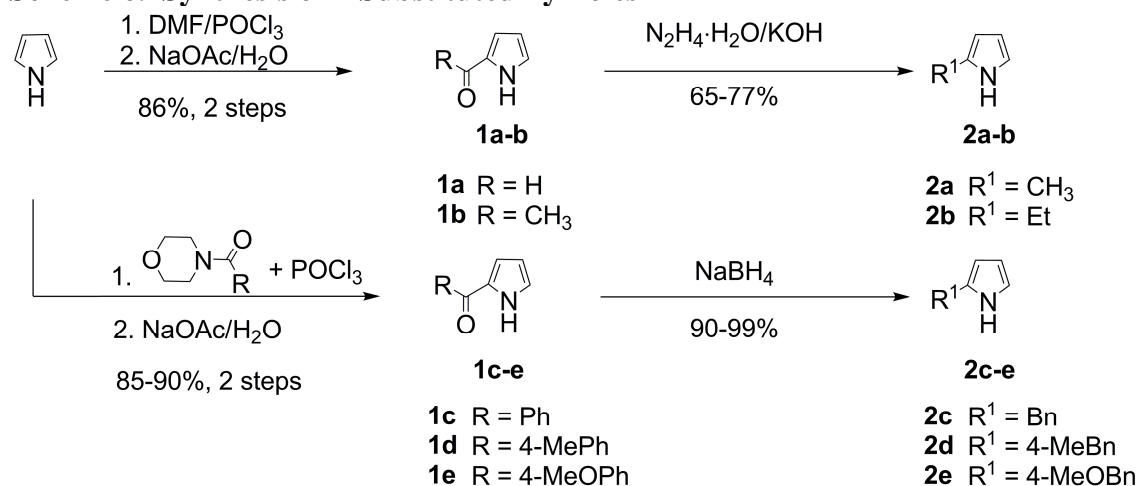
1.2 General, Synthesis of Starting Materials

Pyrrole is a reactive electron-rich heterocycle which, upon condensation with cyclic ketones, followed by proton-transfer, is believed to form a tertiary alcohol. In the presence of an acid catalyst, the alcohol should readily dehydrate, forming a resonance-stabilized 2-vinylpyrrole. The highly reactive 2-vinylpyrrole is then captured *in situ* by the dienophile. Under acidic conditions, pyrroles are known to form polymers.²⁵ Tetrameric calix[4]pyrroles are known to form when pyrroles and ketones react in the presence of an acid catalyst.^{26,27} When producing vinylpyrroles for *in situ* trapping, it has been found that blocking the other 2-position by use of 2-alkyl-substituted pyrroles

is useful in preventing formation of complex polymeric mixtures, which generally appeared as dark sticky tars or black powders.

2-Substituted-5-vinylpyrroles were synthesized as outlined in Scheme 6. Pyrrole-2-carboxaldehyde (**1a**) was synthesized via Vilsmeier-Haack formylation,²⁸ followed by Wolff-Kishner reduction,²⁹ to give 2-methylpyrrole (**2a**). Wolff-Kishner reduction of commercially available 2-acetylpyrrole (**1b**) produced 2-ethylpyrrole (**2b**).²⁹ Vilsmeier-Haack arylation³⁰ of pyrrole gave the 2-phenyl (**1c**), 2-(4-methylphenyl) (**1d**), and 2-(4-methoxyphenyl) (**1e**) ketones, which, after sodium borohydride reduction,³¹ gave the corresponding 2-benzylpyrroles (**2c-e**).

Scheme 6. Synthesis of 2-Substituted Pyrroles



1.3 *In Situ* Diels-Alder Reactions

Condensation of **2a-e** with cyclopentanone (**3a**), variously 4-substituted-cyclohexanones (**3c-h**), or cycloheptanone (**3b**), gave the corresponding vinylpyrroles. These acted as electron-rich dienes for normal electron-demand Diels-Alder reactions, which occurred *in situ* with various substituted maleimides (**4a-j**, Scheme 7). The unrearranged form of the Diels-Alder adduct was not isolated. Instead, spontaneous

isomerization of the double bond into the five-membered ring gave aromatized tetrahydroindoles (**5-112**, Table 1). *cis*-Fusion of the cycloalkyl ring involves less strain, but, since isomerism to the pyrrole is likely irreversible, thermodynamic equilibration may not determine the type of ring-fusion. Orbital symmetry considerations forbid suprafacial 1,3-hydrogen shifts and antarafacial 1,3-hydrogen shifts are geometrically impossible;³² therefore, the isomerism probably takes place through acid catalysis. A proton should approach preferentially from the less sterically hindered face, the face opposite to the maleimide fusion and the same face from which protons 3b-H and 6a-H protrude (in the Experimental, this face is always designated ‘ α ’). This face of hydrogen delivery (in the expected predominant *endo*-addition products) would give *cis*-fusion of the cycloalkyl ring with a *syn* relationship between all four of the protons on the cyclohexene ring.

Scheme 7. In Situ Synthesis of Tetrahydroindoles from Cyclic Ketones

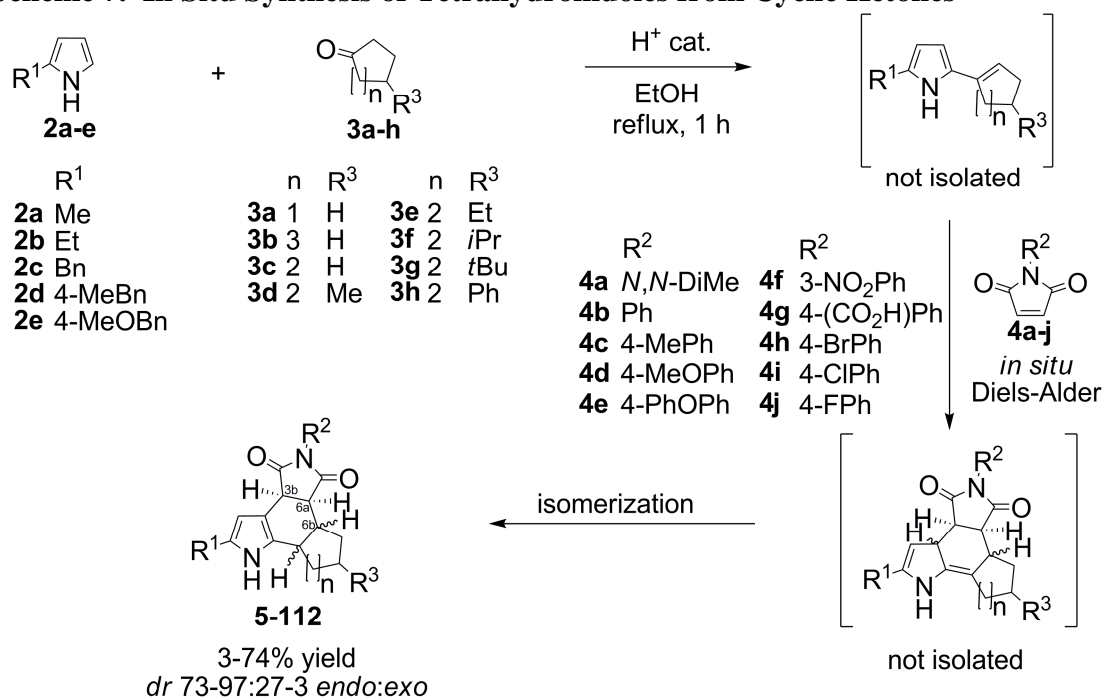


Table 1. Summary of *In Situ* Cycloaddition Results; see Structures in Fig. 1

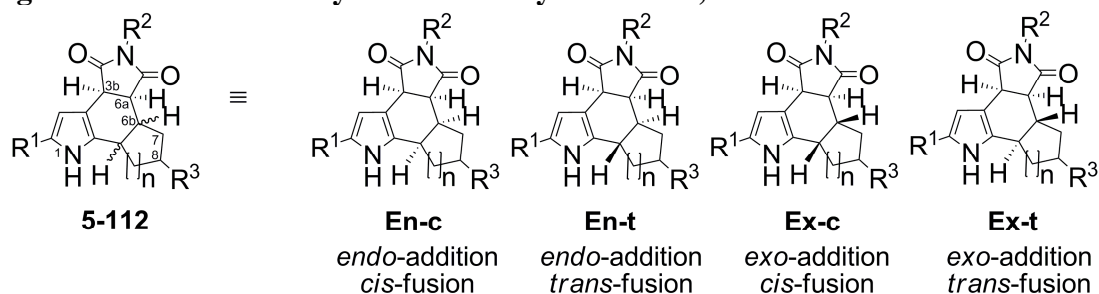
#	R ¹	R ²	n	R ³	Yield %	Ratio of Isomers				#	R ¹	R ²	n	R ³	Yield %	Ratio of Isomers			
						En-c:	En-t:	Ex-c ^a :	Ex-t							En-c:	En-t:	Ex-c ^a :	Ex-t
5	Me	Ph	1	H	62	3.4	1.0	0.1		59	Me	4-BrPh	2	<i>t</i> Bu	31	3.3	1.0	0.5	
6	Me	4-MePh	1	H	42	3.9	1.0			60	Me	4-BrPh	2	Ph	43	2.2	1.0	0.6	0.1
7	Me	4- <i>i</i> PrPh	1	H	50	7.0	1.0			61	Me	4-FPh	2	H	45	1.0	1.8		
8	Me	4-MeOPh	1	H	46	5.4	1.0			62	Me	4-FPh	2	Me	38	1.6	1.0	0.2	
9	Me	4-PhOPh	1	H	52	7.6	1.0			63	Me	4-FPh	2	Et	44	1.0	2.3	0.6	
10	Me	3-NO ₂ Ph	1	H	35	9.0	1.0			64	Me	4-FPh	2	<i>i</i> Pr	41	1.9	1.0	0.2	
11	Me	4-(CO ₂ H)Ph	1	H	20	8.9	1.0	0.7		65	Me	4-FPh	2	<i>t</i> Bu	34	1.6	1.0	0.3	0.2
12	Me	4-BrPh	1	H	63	4.2	1.0			66	Me	4-FPh	2	Ph	49	8.0	1.0	0.5	0.4
13	Me	4-ClPh	1	H	65	2.5	1.0			67	Me	Ph	3	H	21	3.4	1.0	0.9	
14	Me	4-FPh	1	H	59	11.1	1.0			68	Me	4- <i>i</i> PrPh	3	H	3	3.0	1.0		
15	Me	<i>N,N</i> -DiMe	2	H	45	19.2	1.0			69	Me	4-MeOPh	3	H	11	1.9	1.0		
16	Me	<i>N,N</i> -DiMe	2	Et	49	8.4	1.0	0.2		70	Me	3-NO ₂ Ph	3	H	24	4.1	1.0	0.7	
17	Me	<i>N,N</i> -DiMe	2	<i>i</i> Pr	42	1.0				71	Me	4-ClPh	3	H	17	2.8	1.0		
18	Me	<i>N,N</i> -DiMe	2	<i>t</i> Bu	52	2.4	1.0	0.1		72	Et	<i>N,N</i> -DiMe	2	H	28	8.5	1.0		
19	Me	<i>N,N</i> -DiMe	2	Ph	48	1.0				73	Et	<i>N,N</i> -DiMe	2	Et	31	4.1	1.0		
20	Me	Ph	2	H	60	12.5	1.0			74	Et	<i>N,N</i> -DiMe	2	<i>t</i> Bu	23	14.0	1.0		
21	Me	Ph	2	Me	48	1.8	1.0	0.3		75	Et	Ph	2	H	48	1.4	1.0		
22	Me	Ph	2	Et	37	5.6	1.0	0.1		76	Et	Ph	2	Et	35	1.0	1.2	0.2	0.1
23	Me	Ph	2	<i>i</i> Pr	39	5.0	1.0			77	Et	Ph	2	<i>t</i> Bu	27	4.4	1.0	0.3	
24	Me	Ph	2	<i>t</i> Bu	38	8.3	1.0	0.2		78	Et	4-MeOPh	2	H	41	1.0	5.6		
25	Me	Ph	2	Ph	43	3.8	1.0			79	Et	4-MeOPh	2	Et	36	6.5	1.0	0.3	
26	Me	4-MePh	2	H	42	1.0	1.6			80	Et	4-MeOPh	2	<i>t</i> Bu	28	2.1	1.0	0.1	
27	Me	4-MePh	2	Me	37	1.1	1.0	0.1		81	Bn	<i>N,N</i> -DiMe	2	H	35	3.2	1.0		
28	Me	4-MePh	2	Et	38	2.1	1.0			82	Bn	<i>N,N</i> -DiMe	2	Et	29	5.3	1.0	0.3	
29	Me	4-MePh	2	<i>i</i> Pr	41	3.2	1.0			83	Bn	<i>N,N</i> -DiMe	2	<i>t</i> Bu	25	1.0			
30	Me	4-MePh	2	<i>t</i> Bu	27	1.0	12.4	0.6		84	Bn	Ph	2	H	56	3.6	1.0		
31	Me	4-MePh	2	Ph	41	11.9	1.0			85	Bn	Ph	2	Et	36	1.0	1.7	0.6	0.4
32	Me	4-MeOPh	2	H	34	3.5	1.0			86	Bn	Ph	2	<i>i</i> Pr	61	1.0	4.1	0.7	
33	Me	4-MeOPh	2	Me	61	2.3	1.0	0.3		87	Bn	Ph	2	<i>t</i> Bu	39	3.0	1.0	0.5	0.3
34	Me	4-MeOPh	2	Et	36	4.3	1.0	0.1		88	Bn	Ph	2	Ph	63	1.0	2.8		
35	Me	4-MeOPh	2	<i>i</i> Pr	74	2.9	1.0	0.3	0.3	89	Bn	4-MeOPh	2	H	59	3.0	1.0	0.3	
36	Me	4-MeOPh	2	<i>t</i> Bu	35	4.4	1.0	0.3		90	Bn	4-MeOPh	2	Et	36	2.5	1.0	0.3	0.2
37	Me	4-MeOPh	2	Ph	57	4.7	1.0	0.8		91	Bn	4-MeOPh	2	<i>i</i> Pr	63	1.0	3.8	0.8	
38	Me	4-PhOPh	2	H	44	5.0	1.0			92	Bn	4-MeOPh	2	<i>t</i> Bu	24	24.0	1.0	0.3	0.2
39	Me	4-PhOPh	2	Me	52	1.2	1.0	0.1		93	Bn	4-MeOPh	2	Ph	57	1.0	3.2	0.5	
40	Me	4-PhOPh	2	Et	46	1.7	1.0	0.3		94	4-MeBn	Ph	2	H	64	1.0	1.6		
41	Me	4-PhOPh	2	<i>i</i> Pr	42	2.1	1.0	0.3		95	4-MeBn	Ph	2	<i>i</i> Pr	61	1.0	2.7	0.8	
42	Me	4-PhOPh	2	<i>t</i> Bu	30	4.8	1.0	0.9		96	4-MeBn	Ph	2	Ph	64	1.0	5.0		
43	Me	4-PhOPh	2	Ph	48	5.4	1.0	1.0	0.7	97	4-MeBn	4-MeOPh	2	H	65	1.0	1.9		
44	Me	3-NO ₂ Ph	2	H	40	2.8	1.0			98	4-MeBn	4-MeOPh	2	<i>i</i> Pr	57	1.0	3.4	0.9	
45	Me	3-NO ₂ Ph	2	Me	44	3.7	1.0			99	4-MeBn	4-MeOPh	2	Ph	62	1.0	3.0		
46	Me	3-NO ₂ Ph	2	Et	41	1.0	3.3			100	4-MeOBn	<i>N,N</i> -DiMe	2	H	24	3.8	1.0		
47	Me	3-NO ₂ Ph	2	<i>i</i> Pr	30	2.8	1.0	0.2		101	4-MeOBn	<i>N,N</i> -DiMe	2	Et	22	4.0	1.0	0.2	
48	Me	3-NO ₂ Ph	2	<i>t</i> Bu	31	2.1	1.0			102	4-MeOBn	<i>N,N</i> -DiMe	2	<i>t</i> Bu	21	1.0			
49	Me	3-NO ₂ Ph	2	Ph	40	4.2	1.0	0.6		103	4-MeOBn	Ph	2	H	60	1.0	1.8		
50	Me	4-(CO ₂ H)Ph	2	H	31	1.5	1.0			104	4-MeOBn	Ph	2	Et	32	1.1	1.0	0.3	0.3
51	Me	4-(CO ₂ H)Ph	2	Me	31	1.6	1.0			105	4-MeOBn	Ph	2	<i>i</i> Pr	51	1.0	4.5	0.9	
52	Me	4-(CO ₂ H)Ph	2	Et	31	3.7	1.0	0.1		106	4-MeOBn	Ph	2	<i>t</i> Bu	29	5.2	1.0	0.6	
53	Me	4-(CO ₂ H)Ph	2	<i>i</i> Pr	30	5.3	1.0	0.2		107	4-MeOBn	Ph	2	Ph	61	1.0	5.2		
54	Me	4-(CO ₂ H)Ph	2	Ph	46	4.3	1.0			108	4-MeOBn	4-MeOPh	2	H	42	1.2	1.0		
55	Me	4-BrPh	2	H	41	1.8	1.0			109	4-MeOBn	4-MeOPh	2	Et	29	1.9	1.0	0.2	
56	Me	4-BrPh	2	Me	49	3.6	1.0	0.2		110	4-MeOBn	4-MeOPh	2	<i>i</i> Pr	53	1.0	3.8	0.6	
57	Me	4-BrPh	2	Et	47	3.0	1.0	0.3	0.3	111	4-MeOBn	4-MeOPh	2	<i>t</i> Bu	22	2.7	1.0	0.7	0.3
58	Me	4-BrPh	2	<i>i</i> Pr	41	1.8	1.0	0.3		112	4-MeOBn	4-MeOPh	2	Ph	59	1.0	8.1		

(a) Ex-c is assumed to be the major *exo*-addition product.

The ¹H NMR data of **5-112** show mixtures of isomers, which were usually isolated by precipitation from the crude ethanolic reaction mixture, possibly influencing the reported distribution of isomers because of solubility differences. Both *endo*- and *exo*-

Diels-Alder additions are possible, and *cis*- or *trans*-fusion gives the possibility of four isomers, *endo*-addition with *cis*-fusion (**En-c**), *endo*-addition with *trans*-fusion (**En-t**), *exo*-addition with *cis*-fusion (**Ex-c**), and *exo*-addition with *trans*-fusion (**Ex-t**, Figure 3). Between one and four isomers are recognizable in each spectrum, corresponding to these stereoisomeric products. Smaller minor isomer peaks are visible next to or overlapping the peaks belonging to the major isomer, particularly for protons 1-H, 3b-H, 6a-H, 6b-H, and the proton α to the point of cycloalkane ring-fusion to the pyrrole ring, labeled 9a-H, 10a-H, or 11a-H, the numbers depending on which sized cyclic ketone, **3a**, **3b**, or **3c-h**, was used.

Figure 3. Stereochemistry of the Tetrahydroindoles; see Table 1



In some products derived from the 4-substituted-cyclohexanones **3d-h**, additional isomerism is observed due to the stereogenic center at position 8 (see Figure 3 for numbering). This is supported by the observation that the ratio of the integrated areas of proton peaks belonging to the alkyl substituents at position 8 is generally not equal to the ratio of *endo/exo*-addition *cis/trans*-fusion isomers present in the mixture determined from the integrated areas of protons 1-H, 3b-H, and 6a-H. Since the major concern in analyzing the ¹H-NMR data is the diastereoselectivity of the Diels-Alder reaction and subsequent isomerization, it is the distribution of the four isomers **En-c**,

En-t, **Ex-c**, and **Ex-t** that is reported in Table 1 and in the Experimental section, and it is these four isomers to which the text refers in subsequent discussion.

1.4 ¹H NMR, Nuclear Overhauser Effect (NOE), and Computational Analyses

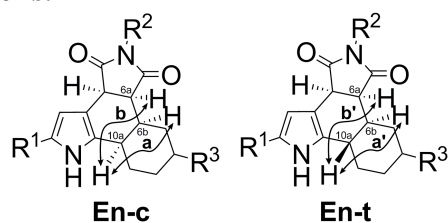
For all products, two isomers are present in greater quantity than the other two, corresponding to the expected *endo*-addition Diels-Alder products. At a minimum, in the isolated products *endo*-addition is preferred over *exo*-addition in a 73:27 diastereomeric ratio, and at a maximum in a 97:3 diastereomeric ratio (in which no **Ex-c** and **Ex-t** isomers are visible by ¹H NMR). The *endo*-addition preference in Diels-Alder reactions is commonly explained by a favorable secondary orbital interaction that occurs in the transition state when the molecular orbitals of the carbonyls of the imide dienophile overlap with the developing molecular orbital from the diene, an interaction not present with an *exo*-approach. Though both stepwise and concerted mechanisms are theoretically possible to give tetrahydroindoles **5-112**,³³ the stereochemical relationships found below in the major isomers are consistent with that expected for an *endo*-addition; therefore, a concerted reaction pathway is likely. To verify the *endo*-addition preference, and to confirm that *cis*-fusion is predominant, NOE experiments were performed on nine representative tetrahydroindoles, compounds **13**, **20**, **26**, **47**, **55**, **61**, **89**, **84**, and **103**.

Consistent NOE interactions were observed between the 3b-H and 6b-H protons of the two major isomers of each of these products, giving evidence that they arise from *endo*-addition. To determine whether *cis*- or *trans*-fusion occurred in a particular *endo*-addition isomer, NOE experiments must compare interactions of the protons at the

points of the cycloalkane ring-fusion. In *trans*-fused products, the distance between the protons should be greater, giving a weaker NOE interaction. For careful comparison of the relative strength of these interactions, a reference NOE interaction of consistent strength should be present in each experiment. Because the distance between the proton α to the point of cycloalkane ring-fusion to the pyrrole ring and the 6a-H proton should be relatively constant for the *cis*- and *trans*-fused products, NOE interactions between these two protons were used as the reference.

In the cyclohexanone-derived products, the ratio of the strength of the NOE interaction for the **En-c** isomer between the 10a-H and 6b-H protons (**a** in Figure 4) to the 10a-H and 6a-H protons (**b**) should appear as markedly less than the ratio for the **En-t** isomer between the 10a-H and 6b-H protons (**a'**) to the 10a-H and 6a-H protons (**b'**). Restating using the labels of Figure 4, **a** is less than **a'**, and **b** is approximately equal to **b'**; therefore **a:b** is less than **a':b'**. For the two predominant isomers in the cyclohexanone-derived products, it was always observed that for one isomer the interaction between the 10a-H and 6b-H protons relative to that between the 10a-H and 6a-H protons was roughly one-third stronger (**En-c**) than for the other (**En-t**). This relationship was also observed for the cyclopentanone-derived product **13**. Thus, NOE evidence supports the assertion that the two most prevalent isomers are **En-c** and **En-t**. Unfortunately, in no ^1H NMR spectrum of the cycloheptanone-derived products were protons at position 11a sufficiently free from overlap to allow accurate observation and comparison of the NOE interactions.

Figure 4. NOE Interactions.



To support the bond-length relationships used to analyze the results of the NOE experiments, a general simplified structure was used to perform computational analysis at the RHF/STO-6G level for the *endo*-addition cyclopentane, cyclohexane, and cycloheptane *cis*- and *trans*-fused products. In these simplified structures, the tetrahydroindole had a phenyl group at the 5-position and was unsubstituted at the 2-position. Calculations indicate that in the **En-c** isomer, the ratio of the distance between the proton at the point of the cycloalkane ring fusion α to the pyrrole and the 6b-H proton should differ significantly from the ratio of the distance between these protons in the **En-t** isomer. The computational models indicate that this ratio in the **En-t** isomer is 72.4, 69.2, and 69.5% of the ratio for the **En-c** isomer for the cyclopentane-, cyclohexane-, and cycloheptane-fused products, respectively.

In all nine of the representative NOE experiments performed, the ¹H NMR peak of the 1-H proton of the **En-c** isomer always appeared upfield from the peak corresponding to the 1-H proton of the **En-t** isomer. This consistent relationship made identifying the number of products having **En-t** as the major isomer a relatively simple process of inspecting the two predominant 1-H peaks in each spectrum; products with **En-t** as the major isomer display the unique signature of having their major 1-H peak farthest downfield. As expected, **En-c** is usually the major isomer. Out of 108 products, only 23 (21%) had **En-t** as the major isomer.

Based on the observation that there are a maximum of four isomers present, and the common general observations of minor *exo*-addition Diels-Alder products in the literature,³⁴ it seems reasonable to assume that the minor peaks appearing in the ¹H NMR spectra indicate *exo*-addition products. Sufficient steric bulk of substituents on the ketone or maleimide may cancel out favorable secondary orbital interactions and allow some *exo*-approach Diels-Alder products. The two minor isomers were not present in sufficient concentration in any sample, nor were the 6b-H protons sufficiently resolved to perform NOE studies to confirm these assertions, or to check whether *cis*- or *trans*-fusion is predominant among the *exo*-addition isomers. Separation of *endo*- and *exo*-addition isomers was not achieved by chromatography nor by crystallization, which prevented analysis of individual isomers.

1.5 Biological Activity

By participating in the Developmental Therapeutics Program at the National Cancer Institute (NCI), 32 representative compounds were submitted to the NCI for a one-dose three-human tumor cell line pre-screen: compounds **20, 22, 24, 32, 34, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 87, 89, 90, 92, 100, 101, 102, 103, 104, 106, 108, 109, and 111**. Of these, seven compounds, **79, 101, 103, 104, 106, 108, and 109**, were judged by the NCI to have activity sufficient to justify screening with 60 human-tumor cell lines at five concentrations with 10-fold dilutions, from 1 x 10⁻⁴ M to 1 x 10⁻⁸ M. Of these seven compounds, compounds **103, 106, 108, and 109**, were found to have high levels of activity against many of the 60 different cell lines tested. Compound **103** was most active against non-small cell lung cancer EKVX, with an IC₅₀ of 113.2

$\mu\text{g/mL}$. Compound **109** was most active against colon cancer KM12, with an IC_{50} of $80.9 \mu\text{g/mL}$. Compounds **106** and **108** were found to be active against several different cell-lines and were the best performing of the 32 compounds. Compound **106** had its highest activities against melanoma SK-MEL-5, colon cancer KM12, and breast cancer MDA-MB-435, with IC_{50} values of 62.5, 73.5, and $113.8 \mu\text{g/mL}$, respectively. Compound **108** was most active against colon cancer HCT-15, with an IC_{50} value of $18.3 \mu\text{g/mL}$. No intention to further test the compounds in Part I was indicated by the NIH at the time this manuscript was submitted.

1.6 Conclusion

In summary, a series of 108 novel tetrahydroindoles has been prepared via a Diels-Alder reaction of maleimides with 5-alkyl-2-vinylpyrroles formed *in situ* from an acid-catalyzed condensation between 2-alkylpyrroles and cyclic ketones. This one-pot method of tetrahydroindole synthesis is convenient and offers a fair-yielding and highly-convergent synthetic route towards substituted indoles with good diastereoselectivity for the **En-c** isomer.

1.7 Notes on ^1H NMR Analysis for Part I

Diastereotopism of the protons on the methylene unit of a benzyl group is sometimes observed as second-order doublets. The $3\beta\text{-H}$ proton appears as a doublet of doublets; COSY experiments indicate that the $3\beta\text{-H}$ proton is coupled not only to the 6a-H proton but also to the proton at the point of cycloalkane ring-fusion α to the pyrrole ring (which would be the 10a-H proton in the cyclohexanone case), with a coupling constant of approximately 2.0 Hz .^{20,35} In the 2-methyl compounds **5-71**, the 2-methyl group

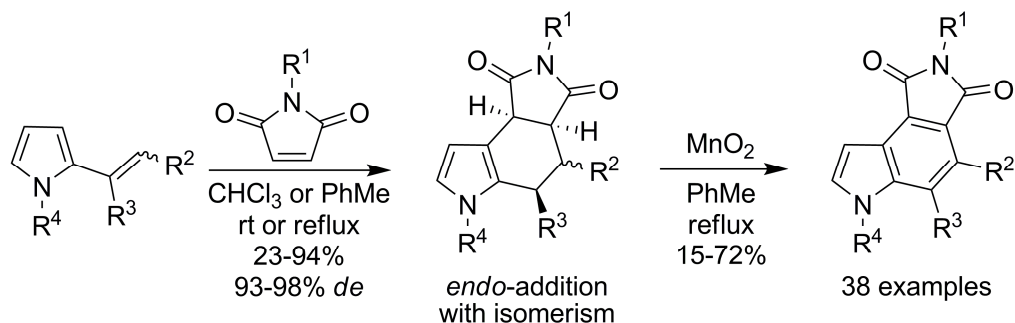
often appears as a doublet of doublets; COSY experiments indicate that this is due in part to an approximately 0.9 Hz coupling with the 3-H proton.³⁶ COSY experiments suggest that the 2-methyl group is also sometimes coupled with the 1-H proton at approximately 0.9 Hz, though no literature precedent for this type of coupling was found.

Part II. Access to Indoles via Diels-Alder Reactions of 2-Vinylpyrroles with Maleimides.¹²

2.1 Introduction

While the *in situ* Diels-Alder approach toward indoles is advantageous with its one-pot method, it is somewhat limited in that acidic conditions are required to catalyze the condensation, and pyrroles are well known to form polymers under acidic conditions.²⁵ Indeed, in Part I formation of polymeric material was an issue when using vinylpyrroles for *in situ* Diels-Alder reactions and it was found that to circumvent the problem, the use of 5-alkyl-substituted pyrroles was essential. These results inspired exploration of the Diels-Alder chemistry of separately-prepared 2-vinylpyrroles (Scheme 8).

Scheme 8. Diels-Alder reactions of 2-Vinylpyrroles with Maleimides



Preparing the vinylpyrrole in a separate step via methods not employing acidic conditions has the advantage of allowing the use of 5-unsubstituted 2-vinylpyrroles in Diels-Alder reactions. In addition, effecting aromatization of the resulting tetrahydroindoles to give indoles was desired. Some studies have been conducted on this route towards indoles using as the dienophiles carboxyl-substituted acetylenes,^{16,17} several acyclic electron-deficient alkenes,^{17,18} maleic anhydride and/or *N*-

phenylmaleimide with *N*-benzenesulfonyl-2-vinylpyrrole^{18,19} and methyl 3-nitroacrylate with *N-p*-toluenesulfonyl-2-vinylpyrroles²⁰ (neither of which were taken through to the aromatic indole), tetrachloro- or tetrabromocyclopropene with *N-p*-toluenesulfonyl-2-vinylpyrrole²¹, *N*-phenylmaleimide with *N*-methyl- and *N*-propanoyloxy-2-vinylpyrrole,¹⁸ *N*-H-maleimide with 3-(*N*-alkyl-2-pyrrolyl)acrylates²² and *N*-alkyl-2-styrylpyrroles,^{22,23} and one report using various maleimides with both *N*-H and *N*-alkyl-2-vinylpyrroles²⁴. Several of these studies report biological activity from this class of compounds, particularly anti-cancer activity.^{22,23,24} No prior broad study of the efficacy of the synthesis of indoles via Diels-Alder reactions of 5-unsubstituted 2-vinylpyrroles with *N*-substituted maleimides has been found. In most of the prior studies, only *N*-alkyl-substituted pyrroles were studied, presumably due both to the higher reactivity of *N*-H pyrroles and the formation of Michael addition products between the adduct and dienophile when certain *N*-H-2-vinylpyrroles are used in Diels-Alder reactions, reported here for the first time. None of the prior studies have characterized the diastereoselective isomerism of the adduct, potentially valuable for synthetic applications. This report is the first demonstration of the use of chiral maleimides in Diels-Alder reactions with 2-vinylpyrroles.

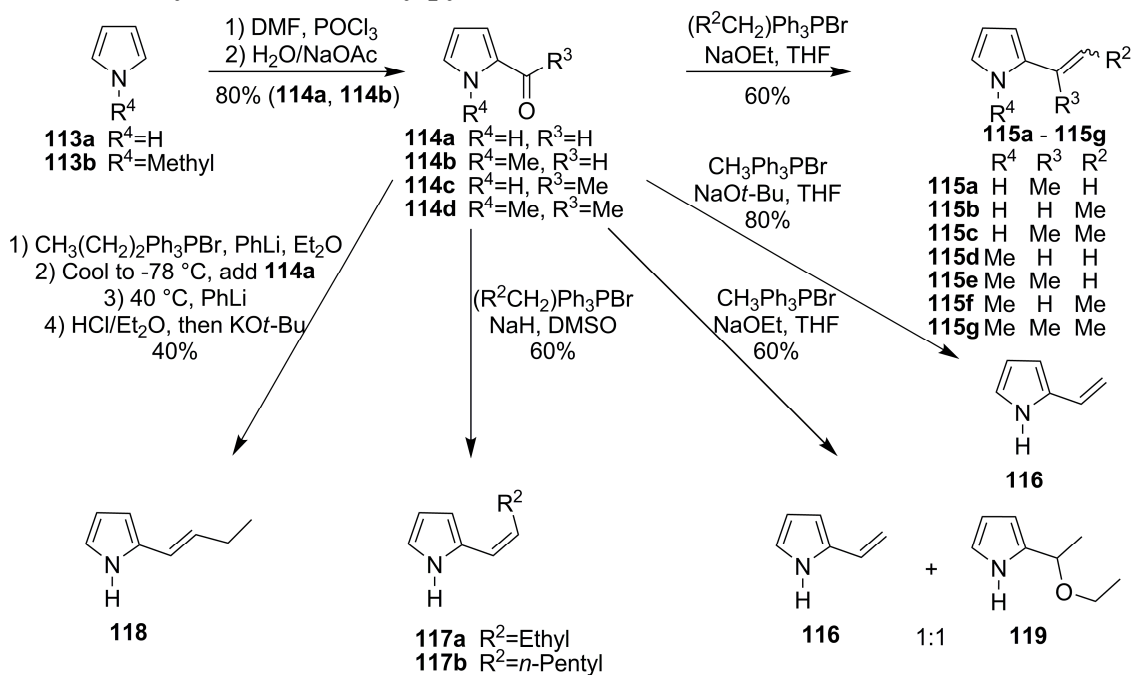
Herein reported are 38 examples where indoles are conveniently available from oxidation of the corresponding tetrahydroindoles, formed via Diels-Alder reactions of both *N*-H and *N*-alkyl-2-vinylpyrroles with a wide range of *N*-substituted maleimides. Also reported is a highly diastereoselective isomerism of the Diels-Alder adduct, and isolation of Michael addition products between the adduct and the dienophile with the

major product being the more sterically congested diastereomer. Additionally, an improved synthesis of *N*-H-2-vinylpyrrole is disclosed.

2.2 Synthesis of Starting Materials

A Vilsmeier-Haack formylation²⁸ was performed on the appropriate pyrrole (**113a** and **113b**, Scheme 9) to give pyrrole-2-carboxaldehydes **114a** and **114b**. Next, a Wittig reaction was conducted on **114a** and **114b** or on commercially available **114c** and **114d** to form the appropriate vinylpyrrole **115-118**.^{16a,17,37,38} Various procedures for the Wittig reaction were used to synthesize the vinylpyrroles. The common procedure for synthesis of 2-vinylpyrroles^{38,39} using sodium ethoxide as the base for formation of the ylide was used to make methyl-substituted vinylpyrroles **115a-g**. For vinylpyrroles **115b**, **115c**, **115f**, and **115g**, this procedure gave approximately 1:3.9, 2.8:1, 1:1.8 and 1:1.5 *E:Z* molar mixtures, respectively, as determined by ¹H NMR, which were used without further purification for formation of the Diels-Alder adducts. Vinylpyrrole **115a** decomposed or polymerized⁴⁰ rapidly at room temperature to a dark viscous liquid before it could be used in any Diels-Alder reaction.

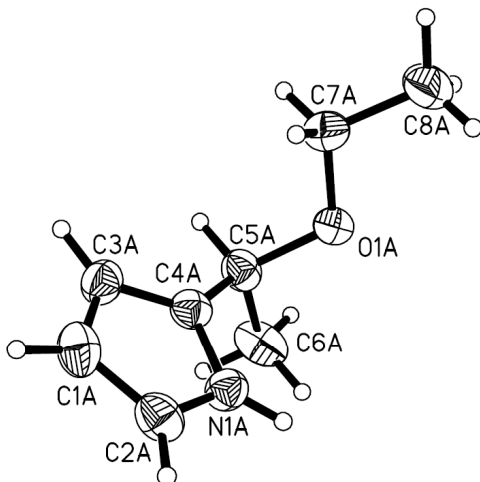
Scheme 9. Synthesis of 2-Vinylpyrroles



While the sodium ethoxide-procedure produced the desired *N*-H-2-vinylpyrrole **116**, it also consistently gave a 1:1 molar ratio of the unwanted and not easily separated byproduct 2-(1-ethoxyethyl)-pyrrole **119**. X-ray crystallography proved the structure of **119** (Figure 5). The isolation of **119** was surprising, considering the lack of mention of this compound in any literature procedure for synthesis of **116**. Though the mixture of **116** and **119** was used as is for formation of the Diels-Alder adducts, a search for a way to avoid contamination with this impurity was sought, which probably comes from an acid-catalyzed addition of ethoxide to the vinyl group in the expected Markovnikov-orientation. Eliminating the acidic aqueous sodium bisulfite wash from the workup had no effect on the proportion of **119** formed. Heating the mixture of **116** and **119** in DMSO was attempted with the hope of effecting deethanolysis, which did occur, but with the destruction of a large amount of the desired **116**, probably from polymerization. It was found that using sodium *t*-butoxide in place of sodium ethoxide

completely eliminated the byproduct and gave a higher efficiency than the sodium ethoxide procedure, with a consistent yield of approximately 80%, and less need for excess methyltriphenylphosphonium bromide and base (1.25 equiv) than was required for complete conversion using the sodium ethoxide procedure (2 equiv).

Figure 5. ORTEP Representation of the X-ray Structure of 119

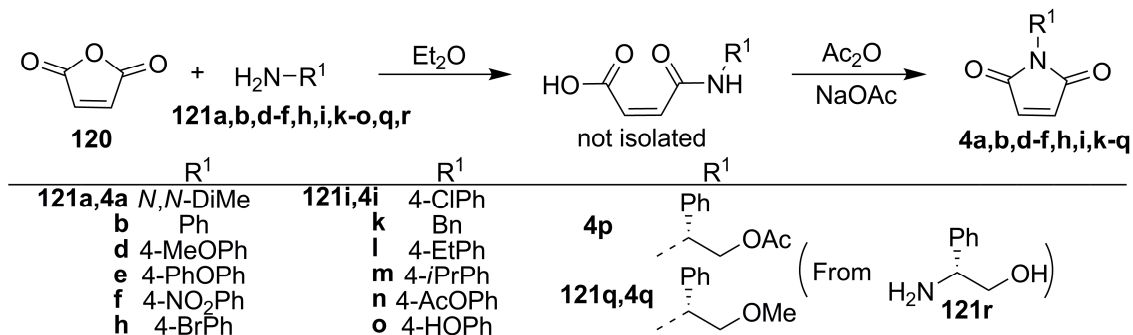


To determine whether the Diels-Alder reactions of 2-vinylpyrroles with maleimides took place with the predicted *endo*-addition, vinylpyrroles with predominantly *E* or *Z* stereochemistry were desired. Ethyl- and pentyl-substituted vinylpyrroles **117a**^{38a} and **117b** were made from aldehyde **114a** with the Corey procedure for the Wittig reaction,⁴¹ using methylsulfinyl carbanion as the base, formed from the reaction of DMSO with sodium hydride. ¹H NMR analysis showed that this procedure gave **117a** exclusively as the *Z* isomer and **117b** in a 1:9 *E*:*Z* mixture. For comparison of the stereochemistry in the resulting Diels-Alder adducts, (*E*)-2-(2-ethylvinyl)pyrrole **118**^{38a}

was synthesized using the Schlosser modification of the Wittig reaction,⁴² giving a 40% yield of an approximately 12:1 *E:Z* molar mixture.

Maleimides were synthesized by the typical procedure⁴³, by reaction of maleic anhydride **120** with the appropriate primary amine **121a**, **121b**, **121d-f**, **121h**, **121i**, **121k-o**, **121q**, and **121r** and then heating the resulting amide-acid in an excess of acetic anhydride (10 equiv) with sodium acetate (0.5 equiv), giving the corresponding *N*-substituted maleimide (**4a**, **4b**, **4d-f**, **4h**, **4i**, and **4k-q**, Scheme 10). When the acid from reaction of **120** with (*R*)-(-)-phenylethanol (**121r**) was cyclized, the primary alcohol group was acetylated, giving acetate **4p**. To make the chiral methyl ether **4q**, (*R*)-2-methoxy-1-phenylethanol (**121q**) was synthesized by methylation of **121r** by reaction of sodium hydride followed by addition of methyl iodide.⁴⁴

Scheme 10. Synthesis of Maleimides



2.3 Diels-Alder Reactions

Diels-Alder reactions of 2-vinylpyrroles **115b-g**, **116**, and **117a** with maleimides **4a**, **4b**, **4d**, **4e**, **4k**, **4l**, **4m**, **4p**, and **4q** in chloroform gave adducts **122-140**, **142**, and **150-162** (Scheme 11, Table 2). The chiral adducts **150-162** were not isolated but were taken directly through to the aromatic indoles **196-208** (Scheme 12, Section 2.4). The reaction solution was refluxed, if necessary, and stopped when complete, as indicated

by TLC. Alternatively, the Diels-Alder reactions of 2-vinylpyrroles **117** and **118** with maleimides **4b**, **4f**, **4h**, **4i**, **4l**, **4n**, and **4o** were run in refluxing toluene, giving adducts **141-149**. In both procedures, vinylpyrroles **115-118** were used in slight excess (1.1 equiv) in order to simplify the required chromatographic purification procedure, since, while the vinylpyrroles were always eluted first, unreacted maleimides generally were eluted very near to the adducts. The unrearranged adducts were not isolated in any case; instead the rearomatized form of the adducts was obtained. While an extensive case-by-case comparison of the efficiency of the two procedures was not undertaken, adduct **142** was produced in both chloroform (70% yield) and toluene (41%). Further, comparing the average yield of the toluene-procedure-derived products **141-149** (38%) to the average yield of the chloroform-procedure-derived products **123**, **125**, **126**, **128-140**, and **142** (73%), the chloroform procedure gave better yields.

Scheme 11. Diels-Alder Reactions of 2-Vinylpyrroles

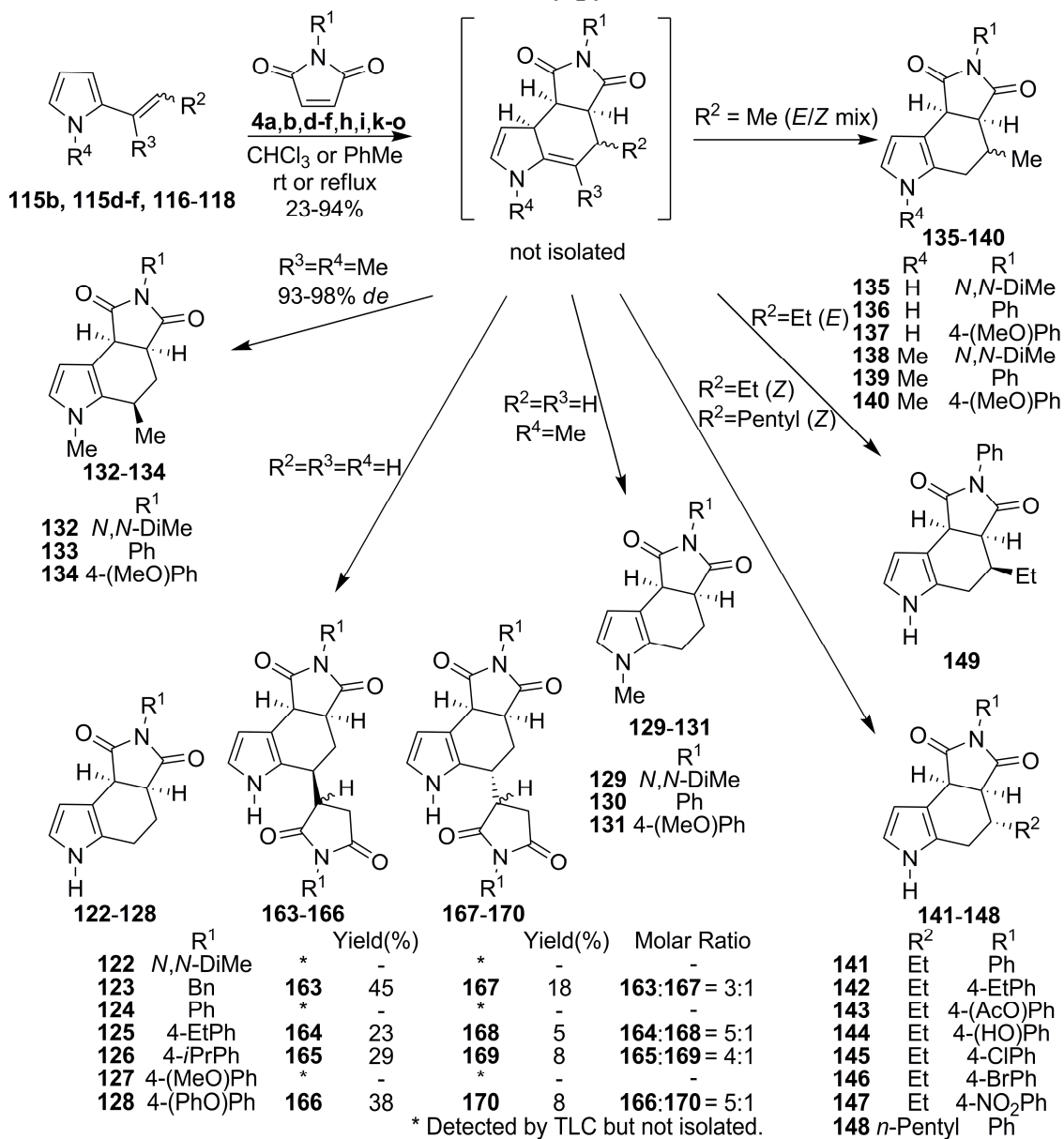
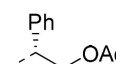
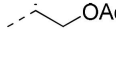
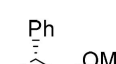
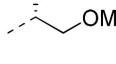


Table 2. Diels-Alder Reactions of 2-Vinylpyrroles

Vinylpyrrole	Maleimide	R ¹	R ²	R ³	R ⁴	Conditions	Adduct	Yield %	PhMe reflux t	Indole	Yield % ^b
4	10a	<i>N,N</i> -DiMe	H	H	H	CHCl ₃ , reflux 24 h	11	64 ^a	24 h	60	64
4	10b	Bn	H	H	H	CHCl ₃ , rt 24 h	12	23	3 h	61	45
4	10c	Ph	H	H	H	CHCl ₃ , reflux 24 h	13	92 ^a	24 h	62	67
4	10d	4-EtPh	H	H	H	CHCl ₃ , rt 24 h	14	49	3 h	63	47
4	10e	4- <i>i</i> PrPh	H	H	H	CHCl ₃ , rt 24 h	15	32	3 h	64	61
4	10f	4-(MeO)Ph	H	H	H	CHCl ₃ , reflux 24 h	16	90 ^a	24 h	65	64
4	10h	4-(PhO)Ph	H	H	H	CHCl ₃ , rt 24 h	17	33	3 h	66	38
3d	10a	<i>N,N</i> -DiMe	H	H	Me	CHCl ₃ , reflux 24 h	18	89	24 h	67	66
3d	10c	Ph	H	H	Me	CHCl ₃ , reflux 24 h	19	94	24 h	68	71
3d	10f	4-(MeO)Ph	H	H	Me	CHCl ₃ , reflux 24 h	20	93	24 h	69	66
3e	10a	<i>N,N</i> -DiMe	H	Me	Me	CHCl ₃ , rt 24 h	21	86	24 h	70	70
3e	10c	Ph	H	Me	Me	CHCl ₃ , rt 24 h	22	91	24 h	71	72
3e	10f	4-(MeO)Ph	H	Me	Me	CHCl ₃ , rt 24 h	23	93	24 h	72	66
3b	10a	<i>N,N</i> -DiMe	Me	H	H	CHCl ₃ , rt 24 h	24	57	24 h	73	57
3b	10c	Ph	Me	H	H	CHCl ₃ , rt 24 h	25	93	24 h	74	61
3b	10f	4-(MeO)Ph	Me	H	H	CHCl ₃ , rt 24 h	26	90	24 h	75	59
3f	10a	<i>N,N</i> -DiMe	Me	H	Me	CHCl ₃ , rt 24 h	27	67	24 h	76	56
3f	10c	Ph	Me	H	Me	CHCl ₃ , rt 24 h	28	89	24 h	77	62
3f	10f	4-(MeO)Ph	Me	H	Me	CHCl ₃ , rt 24 h	29	84	24 h	78	61
5a	10c	Ph	Et	H	H	PhMe, reflux 24 h	30	36	24 h	79	44
5a	10d	4-EtPh	Et	H	H	PhMe, reflux 24 h	31	41	3 h	80	53
5a	10d	4-EtPh	Et	H	H	CHCl ₃ , reflux 24 h	31	70	-	-	-
5a	10g	4-(AcO)Ph	Et	H	H	PhMe, reflux 24 h	32^c	31	24 h	81^c	15
5a	10i	4-(HO)Ph	Et	H	H	PhMe, reflux 24 h	33	54	-	- ^d	- ^d
5a	10j	4-ClPh	Et	H	H	PhMe, reflux 24 h	34	32	24 h	82	33
5a	10k	4-BrPh	Et	H	H	PhMe, reflux 24 h	35	35	24 h	83	36
5a	10l	4-NO ₂ Ph	Et	H	H	PhMe, reflux 24 h	36	45	24 h	84	28
5b	10c	Ph	Pentyl	H	H	PhMe, reflux 24 h	37	30	-	-	-
6	10c	Ph	Et	H	H	PhMe, reflux 24 h	38	41	-	-	-
4	10m		H	H	H	CHCl ₃ , reflux 24 h	39	-	24 h	85	46
3b	10m		Me	H	H	CHCl ₃ , reflux 24 h	40	-	24 h	86	27
3d	10m		H	H	Me	CHCl ₃ , reflux 24 h	41	-	24 h	87	44
3c	10m		Me	Me	H	CHCl ₃ , reflux 24 h	42	-	24 h	88	29
3f	10m		Me	H	Me	CHCl ₃ , reflux 24 h	43	-	24 h	89	26
3g	10m		Me	Me	Me	CHCl ₃ , reflux 24 h	44	-	24 h	90	21
4	10n		H	H	H	CHCl ₃ , reflux 24 h	45	-	24 h	91	39
3b	10n		Me	H	H	CHCl ₃ , reflux 24 h	46	-	24 h	92	30
3e	10n		H	Me	Me	CHCl ₃ , reflux 24 h	47	-	24 h	93	26
3d	10n		H	H	Me	CHCl ₃ , reflux 24 h	48	-	24 h	94	40
3c	10n		Me	Me	H	CHCl ₃ , reflux 24 h	49	-	24 h	95	32
3f	10n		Me	H	Me	CHCl ₃ , reflux 24 h	50	-	24 h	96	29
3g	10n		Me	Me	Me	CHCl ₃ , reflux 24 h	51	-	24 h	97	23

^aYield includes double-addition type products, detected but not isolated.

^bYields for chiral indoles are over two steps.

^cProduct was deacetylated to **33** during the reaction or workup.

^dOnly starting material **33** was recovered, but see note c above.

To determine whether *endo*- or *exo*-addition was predominant, the orientation of a terminal substituent on the vinyl group of the pyrrole was studied in the resulting

isomerized adducts using nuclear Overhauser effect (NOE) experiments (Figure 6). For description of the orientation, the diastereomer with the *syn* 3a-H and 8b-H protons (Figure 7) protruding from the α -face and the fused maleimide protruding from the β -face will always be used, corresponding to the structures at the top of Figure 2, this convention is also used throughout the Experimental.

Figure 6. Effect of Endo- or Exo-Addition on the Stereochemistry of the Diels-Alder Adducts

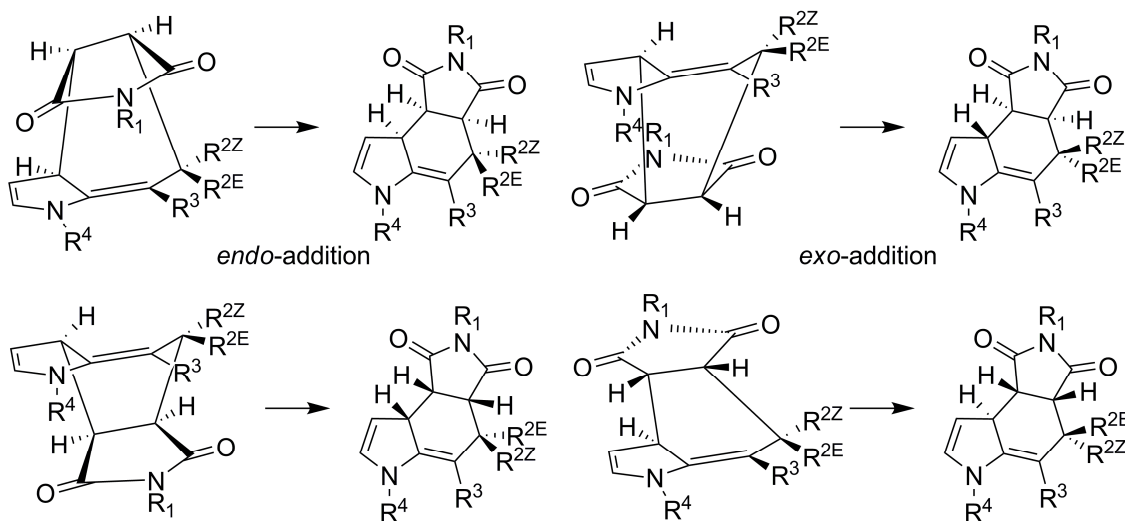
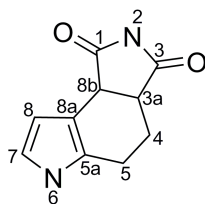


Figure 7. Numbering Scheme



2-(2-Methylvinyl)-pyrroles **115b** and **115f** gave the expected mixture of 4 α -Me and 4 β -Me in rearranged adducts **135-140**, expected for either *endo*- or *exo*-addition. (*Z*)-2-Vinylpyrroles **117a** and **117b** gave adducts **141-148** with exclusively 4 α -Et and 4 α -*n*-pentyl substituents, as shown by ^1H NMR analysis. Correspondingly, adduct **149** from the *E*-vinylpyrrole **118** had mainly 4 β -Et with an approximately 12:1 ratio of 4 β -Et to

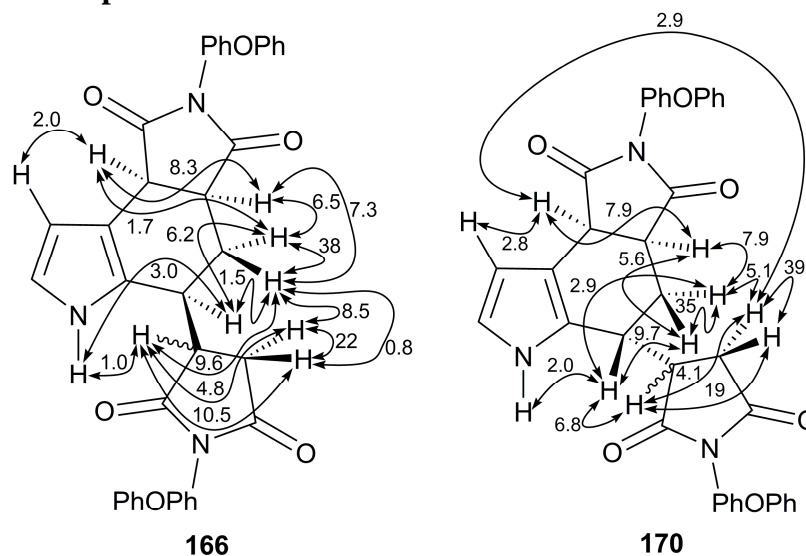
4 α -Et product. To the extent of ^1H NMR sensitivity, this is strong evidence of predominantly *endo*-addition Diels-Alder reactions.

The spontaneous rearrangement of Diels-Alder adducts to their aromatic counterparts was also observed in Part I with *in situ* Diels-Alder reactions of 2-vinylpyrrole with maleimides.¹¹ As noted in that Part, because orbital symmetry considerations forbid suprafacial 1,3-hydride shifts and antarafacial 1,3-hydride shifts are geometrically difficult,³² the isomerism probably takes place via acid catalysis, a “formal 1,3-hydride shift”.⁴⁵ A proton should approach from the least sterically-hindered face of the adduct, the opposite face from which the maleimide protrudes and the same face from which the 8b-H and 3a-H protons protrude (the α -face); thus, the 5-H proton of the rearranged adduct would have the predominant orientation of α . The predominance of a particular diastereomer was observed in the Noland group’s prior work,^{6,11} and to verify it occurred here as well, NOE experiments were performed on the rearranged adducts **133** and **134** which had a methyl substituent at the 5-position; compound **132** had overlapping ^1H NMR peaks which prevented accurate measurement of NOE interactions. The assignment of the two peaks corresponding to the 4 α -H and 4 β -H protons was confirmed by a weak NOE interaction between the 8b α -H and 4 α -H protons, while no interaction between the 8b α -H and 4 β -H protons was observed. Additionally, a much stronger interaction was observed between the 3a α -H and 4 α -H protons than between the 3a α -H and 4 β -H protons. A strong NOE interaction between the 4 α -H and 5-H protons occurred, with no detectable interaction between the 4 α -H proton and the 5-methyl group. Correspondingly, a strong NOE interaction was seen between the 4 β -H proton and the 5-methyl group, while no detectable response was

observed between the 4 β -H and 5-H protons, showing the 5-methyl group to be in the β -orientation. The ^1H NMR integrations of **132-134** showed between a 13:1-54:1 molar ratio of major to minor product, a 93-98% diastereomeric excess. The predominant epimer was the sterically more congested configuration, with the 5-methyl group protruding from the same face as the maleimide.

The high diastereoselectivity of the formal 1,3-hydride shift is further evidenced from products **163-170**. These types of products were detected whenever unsubstituted vinylpyrrole **116** was used in Diels-Alder reactions with maleimides, where they were isolated and characterized in four reactions. Compound **167** was not completely separated from **163**, although sufficient purity was obtained to accurately report ^1H NMR data. In several cases, these products were detected by TLC but not isolated, although their masses were included in determining the percent yield; hence, yields for products **122**, **124**, and **127** do not reflect the actual isolated yield. NOE studies of **166** and **170** verified the structure of products **163-170**, giving evidence of the same kind of stereochemistry as described above for the 5 β -Me adducts **133** and **134** (Figure 8).

Figure 8. NOE Experiments

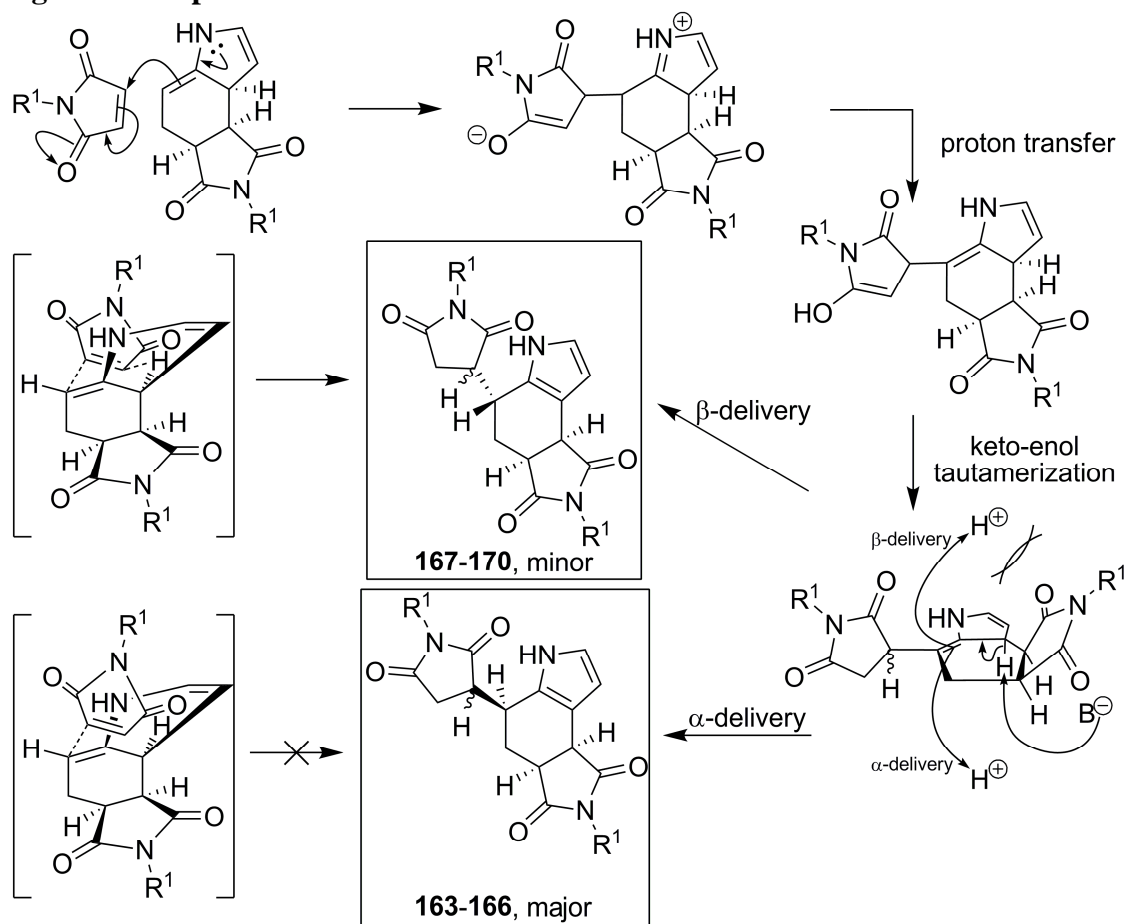


Numbers indicate percent enhancement

For minor product **170**, an NOE interaction was observed between the $8\beta\text{-H}$ proton and a geminal proton of the succinimide substituent, an interaction absent in major product **166**. In **166**, an interaction between the $8\beta\text{-H}$ and $4\alpha\text{-H}$ protons showed a *syn*-relationship. Multiple strong interactions were observed in compound **166** between the $4\beta\text{-H}$ proton and the succinimide protons, while no such interactions were observed with the $4\alpha\text{-H}$ proton, giving evidence that the succinimide is attached to the β -face in the major product. In compounds **163-170**, the stereochemistry of the succinimidyl proton at the point of attachment was not determined. However, coupling constants and NOE interactions between the geminal protons of the succinimide and the succinimidyl proton at the point of attachment did allow determination of a probable *syn*- or *anti*-relationship. In compound **166**, the ^1H NMR peaks of the $5\alpha\text{-H}$ proton and the proton at the point of succinimide attachment overlapped too greatly to allow accurate measurement of NOE interactions.

When first detected, products **163-170** were assumed to be the result of ene-reactions between the Diels-Alder adduct and the maleimide, as there are several reports of ene-products formed between Diels-Alder adducts and their corresponding dienophiles.⁴⁶ However, after determining the stereochemistry at C5, it was realized that an ene reaction could not adequately explain the formation of both epimers. While an ene reaction could justify formation of minor products **167-170**, the tight transition state required⁴⁷ makes the ene reaction an impossible route towards major products **163-166** (Figure 9). Because the more sterically congested epimers **163-166** were the predominant products, thermodynamic equilibration of the feasibly ene-reaction-formed **167-170** is also highly unlikely.

Figure 9. Proposed Mechanism for Formation of 163-170



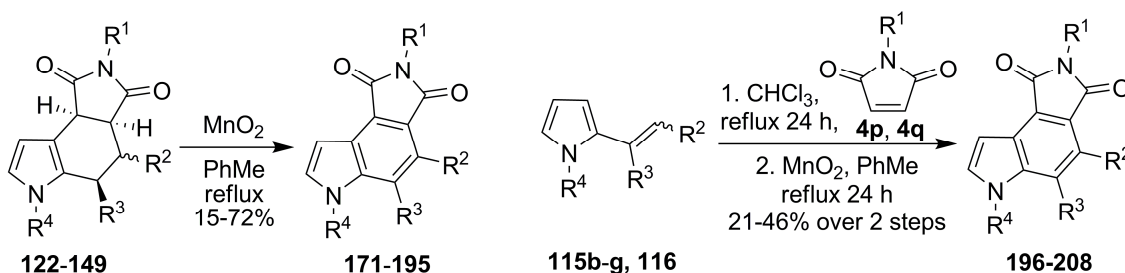
In light of the diastereoselective rearrangement at C5 noted in this Part, Part I,¹¹ and in the Noland group's prior *in situ* Diels-Alder reaction work with vinylindoles,⁶ it was realized that the mechanistic explanation offered in Part I¹¹ for formation of the rearranged adducts could also explain the formation of **163-170**. A Michael addition of the unrearranged adduct to the maleimide would result in 5-succinimide-substituted adducts. When a proton approaches the molecule to cause the formal 1,3-hydride shift, an addition from the least sterically congested face (the α -face in the Figures) would predominate and would result in products **163-166**, with a smaller amount of hydrogen delivery occurring from the more sterically occluded face to give minor products **167-**

170. The presence of the succinimide substituent at C5 may cause the steric environment of the α -face to be more similar to the β -face than does a 5-methyl group; this would explain the 3:1-5:1 ratios of products **163-170** (75-83% *de*) as contrasted with the higher diastereomeric excess observed in 5-methyl products **132-134** (93-98% *de*).

2.4 Aromatization of Diels-Alder Adducts

Diels-Alder adducts **122-143**, **145-147**, and **150-162** were dehydrogenated using activated MnO₂, giving the corresponding indoles **171-195** in 15-72% yield, and giving chiral indoles **196-208** with 21-46% yield over two steps (Scheme 12, Table 2). Using manganese sulfate with potassium permanganate⁴⁸ to make the activated MnO₂ gave consistent and moderate-yielding aromatizations. Some restrictions to this technique apply, as when aromatization of hydroxyl-adduct **144** was attempted, only starting material was obtained. Competition for adsorption on the oxide surface of the activated MnO₂ from the phenol group of **144** may have partially deactivated the reagent. When MnO₂ treatment of acetoxy-adduct **143** was conducted, the hydroxy-indole **192** was the exclusive product isolated. When oxidation occurs, water can be produced, but deacetylation appears to be unprecedented under these oxidative conditions; therefore, the aromatized product was more likely deacetylated on silica gel during chromatography, giving **192**. Aromatization and purification of chiral adducts **150-155** gave indoles **196-201** with no deacetylation.

Scheme 12. Aromatization of Diels-Alder Adducts



2.5 Biological Activity

While participating in the Developmental Therapeutics Program at the National Cancer Institute (NCI), 11 compounds were submitted to the NCI for a one-dose 60-human tumor cell line pre-screen: compounds **123**, **125**, **128**, **141**, **143**, **144**, **172**, **174**, **177**, and **190**. Of these, two compounds, **174** and **177**, were judged by the NCI to have sufficient activity to justify screening with 60 human-tumor cell lines at five concentrations with 10-fold dilutions, from 1×10^{-4} M to 1×10^{-8} M. Both of these compounds were found to have high levels of activity against many of the 60 different cell lines tested. Compound **174** was most active against non-small cell lung cancer HOP-92, and melanoma cell lines SK-MEL-5 and LOX IMVI with an IC_{50} of 322 ng/mL, 412 ng/mL, and 462 ng/mL, respectively. Compound **177** was most active against breast cancer HS 578T, melanoma UACC-257, and leukemia RPMI-8226, with an IC_{50} of 3.5 ng/mL, 34 ng/mL, and 230 ng/mL, respectively. No intention to further test the compounds in Part II was indicated by the NIH at the time this manuscript was submitted.

2.6 Conclusion

Variously-substituted 2-vinylpyrroles undergo *endo*-addition Diels-Alder additions with maleimides, followed by a highly diastereoselective (93-98% *de*) rearrangement to tetrahydroindoles in moderate to excellent yield. Treatment with activated MnO₂ in refluxing toluene gives the corresponding indole aromatized products in moderate to good yield. This highly convergent methodology for formation of indoles is flexible and the starting materials are conveniently prepared.

2.7 Notes on ¹H NMR Analysis for Part II.

In the ¹H NMR spectra of adducts **122-149**, the 8 β α -H proton often appears as a doublet of doublet of doublets in 5-unsubstituted adducts; COSY experiments indicate that the 8 β α -H proton is coupled not only to the 3 α α -H proton but also to the 5-bond-distant 5-H protons with a coupling constant of about 1.5 Hz.^{19,35} In 5-methyl adducts, the 3 α α -H proton was sometimes observed to couple to the 5 α -H proton at 0.6-0.9 Hz. Additionally, in 4-alkyl adducts the 3 α α -H proton was coupled to the 5 α -H proton at approximately 1.0 Hz. For indoles **171-208** the 8-H proton and the 5-H proton were consistently coupled at about 1.0 Hz.⁴⁹

Part III. Access to Indoles via Diels-Alder Reactions of 3-Vinylpyrroles.¹³

3.1 Introduction

Pyrrole preferentially undergoes electrophilic attack at its 2-position since the most stable resonance structure of the reactive species has its greatest electron density alpha to the iminium nitrogen. Therefore, 2-vinylpyrroles are the most obviously accessible vinylated pyrroles, and there are numerous examples of 2-vinylpyrroles being used as dienes in Diels-Alder reactions.^{11,16-24} Several of these studies report biological activity from the resulting class of compounds and the corresponding aromatized indoles, particularly anti-cancer activity.^{11,22-24} To expand upon this general methodology, in a desire to find improved synthetic methods towards indole and to generate novel indoles for biological testing, it was chosen to study the use of 3-vinylpyrroles as the diene in Diels-Alder reactions.

Only four reports of 3-vinylpyrroles being used in Diels-Alder reactions were found to exist.^{17,19,50,51} Jones et al. reported the Diels-Alder reaction of *N*-*t*-butyl-3-vinylpyrrole with DMAD and oxidation with DDQ to give the corresponding indoles.¹⁷ Murase et al. reported Diels-Alder reactions of sulfur-substituted *N*-methyl-3-vinylpyrrole generated *in situ* from the corresponding 3-thioacetylpyrrole, using as the dienophile DMAD, maleic anhydride, *N*-methylmaleimide, 1,4-naphthoquinone, and several unsymmetrical alkenes, followed by DDQ aromatization to the indoles.⁵¹ The Diels-Alder adducts were not isolated, but were oxidized directly to the indoles in a maximum of 31% yield over three steps. Xiao and Ketcha reported Diels-Alder reactions of *N*-benzenesulfonyl-3-vinylpyrrole and ethyl 3-(1-(benzenesulfonyl)-1*H*-2-

pyrrolyl)acrylate with *N*-phenylmaleimide and maleic anhydride, without taking the adducts through to the indoles.¹⁹ Most recently, Hodges et al. reported Diels-Alder reactions of osmium-complexed *N*-methyl-3-vinylpyrroles with *N*-phenylmaleimide to give tetrahydroindoles, which were then oxidized with DDQ to give the corresponding indoles, but difficulties with oxidation and pyrrole polymerization were experienced.⁵⁰ In most of the prior examples of Diels-Alder reactions of 3-vinylpyrroles, the isolated tetrahydroindole had isomerized from the originally formed adducts, with a double bond having moved into the 5-membered ring to form the aromatic pyrrole. In the one exception, the work by Hodges et al.,⁵⁰ the unrearranged adduct was complexed with osmium when isolated.

The synthesis of 3-vinylpyrrole was first found to be reported in 1979 by Jones and Gilow et al., by the photoaddition of acetaldehyde and *N*-methylpyrrole followed by dehydration of the resulting alcohol give *N*-methyl-3-vinylpyrrole in 32% overall yield.⁵² A more efficient method uses 3-(*N*-*t*-butylpyrrole)carboxaldehyde in a Wittig methylenation in 55% overall yield.⁵³ The *t*-butyl group, due to its steric bulk, directs selective Vilsmeier-Haack formylation to the 3-position. The most efficient method to 3-vinylate pyrrole is likely via *N*-benzenesulfonylation followed by 3-acetylation under Friedel-Crafts acylation conditions using AlCl₃ as the Lewis acid, selectively acetylating the 3-position.^{54,55,56} The resulting acetylpyrrole is then reduced and dehydrated to the 3-vinylpyrrole.^{19,56} An extensive study by Huffman et al. indicates that subjecting *N*-*p*-toluenesulfonylpyrrole to Friedel-Crafts acylation conditions using AlCl₃ does not result in a Friedel-Crafts-type acylation, but instead causes reversible formation of 2- and 3-dichloroaluminum intermediates, the latter being sterically

avored, and the former possibly experiencing a stabilizing electronic interaction between the electrophilic aluminum and an oxygen of the *N*-sulfonyl group.⁵⁷ The predominant and more reactive 3-substituted organoaluminum intermediate then reacts with the acylating agent to give mainly 3-acylpyrroles.

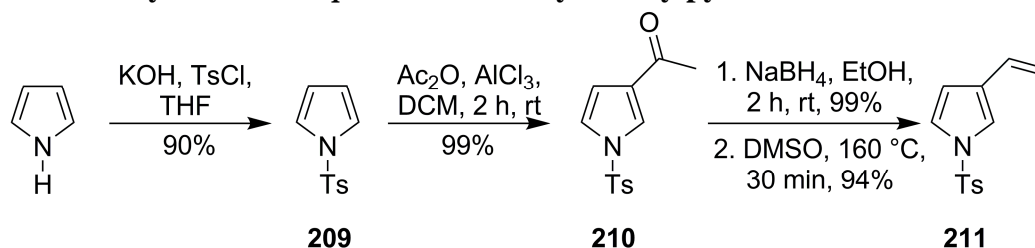
While altering the side to which the dienophile-component is fused in the resulting tetrahydroindole, using 3-vinylpyrroles in Diels-Alder reactions is significantly advantageous over the use of 2-vinylpyrroles. 2-Vinylpyrroles are generally volatile liquids which polymerize or decompose on exposure to air and light, but *N-p*-toluenesulfonyl-3-vinylpyrroles are robust crystalline solids which are easy to store and handle. 2-Vinylpyrroles are most efficiently made from pyrrole-2-carboxaldehyde or from the 2-acylpyrrole via a Wittig reaction in approximately 50% yield over two steps from *N*-H-pyrrole.^{12,38,39} In comparison, *N-p*-toluenesulfonyl-3-vinylpyrrole is generated using the Lewis Acid-catalyzed process outlined above in 83% yield from *N*-H-pyrrole over four steps, a sizable increase in efficiency. In most of the prior examples, the 2-vinylpyrroles are *N*-alkylated due to the high reactivity and tendency towards polymerization and decomposition of *N*-H-2-vinylpyrroles, whereas an *N-p*-toluenesulfonyl group decreases reactivity, increases stability, and may be removed later to give the *N*-H-indole derivative and further replaced with the group of choice.

3.2 Synthesis of Starting Materials

Pyrrole was *N*-tosylated with potassium hydroxide and *p*-toluenesulfonyl chloride in THF to give *N-p*-toluenesulfonylpyrrole **209** in 90% yield (Scheme 13).⁵⁸ Pyrrole **209** was then subjected to Friedel-Crafts acylation conditions using AlCl₃ and acetic

anhydride, giving 3-acetyl-*N-p*-toluenesulfonylpyrrole **210** in 99% yield; ¹H NMR analysis detected no 2-acetylated pyrrole.^{54,56} Sodium borohydride reduction gave the alcohol in 99% yield,¹⁹ which was subsequently dehydrated by heating in DMSO at 160 °C, giving *N-p*-toluenesulfonyl-3-vinylpyrrole **211** in 94% yield.⁵⁶ Over four steps, vinylpyrrole **211** was prepared in 83% overall yield.

Scheme 13. Synthesis of *N-p*-Toluenesulfonyl-3-vinylpyrrole **211**



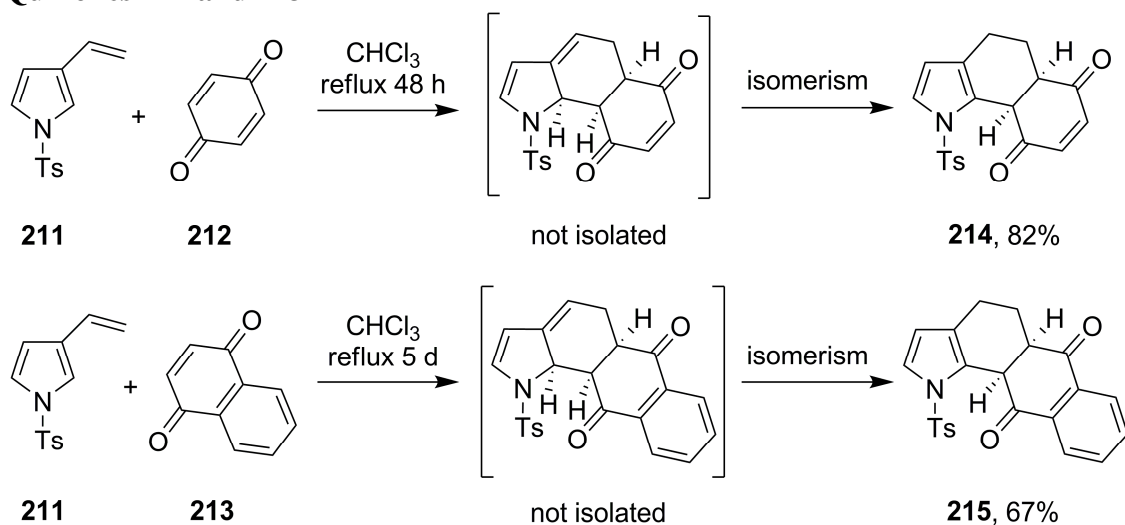
Commercial *p*-benzoquinone and 1,4-naphthoquinones **212** and **213** were used. *N*-(4-Isopropylphenyl)maleimide **4m** and *N*-(4-phenoxyphenyl)maleimide **4e** were synthesized by the reaction of maleic anhydride with the appropriate aniline and heating the resulting maleanilic acid in excess acetic anhydride with sodium acetate to dehydratively close the 5-membered ring.^{12,43} Flash chromatography on silica gel, followed by recrystallization, was used to purify the maleimides.

3.3 Diels-Alder Reactions

Diels-Alder reactions of *N-p*-toluenesulfonyl-3-vinylpyrrole **211** with *p*-benzoquinone **212**, 1,4-naphthoquinone **213**, *N*-(4-isopropylphenyl)maleimide **4m**, and *N*-(4-phenoxyphenyl)maleimide **4e** in chloroform gave compounds **214**, **215**, **216**, and **217**, respectively (Scheme 14 and Scheme 15). The reactions were monitored by TLC. While the maleimide-containing reactions giving adducts **216** and **217** went to completion at room temperature over five days, the Diels-Alder reactions giving **214**

and **215** required for completion refluxing for 48 hours and five days, respectively. In each reaction, the vinylpyrrole was used in slight excess (1.1 equiv) to simplify the required chromatographic purification procedure, since, while the vinylpyrroles were always eluted first, unreacted maleimides or quinones were eluted very close to the adducts. Chromatography on silica gel, followed by recrystallization, was used to purify the adducts. Conditions for the Diels-Alder reactions were not optimized, except that chloroform was used as the solvent based on the considerably higher yields obtained in Part II with Diels-Alder reactions with 2-vinylpyrroles in chloroform versus toluene.¹²

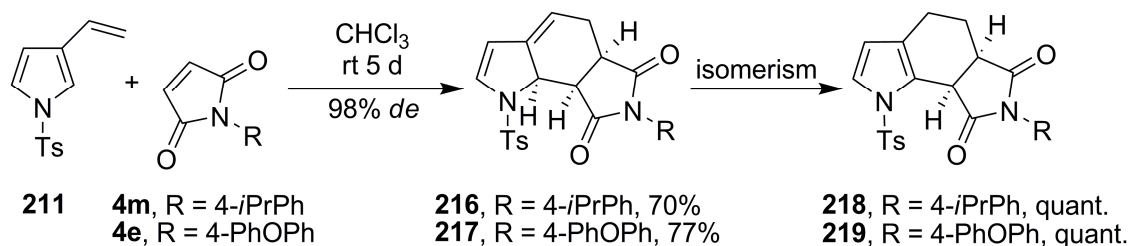
Scheme 14. Diels-Alder Reactions of *N*-*p*-Toluenesulfonyl-2-vinylpyrrole **211 with Quinones **212** and **213****



In Diels-Alder reactions with *p*-benzoquinone and 1,4-naphthoquinone, unisomerized adducts were not isolated or detected; instead compounds **214** and **215** were isolated, in which a double-bond had moved into the 5-membered ring, giving the more stable aromatic pyrrole. In Diels-Alder reactions with maleimides, however, the unisomerized adducts **216** and **217** were isolated first, and quantitative isomerization of

these compounds into the aromatic **218** and **219** occurred in chloroform at rt over about a month, or over several days at reflux (Scheme 15). Although unisomerized adducts were not isolated in Part II's 2-vinylpyrrole work, evidence of them as intermediates was provided by the isolation of products likely resulting from a Michael addition between an unisomerized adduct and a maleimide (see Part II).¹² NOE experiments were used to confirm the stereochemistry of **216** and **217**. This appears to be the first report of the isolation of unisomerized Diels-Alder adducts being formed from vinylpyrroles. The average yield of the Diels-Alder products **214**, **215**, **216**, and **217** was 74%, nearly identical with the 73% average for Diels-Alder products from 2-vinylpyrrole obtained in chloroform in Part II,¹² although a greater number of Diels-Alder reactions of 3-vinylpyrroles would be needed for an accurate comparison of the relative efficiency of the two procedures.

Scheme 15. Diels-Alder Reactions of *N*-*p*-Toluenesulfonyl-2-vinylpyrrole **211 with Maleimides **4m** and **4e****



3.4 Diels-Alder Dimerization

In an effort to extend the general methodology to allow for a highly convergent synthetic step after indole formation via a potential Suzuki coupling,⁵⁹ a Diels-Alder reaction between *N*-toluenesulfonyl-3-vinylpyrrole **211** and commercially available vinylboronic acid 2-methyl-2,4-pentanediol ester **220** was attempted (Scheme 16).⁶⁰

Although Diels-Alder reactions of vinylboranes,⁶¹ vinylboronates,^{60i,62} and of **220**^{60g} are known, they were not found to have been reported with vinylpyrroles. No reaction was observed to occur in chloroform at room temperature over five days, so the solution was refluxed. After three days, a new TLC spot had appeared, and no further consumption of the vinylpyrrole **211** seemed to be occurring. Isolation and purification revealed via ¹H NMR that the new compound was in fact not the expected Diels-Alder adduct **221** and/or **222**, as it lacked any of the characteristic aliphatic methyl groups from vinyl boronate **220**. Characterization of this product using HRMS, COSY, and NOE studies showed it to be the result of a formal Diels-Alder reaction between two molecules of *N*-toluenesulfonyl-3-vinylpyrrole **211**, giving dimer **223** (Figure 10). For descriptions of orientation, the diastereomer with the *syn*-protons at the points of diene fusion protruding from the α -face and the fused-dieneophile protruding from the β -face will always be used, this convention is also used throughout the Experimental. In the ¹H NMR, the 4 α -H and 4 β -H protons were overlapped, which prevented distinguishing between them in the NOE study.

Scheme 16. Attempted Diels-Alder Reaction of *N*-*p*-Toluenesulfonyl-3-vinylpyrrole **211 with Vinylboronate **220****

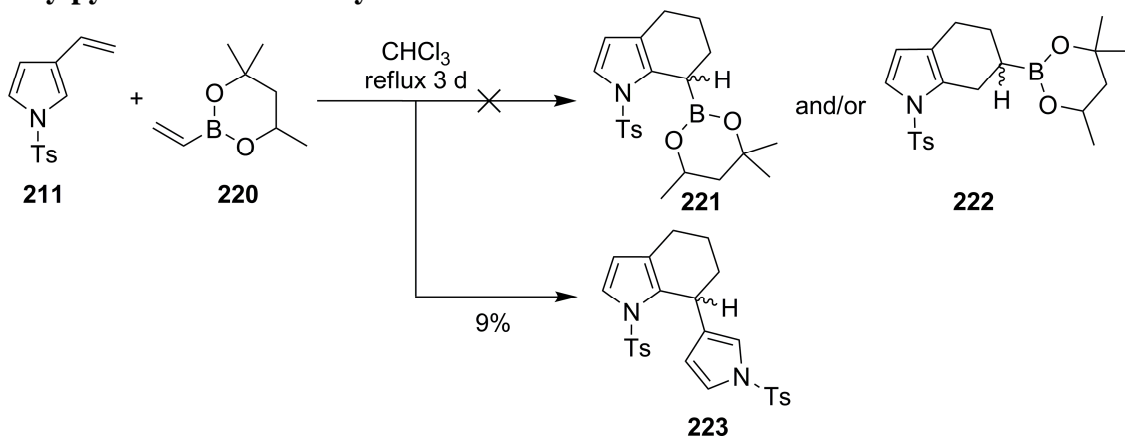
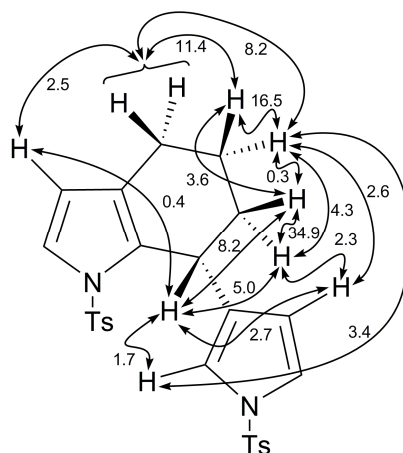


Figure 10. Relevant NOE Interactions for Diels-Alder Dimer 223



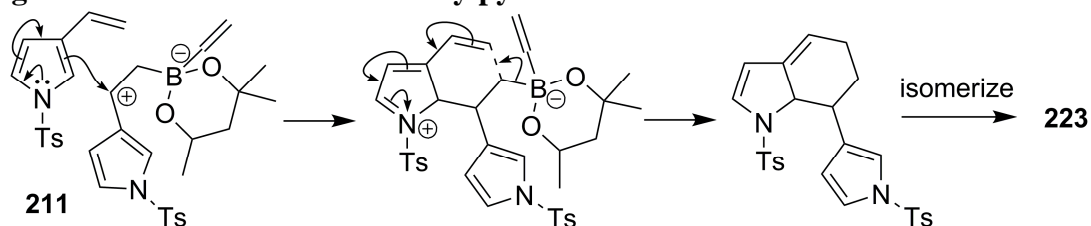
Formation of dimer **223** would occur when two vinylpyrroles approach each other with the terminal ends of their vinyl groups nearest to one-another, seeming to maximize proximity of like partial-charge and to violate the *ortho/para* rule of adduct substitution in Diels-Alder reactions. Refluxing *N-p*-toluenesulfonyl-3-vinylpyrrole **211** in toluene or chloroform without vinylboronate **220** for two weeks produced no sign of dimer **223** by ^1H NMR and HRMS analysis; only starting materials were recovered. Refluxing 100 mg of *N-p*-toluenesulfonyl-3-vinylpyrrole **211** in 10 mL of chloroform with one drop of concentrated hydrochloric acid for several days produced no sign of dimer **223** by TLC analysis; only starting materials were present. Therefore, it is likely that the vinylboronate acted as a Lewis Acid and activated the vinylpyrrole to form the dimer **223**.

Considering the electron-rich nature of vinylpyrrole systems, the reaction reported above seems otherwise unexpected, especially in light of the comparatively electron-deficient nature of the available vinylboronate in this reaction system. Examples of compounds undergoing Diels-Alder-dimerization include butadiene,⁶³ natural

products,⁶⁴ 2-styrylindolizine,⁶⁵ 2-vinylindoles,^{66,67} 3-vinylindoles,^{68,69} and 2-vinylpyrroles.⁷⁰ Several of these dimeric products violate the ‘*ortho/para*’ rule,^{67,69,70} and in each case the diene and the dienophile is connected to an electron-donating substituent, the nitrogen atom of the pyrrole ring, as in the present case, but no Lewis Acid was present. This type of ‘*meta*’ regioselectivity in Diels-Alder reactions having electron-donating substituents on the diene and dienophile was predicted by Houk in 1972 using frontier molecular orbital theory,^{71,72} and it has been experimentally observed in non-dimerization Diels-Alder reactions not involving pyrrole as well (between the diene generated from benzocyclobutenes with the dienophiles propyne and ethoxyethene).⁷³ As in some of the examples of ‘*ortho/para*’ rule violation,^{67,69,70,73} a steric argument may also be made to help explain formation of the dimer **223**, especially considering that in the present case dimer formation did not occur without the Lewis acid. This can be rationalized if one molecule of **211** complexes with the boronate **220** acting as a Lewis acid at the more basic, terminal end of **211**. This may cause the terminal end of the vinylpyrrole to be so sterically bulky as to prohibit approach by either a non-Lewis acid-complexed vinylpyrrole in the normal *ortho/para* regiochemistry or another Lewis acid-complexed vinylpyrrole (statistically unlikely), allowing only the approach of a non-Lewis acid-complexed vinylpyrrole with the pyrrole ring farthest from the complexing-Lewis acid. The electrons of the nitrogen of the non-complexed vinylpyrrole may then drive an attack from the α -carbon of that pyrrole to the α -carbon of the vinyl group of the complexed pyrrole, the positive charge of which is enhanced by complexation with the Lewis acid (Figure 11). This is followed by dissociation of the catalyst and concomitant bond formation between the

terminal carbons of each vinylpyrrole. Then, isomerization of the double bond in the adduct gives the observed 7-pyrrolyl-substituted tetrahydroindole **223**. In this proposed mechanism, nucleophilic attack of the free pyrrole in the first step effectively allows reversal of the normal polarity of the terminus of its vinyl group, allowing the second carbon-carbon bond formation, an example of umpolung.⁷⁴ Further studies are needed to discern the limits of such a dimerization approach towards indoles.

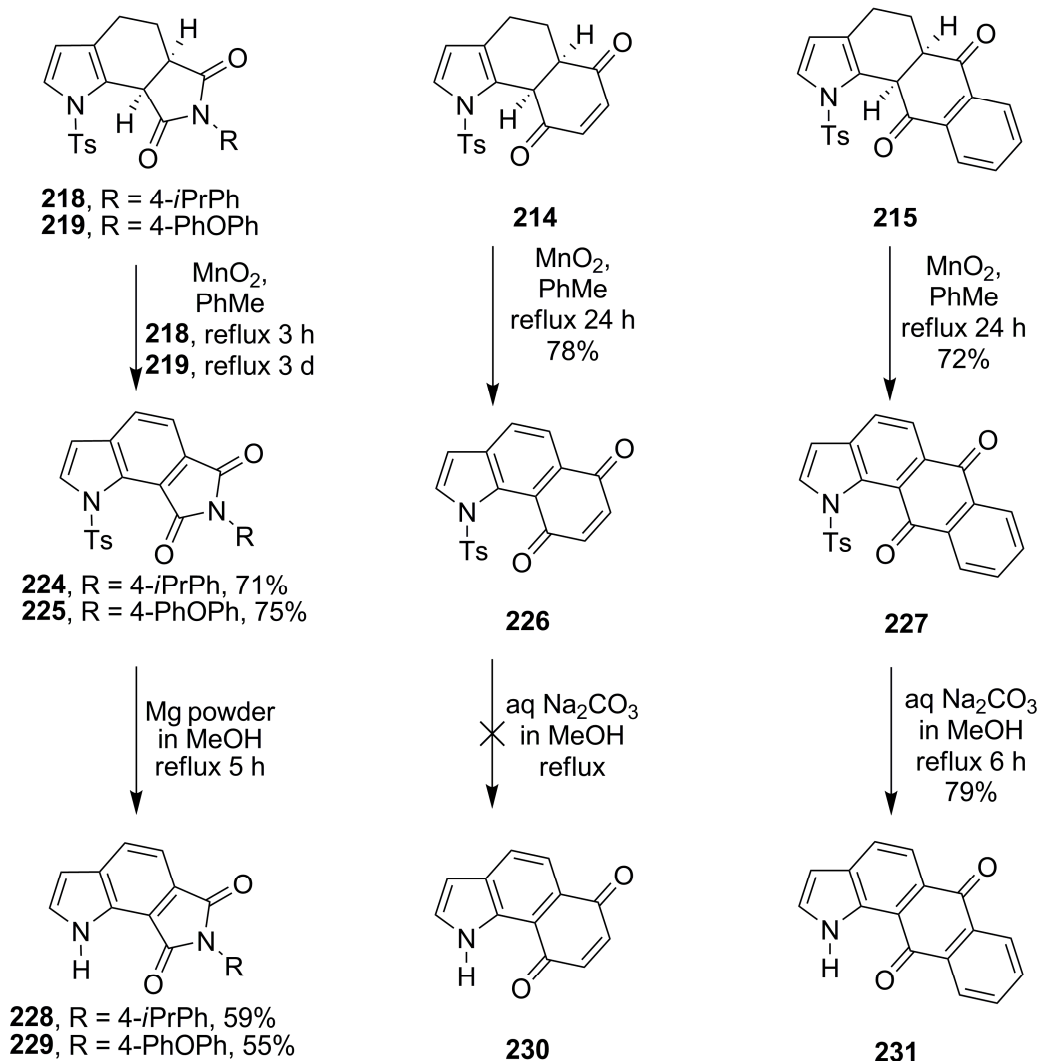
Figure 11. Formation of the 3-Vinylpyrrole Dimer 223



3.5 Aromatization of Diels-Alder Adducts

Tetrahydroindoles **218**, **219**, **214**, and **215** were aromatized using MnO_2 in refluxing toluene for 3-72 hours, giving **224**, **225**, **226**, and **227** in 71, 75, 78, and 72% yields, respectively (Scheme 17). The most consistent and high-yielding results were achieved using MnO_2 generated from manganese(II) sulfate and potassium permanganate,⁴⁸ which was also used in Part II's 2-vinylpyrrole work.¹² The average yield from dehydrogenations was 74%, higher than the 54% average achieved in aromatizing the adducts resulting from 2-vinylpyrrole, indicating that the tosyl group may help to facilitate the reaction or provide some degree of stability to the tetrahydroindoles during the aromatization process.¹²

Scheme 17. Aromatization and Detosylation of Tetrahydroindoles **214, **215**, **218**, and **219****



3.6 Detosylation of *N*-*p*-Toluenesulfonylindoles

Detosylation of maleimide-derived indoles **24** and **225** was accomplished with magnesium in refluxing methanol for five hours, giving **228** and **229** in 59 and 55% yield, respectively (Scheme 17).⁷⁵ Detosylation of 1,4-naphthoquinone-derived indole **227**⁷⁶ was effected by saponification with aqueous sodium carbonate in methanol under reflux for six hours. With saponification of **224** and **225**, competition between removal

of the toluenesulfonyl-group and hydrolysis of the imide was observed. When these two methods were applied to the *p*-benzoquinone derived indole **226**, decomposition occurred with no recovery of starting materials. Various other methods were attempted, such as TBAF in refluxing THF/MeOH,⁷⁷ the dilithium salt of thioglycolate in DMF,⁷⁸ 5% sodium-mercury amalgam in THF/MeOH,⁷⁹ and concentrated sulfuric acid,⁸⁰ but none of these methods gave the desired *N*-H indole **230**. The failure to achieve compound **230** is likely due to the α,β -unsaturated dione portion of indole **226** acting as a strong Michael acceptor. An example exists of saponification failing to detosylate an *N*-tosyl compound containing such a dione portion,⁸¹ an *N*-*p*-toluenesulfonyl-1*H*-indole-4,7-dione, but some precedent exists for detosylation of such compounds using TBAF in THF.⁸² However, 1*H*-indole-4,7-diones may be distinguished from **226** because the carbonyls of these compounds are in more direct conjugation with the electron-releasing nitrogen, causing deactivation. If the conjugated dione of compound **226** indeed prevented its detosylation by the means attempted, then a masking technique could be used, such as reduction of **226** and formation of the *bis*-silyl ether,⁸³ detosylation via conventional means, then desilylation followed by tautomerization to the quinone⁸⁴ to give *N*-H indole **230**.

3.7 Biological Activity

While participating in the Developmental Therapeutics Program at the National Cancer Institute (NCI), eight compounds were submitted to the NCI for a one-dose 60-human tumor cell line pre-screen: compounds **214**, **215**, **218**, **219**, **224**, **225**, **226**, and **227**. Of these, four compounds, **214**, **215**, **226**, and **227**, were judged by the NCI to

have sufficient activity to justify screening with 60 human-tumor cell lines at five concentrations with 10-fold dilutions, from 1×10^{-4} M to 1×10^{-8} M. All four of these compounds were found to have high levels of activity against many of the 60 different cell lines tested. Compound **214** was most active against colon cancer HCT-116, melanoma M14, and non-small cell lung cancer, with IC_{50} 's of 67, 63, and 37 ng/mL, respectively. Compound **215** was most active against melanoma M14, and leukemia cell lines CCRF-CEM and HL-60(TB), with IC_{50} 's of 11, 13, and 11 ng/mL, respectively. Compound **226** was most active against melanoma UACC-257, and leukemia cell lines MOLT-4 and SR, with IC_{50} 's of 21, 56, and 50 ng/mL, respectively. Compound **227** was most active against CNS cancer SF-295, ovarian cancer OVCAR-3, and melanoma MDA-MB-435, with IC_{50} 's of 10, 9.6, and 9.1 ng/mL, respectively. Compounds **214** and **226** were selected by the NCI for toxicity testing and subsequent hollow fiber testing. Compound **214** had a maximum tolerated dose of 100 mg/Kg body wt in athymic nude mice, with death resulting in 3 days at 200 mg/Kg body wt and 2 days at 400 mg/Kg body wt. Hollow fiber testing of compound **214** against breast cancer MDA-MB-231, non-small cell lung cancer NCI-H23 and NCI-H522, colon cancer SW-620 and COLO 205, melanoma LOX IMVI, UACC-62, and MDA-MB-435, ovarian cancer OVCAR-3, CNS cancer U251 and SF-295 gave a score of 4/96 with no cell kill, below the 20/96 minimum score required for selection for xenograft testing. Toxicity and hollow fiber testing data for compound **226** were pending at the time of submission of this dissertation. No intention to further test the compounds in Part III was indicated by the NIH at the time this manuscript was submitted.

3.8 Conclusion

N-p-Toluenesulfonyl-3-vinylpyrrole underwent *endo*-addition [4+2] cycloaddition reactions with *p*-benzoquinone, 1,4-naphthoquinone, and maleimides, giving isomerized tetrahydroindoles with *p*-benzoquinone and 1,4-naphthoquinone, and unrearranged tetrahydroindoles with maleimides. In the presence of vinylboronic acid 2-methyl-2,4-pentanediol ester, *N*-tosyl-3-vinylpyrrole underwent a Diels-Alder dimerization. Dehydrogenation of the tetrahydroindoles with activated MnO₂ in refluxing toluene gave the corresponding indoles. The maleimide-fused indoles were detosylated via saponification, and the 1,4-naphthoquinone-fused indole was detosylated with magnesium in refluxing methanol, giving the *N*-H indoles in moderate to good yields. This efficient methodology for formation of indoles offers high convergency and easily accessible starting materials.

3.9 Notes on ¹H NMR Analysis for Part III

In the ¹H NMR spectra of unisomerized adducts **216** and **217**, the 5 α -H proton appears as a doublet of doublet of doublet of doublets; COSY experiments indicate that the 5 α -H proton is coupled not only to the 5 β -H, 4-H, and 5 $\alpha\alpha$ -H protons, but also to the 8 $\beta\alpha$ -H proton at approximately 3.0 Hz.^{19,35} For isomerized adduct **214**, the 7-H proton is coupled not only to the 8-H proton but also to the 5 $\alpha\alpha$ -H proton at approximately 1.2 Hz.⁸⁵

Part IV. Access to Indoles via Diels-Alder Reactions of 2-Methylthio-5-Vinylpyrroles.¹⁴

4.1 Introduction

In comparing the efficiency of the Diels-Alder reactions of *N*-H-2-vinylpyrroles and *N*-tosyl-3-vinylpyrrole, it was inspiring to note the apparent increase in yields caused by the use of the *N*-tosyl group, which was later able to be removed. Seeking to expand the usefulness of the technique of approaching indoles via vinylpyrroles, it was chosen to study the use of electron-donating protective groups on the 2-vinylpyrrole-diene with the objective of enhancing efficiency by simultaneously preventing unwanted side-reactions while maintaining or increasing reactivity. The α -position of pyrrole is the most reactive, therefore blocking that location was desired, however, placing removable electron-donating functionalities on the vinyl group solely for temporary enhancement of reactivity was another goal. It was hoped that any increase in the electron density of the diene caused by the use of removable groups would broaden the library of indoles conceivably achievable via normal-demand Diels-Alder reactions of vinylpyrroles by allowing the use of less electron-deficient dienophiles.

Due to the high reactivity of the pyrrole system, several types of removable groups at the α -position have been used with pyrrole to prevent unwanted reactions.⁸⁶ Often used in the setting of porphyrin synthesis,⁸⁷ most of the methods developed involve electron-withdrawing protecting groups, due partially to a desire to temper the reactivity of pyrrole.⁸⁸ These include carboxylate⁸⁹ and aldehyde groups,⁸⁶ which are commonly removed (with aldehydes being first oxidized) using high temperature treatment with

strong base or acid to cause saponification followed by decarboxylation. Due to its reactivity, the 2-carboxaldehyde group is itself often further protected.⁸⁷ Other electron-withdrawing protective groups used are the more mildly-cleaved sulfinyl and sulfonyl groups,⁹⁰ removed using Raney nickel or using radical-induced reductive desulfonylation with Bu₃SnH/AIBN,⁹¹ and 2,4-dinitrobenzenesulfinyl which can be removed by oxidation and then treatment with phenylthiol.⁹⁰ These protecting groups were not suited to this project's goals since they would decrease the electron density of 2-vinylpyrrole and would therefore likely cause an undesirable decrease in normal-demand [4+2] cycloaddition reactivity.

Comparatively few examples exist of electron-donating functionalities being used to α -protect pyrrole. The only example found was the alkylthio group, recently reported by Lindsey and coworkers.^{92,93} The alkylthio group has the advantage of being readily removed using Raney nickel, and a variety of 2-alkylthiopyrroles are readily available from the corresponding 2-thiocyanatopyrrole.^{92,93} After protection, further functionalization of pyrrole to the aldehyde via aromatic electrophilic substitution might be enhanced due to the electron-releasing characteristics of the thio group.⁹⁴ It was hoped the group would provide adequate electron donation to enhance or maintain Diels-Alder reactivity, while not deactivating the aldehyde towards Wittig methylenation and causing sluggish formation of the vinyl functionality.

Several examples exist that demonstrate the use of removable groups to enhance the efficiency of Diels-Alder reactions. Removable hydrophilic 2-pyridyldimethylsilyl groups on a diene were shown to enhance water solubility as a means of increasing Diels-Alder reaction efficiency.⁹⁵ Furan has been shown to have increased reactivity as

a Diels-Alder diene when substituted at the 2-position with methylthio^{96,97} and phenylthio⁹⁷ groups, which were not removed later; these results were encouraging since with direct substitution on a diene the electron-donating effect of the electronegative sulfur atom did not overpower its inductive effect. There were no prior studies found which examine the use of removable electron-donating groups that are in distant conjugation with the diene used as a means to enhance Diels-Alder reactivity.

By placing removable electron-donating functionalities directly on the vinyl group in combination with α -alkylthio protection, a dialkylthio-substituted hyper-electron rich diene was envisioned, which later could be di-deprotected in a single step. Diels-Alder reactions of sulfonyl-,^{98,99} sulfinyl-,¹⁰⁰ and sulfanyl-substituted^{99,101} dienes are known, though none of the examples found remove the sulfur group after the Diels-Alder reaction. Murase et al. showed 3-(1-(methylthio)vinyl)indoles and 3-(1-(benzylthio)vinyl)indoles underwent [4+2] cycloadditions with DMAD at 67% and 70% yield, respectively.¹⁰² However, in the only example found of Diels-Alder reactions of vinylpyrroles with an alkylthio-substituted vinyl group, Murase et al. showed the corresponding 3-(1-(benzylthio)vinyl)pyrrole gave the Diels-Alder adduct with DMAD at 31% yield,⁵¹ surprisingly the yields achieved in Part III with Diels-Alder reactions of the comparatively deactivated *N*-toluenesulfonyl-3-vinylpyrrole with maleimides were much higher.¹³ The poor yield in Murase et al.'s 3-vinylpyrrole case could have been caused by predominance of *s-trans* geometry in the diene system due to steric repulsion between the pyrrole and the benzylthio functionality. However, this explanation does not adequately explain the 70% yield achieved with 3-vinylindole, as steric interactions between indole and the benzylthio-group would be, if anything, greater by comparison.

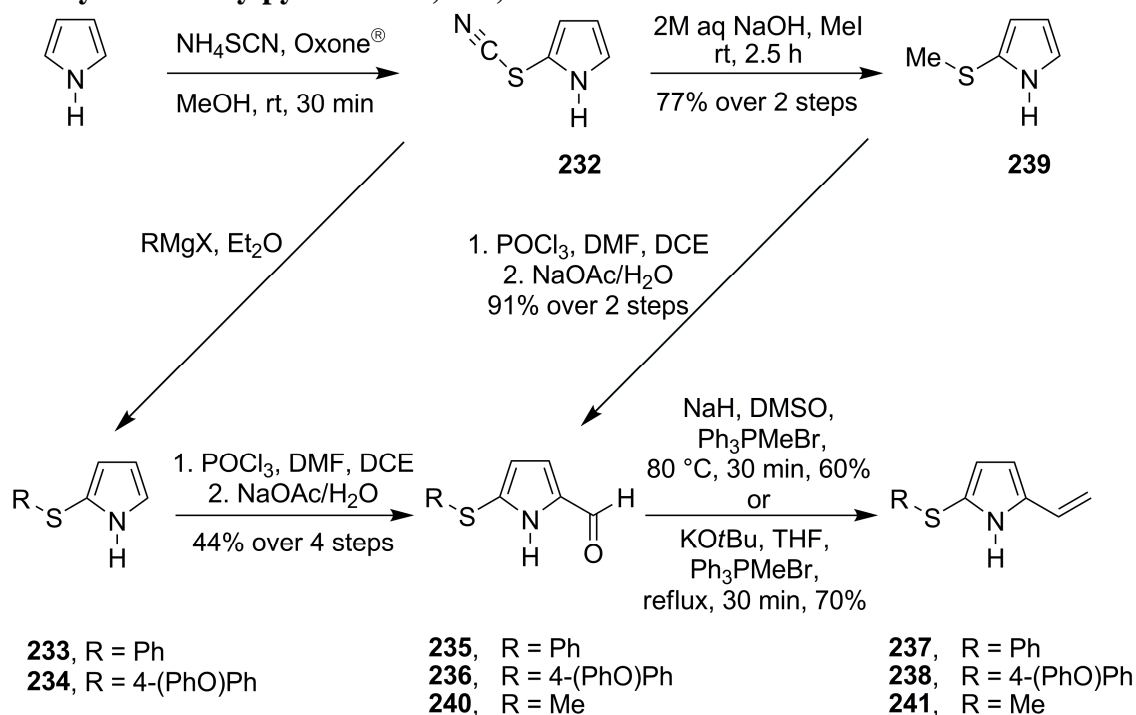
Rather, unintended reactions of the thio-activated pyrrole at the reactive α -unsubstituted site could be more likely to blame for the differences in yield, a hypothesis that was desired to be tested by examining the reactivity of pyrrole substituted with an α -protecting group in combination with an alkylthio-substituted vinyl group.

4.2 Synthesis of Starting Materials, and Diels-Alder Reactions

Initially, it was hoped that use of a bulky aromatic-substituted thio group would imbue crystallinity to the vinylpyrrole at room temperature, potentially allowing the benefit of purification via recrystallization, as vinylpyrroles are often unstable on silica gel. With this in mind, 2-phenylthio- and 2-(4-phenoxyphenylthio)-5-vinylpyrroles **237**¹⁰³ and **238** were chosen to be generated first (Scheme 18). Although Lindsey et al. demonstrated that 2-phenylthiopyrrole **232** is deactivated towards deuterium exchange relative to pyrrole itself, it was hoped that any lessening of reactivity would be slight and would be outweighed by ease of purification.⁹² Pyrrole was treated with ammonium thiocyanate, giving thiocyanatopyrrole **232**,¹⁰⁴ which was immediately subjected to Grignard reaction conditions to give, after a time-consuming workup, **233** and **234**.¹⁰³ The crude Grignard products were then used in a Vilsmeier-Haack reaction, giving, following flash chromatography, aldehydes **235** and **236** at 44% yield over four steps.^{28,94} A Wittig reaction using Corey's modification⁴¹ followed by flash chromatography gave 2-arylthio-5-vinylpyrroles **237** and **238** at approximately 60% yield. Unfortunately, all attempts at crystallizing these vinylpyrroles in a freezer failed, thus they are probably liquids at room temperature. During chromatography on silica gel several closely-eluting impurities were not fully removed and some decomposition

occurred; therefore, it was decided to not bring vinylpyrroles **237** and **238** to analytical purity unless their success as Diels-Alder dienes could be established.

Scheme 18. Synthesis of 2-Phenylthio-, and 2-(4-Phenoxyphenyl)thio-, and 2-Methylthio-5-vinylpyrroles **237, **238**, and **241****



Vinylpyrroles **237** and **238** (1.1 equiv) were stirred individually with the dienophile 4-ethylphenylmaleimide **41** in chloroform for several days, no reaction was observed to occur by TLC. The vinylpyrrole was used in excess because past experience in Parts II and III with vinylpyrroles indicated any adduct formed would be eluted during chromatography likely very near to the maleimide.^{12,13} The reactions were refluxed for five days, but still no new TLC spots had appeared, ¹H NMR confirmed that only starting materials were present in the reaction mixture. The same results were observed when DMAD was employed as the dienophile.

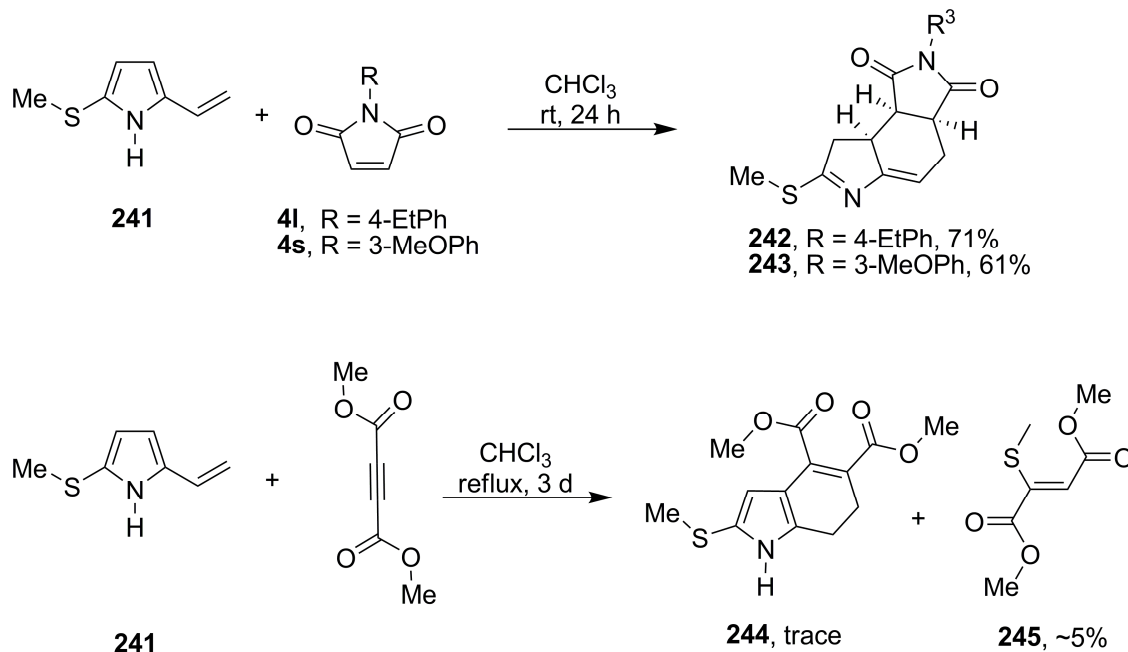
With arylthio substituents apparently too electron-withdrawing to maintain reactivity of the diene, the methylthio substituent was tried next, with confidence; studies by

Lindsey et al. have demonstrated that 2-alkylthio substituents slightly activate pyrrole towards deuterium exchange at the 5-position 1.4- to 4-fold, with the 4-position deactivated 5- to 7-fold, and the 3-position strongly activated 8- to 25-fold, as compared to *N*-H-pyrrole.⁹² 2-Thiocyanatopyrrole **232** was treated with 2M sodium hydroxide and methyl iodide for 2.5 hours to give the 2-methylthiopyrrole **239** in 77% yield over two steps from pyrrole, a small amount of *N*-methyl-2-methylthiopyrrole was also generated (about 5% by mass, as determined by ¹H NMR).¹⁰⁵ The crude **239** was then subjected to a Vilsmeier-Haack reaction^{28,94} to give aldehyde **240** at 91% yield, which was conveniently vacuum-distilled for purification, any codistilled *N*-methyl-2-methylthio-pyrrole-2-carboxaldehyde was easily removed by trituration with hexanes. Lastly, a Wittig reaction was performed on **240** using potassium *t*-butoxide in THF,¹² which, following vacuum-distillation, gave the desired 2-methylthio-5-vinylpyrrole **241** at 69% yield.

Methylthio-protected vinylpyrrole **241** (1.1 equiv) was stirred with 4-ethylphenylmaleimide **41** in chloroform for 24 hours, at which point TLC indicated one new product had been formed, and the limiting reagent had been completely consumed (Scheme 19). At first, the ¹H NMR of Diels-Alder adduct **242** was baffling, as there was no *N*-H peak. However, an extra peak in the carbonyl region of the ¹³C NMR indicated the distinctive thio-imine functionality of the adduct,¹⁰⁶ COSY and NOE experiments verified the structure. In Diels-Alder reactions with vinylpyrrole **241**, the dienophiles *N*-(4-ethylphenyl)maleimide and *N*-(3-methoxyphenyl)maleimide **41** and **4s** were used, stirring in chloroform for 24 hours, giving adducts **242**, and **243** at 71%, and 61% yield, respectively. Although a greater number of reactions would be required for

a thorough comparison, these yields are comparable or slightly lower than those observed with 2-vinylpyrrole in Part II,¹² which had a 73% average yield for Diels-Alder reactions run in chloroform.

Scheme 19. Diels-Alder Reactions of 2-Methylthio-5-vinylpyrrole **241**



These results demonstrate that the methylthio group probably very slightly deactivates the vinylpyrrole toward Diels-Alder chemistry; thus, the inductive effect of the sulfur overcomes the effect of its electron donation to the diene. It is notable that no double-addition Michael addition type products were detected as were seen in Part II; just as the methylthio group may be slightly decreasing the electron-density of the diene, the methylthio group may also make the adduct a worse Michael component by decreasing its nucleophilicity through the inductive effect of sulfur. Additionally, because no adduct which had rearranged into the aromatic pyrrole was isolated, the conjugated thio-imine functionality of **242** and **243** is likely quite stable, in contrast with Part II in which all isolated adducts had rearranged to the aromatic pyrrole form.

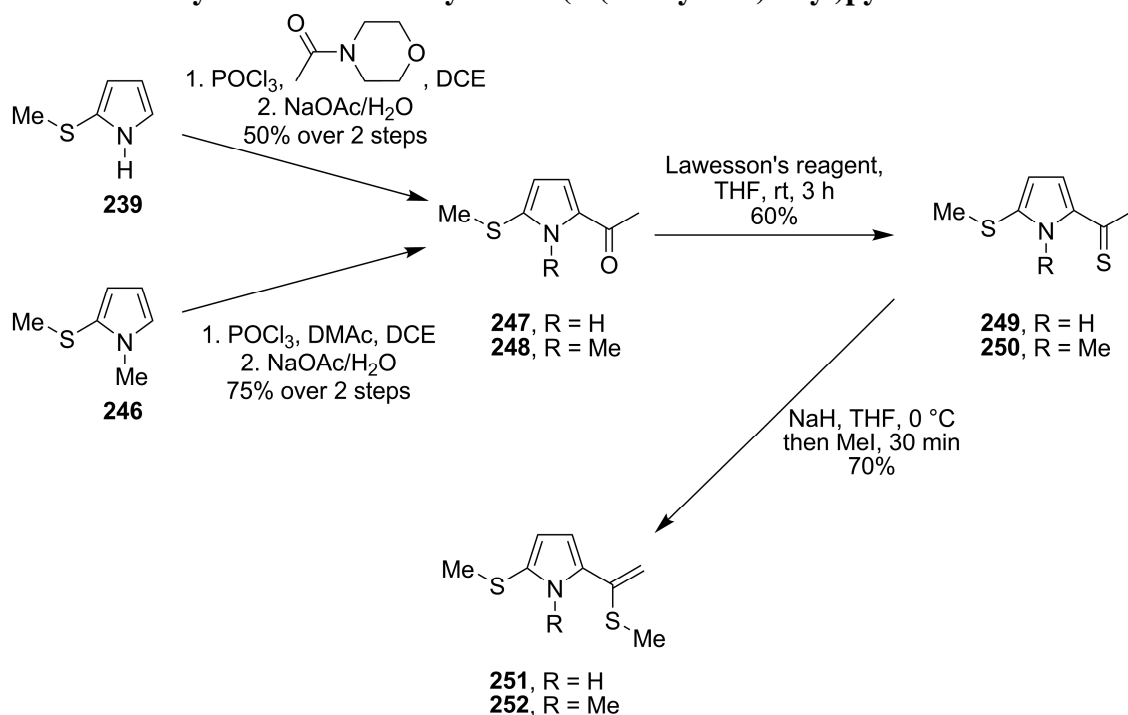
This may mean that the activation energy for formation of a double-addition type Michael addition product from a methylthioated adduct is significantly higher than for the adducts in Part II.

The Diels-Alder reaction of vinylpyrrole **241** with DMAD was also attempted (Scheme 19). Heat was generated upon addition of the DMAD, and black tars formed in the first five minutes, potentially indicating a polymerization reaction. When subjected to flash chromatography with ethyl acetate/hexanes, only ~25% mass recovery occurred, with most of the black material staying at the top of the column, further evidencing that the main reaction occurring was not the desired Diels-Alder reaction. The mass corresponding to expected adduct **244** was detected via HRMS but the adduct was not generated in sufficient quantity to isolate and characterize. Rather, the major product isolated (~%5 yield) was dimethyl 2-methylthiomaleate **245**,¹⁰⁷ corresponding to a Michael addition of the methylthio group to DMAD, with demethylthioation of the vinylpyrrole. Because DMAD is a soft electrophile, this may make a Michael addition from sulfur, a soft nucleophile, preferred over a Diels-Alder reaction,¹⁰⁸ although extensive variation of reaction conditions was not attempted.

To synthesize dimethylthioated vinylpyrroles **251** and **252**, 2-thiocyanatopyrroles **232** and **246**¹⁰⁴ were first acetylated using a Vilsmeier-Haack reaction to give 5-acetyl-2-methylthiopyrroles **247** and **248** (Scheme 20);^{91,109} Muchowski et al. has demonstrated that the 2-methylthio group has a directing effect to give acylation at exclusively the 5-position.⁹⁴ While **247** was a crystalline solid which could be recrystallized for facile purification, acetylpyrrole **248** was a liquid that included several closely spotting impurities which were revealed by ¹H NMR to be unmethylthioated 2-

and 3-acetylpyrrole, caused by incomplete conversion of *N*-methylpyrrole during the initial thiocyanation step towards generation of **246**. Fractional vacuum distillation was performed twice to give 5-acetyl-1-methyl-2-methylthiopyrrole **248** at a maximum purity of 7:1 by mass. Acetylpyrroles **247** and **248** were then treated with Lawesson's reagent's reagent to give the thioacetylpyrroles **249** and **250**.^{51,102}

Scheme 20. Synthesis of 2-Methylthio-5-(1-(methylthio)vinyl)pyrroles 251 and 252



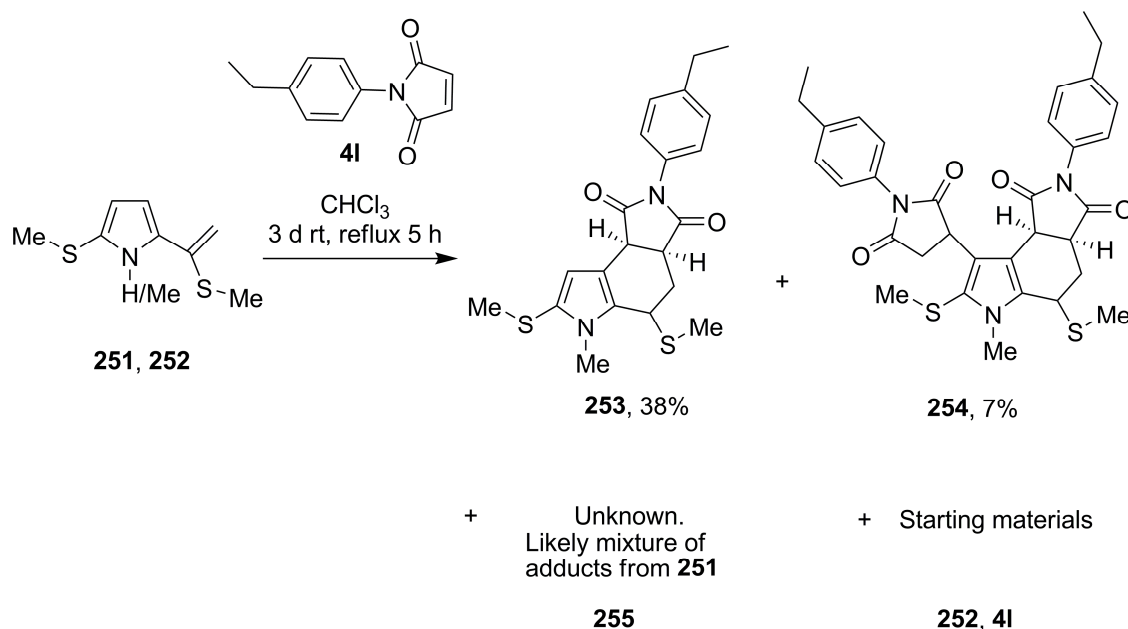
The thioacetylpyrroles **249** and **250** were then allowed to react at 0 °C with sodium hydride (1.5 equiv) for 10 minutes, followed by addition of methyl iodide (1.5 equiv) and stirring for 30 minutes at 0 °C, giving the 2-methylthio-5-(1-(methylthio)vinyl)pyrroles **251** and **252**.^{51,102} From TLC analysis, it could be seen that the *N*-H-thioacetylpyrrole **249** at first gave one product in the first 15 minutes, which then rapidly began to form into another higher-spotting product. Further comparison of

TLCs and also ^1H NMR analysis of the products revealed that the *N*-H-vinylpyrrole **251** was being transformed into *N*-methylvinylpyrrole **252** in the presence of sodium hydride and methyl iodide. The ratio of *N*-methyl to *N*-H products depended on the time allowed to pass before the reaction was quenched with aqueous ammonium chloride, and was generally equal to or more than 1:1 by mass, but for complete conversion of the thioacetylpyrrole, the ratio of **252** to **251** was approximately 2:1 by mass. Perhaps the use of lower temperatures could help to avoid this problem in the future. When generated from thioacetylpyrrole **250**, vinylpyrrole **252** had small amounts of impurities caused by the use of impure starting material **250** (which had approximately 13% impurities by mass). Flash chromatography of the mixture of **251** and **252** was attempted on silica gel using ethyl acetate and hexanes, significant degradation of the products was observed. Since the *N*-H-thioacetylpyrrole **249** was pure and provided a mixture of pure *N*-H and *N*-methyl-vinylpyrroles, it was used as the source of dimethylthioated vinylpyrroles for the remainder of this Part.

The approximately 2:1 mixture of dimethylthioated *N*-methyl and *N*-H-vinylpyrroles **251** and **252**, generated from *N*-H-thioacetylpyrrole **249**, was then allowed to react with 1-(4-ethylphenyl)maleimide **4I** (0.8 equiv) in chloroform at room temperature (Scheme 21). The vinylpyrrole was used in excess to simply purification, since previous experience has shown that the Diels-Alder adduct is generally eluted during column chromatography very near to the maleimide starting material. After 3 days, all *N*-H-vinylpyrrole **251** was consumed, but both *N*-methylvinylpyrrole **252** and maleimide **4I** remained. The reaction was refluxed, and after five hours very little change was observed by TLC analysis. In a desire to prevent destruction or rearrangement of the

products that were anticipated to have formed, the reaction was stopped after five hours reflux, with some *N*-methylvinylpyrrole **252** and maleimide **41** still remaining in the reaction mixture.

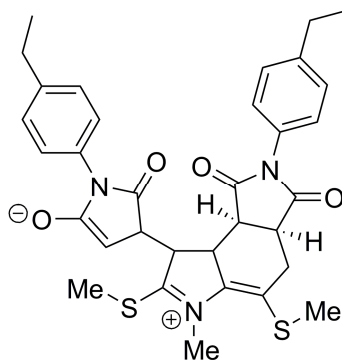
Scheme 21. Diels Alder reactions of 2-methylthio-5-(1-(methylthio)vinyl)pyrroles **251 and **252****



The crude reaction mixture was subjected to chromatography, and not unexpectedly, vinylpyrrole **251** suffered degradation and several other new TLC spots formed. However, along with maleimide **41**, three new products were isolated. The major product was the expected rearranged adduct **255** from *N*-methylvinylpyrrole **252**. Another product isolated was **254**, a double-addition type product also formed from vinylpyrrole **252**. Though in Part II double-addition products were observed to have formed via a Michael addition from the 5-position carbon of the adducts, this is the first example of a Michael addition from an adduct at the β -position of pyrrole. There appears to be no precedent for this type of product in the literature. These types of products may not have been observed in Part II, or earlier in this Part, because the

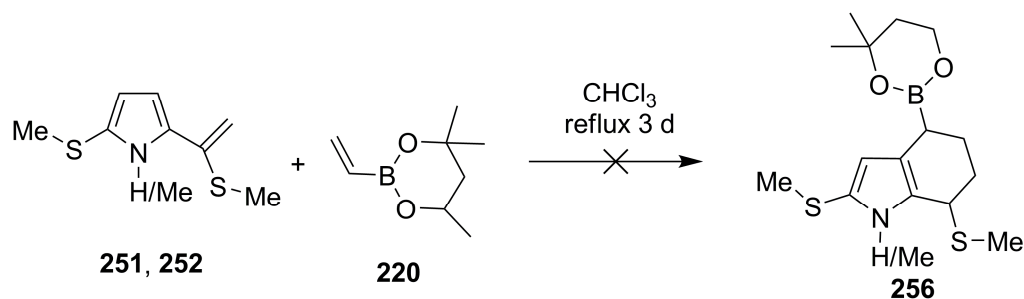
activation energy required to form compound **254** might be lowered by resonance stabilization of the Michael addition intermediate, if the addition occurs before the adduct rearranges to the aromatic pyrrole (Figure 12). A third new product was isolated from the MPLC, compound(s) **255**, but was not able to be purified enough to fully characterize. However, it is likely from the ^1H NMR, ^{13}C NMR, and HRMS data ($\text{M}+\text{Na}^+$ calcd 409.1016, found 409.1026), that **255** (a single TLC spot in 1:1 ethyl acetate/hexanes, $R_f \approx 0.42$) is a mixture of rearranged and unrearranged adducts formed from the *N*-H-vinylpyrrole **251**. The isolated vinylpyrrole **252** in combination with the uncharacterized likely degradation products resulting from chromatography of **252** approximately completed the mass balance for this reaction.

Figure 12. Stabilized Intermediate in Formation of Double-Addition Adduct 254



The mixture of dimethylthioated *N*-methyl and *N*-H-vinylpyrroles **251** and **252** was also allowed to react with vinylboronate **220** (0.8 equiv) in chloroform at room temperature (Scheme 22). After three days at room temperature no reaction was observed by TLC, so the mixture was refluxed. After five days, disappointingly, no reaction was detected by TLC, and ^1H NMR of the crude reaction showed no sign of the desired Diels-Alder products.

Scheme 22. Attempted Diels-Alder Reaction between Vinylpyrroles 251 and 252 and Vinylboronate 220



A more thorough comparison of the reactivity of vinylpyrroles was desired, but finding dienophiles that were on the cusp between reacting and not reacting with a diene to compare the electron density of each diene seemed unduly time-consuming. Instead, by inspecting the ^1H NMRs of the vinylpyrroles and comparing the chemical shifts of the vinylogous protons, the electron-densities of each diene system may be more efficiently compared (Table 3). The more shielded the vinyl protons, the more relative electron density there should be on the diene, and thus the greater reactivity of the diene in a normal-demand Diels-Alder reaction. There is infrequent precedent for this method of comparing reactivity in Diels-Alder reactions.¹¹⁰ This method of comparison does not take into account the geometry of the diene, as certain steric situations may cause an *s-trans* configuration to be favored over the *s-cis* configuration required for a Diels-Alder reaction.

Table 3. ^1H NMR Chemical Shifts of the Vinylogous Protons of Vinylpyrroles in CDCl_3 .

<u>Compound</u>	<u>1'-H</u>	<u>2'-H</u>
2-Vinyl- <i>N</i> -H-pyrrole, 116	6.60	5.29, 5.03
2-Vinyl- <i>N</i> -Me-pyrrole, 115d	6.65	5.55, 5.11
5-PhS-2-vinyl- <i>N</i> -H-pyrrole, 237	6.79	5.61, 5.17
5-PhOPh-2-vinyl- <i>N</i> -H-pyrrole, 238	6.82	5.60, 5.18
2-MeS-5-vinyl- <i>N</i> -H-pyrrole, 241	6.73	5.31, 5.04
2-MeS-5-(MeSvinyl)- <i>N</i> -H-pyrrole, 251	NA	5.40, 4.85
2-MeS-5-(MeSvinyl)- <i>N</i> -Me-pyrrole, 252	NA	5.22, 5.12

The vinylogous protons of 2-vinyl-*N*-methyl-pyrrole **115d** are deshielded as compared to those of 2-vinyl-*N*-H-pyrrole **116**, due to the ability of the *N*-H nitrogen to donate electrons into the diene system while partially losing its mildly acidic proton, stabilizing the resulting positive charge on the nitrogen. The vinyl protons of 2-phenoxyphenylthio- and 2-phenylthio-5-vinylpyrroles **237** and **238** are significantly more deshielded than those of the unthioated pyrroles **115d** and **116**, due to the electron-withdrawing effect of the phenyl groups and due to inductive effects from the sulfur. This relationship correlates with the observation that phenylthioated vinylpyrroles **237** and **238** are unsuitable as Diels-Alder dienes. The degree to which the phenyl groups contribute to deshielding the vinyl protons of **237** and **238** as contrasted with the inductive and resonance effects of sulfur is partially evident when examining the shifts for the vinyl protons of 2-methylthio-5-vinylpyrrole **241**, which appear very near but slightly downfield from those of unthioated *N*-H vinylpyrrole **116**.

These relationships correlate nicely with the slightly lower yield achieved in Diels-Alder reactions of methylthioated **241** as compared to those achieved with unthioated *N*-H and *N*-methyl vinylpyrroles **115d** and **116** in Part II. These values seem to indicate that greater activation is required if a methylthio group is indeed to serve as a removable activating group for enhancing the efficiency of Diels-Alder reactions of vinylpyrroles.

One vinyl proton of *N*-methyl dimethylthioated vinylpyrrole **252** appears very slightly deshielded as compared to those of the less reactive of the unthioated vinylpyrroles, **115d**, but the other vinyl proton of **252** is slightly more shielded than those of either **115d** or **116**. Similarly, while one vinyl proton of *N*-H dimethylthioated vinylpyrrole **251** appears in-between those of unthioated **115d** and **116**, the other proton appears dramatically upfield from those of **115d** and **116**.

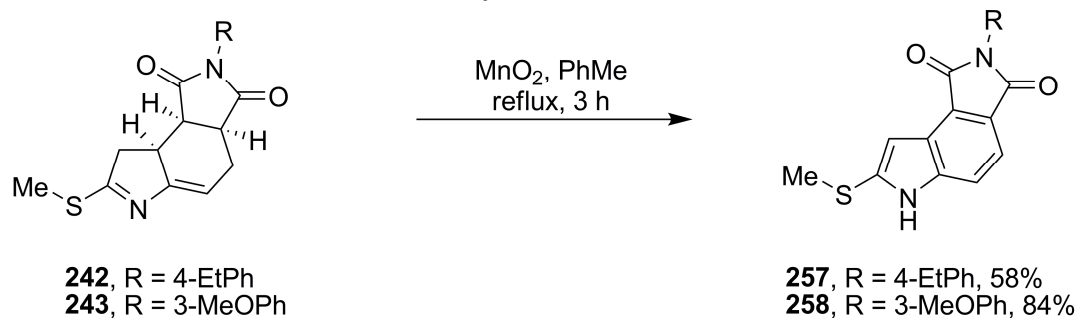
If the electron density as shown by chemical shift alone were the indication of how well dienes perform in Diels-Alder reactions, it would seem that dimethylthioated vinylpyrroles **251** and **252** ought to perform at least as well as unmethylthioated *N*-methylvinylpyrrole **115d**, with a chance of **251** performing better than either **115d** or **116** due to its one very shielded vinyl proton. Though the amount of data available to make the comparison is less than ideal, both the amount of time required for and the yields of the one successful Diels-Alder reaction of dimethylthioated vinylpyrroles **251** and **252**, when viewed in light of the relative chemical shifts of the vinyl protons, seem to suggest that either an *s-trans* configuration preference of the dienes interferes with reactivity, or that steric hindrance caused by the methylthio group on the vinyl moiety encumbers the approach of dienophiles to these vinylpyrroles. However, a *s-trans*

preference could be caused from steric interactions between the *N*-methyl group of **252** and the methylthio group on the vinyl functionality, while the dimethylthioated *N*-H vinylpyrrole **251** was observed to react completely within three days at room temperature, although the product generated from **251** has yet to be fully characterized. More thorough study is needed before the effectiveness of dual-methylthioation as a reversible method for enhancing the reactivity of vinylpyrroles in Diels-Alder reactions can be fully assessed.

4.3 Aromatization of Diels-Alder Adducts

Tetrahydroindoles **242** and **243** were aromatized using MnO₂ (5 equiv) in refluxing toluene for three hours, giving indoles **257** and **258** in 58 and 84% yields, respectively (Scheme 23). The MnO₂ was generated from manganese(II) sulfate and potassium permanganate,⁴⁸ which was also used in Part II and III's 2- and 3-vinylpyrrole work.^{12,13} Though more data is needed for a thorough comparison, the average yield from these two dehydrogenations was 71%, slightly less than the 74% average yield from aromatizations in Part III, and higher than the 54% average achieved in aromatizing the adducts resulting from 2-vinylpyrrole in Part II, indicating that the methylthio group may provide some degree of stability to the tetrahydroindoles during the aromatization process.¹²

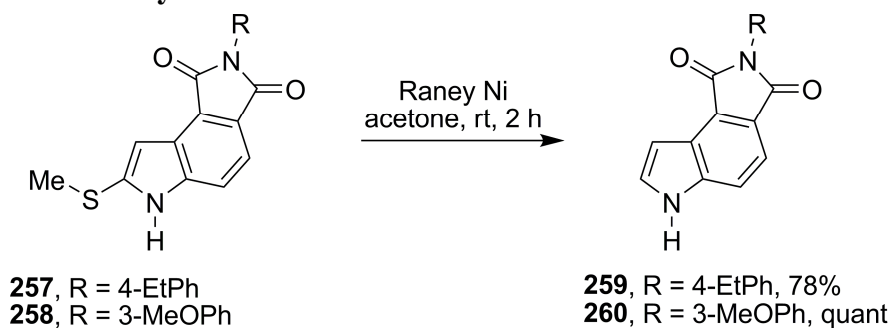
Scheme 23. Aromatization of Tetrahydroindoles 242 and 243



4.4 Deprotection of Indoles

To cleave carbon-sulfur bonds, a variety of organometallic or metallic reagents may be used, of which Raney nickel is employed most frequently.^{92,111} Methylthioated indoles **257** and **258** were deprotected using excess Raney nickel in acetone over two hours at room temperature to give indoles **259** and **260** in 78 and 100% yields, respectively (Scheme 24).

Scheme 24. Demethylthioation of Indoles 257 and 258



4.5 Conclusion

Diels-Alder reactions of 2-methylthio-5-vinyl-1*H*-pyrroles with maleimides followed by isomerization gave tetrahydroindoles in good yield. Aromatization using MnO₂ in refluxing toluene gave the corresponding 2-methylthioindoles in good yields, and demethylthioation gave the indoles in excellent yields. 5-Methylthio-2-vinylpyrrole

was shown to perform with approximately the same efficiency as 2-vinylpyrrole in Diels-Alder reactions, and the protected adducts underwent aromatization at higher yield, demonstrating the effectiveness of the methylthio group as a non-deactivating protecting group for pyrroles. *N*-H-2-Methylthio-5-(1-(methylthio)vinyl)-pyrrole was shown to have potentially greater electron density than 2-vinylpyrrole, and to function successfully as Diels-Alder diene, demonstrating the possible use of the methylthio group as a removable group for activating vinylpyrroles towards normal electron demand Diels-Alder reactions.

Part V. Potential Future Applications

5.1 Introduction

The intent of this Part is to summarize some of the research ideas inspired by the findings of Parts I-IV, the execution of which was prevented by time constraints.

5.2 Summary

Parts I, II, and III show that 2- and 3-vinylpyrroles are effective dienes in Diels-Alder reactions. In Part IV it was shown that a methylthio group may be added to the 5-position of 2-vinylpyrrole to serve as a non-deactivating protecting group for use in vinylpyrrole Diels-Alder chemistry. In addition, the results from Part IV suggest that the reactivity of vinylpyrroles may possibly be enhanced by the addition of an additional methylthio group on the vinyl moiety, and that dimethylthioated pyrroles indeed participate in [4+2] cycloaddition chemistry. In all, Parts I-IV demonstrate that vinylpyrroles are versatile dienes for Diels-Alder reactions, a potentially useful synthetic approach towards indole systems.

The dienophiles successfully employed in Parts I-IV were maleimides or quinones, and in Parts III and IV it was found that vinylboronic acid 2-methyl-2,4-pentanediol ester **222** did not undergo Diels-Alder chemistry with vinylpyrroles.

5.3 Stereocontrol of Diels-Alder Reactions

Bernardi and Ricci et al. have demonstrated that Diels-Alder reactions of 2-vinylindoles can give enantiopure products ($\leq 98\%$ *ee*) at high yields (55-91%) when performed in the presence of asymmetric thiourea-derived catalysts.¹¹² Similar

conditions might effect similar stereocontrol over the Diels-Alder reactions of vinylpyrroles. Although there appears to be no direct precedent in the literature for this, extending the potential application of the methods in Parts I-IV to asymmetric synthesis would be powerful, enabling the creation of as many as four stereocenters in a single convergent step.

5.3 Vinylborane Chemistry

It was disappointing that vinylboronate **222** did not perform the desired chemistry in Parts III and IV, as Woods and Bengelsdorf have reported that **222** undergoes Diels-Alder reactions with cyclopentadiene in a sealed tube at 150-153 °C in 78% yield.^{60g} Additionally, Waldbillig et al. has reported Diels-Alder reactions of dibutyl vinylboronate with cyclopentadiene at 100 °C over four hours at 83% yield,⁶⁰ⁱ while Evans et al. has reported the low reactivity of vinylboronic esters with 1,3-cyclohexadiene derivatives.^{62,113}

In 1990, Singleton et al. surveyed the literature reports of vinylboronate Diels-Alder chemistry and found that generally harsh conditions are required for success and often yields were low.^{61a} Appreciating the implications of the synthetic doorways that would be opened from accomplishing high-yielding [4+2] cycloaddition chemistry of a vinyl-substituted boron compound, Singleton et al. investigated vinylboranes as dienophiles and found that they were dramatically more activated towards Diels-Alder chemistry than vinylboronates.^{61a} In addition, multiple later studies confirm that vinylboranes are exceptionally reactive with both electron rich and electron poor dienes, and are highly regioselective and stereoselective dienophiles.^{61b,114} This precedent gives great hope

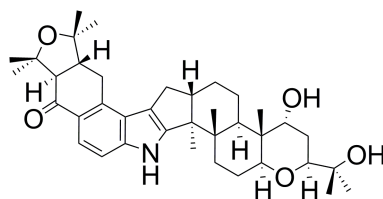
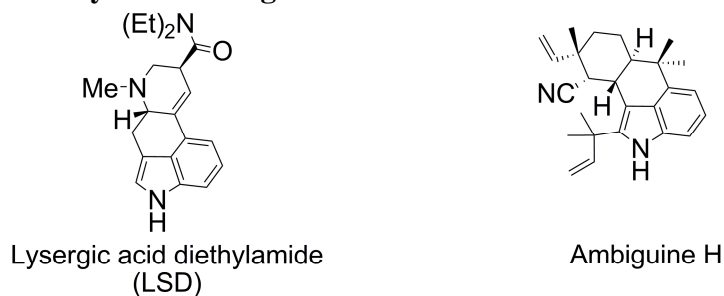
that vinylboranes will undergo high-yielding and highly regioselective Diels-Alder reactions with 2- and 3-vinylpyrroles.

As discussed in Part 3.4, aromatization followed by Suzuki coupling⁵⁹ of the indole-boron adduct would allow a highly convergent addition, giving access to a wide variety of 4- and 7-substituted indoles. There are relatively few entry points to 4-^{1c,115} and 7-¹¹⁶ substituted indoles known, therefore this would be a valuable contribution to synthetic organic chemistry.

5.4 Cyclization of 4-Substituted Indoles

Indoles which are 3-4 bridged or 4-5 fused occur in many important bioactive products, including the ergot alkaloids (such as the famous lysergic acid), lolitremes and lolicines,¹¹⁷ and hapalindoles/ambiguines¹¹⁸ (Figure 13).

Figure 13. Possible Synthetic Targets



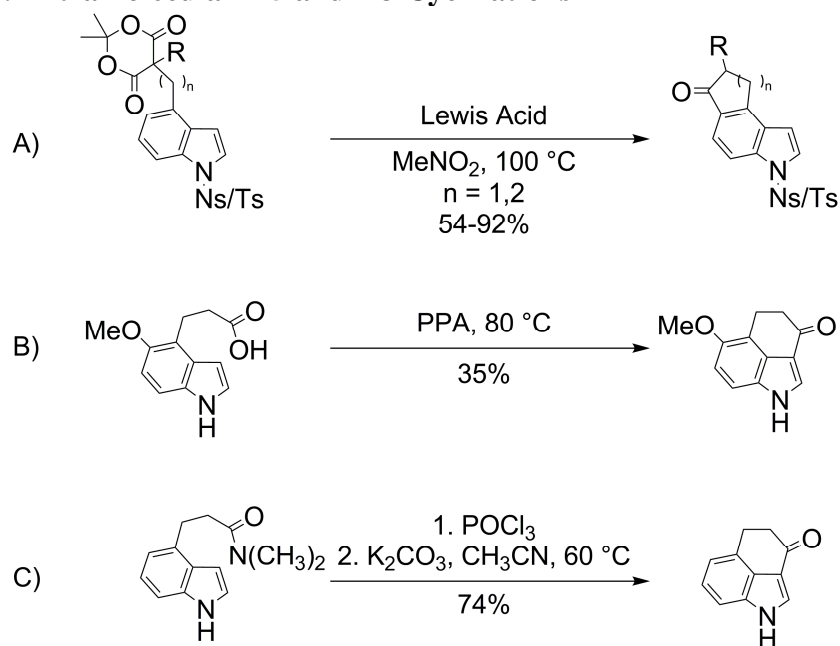
Lolicine A

Fillion and Dumas have recently demonstrated that using an intramolecular Friedel-Crafts reaction, 4-substituted indoles protected with electron-withdrawing *N*-

substituents preferentially cyclize at the 5-position (Scheme 25 reaction A).¹¹⁹

Exclusive cyclization from the 4- to the 3-position has been reported by Friedel-Crafts acylation from carboxylic acids¹²⁰ and also from the Vilsmeier-Haack reagents derived from *N,N*-dimethylamides¹²¹ (Scheme 25 reactions B and C).

Scheme 25. Intramolecular 4-5 and 4-3 Cyclizations



A [4+2] cycloaddition between a vinylborane and a vinylpyrrole followed by Suzuki coupling and then 4-3 or 4-5 cyclization could represent a powerful synthetic entry point into a wide array of bioactive compounds.

Part VI. Experimental

General. Solvents and reagents were purchased and used as received. Flash chromatography was performed using 230-450 mesh silica gel. TLC analyses were performed on plastic-backed plates pre-coated with 0.2 mm silica with F₂₅₄ indicator. Infrared spectra were recorded on a 4000 FT-IR spectrometer; only the most intense and/or diagnostic peaks are reported. High-resolution mass spectra were recorded with a time-of-flight instrument using electrospray ionization with PEG as an internal calibrant. For NMR spectra, chemical shifts (δ) were referenced to the solvent. ¹³C NMR spectra were proton-decoupled. Melting points are uncalibrated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Petroleum ether refers to the fraction boiling at 35-60 °C. Computational analysis for Part I was performed using ChemBio3D Ultra 3.0 by first minimizing the energy using the MM2 method, and then minimizing the energy using the GAMESS interface with the RHF/STO-6G method, without extensive variation of conformations prior to energy minimization.

6.1 Experimental for Part I

Note on ¹H NMR Analysis for Part I.

All the Diels-Alder products are identified such that both *endo*- and *exo*-addition products have their protons 3b-H and 6a-H in the α -orientation, as shown in Figure 1. Major and minor isomers are identified when possible with the abbreviations maj and min. The ratio of products is given such that the most prevalent minor isomer is 1.0 for easy readability of the *cis:trans* or *trans:cis* ratio of the *endo*-addition isomers. When

the orientation of a proton is unclear, the orientation is omitted from the identification. Insufficient resolution or peak overlap sometimes leads to the labeling of a splitting pattern as “apparent” (app.), which is used when there are discrepancies between the splitting of the same proton of several isomers in a single ^1H NMR spectrum, or when it is certain that coupling from a particular proton occurs but is not visible.

Most of the protons of the fused cycloalkane rings appear upfield as multiplets. For compounds with more than one isomer present, it would be confusing and nonintuitive to label the integration of these multiplets with multiplicity that varies depending on the number of isomers present in the mixture. Therefore, when the peaks of all the isomers overlap into a single peak, the integration is designated as 1H. When it is clear that the protons of several but not all isomers overlap in a particular peak, this multiplicity is indicated with an integration larger than 1H. When it is not clear whether multiple peaks overlap, the integration reflects the number of protons which are thought to be definitely in the peak. Thus, sometimes, fewer isomers are identified for a particular proton than there are isomers present in the mixture, because it is not clear where the peak(s) from one isomer occurs.

With some protons, the peaks belonging to the various isomers overlap. In these cases, sometimes the peak is identified as it would be if there was a single isomer present, omitting the designation maj and min, and also omitting the designation α or β if the orientation is unknown or mixed. These designations are only omitted when it is clear which isomers overlap into a single identified peak, and when it is clear the protons are of mixed or unknown orientation. Overlap of signals from a proton with multiple orientations occurs most frequently with protons at the 6b-position in

compounds with more than one minor isomer present. In the case of a compound with three isomers present, with the peak from $6\beta\text{maj-H}$ distinct but the peaks from the $6\beta\text{min-H}$ and $6\beta\text{min-H}$ protons overlapping into one, the overlapped peak is labeled $6\beta\text{-H}$ and is assigned an integration of two. This situation also occurs with peaks belonging to protons α to the point of cycloalkane ring fusion to the pyrrole ring in compounds with more than one isomer present.

General Reaction Conditions.

Method A: A solution of the pyrrole (3.00 mmol), the cyclohexanone (4.00 mmol), and the maleimide (4.00 mmol) was heated to reflux in ethanol (5.0 mL). Hydrochloric acid (0.20 mL, 37% aqueous solution) was added to the hot solution, causing it to turn red-brown in color. The solution was refluxed for one hour. In most cases, slow precipitation of the *in situ* product was observed throughout this time. After the mixture had cooled to rt, the precipitate was vacuum-filtered, washed with ethanol (5.0 mL), and reprecipitated from ethanol (5.0 mL). In cases where no precipitate was observed during reflux, which occurred particularly when 4-*tert*-butylcyclohexanone and/or 4-methoxyphenylmaleimide were used, the desired product was isolated by flash chromatography on silica gel using ethyl acetate:hexane as the eluent.

Method B: Hydrochloric acid (0.10 mL, 37% aqueous solution) was added to a solution of the pyrrole (5.00 mmol), the cyclic ketone (6.50-9.82 mmol), and the maleimide (4.80 mmol) in ethanol (15.0 mL) and the resulting solution was refluxed with stirring for 1-6 h, as determined by TLC. As the solution was allowed to cool to rt, a precipitate developed, which was vacuum-filtered. Purification to give the desired

product was accomplished in one of several ways: (1) washing with diethyl ether (5-20 mL) and/or ethanol (5-20 mL), (2) reprecipitation from ethanol (15-20 mL) and/or diethyl ether (15-20 mL) and then, if necessary, washing with diethyl ether (5-20 mL), (3) purified using flash chromatography on silica gel, or (4) a combination of the above techniques, as noted.

Compounds 5 through 112

2-Methyl-5-phenyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (5). Method B with **3a** (800 mg, 9.50 mmol), 2-h reflux, ethanol wash (10 mL) and then a diethyl ether wash (10 mL) gave **5** (950 mg, 62%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.4:1.0:0.1): mp 260-262 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.55 (bs, 1H, 1min-H), 8.22 (bs, 1H, 1min-H), 7.64 (bs, 1H, 1maj-H), 7.36-7.52 (m, 3H, Ph), 7.26-7.31 (m, 2H, Ph), 6.11 (dd, *J* = 2.6, 1.1 Hz, 1H, 3maj-H), 6.03-6.05 (m, 1H, 3min-H), 5.76 (app. d, *J* = 3.0 Hz, 1H, 3min-H), 4.02 (dd, *J* = 8.3, 1.7 Hz, 1H, 3bαmin-H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.63 (dd, *J* = 8.9, 6.2 Hz, 1H, 6aαmin-H), 3.55 (dd, *J* = 8.4, 6.0 Hz, 1H, 6aαmaj-H), 3.20-3.27 (m, 1H, 9aαmaj-H), 3.10-3.16 (m, 1H, 9aβmin-H), 2.75-2.88 (m, 1H, 6b-H), 2.29 (s, 3H, 2-CH₃), 1.88-2.08 (m, 2H, cyclopent.), 1.57-1.75 (m, 3H, cyclopent.), 1.38-1.49 (m, 1H, cyclopent.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.48 (bs, 1H, 1min-H), 10.29 (bs, 1H, 1maj-H), 7.38-7.54 (m, 3H, Ph), 7.19-7.25 (m, 2H, Ph), 5.76 (dd, *J* = 2.3, 1.1 Hz, 1H, 3maj-H), 5.57 (dd, *J* = 2.3, 1.1 Hz, 1H, 3min-H), 4.18 (app. d, *J* = 8.7 Hz, 1H, 3bαmin-H), 4.05 (dd, *J* = 8.3, 2.0 Hz, 1H, 3bαmaj-H), 3.53 (dd, *J* = 8.3, 5.9 Hz, 1H, 6aαmin-H), 3.48 (dd, *J* = 8.3, 5.9 Hz, 1H, 6aαmaj-H), 3.07-3.14 (m, 1H, 9aαmaj-H), 2.99-3.04 (m, 1H, 9aβmin-H), 2.56-2.66 (m, 1H, 6b-H), 2.04-2.18 (m, 1H, cyclopent.),

2.15 (s, 3H, 2-CH₃), 1.77-1.94 (m, 1H, cyclopent.), 1.36-1.61 (m, 3H, cyclopent.), 1.15-1.30 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.4, 177.0, 132.2, 131.0, 129.3, 129.2, 128.5, 128.1, 127.8, 126.6, 115.5, 109.3, 108.7, 105.6, 104.1, 41.9, 41.7, 38.5, 37.2, 36.5, 31.1, 30.5, 24.9, 22.4, 21.9, 13.3; IR (thin film, cm⁻¹) 3397(bs), 3059(m), 2934(m), 2857(m), 1775(s), 1695(s), 1498, 1391(m), 1189(m), 1170(m); HRMS *m/z* (M + Na⁺) calcd 343.1418, found 343.1417. Anal. Calcd for C₂₀H₂₀N₂O₂: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.20; H, 6.16; N, 8.90.

2-Methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-*e*]indole-4,6-dione (6). Method B with **3a** (800 mg, 9.50 mmol), 3.5-h reflux, reprecipitation from ethanol (15 mL), and then a diethyl ether wash (10 mL) gave **6** (670 mg, 42%) as a colorless solid, a mixture of two isomers (maj:min = 3.9:1.0): mp 214-216 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.23 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1maj-H), 7.27 (d, *J* = 7.8 Hz, 2H, Ph), 7.16 (d, *J* = 7.8 Hz, 2H, Ph), 6.11 (dd, *J* = 2.6, 1.1 Hz, 1H, 3maj-H), 5.75 (dd, *J* = 2.6, 0.75 Hz, 1H, 3min-H), 3.99 (dd, *J* = 8.6, 2.0 Hz, 1H, 3b α -H), 3.62 (dd, *J* = 8.9, 6.2 Hz, 1H, 6a α min-H), 3.53 (dd, *J* = 8.3, 6.2 Hz, 1H, 6a α maj-H), 3.19-3.26 (m, 1H, 9a α maj-H), 3.10-3.16 (m, 1H, 9a β maj-H), 2.73-2.88 (m, 1H, 6b α -H), 2.40 (s, 3H, 4'-CH₃ min), 2.39 (s, 3H, 4'-CH₃ maj), 2.28 (s, 3H, 2-CH₃), 1.88-2.07 (m, 2H, cyclopent.), 1.50-1.75 (m, 3H, cyclopent.), 1.25-1.49 (m, 1H, cyclopent.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.47 (d, *J* = 2.1 Hz, 1H, 1min-H), 10.28 (d, *J* = 1.8 Hz, 1H, 1maj-H), 7.28 (d, *J* = 7.8 Hz, 2H, Ph), 7.08 (d, *J* = 8.4 Hz, 2H, Ph), 5.75 (dd, *J* = 2.3, 1.1 Hz, 1H, 3maj-H), 5.57 (dd, *J* = 2.4, 0.6 Hz, 1H, 3min-H), 4.15 (dd, *J* = 7.2, 1.2 Hz, 1H, 3b α min-H), 4.02 (dd, *J* = 8.4, 1.8 Hz, 1H, 3b α maj-H), 3.51 (dd, *J* = 8.3, 5.9 Hz, 1H, 6a α min-H), 3.46 (dd, *J* = 8.4, 6.0 Hz, 1H, 6a α maj-H),

3.07-3.13 (m, 1H, 9 α maj-H), 2.98-3.04 (m, 1H, 9 α βmin-H), 2.52-2.65 (m, 1H, 6 β α -H), 2.35 (s, 3H, 4'-CH₃ maj), 2.34 (s, 3H, 4'-CH₃ min), 2.02-2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH₃), 1.77-1.89 (m, 1H, cyclopent.), 1.34-1.60 (m, 3H, cyclopent.), 1.14-1.29 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.6, 177.1, 138.6, 130.0, 129.9, 129.5, 128.0, 127.8, 126.4, 108.7, 105.6, 104.1, 41.9, 41.8, 41.2, 38.5, 37.2, 36.5, 31.4, 30.5, 24.9, 24.5, 22.4, 21.9, 21.3, 13.3; IR (thin film, cm⁻¹) 3381(bs), 2948(m), 2871(m), 2366(w), 1775(w), 1706(s), 1514(m), 1383(m), 1194(m), 1179(m), 1162(m); HRMS *m/z* (M + Na⁺) calcd 357.1574, found 357.1572. Anal. Calcd for C₂₁H₂₂N₂O₂: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.38; H, 6.58; N, 8.55.

5-(4-Isopropylphenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-

cyclopenta[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (7). Method B with **3a** (800 mg, 9.50 mmol), 4-h reflux and then a diethyl ether wash (20 mL) gave **7** (760 mg, 50%) as a colorless solid, a mixture of two isomers (maj:min = 7.0:1.0): mp 199-201 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.30 (bs, 1H, 1min-H), 7.69 (bs, 1H, 1maj-H), 7.32 (d, *J* = 8.4 Hz, 2H, Ph), 7.19 (d, *J* = 8.4 Hz, 2H, Ph), 6.11 (d, *J* = 1.8 Hz, 1H, 3maj-H), 5.75 (d, *J* = 2.1 Hz, 1H, 3min-H), 4.01 (dd, *J* = 8.3, 1.7 Hz, 1H, 3 β amin-H), 3.99 (dd, *J* = 8.4, 1.8 Hz, 1H, 3 β amaj-H), 3.62 (dd, *J* = 8.9, 6.2 Hz, 1H, 6 α amin-H), 3.53 (dd, *J* = 8.4, 5.7 Hz, 1H, 6 α maj-H), 3.19-3.25 (m, 1H, 9 α maj-H), 3.10-3.16 (m, 1H, 9 α βmin-H), 2.96 (septet, *J* = 6.9 Hz, 1H, CH(CH₃)₂ min), 2.95 (septet, *J* = 6.9 Hz, 1H, CH(CH₃)₂ maj), 2.75-2.88 (m, 1H, 6 β α -H), 2.28 (s, 3H, 2-CH₃), 1.88-2.09 (m, 2H, cyclopent.), 1.33-1.74 (m, 4H, cyclopent.), 1.271 (d, *J* = 6.9 Hz, 1H, CH(CH₃)₂ min), 1.269 (d, *J* = 6.6 Hz, 6H, CH(CH₃)₂ maj); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.48 (d, *J* = 2.1 Hz, 1H, 1min-H), 10.28 (bs, *J* = 1.8 Hz, 1H, 1maj-H), 7.35 (d, *J* = 8.4 Hz, 2H, Ph), 7.12 (d, *J* = 8.4

Hz, 2H, Ph), 5.76 (d, $J = 1.2$ Hz, 1H, 3maj-H), 5.57 (d, $J = 1.5$ Hz, 1H, 3min-H), 4.16 (app. d, $J = 8.4$ Hz, 1H, 3 β amin-H), 4.03 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β amaj-H), 3.52 (dd, $J = 8.3, 5.9$ Hz, 1H, 6 α amin-H), 3.46 (dd, $J = 8.4, 6.0$ Hz, 1H, 6 α amaj-H), 3.03-3.14 (m, 1H, 9 α amaj-H), 2.97-3.04 (m, 1H, 9 β min-H), 2.94 (septet, $J = 6.9$ Hz, 1H, $CH(CH_3)_2$ min), 2.93 (septet, $J = 6.9$ Hz, 1H, $CH(CH_3)_2$ maj), 2.53-2.65 (m, 1H, 6 $\beta\alpha$ -H), 2.03-2.19 (m, 1H, cyclopent.), 2.15 (s, 3H, 2- CH_3), 1.77-1.91 (m, 1H, cyclopent.), 1.35-1.61 (m, 4H, cyclopent.), 1.23 (d, $J = 6.9$ Hz, 6H, $CH(CH_3)_2$ min), 1.22 (d, $J = 6.9$ Hz, 6H, $CH(CH_3)_2$ maj); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.6, 177.2, 149.3, 129.7, 128.0, 127.9, 127.3, 126.3, 108.7, 105.6, 41.9, 41.7, 38.5, 36.5, 34.0, 30.5, 24.9, 24.0, 22.4, 13.3; IR (thin film, cm^{-1}) 3378(bs), 2961(m), 2872(m), 1774(w), 1701(s), 1515(m), 1384(m), 1182(m), 1162(m); HRMS m/z ($M + Na^+$) calcd 385.1887, found 385.1886. Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.18; H, 7.41; N, 7.51.

5-(4-Methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-

cyclopenta[g]pyrrolo[3,4-*e*]indole-4,6-dione (8). Method B with **3a** (800 mg, 9.50 mmol), 1.5-h reflux and then reprecipitation from ethanol (15 mL) gave **8** (850 mg, 46%) as a colorless solid, a mixture of two isomers (maj:min = 5.4:1.0): mp 213-215 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.25 (bs, 1H, 1min-H), 7.69 (bs, 1H, 1maj-H), 7.15-7.23 (m, 2H, Ph), 6.95-7.02 (m, 2H, Ph), 6.11 (d, $J = 1.5$ Hz, 1H, 3maj-H), 5.75 (d, $J = 2.1$ Hz, 1H, 3min-H), 3.99 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 $\beta\alpha$ -H), 3.84 (s, 3H, OCH_3 min), 3.83 (s, 3H, OCH_3 maj), 3.61 (dd, $J = 8.7, 6.3$ Hz, 1H, 6 α amin-H), 3.53 (dd, $J = 8.6, 5.9$ Hz, 1H, 6 α amaj-H), 3.18-3.25 (m, 1H, 9 α amaj-H), 3.09-3.16 (m, 1H, 9 β min-H), 2.74-2.87 (m, 1H, 6 β -H), 2.28 (s, 3H, 2- CH_3), 1.88-2.07 (m, 2H, cyclopent.), 1.26-1.70

(m, 4H, cyclopent.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.46 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 7.12 (d, *J* = 9.0 Hz, 2H, Ph), 7.02 (d, *J* = 9.0 Hz, 2H, Ph), 5.74-5.77 (m, 1H, 3maj-H), 5.55-5.58 (m, 1H, 3min-H), 4.12-4.16 (m, 1H, 3b α min-H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H, 3b α maj-H), 3.78 (s, 3H, OCH₃), 3.45-3.52 (m, overlapped, 1H, 6 α min-H), 3.45 (dd, *J* = 8.3, 5.9 Hz, 1H, 6 α maj-H), 3.06-3.13 (m, 1H, 9 α maj-H), 2.98-3.04 (m, 1H, 9 α β min-H), 2.52-2.65 (m, 1H, 6b α -H), 1.99-2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH₃), 1.78-1.96 (m, 1H, cyclopent.), 1.32-1.62 (m, 3H, cyclopent.), 1.12-1.28 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.7, 177.3, 159.5, 128.0, 127.8, 124.8, 114.7, 114.6, 108.7, 105.6, 55.6, 41.9, 41.7, 38.5, 37.2, 36.5, 30.5, 31.5, 24.9, 22.3, 22.0, 13.3; IR (KBr, cm⁻¹) 3384(bs), 2869(m), 1773(w), 1704(s), 1697(bs), 1515(s), 1391(m), 1252(m), 1176(m); HRMS *m/z* (M + Na⁺) calcd 373.1523, found 373.1528. Anal. Calcd for C₂₁H₂₂N₂O₃: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.12; H, 6.51; N, 7.82.

2-Methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-

cyclopenta[g]pyrrolo[3,4-*e*]indole-4,6-dione (9). Method B with **3a** (800 mg, 9.50 mmol), 3-h reflux, reprecipitation from ethanol (15 mL), and then a diethyl ether wash (15 mL) gave **9** (1130 mg, 52%) as a colorless solid, a mixture of two isomers (maj:min = 7.6:1.0): mp 227-228 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.22 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1maj-H), 7.34-7.41 (m, 2H, Ph), 7.13-7.28 (m, 3H, Ph), 7.04-7.10 (m, 4H, Ph), 6.11 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 5.76 (app. d, *J* = 2.4 Hz, 1H, 3min-H), 4.00 (dd, *J* = 8.4, 1.8 Hz, 1H, 3b α -H), 3.84 (dd, *J* = 8.4, 6.0 Hz, 1H, 6 α maj-H), 3.63 (dd, *J* = 8.6, 6.2 Hz, 1H, 6 α min-H), 3.20-3.27 (m, 1H, 9 α maj-H), 3.13-3.17 (m, 1H, 9 α β min-H), 2.75-2.88 (m, 1H, 6b α -H), 2.29 (s, 3H, 2-CH₃), 1.88-2.08 (m, 2H, cyclopent.), 1.53-

1.73 (m, 3H, cyclopent.), 1.30-1.48 (m, 1H, cyclopent.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.48 (d, *J* = 2.4 Hz, 1H, 1min-H), 10.28 (d, *J* = 2.1 Hz, 1H, 1maj-H), 7.40-7.47 (m, 2H, Ph), 7.16-7.26 (m, 3H, Ph), 7.07-7.11 (m, 4H, Ph), 5.76 (dd, *J* = 2.1, 0.9 Hz, 1H, 3maj-H), 5.57 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 4.17 (app. d, *J* = 8.4 Hz, 1H, 3βamin-H), 4.03 (dd, *J* = 8.4, 1.8 Hz, 1H, 3βαmaj-H), 3.52 (dd, *J* = 8.3, 5.9 Hz, 1H, 6αamin-H), 3.47 (dd, *J* = 8.3, 5.9 Hz, 1H, 6ααmaj-H), 3.07-3.13 (m, 1H, 9ααmaj-H), 2.98-3.04 (m, 1H, 9αβmin-H), 2.54-2.65 (m, 1H, 6bα-H), 2.15 (s, 3H, 2-CH₃), 2.02-2.15 (m, 1H, cyclopent.), 1.76-1.90 (m, 1H, cyclopent.), 1.35-1.61 (m, 3H, cyclopent.), 1.13-1.29 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.5, 177.1, 157.5, 156.5, 130.0, 128.1, 128.0, 127.8, 126.9, 124.0, 119.6, 118.9, 108.6, 105.6, 41.9, 41.7, 38.5, 37.2, 36.5, 30.5, 24.9, 22.4, 13.3; IR (thin film, cm⁻¹) 3381(bs), 2950(m), 2872(m), 2365(w), 2343(w), 1775(w), 1706(s), 1590(w), 1507(m), 1489(m), 1385(m), 1240(m), 1163(m); HRMS *m/z* (M + Na⁺) calcd 435.1680, found 435.1682. Anal. Calcd for C₂₆H₂₄N₂O₃: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.86; H, 5.73; N, 6.76.

4-(2-Methyl-4,6-dioxo-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-cyclopenta[*g*]pyrrolo[3,4-*e*]-5-indolyl) benzoic acid (10). Method B with **3a** (800 mg, 9.50 mmol), 1.5-h reflux, reprecipitation from ethanol (15 mL), and then a diethyl ether wash (10 mL) gave **10** (600 mg, 35%) as a colorless solid, a mixture of two isomers (maj:min = 9.0:1.0): mp 262-264 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 13.10 (bs, 1H, CO₂H), 10.49 (d, *J* = 3.0 Hz, 1H, 1min-H), 10.29 (d, *J* = 3.0 Hz, 1H, 1maj-H), 8.05 (d, *J* = 8.4 Hz, 2H, Ph), 7.39 (d, *J* = 8.7 Hz, 2H, Ph), 5.76 (d, *J* = 1.5 Hz, 1H, 3maj-H), 5.58 (d, *J* = 1.8 Hz, 1H, 3min-H), 4.21 (app. d, *J* = 8.7 Hz, 1H, 3αamin-H), 4.04 (dd, *J* = 8.3, 1.7 Hz, 1H, 3ααmaj-H), 3.56 (dd, *J* = 8.1, 5.4 Hz, 1H, 6αamin-H),

3.51 (dd, $J = 8.3, 5.9$ Hz, 1H, 6 α maj-H), 3.08-3.15 (m, 1H, 9 α maj-H), 3.00-3.05 (m, 1H, 9 α min-H), 2.56-2.67 (m, 1H, 6 β -H), 2.15 (s, 3H, 2-CH₃), 2.02-2.15 (m, 1H, cyclopent.), 1.77-1.90 (m, 1H, cyclopent.), 1.33-1.64 (m, 3H, cyclopent.), 1.15-1.27 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.4, 177.3, 167.9, 157.2, 136.8, 130.9, 130.6, 127.6, 127.4, 127.1, 108.0, 105.2, 42.1, 41.7, 38.5, 36.8, 31.2, 30.4, 25.1, 22.4, 13.4; IR (thin film, cm⁻¹) 3394(bs), 2910(m), 1773(w), 1696(s), 1515(w), 1391(m), 1289(m), 1172(m); HRMS m/z (M + Na⁺) calcd for C₂₁H₂₀N₂O₄: 387.1316, found 387.1302.

2-Methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-

cyclopenta[g]pyrrolo[3,4-*e*]indole-4,6-dione (11). Method B with **3a** (800 mg, 9.50 mmol), 4-h reflux and then purification with column chromatography (CH₂Cl₂) gave **11** (350 mg, 20%) as a yellow solid, a mixture of three isomers (maj:min:min = 8.9:1.0:0.7): mp 212-216 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.24-8.28 (m, 3H, Ph, Ph, 1min-H), 7.63-7.74 (m, 3H, Ph, 1maj-H), 6.10 (dd, $J = 2.6, 1.1$ Hz, 1H, 3maj-H), 6.03 (dd, $J = 2.9, 1.1$ Hz, 1H, 3min-H), 5.77 (dd, $J = 2.6, 1.1$ Hz, 1H, 3min-H), 4.20 (dd, $J = 8.1, 1.8$ Hz, 1H, 3 β amin-H), 4.05 (dd, $J = 8.4, 2.1$ Hz, 1H, 3 β maj-H), 3.68 (dd, $J = 8.6, 6.2$ Hz, 1H, 6 α min-H), 3.63 (dd, $J = 8.1, 4.2$ Hz, 1H, 6 α min-H), 3.60 (dd, $J = 8.6, 5.9$ Hz, 1H, 6 α maj-H), 3.21-3.29 (m, 1H, 9 α maj-H), 3.10-3.19 (m, 1H, 9amin-H), 2.79-2.89 (m, 1H, 6 β -H), 2.30 (dd, $J = 0.8$ Hz, 3H, 2-CH₃), 1.90-2.05 (m, 2H, cyclopent.), 1.58-1.74 (m, 3H, cyclopent.), 1.34-1.49 (m, 1H, cyclopent.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.52 (d, $J = 1.2$ Hz, 1H, 1min-H), 10.46 (d, $J = 1.8$ Hz, 1H, 1min-H), 10.32 (d, $J = 1.8$ Hz, 1H, 1maj-H), 8.25-8.32 (m, 1H, Ph), 8.15-8.17 (m, 1H, Ph), 7.73-7.86 (m, 2H, Ph), 5.78 (d, $J = 1.5$ Hz, 1H, 3maj-H), 5.72 (d, $J = 1.8$ Hz, 1H,

3min-H), 5.58 (d, $J = 1.8$ Hz, 1H, 3min-H), 4.22 (app. d, $J = 8.1$ Hz, 1H, 3b α min-H), 4.09 (dd, $J = 8.4, 2.1$ Hz, 1H, 3b α maj-H), 4.03 (dd, $J = 8.3, 1.7$ Hz, 1H, 3b α min-H), 3.72 (dd, $J = 4.7, 8.0$ Hz, 1H, 6a α min-H), 3.60 (dd, $J = 8.3, 5.6$ Hz, 1H, 6a α min-H), 3.54 (dd, $J = 8.1, 6.0$ Hz, 1H, 6a α maj-H), 3.09-3.15 (m, 1H, 9a α maj-H), 2.99-3.06 (m, 1H, 9amin-H), 2.58-2.67 (m, 1H, 6b-H), 2.03-2.17 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH₃), 1.74-1.91 (m, 1H, cyclopent.), 1.37-1.64 (m, 3H, cyclopent.), 1.15-1.33 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 177.6, 176.3, 133.2, 132.3, 130.0, 128.3, 127.8, 123.1, 121.7, 108.1, 105.5, 42.0, 41.6, 38.6, 36.5, 30.5, 25.0, 22.4, 13.3; IR (thin film, cm⁻¹) 3388(bs), 2953(m), 2926(m), 1779(w), 1712(s), 1532(s), 1376(m), 1349(m), 1159(m); HRMS m/z (M + Na⁺) calcd for C₂₀H₁₉N₃O₄: 388.1269, found 388.1258.

5-(4-Bromophenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-

cyclopenta[g]pyrrolo[3,4-*e*]indole-4,6-dione (12). Method B with **3a** (800 mg, 9.50 mmol), 1.5-h reflux, and then reprecipitation from ethanol (15 mL) gave **12** (1250 mg, 63%) as a colorless solid, a mixture of two isomers (maj:min = 4.2:1.0): mp 266-268 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.20 (bs, 1H, 1min-H), 7.63 (bs, overlapped, 1H, 1maj-H), 7.60 (d, $J = 8.7$ Hz, 2H, Ph), 7.20 (d, $J = 8.7$ Hz, 2H, Ph), 6.10 (dd, $J = 2.6, 1.1$ Hz, 1H, 3maj-H), 5.75 (dd, $J = 2.9, 0.8$ Hz, 1H, 3min-H), 4.00 (dd, $J = 8.6, 1.5$ Hz, 1H, 3b α -H), 3.63 (dd, $J = 8.6, 6.2$ Hz, 1H, 6a α min-H), 3.54 (dd, $J = 8.4, 6.0$ Hz, 1H, 6a α maj-H), 3.20-3.27 (m, 1H, 9a α maj-H), 3.10-3.16 (m, 1H, 9a β min-H), 2.74-2.88 (m, 1H, 6b α -H), 2.29 (s, 3H, 2-CH₃), 1.87-2.08 (m, 2H, cyclopent.), 1.52-1.72 (m, 3H, cyclopent.), 1.23-1.48 (m, 1H, cyclopent.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.49 (d, $J = 2.4$ Hz, 1H, 1min-H), 10.29 (d, $J = 1.8$ Hz, 1H, 1maj-H), 7.70 (d, $J = 8.4$ Hz, 2H, Ph), 7.20 (d, $J = 8.7$ Hz, 2H, Ph), 5.75 (d, $J = 2.3, 0.75$ Hz, 1H, 3maj-H), 5.57 (d, $J =$

2.4, 0.6 Hz, 1H, 3min-H), 4.17 (app. d, $J = 8.4$ Hz, 1H, 3b α min-H), 4.04 (dd, $J = 8.1$, 1.8 Hz, 1H, 3b α maj-H), 3.54 (dd, $J = 8.4$, 5.7 Hz, 1H, 6a α min-H), 3.48 (dd, $J = 8.3$, 5.9 Hz, 1H, 6a α maj-H), 3.07-3.13 (m, 1H, 9a α maj-H), 2.98-3.04 (m, 1H, 9a β min-H), 2.53-2.65 (m, 1H, 6b-H), 2.02-2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH₃), 1.77-1.89 (m, 1H, cyclopent.), 1.33-1.61 (m, 3H, cyclopent.), 1.13-1.25 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.5, 132.5, 132.4, 128.0, 127.8, 105.6, 41.9, 41.6, 38.5, 36.5, 24.9, 22.4, 13.3; IR (thin film, cm⁻¹) 3396(bs), 2872(m), 2364(m), 1774(w), 1697(s), 1490(m), 1387(m), 1177(m), 1167(m); HRMS m/z ($M + Na^+$) calcd 421.0523, found 421.0519. Anal. Calcd for C₂₀H₁₉BrN₂O₂: C, 60.16; H, 4.80; N, 7.02. Found: C, 60.25; H, 4.98; N, 7.14.

5-(4-Chlorophenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-

cyclopenta[g]pyrrolo[3,4-*e*]indole-4,6-dione (13). Method B with **3a** (800 mg, 9.50 mmol), 2-h reflux, reprecipitation from ethanol (10 mL), and then a diethyl ether wash (10 mL) gave **13** (1100 mg, 65%) as a colorless solid, a mixture of two isomers (maj:min = 2.5:1.0): mp 257-260 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.22 (bs, 1H, 1min-H), 7.67 (bs, 1H, 1maj-H), 7.44 (d, $J = 8.7$ Hz, 2H, Ph), 7.26 (d, $J = 9.0$ Hz, 2H, Ph), 6.10 (dd, $J = 2.6$, 1.1 Hz, 1H, 3maj-H), 5.76 (dd, $J = 2.7$, 0.9 Hz, 1H, 3min-H), 4.01 (dd, $J = 8.7$, 2.1 Hz, 1H, 3b α min-H), 4.00 (dd, $J = 8.4$, 1.8 Hz, 1H, 3b α maj-H), 3.62 (dd, $J = 8.9$, 6.2 Hz, 1H, 6a α min-H), 3.54 (dd, $J = 8.4$, 5.7 Hz, 1H, 6a α maj-H), 3.20-3.26 (m, 1H, 9a α maj-H), 3.10-3.16 (m, 1H, 9a β min-H), 2.72-2.87 (m, 1H, 6b α -H), 2.29 (s, 3H, 2-CH₃), 1.87-2.07 (m, 2H, cyclopent.), 1.52-1.75 (m, 3H, cyclopent.), 1.22-1.49 (m, 1H, cyclopent.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.49 (d, $J = 1.8$ Hz, 1H, 1min-H), 10.29 (d, $J = 2.7$ Hz, 1H, 1maj-H), 7.57 (d, $J = 8.7$ Hz, 2H, Ph), 7.27 (d, $J =$

8.7 Hz, 2H, Ph), 5.76 (d, $J = 2.1$ Hz, 1H, 3maj-H), 5.57 (d, $J = 1.8$ Hz, 1H, 3min-H), 4.17 (app. d, $J = 8.1$ Hz, 1H, 3b α min-H), 4.04 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α maj-H), 3.54 (dd, $J = 8.3, 5.9$ Hz, 1H, 6a α min-H), 3.49 (dd, $J = 8.3, 5.9$ Hz, 1H, 6a α maj-H), 3.07-3.14 (m, 1H, 9a α maj-H), 2.98-3.04 (m, 1H, 9a β min-H), 2.53-2.65 (m, 1H, 6b α -H), 2.02-2.17 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH₃), 1.76-1.93 (m, 1H, cyclopent.), 1.35-1.62 (m, 3H, cyclopent.), 1.12-1.28 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.1, 176.7, 134.3, 130.6, 129.6, 129.4, 128.1, 127.8, 121.2, 115.8, 108.4, 105.6, 104.1, 41.6, 41.1, 38.5, 37.2, 36.5, 31.4, 31.1, 30.5, 24.9, 24.5, 22.4, 21.9, 13.3; IR (thin film, cm⁻¹) 3398(bs), 2929(m), 1774(w), 1696(s), 1494(m), 1391(m), 1177(m), 1168(m); HRMS m/z (M + Na⁺) calcd 377.1028, found 377.1023. Anal. Calcd for C₂₀H₁₉ClN₂O₂: C, 67.70; H, 5.40; N, 7.89. Found: C, 67.81; H, 5.35; N, 8.07.

5-(4-Fluorophenyl)-2-methyl-3b,6a,6b,7,8,9,9a-heptahydro-1H,5H-

cyclopenta[g]pyrrolo[3,4-*e*]indole-4,6-dione (14). Method B with **3a** (800 mg, 9.50 mmol), 2-h reflux, reprecipitation from ethanol (20 mL), and then a diethyl ether wash (10 mL) gave **14** (950 mg, 59%) as a colorless solid, a mixture of two isomers (maj:min = 11.1:1.0): mp 230-232 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.24 (bs, 1H, 1min-H), 7.69 (bs, 1H, 1maj-H), 7.24-7.31 (m, 2H, Ph), 7.11-7.20 (m, 2H, Ph), 6.10 (dd, $J = 2.7, 1.2$ Hz, 1H, 3maj-H), 5.75 (d, $J = 3.3$ Hz, 1H, 3min-H), 4.00 (dd, $J = 8.4, 2.1$ Hz, 1H, 3b α -H), 3.62 (dd, $J = 8.6, 6.2$ Hz, 1H, 6a α min-H), 3.54 (dd, $J = 8.4, 6.0$ Hz, 1H, 6a α maj-H), 3.19-3.26 (m, 1H, 9a α maj-H), 3.10-3.16 (m, 1H, 9a β min-H), 2.76-2.87 (m, 1H, 6b α -H), 2.28 (s, 3H, 2-CH₃), 1.88-2.07 (m, 2H, cyclopent.), 1.53-1.72 (m, 3H, cyclopent.), 1.33-1.48 (m, 1H, cyclopent.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.49 (bs, 1H, 1min-H), 10.29 (bs, 1H, 1maj-H), 7.24-7.39 (m, 4H, Ph), 5.76 (dd, $J = 2.1, 0.6$

Hz, 1H, 3maj-H), 5.57 (app. d, $J = 1.8$ Hz, 1H, 3min-H), 4.17 (app. d, $J = 9.3$ Hz, 1H, 3b α min-H), 4.04 (dd, $J = 8.1, 1.8$ Hz, 1H, 3b α maj-H), 3.48 (dd, $J = 8.4, 5.7$ Hz, 1H, 6 α maj-H), 3.44 (dd, $J = 7.1, 5.0$ Hz, 1H, 6 α min-H), 3.07-3.14 (m, 1H, 9 α maj-H), 2.98-3.04 (m, 1H, 9 β min-H), 2.53-2.65 (m, 1H, 6b α -H), 2.02-2.18 (m, 1H, cyclopent.), 2.15 (s, 3H, 2-CH₃), 1.76-1.89 (m, 1H, cyclopent.), 1.34-1.61 (m, 3H, cyclopent.), 1.13-1.29 (m, 1H, cyclopent.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.3, 176.9, 163.9, 160.1, 128.4, 128.3, 128.1, 127.8, 116.5, 116.4, 116.1, 108.5, 105.6, 41.9, 41.6, 38.5, 36.5, 31.0, 30.5, 24.9, 22.3, 13.3; IR (thin film, cm⁻¹) 3387(bs), 2876(m), 1775(w), 1706(s), 1510(s), 1510(m), 1387(m), 1229(m), 1189(m), 1159(m); HRMS m/z ($M + Na^+$) calcd 361.1324, found 361.1323. Anal. Calcd for C₂₀H₁₉FN₂O₂: C, 70.99; H, 5.66; N, 8.28. Found: C, 71.03; H, 5.71; N, 8.21.

5-Dimethylamino-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (15). Method A gave **15** (407 mg, 45%) as a light-orange solid, a mixture of two isomers (maj:min = 19.2:1.0): mp 234-236 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.25 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1maj-H), 6.15 (dd, $J = 2.4, 1.2$ Hz, 1H, 3maj-H), 5.74 (dd, $J = 2.6, 0.7$ Hz, 1H, 3min-H), 3.68 (dd, $J = 2.0$ Hz, 1H, 3b α -H), 3.23 (dd, $J = 8.9, 5.6$ Hz, 1H, 6 α min-H), 3.17 (dd, $J = 8.6, 5.6$ Hz, 1H, 6 α maj-H), 3.04-3.09 (m, 1H, 10 α maj-H), 2.92 (s, 6H, N(CH₃)₂), 2.30 (dd, $J = 1.1, 1.1$ Hz, 3H, 2-CH₃), 2.43-2.53 (m, 1H, 6b-H), 2.08-2.16 (m, 1H, cyclohex.), 1.45-1.79 (m, 3H, cyclohex.), 1.05-1.32 (m, 4H, cyclohex.); ¹³C NMR (75 MHz, CDCl₃, δ) 177.5, 176.6, 127.4, 127.0, 108.9, 105.6, 44.2, 44.1, 38.2, 37.0, 32.7, 27.9, 25.5, 22.8, 21.0, 13.3; IR (thin film, cm⁻¹) 3426(bs), 2930(m), 2859(m), 2124(bw), 1770(bw), 1705(s), 1648(bs), 1446(m), 1362(m), 1193(m), 1146(m); HRMS m/z ($M + Na^+$) calcd 324.1683,

found 324.1707. Anal. Calcd for C₁₇H₂₃N₃O₂: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.92; H, 7.69; N, 13.76.

5-Dimethylamino-8-ethyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (16). Method A gave **16** (484 mg, 49%) as a light-orange solid, a mixture of three isomers (maj:min:min = 8.4:1.0:0.2): mp 230-231 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.24 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1maj-H), 6.15 (dd, *J* = 2.4 Hz, 0.9 Hz, 1H, 3maj-H), 5.75 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 5.71 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 3.68 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bα-H), 3.22 (dd, *J* = 9.0 Hz, 5.4 Hz, 1H, 6αmin-H), 3.21 (dd, *J* = 8.4, 5.4 Hz, 1H, 6αmin-H), 3.17 (dd, *J* = 8.4, 5.4 Hz, 1H, 6αmaj-H), 2.99-3.04 (m, 1H, 10αmaj-H), 2.93 (s, 6H, N(CH₃)₂), 2.59-2.70 (m, 1H, 6bαmaj-H), 2.48-2.56 (m, 1H, 6bmin-H), 2.30 (dd, *J* = 0.9, 0.9 Hz, 1H, 2-CH₃), 1.70-1.99 (m, 2H, cyclohex.), 1.00-1.60 (m, 7H, cyclohex., CH₂CH₃), 0.86 (t, *J* = 7.2 Hz, 3H, CH₂CH₃ maj), 0.76 (t, *J* = 7.2 Hz, 3H, CH₂CH₃ min); ¹³C NMR (75 MHz, CDCl₃, δ) 177.5, 177.4, 176.6, 127.5, 127.4, 127.0, 126.8, 109.1, 105.6, 103.7, 44.1, 43.9, 39.0, 38.3, 37.0, 36.0, 34.4, 34.0, 32.8, 32.7, 32.6, 29.6, 29.3, 27.8, 27.5, 26.1, 24.3, 23.6, 22.6, 13.3, 12.2, 11.4; IR (thin film, cm⁻¹) 3455(bs), 2957(m), 1704(m), 2125(bw), 1770(w), 1704(s), 1651(bs), 1558(m), 1446(m), 1194(m), 1142(m); HRMS *m/z* (M + Na⁺) calcd 352.1996, found 352.2002. Anal. Calcd for C₁₉H₂₇N₃O₂: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.50; H, 8.09; N, 12.67.

5-Dimethylamino-8-isopropyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (17). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL) and then a diethyl ether wash (10 mL) gave **17** (690 mg, 42%) as light-orange crystals, a single isomer: mp 237-238 °C; ¹H NMR (300 MHz,

CDCl₃, δ) 7.65 (bs, 1H, 1-H), 6.15 (dd, $J = 2.4, 0.9$ Hz, 1H, 3-H), 3.69 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α -H), 3.16 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α -H), 3.00-3.05 (m, 1H, 10a α -H), 2.93 (s, 6H, N(CH₃)₂), 2.57-2.72 (m, 1H, 6b α -H), 2.31 (s, 3H, 2-CH₃), 1.77-1.96 (m, 3H, cyclohex.), 1.52-1.63 (m, 1H, cyclohex.), 1.10-1.44(m, 4H, CH(CH₃)₂, cyclohex.), 0.88 (d, $J = 6.6$ Hz, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃, δ) 177.5, 176.6, 127.4, 127.1, 109.2, 105.6, 44.0, 43.8, 39.7, 37.0, 33.0, 32.7, 25.6, 25.0, 23.0, 21.3, 20.8, 13.3; IR (thin film, cm⁻¹) 3369 (bs), 2952(s), 2868(s), 2363(w), 1769(m), 1706(s), 1602(w), 1522(w), 1449(m), 1365(m), 1312(w), 1244(w), 1192(m), 1144(m), 1046(m); HRMS m/z (M + Na⁺) calcd 366.2153, found 366.2160. Anal. Calcd for C₂₀H₂₉N₃O₂: C, 69.94; H, 8.51; N, 12.23. Found: C, 69.87; H, 8.41; N, 12.08.

8-tert-Butyl-5-dimethylamino-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (18). Method A gave **18** (558 mg, 52%) as an orange solid, a mixture of three isomers (maj:min:min = 2.4:1.0:0.1): mp 175-176 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.65 (bs, 1H, 1min-H), 7.61 (bs, 1H, 1maj-H), 6.12 (dd, $J = 2.7, 1.2$ Hz, 1H, 3min-H), 5.99 (dd, $J = 2.6, 1.1$ Hz, 1H, 3maj-H), 5.75 (dd, $J = 2.7, 1.2$ Hz, 1H, 3min-H), 3.77 (dd, $J = 7.8, 1.5$ Hz, 1H, 3b α maj-H), 3.68 (dd, $J = 8.3, 2.0$ Hz, 1H, 3b α min-H), 3.21 (dd, $J = 8.6, 5.6$ Hz, 1H, 6a α min-H), 3.09 (dd, $J = 7.8, 6.0$ Hz, 1H, 6a α maj-H), 3.00-3.05 (m, 1H, 10a β min-H), 2.94 (s, 6H, N(CH₃)₂ min), 2.86 (s, 6H, N(CH₃)₂ maj), 2.45-2.75 (m, 2H, 6b-H, 10a α maj-H), 2.29 (dd, $J = 0.9, 0.9$ Hz, 3H, 2-CH₃ min), 2.24 (d, $J = 0.9$ Hz, 3H, 2-CH₃ maj), 0.98-2.20 (m, 7H, cyclohex.), 0.90 (s, 9H, *t*-Bu), 0.70 (s, 9H, *t*-Bu); ¹³C NMR (75 MHz, CDCl₃, δ) 177.6, 177.2, 176.65, 176.61, 130.0, 127.6, 127.4, 126.9, 109.1, 108.7, 105.5, 104.6, 58.3, 47.8, 44.2, 44.1,

43.8, 43.3, 40.8, 39.3, 38.9, 37.1, 34.2, 34.0, 32.9, 32.42, 32.40, 30.2, 28.3, 27.6, 27.5, 25.0, 24.2, 22.2, 18.4, 13.3, 13.2; IR (thin film, cm^{-1}) 3411(bs), 2953(m), 2866(m), 2114(bw), 1774(w), 1711(s), 1646(bm), 1365(m), 1200(m), 1148(m); HRMS m/z ($M + \text{Na}^+$) calcd 380.2309, found 380.2335. Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{N}_3\text{O}_2$: C, 70.55; H, 8.74; N, 11.75. Found: C, 69.84; H, 8.82; N, 11.09.

5-Dimethylamino-2-methyl-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (19). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **19** (870 mg, 48%) as light-orange crystals, a single isomer: mp 220-222 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.67 (bs, 1H, 1-H), 7.18-7.34 (m, 5H, Ph), 6.14-6.16 (m, 1H, 3-H), 3.75 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α -H), 3.19 (dd, $J = 8.3, 5.6$ Hz, 1H, 6a α -H), 2.96-3.00 (m, 1H, 10a α -H), 2.96 (s, 6H, $\text{N}(\text{CH}_3)_2$), 2.72-2.80 (m, 1H, 6b α -H), 2.32 (s, 3H, 2- CH_3), 1.70-2.05 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, CDCl_3 , δ) 177.4, 176.5, 128.6, 127.6, 127.3, 127.1, 125.8, 109.4, 105.5, 44.1, 43.7, 32.9-33.5 (overlapped peaks), 13.3; IR (thin film, cm^{-1}) 3380(bs), 3085(w), 3058(w), 3026(w), 2933(s), 2867(m), 2800(w), 1772(w), 1709(s), 1601(w), 1495(w), 1448(m), 1361(m), 1243(w), 1195(m), 1150(w), 1106(w), 1028(m); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_2$: 400.1996, found 400.2008.

2-Methyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (20). Method A gave **20** (602 mg, 60%) as a white solid, a mixture of two isomers (maj:min = 12.5:1.0): mp 268-269 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 8.30 (bs, 1H, 1min-H), 7.68 (bs, 1H, 1maj-H), 7.43-7.52 (m, 3H, Ph), 7.27-7.33 (m, 2H, Ph), 6.19 (dd, $J = 2.6, 1.1$ Hz, 1H, 3maj-H), 5.78 (dd, $J = 3.0, 0.9$ Hz, 1H, 3min-H),

3.96 (dd, $J = 8.6, 2.0$ Hz, 1H, 3b α -H), 3.47 (dd, $J = 8.7, 5.7$ Hz, 1H, 6a α min-H), 3.40 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α maj-H), 3.12-3.18 (m, 1H, 10a α maj-H), 3.01-3.07 (m, 1H, 10a β min-H), 2.51-2.60 (m, 1H, 6b α -H), 2.32 (dd, 3H, $J = 0.9, 0.9$ Hz, 2-CH₃), 2.11-2.20 (m, 1H, cyclohex.), 1.18-1.83 (m, 7H, cyclohex.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.52 (bs, 1H, 1maj-H), 10.26 (bs, 1H, 1min-H), 7.35-7.54 (m, 3H, Ph), 7.19-7.26 (m, 2H, Ph), 5.84 (dd, $J = 2.1$ Hz, 0.6 Hz, 1H, 3maj-H), 5.60 (app. d, $J = 2.4$ Hz, 1H, 3min-H), 4.16 (app. d, $J = 7.5$ Hz, 1H, 3b α min-H), 4.02 (dd, $J = 8.7, 1.8$ Hz, 1H, 3b α maj-H), 3.39 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α min-H), 3.34 (dd, $J = 8.6, 5.3$ Hz, 1H, 6a α maj-H), 2.99-3.06 (m, 1H, 10a α maj-H), 2.90-2.96 (m, 1H, 10a β -H), 2.04-2.40 (m, 1H, 6b α -H), 2.18 (s, 3H, 2-CH₃), 1.50-1.64 (m, 2H, cyclohex.), 1.32-1.46 (m, 1H, cyclohex.), 0.98-1.28 (m, 5H, cyclohex.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.1, 176.8, 154.8, 132.1, 129.3, 129.2, 128.8, 128.5, 127.4, 127.1, 126.5, 109.4, 105.9, 103.7, 46.0, 38.9, 38.7, 38.4, 37.8, 33.1, 32.9, 29.1, 28.1, 26.1, 25.6, 23.1, 22.7, 21.1, 20.6, 13.3; IR (thin film, cm⁻¹) 3392(bs), 2943(m), 2855(m), 2181 (bw), 1775 (w), 1697(s), 1645(bs), 1387(m), 1186 (m), 1162(m); HRMS m/z (M + Na⁺) calcd 357.1574, found 357.1584. Anal. Calcd for C₂₁H₂₂N₂O₂: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.53; H, 6.80; N, 8.38.

2,8-Dimethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (21). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **21** (800 mg, 48%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.8:1.0:0.3): mp 270-272 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.52 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 7.38-7.55 (m, 3H, Ph), 7.20-7.25 (m, 2H, Ph), 5.83 (d, $J =$

1.2 Hz, 1H, 3maj-H), 5.61 (d, $J = 2.1$ Hz, 1H, 3min-H), 5.59 (d, $J = 2.4$ Hz, 1H, 3min-H), 4.16 (app. d, $J = 8.4$ Hz, 1H, 3b α min-H), 4.02 (dd, $J = 8.6, 1.7$ Hz, 1H, 3b α min-H), 4.01 (dd, $J = 9.9, 1.5$ Hz, 1H, 3b α maj-H), 3.40 (dd, $J = 8.1, 4.8$ Hz, 1H, 6a α min-H), 3.36 (dd, $J = 8.1, 5.4$ Hz, 1H, 6a α maj-H), 2.93-3.02 (m, 1H, 10a α -H), 2.85-2.92 (m, 1H, 10a β -H), 2.48-2.58 (m, 1H, 6b α maj-H), 2.30-2.42 (m, 1H, 6bmin-H), 2.18 (s, 3H, 2-CH₃), 1.74-2.16 (m, 2H, cyclohex.), 0.89-1.65 (m, 5H, cyclohex.), 0.95 (d, $J = 7.2$ Hz, 3H, 8-CH₃ maj), 0.73 (d, $J = 6.3$ Hz, 3H, 8-CH₃ min); ¹³C NMR (75 MHz, CDCl₃, δ) 178.0, 176.8, 132.1, 129.3, 129.2, 128.7, 128.5, 127.4, 126.5, 117.0, 109.5, 105.8, 103.8, 45.7, 38.9, 37.8, 33.1, 33.0, 32.7, 32.6, 27.1, 26.7, 22.5, 22.4, 17.7, 13.3; IR (thin film, cm⁻¹) 3384(bs), 3063(m), 2950(s), 2866(s), 2361(m), 1778(m), 1712(s), 1598(m), 1501(m), 1457(m), 1384(m), 1182(m); HRMS m/z ($M + Na^+$) calcd 371.1731, found 371.1737. Anal. Calcd for C₂₂H₂₄N₂O₂: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.70; H, 7.08; N, 7.88.

8-Ethyl-2-methyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (22). Method A gave **22** (402 mg, 37%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 5.6:1.0:0.1): mp 257-258 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.30 (bs, 1H, 1min-H), 7.69 (bs, 1H, 1maj-H), 7.36-7.51 (m, Ph, 3H), 7.27-7.32 (m, Ph, 2H), 6.19 (dd, $J = 2.4, 1.2$ Hz, 1H, 3maj-H), 5.79 (dd, $J = 2.9, 1.1$, 1H, 3min-H), 5.76 (dd, $J = 2.7, 1.2$ Hz, 1H, 3min-H), 3.96 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α -H), 3.46 (dd, $J = 8.7, 5.7$ Hz, 1H, 6a α min-H), 3.43 (dd, $J = 8.4, 5.1$ Hz, 1H, 6a α min-H), 3.39 (dd, $J = 8.4, 5.7$ Hz, 1H, 6a α maj-H), 3.06-3.12 (m, 1H, 10a α maj-H), 2.96-2.02 (m, 1H, 10a β min-H), 2.65-2.75 (m, 1H, 6b α maj-H), 2.52-2.63 (m, 1H, 6b α min-H), 2.32 (dd, $J = 0.9, 0.9$ Hz, 3H, 2-CH₃), 1.72-2.02 (m, 2H,

cyclohex.), 1.26-1.64 (m, 5H, cyclohex.), 1.42 (app. q, $J = 7.5$ Hz, 2H, CH_2CH_3), 0.86 (t, $J = 7.2$ Hz, 3H, CH_2CH_3); ^1H NMR (300 MHz, $\text{DMSO-}d_6$, δ) 10.52 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 10.27 (bs, 1H, 1min-H), 7.39-7.54 (m, 3H, Ph), 7.20-7.25 (m, 2H, Ph), 5.83 (d, $J = 1.5$ Hz, 1H, 3maj-H), 5.61 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.59 (d, $J = 2.4$ Hz, 1H, 3min-H), 4.15 (app. d, $J = 8.4$ Hz, 1H, 3 β min-H), 4.02 (dd, $J = 8.4$, 2.1 Hz, 1H, 3 β min-H), 4.01 (dd, $J = 8.4$, 1.8 Hz, 1H, 3 β amaj-H), 3.42 (dd, $J = 8.3$, 5.3 Hz, 1H, 6 α min-H), 3.39 (dd, $J = 8.4$, 5.4 Hz, 1H, 6 α min-H), 3.35 (dd, $J = 8.3$, 5.3 Hz, 1H, 6 α amaj-H), 2.94-3.00 (m, 1H, 10 α amaj-H), 2.85-2.91 (m, 1H, 10 α β min-H), 2.41-2.52 (m, 1H, 6 β amaj-H), 2.27-2.39 (m, 1H, 6 β min-H), 2.18 (s, 3H, 2- CH_3), 1.70-2.18 (m, 2H, cyclohex.), 0.98-1.84 (m, 5H, cyclohex.), 1.38 (app. q, $J = 7.5$ Hz, 2H, CH_2CH_3), 0.80 (t, $J = 7.2$ Hz, 3H, CH_2CH_3 maj), 0.79 (t, $J = 7.2$ Hz, 3H, CH_2CH_3 min); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$, δ) 178.4, 178.2, 177.4, 176.3, 133.0, 132.9, 129.6, 129.5, 128.8, 128.7, 128.2, 127.4, 127.3, 126.5, 117.0, 114.8, 108.9, 105.4, 103.0, 46.5, 45.7, 45.5, 38.1, 34.2, 34.0, 32.6-33.2 (overlapped peaks), 23.9, 23.8, 23.7, 13.5, 13.4, 12.6; IR (thin film, cm^{-1}) 3420(bs), 2955(m), 2930(m), 2866(m), 2100 (bw), 1771 (w), 1695(s), 1644(bs), 1389(m), 1193(m), 1178(m), 1164(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 385.1887, found 385.1881. Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.40; H, 7.38; N, 7.84.

8-Isopropyl-2-methyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (23). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **23** (700 mg, 39%) as a colorless solid, a mixture of two isomers (maj:min = 5.0:1.0): mp 278-281 °C; ^1H NMR (300 MHz, $\text{DMSO-}d_6$, δ) 10.53 (bs, 1H, 1min-H), 10.28 (bs, 1H,

1maj-H), 7.38-7.55 (m, 3H, Ph), 7.17-7.24 (m, 2H, Ph), 7.82 (app. d, $J = 1.5$ Hz, 1H, 3maj-H), 5.62 (dd, $J = 2.4, 0.6$ Hz, 1H, 3min-H), 4.15 (app. d, $J = 7.2$ Hz, 1H, 3bamin-H), 4.01 (dd, $J = 8.4, 1.5$ Hz, 1H, 3bamaj-H), 3.39 (dd, $J = 8.7, 5.4$ Hz, 1H, 6aamin-H), 3.35 (dd, $J = 8.4, 5.4$ Hz, 1H, 6aamaj-H), 2.94-3.01 (m, 1H, 10aamaj-H), 2.86-2.92 (m, 1H, 10aamin-H), 2.41-2.50 (m, 1H, 6b α -H), 2.18 (s, 3H, 2-CH₃), 1.64-2.12 (m, 2H, cyclohex.), 1.08-1.58 (m, 6H, cyclohex, CH(CH₃)₂), 0.86 (d, $J = 6.3$ Hz, 6H, CH(CH₃)₂ maj), 0.79 (d, $J = 6.6$ Hz, 6H, CH(CH₃)₂ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.5, 177.4, 144.7, 133.0, 129.6, 128.7, 127.3, 126.5, 108.9, 105.4, 45.5, 32.9-33.2 (overlapped peaks), 21.7, 21.0, 13.5; IR (thin film, cm⁻¹) 3467(m), 3393(bs), 3061(w), 2951(m), 2868(m), 1773(w), 1705(s), 1599(w), 1502(m), 1454(m), 1384(s), 1193(m), 1177(m), 1161(m); HRMS m/z (M + Na⁺) calcd 399.2044, found 399.2047. Anal. Calcd for C₂₄H₂₈N₂O₂: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.72; H, 7.63; N, 7.33.

8-tert-Butyl-2-methyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (24). Method A gave **24** (445 mg, 38%) as a light-orange solid, a mixture of three isomers (maj:min:min = 8.3:1.0:0.2): mp 221-222 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.08 (bs, 1H, 1min-H), 7.65 (bs, 1H, 1min-H), 7.61 (bs, 1H, 1maj-H), 7.21-7.56 (m, 5H, Ph), 6.17 (dd, $J = 2.7, 1.2$ Hz, 1H, 3min-H), 6.03 (dd, $J = 2.6, 1.1$ Hz, 1H, 3maj-H), 5.74 (dd, $J = 2.7, 1.1$ Hz, 1H, 3min-H), 4.04 (dd, $J = 7.8, 1.5$ Hz, 1H, 3bamaj-H), 3.96 (dd, $J = 8.4, 1.8$ Hz, 1H, 3bamin-H), 3.43 (dd, $J = 8.6, 5.6$ Hz, 1H, 6aamin-H), 3.34 (dd, $J = 7.7, 5.6$ Hz, 1H, 6aamaj-H), 3.10-3.15 (m, 1H, 10aamin-H), 2.69-2.78 (m, 1H, 6bamaj-H), 2.61-2.68 (m, 1H, 10aamaj-H), 2.53-2.62 (m, 1H 6bmin-H), 2.26 (d, $J = 0.9$ Hz, 3H, 2-CH₃), 1.77-2.07 (m, 3H, cyclohex.), 1.62 (ddd, $J = 13.9, 10.1, 7.1$ Hz, 1H, cyclohex.), 0.83-1.43 (m, 3H, cyclohex.), 0.91 (s,

9H, *t*-Bu), 0.74 (s, 9H, *t*-Bu); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.37 (bs, 1H, 1min-H), 10.34 (bs, 1H, 1maj-H), 10.29 (bs, 1H, 1min-H), 7.36-7.50 (m, 3H, Ph), 7.10-7.13 (m, 2H, Ph), 5.67 (dd, *J* = 2.3, 0.8 Hz, 1H, 3maj-H), 5.55 (dd, *J* = 2.1, 0.6 Hz, 1H, 3min-H), 4.12 (app. d, *J* = 8.7 Hz, 1H, 3βamin-H), 4.03 (dd, *J* = 8.4, 1.5 Hz, 1H, 3βamin-H), 3.90 (dd, *J* = 7.7, 1.4 Hz, 1H, 3βmaj-H), 3.50 (dd, *J* = 8.4, 6.6 Hz, 1H, 6αamin-H), 3.47 (dd, *J* = 7.7, 5.6 Hz, 1H, 6αmaj-H), 3.38 (dd, *J* = 8.3, 5.3 Hz, 1H, 6αamin-H), 2.98-3.03 (m, 1H, 10αβmin-H), 2.56-2.65 (m, 1H, 10αmaj-H), 2.42-2.53 (m, 1H, 6b-H), 0.90-2.20 (m, 7H, cyclohex.), 2.12 (s, 3H, 2-CH₃), 0.86 (s, 9H, *t*-Bu maj), 0.68 (s, 9H, *t*-Bu min); ¹³C NMR (75 MHz, CDCl₃, δ) 177.9, 177.1, 176.3, 173.8, 146.2, 134.3, 132.3, 130.4, 129.7, 129.4, 129.3, 129.29, 129.26, 129.20, 129.1, 128.6, 128.5, 127.0, 126.8, 126.5, 126.4, 126.2, 119.7, 114.0, 109.7, 104.7, 53.1, 47.8, 46.2, 45.7, 43.9, 43.7, 41.7, 41.2, 40.7, 39.2, 39.0, 38.3, 34.3, 34.2, 32.9, 32.6, 32.5, 32.4, 31.4, 30.5, 28.7, 28.5, 27.7, 27.5, 27.4, 25.5, 24.8, 24.3, 22.2, 13.2; IR (thin film, cm⁻¹) 3390(bs), 2951(m), 2866(w), 2357 (w), 2088(bw), 1772(w), 1708(s), 1647(bs), 1500(m), 1386(m), 1372(m), 1199(m), 1176(m); HRMS *m/z* (M + Na⁺) calcd 413.2200, found 413.2181. Anal. Calcd for C₂₅H₃₀N₂O₂: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.65; H, 7.43; N, 7.39.

2-Methyl-5,8-diphenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (25). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **25** (850 mg, 43%) as a colorless solid, a mixture of two isomers (maj:min = 3.8:1.0): mp 282-285 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.56 (bs, 1H, 1min-H), 10.38 (bs, 1H, 1maj-H), 7.15-7.56 (m, 10H, Ph), 5.78-5.87 (m, 1H, 3maj-H), 5.68-5.67 (m, 1H,

3min-H), 4.19 (d, $J = 8.1$ Hz, 1H, 3b α min-H), 4.02 (d, $J = 7.5$ Hz, 1H, 3b α maj-H), 3.36-3.54 (m, 1H, 6a α -H), 2.82-2.98 (m, 1H, 10a-H), 2.48-2.60 (m, 1H, 6b α -H), 2.19 (s, 3H, 2-CH₃), 1.34-2.10 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.0, 176.8, 129.3, 128.6, 127.7, 127.3, 126.6, 125.8, 109.8, 105.6, 105.5, 105.4, 45.6, 33.2-33.6 (overlapped peaks), 13.3; IR (thin film, cm⁻¹) 3462(m), 3431(m), 3394(bs), 3060(w), 3024(w), 2934(s), 2868(m), 1776(w), 1706(s), 1599(w), 1499(m), 1383(m), 1189(m), 1168(m); HRMS m/z (M + Na⁺) calcd 433.1887, found 433.1908. Anal. Calcd for C₂₇H₂₆N₂O₂: C, 79.00; H, 6.38; N, 6.82. Found: C, 78.88; H, 6.58; N, 6.68.

2-Methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (26). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **26** (700 mg, 42%) as a colorless solid, a mixture of two isomers (maj:min = 1.6:1.0): mp 276-278 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.51 (bs, 1H, 1maj-H), 10.25 (bs, 1H, 1min-H), 7.30 (d, $J = 8.1$ Hz, 2H, Ph maj), 7.28 (d, $J = 7.8$ Hz, 2H, Ph min), 7.12 (d, $J = 8.1$ Hz, 2H, Ph maj), 7.09 (d, $J = 8.4$ Hz, 2H, Ph min), 5.83 (dd, $J = 2.4, 1.2$ Hz, 1H, 3min-H), 5.59 (dd, $J = 2.4, 0.6$ Hz, 1H, 3maj-H), 4.14 (app. d, $J = 7.8$ Hz, 1H, 3b α maj-H), 3.99 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α min-H), 3.37 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α maj-H), 3.32 (dd, $J = 8.6, 5.3$ Hz, 1H, 6a α min-H), 2.99-3.04 (m, 1H, 10a α min-H), 2.92 (m, 1H, 10a β maj-H), 2.06-2.40 (m, 2H, cyclohex., 6b α -H), 2.35 (s, 3H, 4'-CH₃ maj), 2.34 (s, 3H, 4'-CH₃ min), 2.18 (s, 3H, 2-CH₃), 0.98-1.64 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.5, 178.3, 177.6, 176.4, 138.4, 138.3, 130.4, 130.2, 130.1, 130.0, 128.2, 127.2, 126.9, 126.5, 119.0, 116.9, 108.8, 105.5, 102.8, 46.2, 45.9, 38.7, 38.5, 38.4, 38.2, 33.1, 33.0, 29.3, 27.6, 26.1, 25.7, 23.2, 22.9, 21.4, 21.3, 20.8, 13.52,

13.45; IR (thin film, cm^{-1}) 3400(bs), 2927(m), 2857(m), 1776(w), 1702(s), 1516(m), 1387(m), 1182(m), 1161(m); HRMS m/z ($M + \text{Na}^+$) calcd 371.1731, found 371.1743. Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.98; H, 6.92; N, 7.90.

2,8-Dimethyl-2-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (27). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **27** (650 mg, 37%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.1:1.0:0.1): mp 255-257 °C; ^1H NMR (200 MHz, $\text{DMSO-}d_6$, δ) 10.50 (bs, 1H, 1min-H), 10.25 (bs, 1H, 1maj-H), 7.29 (d, $J = 8.4$ Hz, 2H, Ph min), 7.27 (d, $J = 8.2$ Hz, 2H, Ph maj), 7.09 (d, $J = 8.2$ Hz, 1H, Ph min), 7.07 (d, $J = 8.2$ Hz, 1H, Ph maj), 5.80 (app. d, $J = 1.8$ Hz, 1H, 3maj-H), 5.58 (dd, $J = 2.2, 0.8$ Hz, 1H, 3min-H), 5.56-5.58 (m, overlapped, 1H, 3min-H), 4.12 (app. d, $J = 7.8$ Hz, 1H, 3 β amin-H), 3.97 (dd, $J = 8.3, 1.7$ Hz, 1H, 3 β amaj-H), 3.38 (dd, $J = 7.8, 5.0$ Hz, 1H, 6 α amin-H), 3.37 (dd, $J = 8.6, 5.4$ Hz, 1H, 6 α min-H), 3.32 (dd, $J = 8.6, 5.4$ Hz, 1H, 6 α amaj-H), 2.91-2.98 (m, 1H, 10amaj-H), 2.83-2.89 (m, 1H, 10amin-H), 1.64-2.60 (m, 3H, cyclohex., 6 β α -H), 2.32 (s, 3H, 4'- CH_3), 2.16 (s, 3H, 2- CH_3), 0.98 (m, 5H, cyclohex.), 0.94 (d, $J = 7.0$ Hz, 3H, 8- CH_3 maj), 0.70 (d, $J = 6.2$ Hz, 3H, 8- CH_3 min); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$, δ) 178.4, 178.2, 177.5, 176.4, 138.2, 130.4, 130.1, 130.0, 127.2, 126.5, 109.0, 105.4, 45.6, 38.8, 38.0, 33.1, 32.3-32.7 (overlapped peaks), 26.8, 26.7, 21.3, 13.4; IR (thin film, cm^{-1}) 3460(m), 3396(bs), 3075(w), 3040(w), 2927(s), 2892(m), 2867(m), 2362(w), 2336(w), 1776(m), 1708(s), 1516(s), 1387(s), 1180(s); HRMS m/z ($M + \text{Na}^+$) calcd

385.1887, found 385.1900. Anal. Calcd for C₂₃H₂₆N₂O₂: C, 76.21; H, 7.23; N, 7.73.

Found: C, 76.01; H, 7.03; N, 7.58.

8-Ethyl-2-methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (28). Method B with **3e** (883 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **28** (680 mg, 38%) as a colorless solid, a mixture of two isomers (maj:min = 2.1:1.0): mp 269-271 °C; ¹H NMR (200 MHz, DMSO-*d*₆, δ) 10.50 (bs, 1H, 1min-H), 10.25 (bs, 1H, 1maj-H), 7.29 (d, *J* = 8.0 Hz, 2H, Ph min), 7.27 (d, *J* = 8.2 Hz, 2H, Ph maj), 7.08 (d, *J* = 8.2 Hz, 2H, Ph min), 7.06 (d, *J* = 8.4 Hz, 2H, Ph maj), 5.80 (dd, *J* = 2.0, 0.8 Hz, 1H, 3maj-H), 5.59 (app. d, *J* = 2.2 Hz, 1H, 3min-H), 4.11 (app. d, *J* = 8.2 Hz, 1H, 3bαmin-H), 3.96 (dd, *J* = 8.6, 1.4 Hz, 1H, 3bαmaj-H), 3.35 (dd, *J* = 8.7, 5.3 Hz, 1H, 6aαmin-H), 3.31 (dd, *J* = 8.5, 5.3 Hz, 1H, 6aαmaj-H), 2.92-2.99 (m, 1H, 10aαmaj-H), 2.83-2.88 (m, 1H, 10aβmin-H), 1.64-2.50 (m, 2H, cyclohex., 6bα-H), 2.38 (s, 3H, 4'CH₃), 2.16 (s, 3H, 2-CH₃), 1.00-1.88 (m, 6H, cyclohex.), 1.35 (app. q, *J* = 7.4 Hz, 2H, CH₂CH₃), 0.78 (t, *J* = 7.2 Hz, 3H, CH₂CH₃ maj), 0.77 (t, *J* = 7.2 Hz, 1H, CH₂CH₃ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.4, 178.3, 177.5, 176.4, 138.4, 138.2, 130.4, 130.4, 130.1, 130.0, 128.2, 127.2, 126.8, 126.5, 117.0, 108.9, 105.4, 104.5, 103.0, 45.6, 33.8-34.2 (overlapped peaks), 33.1, 32.6-32.8 (overlapped peaks), 23.8, 23.7, 21.3, 13.5, 12.6; IR (thin film, cm⁻¹) 3468(m), 3394(bs), 3038(w), 2958(m), 2932(s), 2867(m), 1776(m), 1706(s), 1516(s), 1386(s), 1181(m), 1165(m); HRMS *m/z* (M + Na⁺) calcd 399.2044, found 399.2051. Anal. Calcd for C₂₄H₂₈N₂O₂: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.70; H, 7.49; N, 7.43.

8-Isopropyl-2-methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (29). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **29** (760 mg, 41%) as a colorless solid, a mixture of two isomers (maj:min = 3.2:1.0): mp 296-298 °C; ¹H NMR (200 MHz, DMSO-*d*₆, δ) 10.50 (bs, 1H, 1min-H), 10.26 (bs, 1H, 1maj-H), 7.30 (d, *J* = 8.2 Hz, 2H, Ph min), 7.28 (d, *J* = 8.0 Hz, 2H, Ph maj), 7.07 (d, *J* = 8.2 Hz, 2H, Ph min), 7.05 (d, *J* = 8.2 Hz, 2H, Ph maj), 5.80 (app. d, *J* = 1.2 Hz, 1H, 3maj-H), 5.59 (dd, *J* = 2.8, 0.6 Hz, 1H, 3min-H), 4.11 (app. d, *J* = 9.0 Hz, 1H, 3bamin-H), 3.96 (dd, *J* = 8.3, 1.7 Hz, 1H, 3bαmaj-H), 3.35 (dd, *J* = 8.0, 5.2 Hz, 1H, 6αamin-H), 3.31 (dd, *J* = 8.4, 5.4 Hz, 1H, 6αmaj-H), 2.91-2.99 (m, 1H, 10αmaj-H), 2.84-2.89 (m, 1H, 10αβmin-H), 2.29-2.49 (m, 1H, 6bα-H), 2.32 (s, 3H, 4'-CH₃), 0.73-2.20 (m, 8H, cyclohex., CH(CH₃)₂), 2.16 (s, 3H, 2-CH₃), 0.84 (d, *J* = 6.6 Hz, 6H, CH(CH₃)₂), 0.77 (d, *J* = 6.4 Hz, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.6, 177.5, 138.2, 130.5, 130.0, 128.4, 127.1, 126.5, 108.9, 105.4, 45.5, 32.7-33.2 (overlapped peaks), 21.7, 21.3, 21.0, 13.5; IR (thin film, cm⁻¹) 3393(bs), 2948(m), 2925(m), 2867(m), 1773(w), 1696(s), 1516(m), 1387(m), 1192(m), 1180(m), 1162(m); HRMS *m/z* (M + Na⁺) calcd 413.2200, found 413.2201. Anal. Calcd for C₂₅H₃₀N₂O₂: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.58; H, 7.82; N, 6.93.

8-tert-Butyl-2-methyl-5-(4-methylphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (30). Method B with **3g** (1079 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **30** (530 mg, 27%) as a pink solid, a mixture of three isomers (maj:min:min = 12.4:1.0:0.6): mp 220-222 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.32 (bs, 1H, 1maj-

H), 10.28 (bs, 1H, 1min-H), 10.22 (bs, 1H, 1min-H), 7.25 (d, $J = 7.8$ Hz, 2H, Ph), 6.99 (d, $J = 7.8$ Hz, 2H, Ph), 5.79-5.82 (m, 1H, 3min-H), 5.75-5.77 (m, 1H, 3min-H), 5.65-5.68 (m, 1H, 3maj-H), 4.06 (d, $J = 6.9$ Hz, 1H, 3 β amin-H), 3.89 (d, $J = 7.5$ Hz, 1H, 3 β amaj-H), 3.44 (dd, $J = 7.4, 5.9$ Hz, 1H, 6 α amaj-H), 1.46-2.68 (m, 7H, cyclohex., 10a-H, 6b-H), 2.32 (s, 3H, 4'-CH₃), 2.12 (s, 3H, 2-CH₃), 0.90-1.20 (m, 2H, cyclohex.), 0.85 (s, 9H, *t*-Bu maj), 0.68 (s, 9H, *t*-Bu min); ¹³C NMR (75 MHz, CDCl₃, δ) 178.0, 177.6, 141.5, 137.7, 133.3, 133.1, 131.3, 129.8, 129.7, 126.9, 126.5, 114.2, 109.9, 104.9, 51.9, 47.0, 45.6, 44.2, 41.6, 40.6, 34.2, 32.8, 32.5, 31.9, 27.7, 27.5, 26.8, 24.7, 23.9, 23.8, 23.5, 23.4, 21.3, 18.6, 13.2; IR (thin film, cm⁻¹) 3390(bs), 3038(w), 2953(s), 2869(m), 2360(w), 2340(w), 1767(m), 1708(s), 1516(m), 1384(s), 1367(m), 1175(m), 1169(m); HRMS m/z (M + Na⁺) calcd for C₂₆H₃₂N₂O₂: 427.2357, found 427.2356

2-Methyl-5-(4-methylphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (31). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **31** (830 mg, 41%) as a colorless solid, a mixture of two isomers (maj:min = 11.9:1.0): mp 298-300 °C; ¹H NMR (200 MHz, DMSO-*d*₆, δ) 10.53 (bs, 1H, 1min-H), 10.35 (bs, 1H, 1maj-H), 6.96-7.30 (m, 9H, Ph), 5.78-5.83 (m, 1H, 3maj-H), 5.63 (dd, $J = 2.1, 1.5$ Hz, 1H, 3min-H), 4.15 (d, $J = 9.2$ Hz, 1H, 3 β amin-H), 3.98 (d, $J = 7.4$ Hz, 1H, 3 β amaj-H), 3.36-3.45 (m, 1H, 6 α -H), 2.80-2.96 (m, 1H, 10a-H), 1.70-2.60 (m, 8H, cyclohex., 6 β -H), 2.33 (s, 3H, 4'-CH₃), 2.17 (s, 3H, 2-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.7, 177.5, 138.3, 130.5, 130.0, 128.9, 127.6, 127.3, 126.8, 126.1, 109.2, 45.4, 33.1-33.7 (overlapped peaks), 21.3, 13.5; IR (thin film, cm⁻¹) 3431(bs), 3025(w), 2941(m), 2872(m), 1772(m), 1688(m), 1516(m), 1452(m), 1379(m), 1192(m); HRMS m/z (M +

Na⁺) calcd 447.2044, found 447.2065. Anal. Calcd for C₂₈H₂₈N₂O₂: C, 79.22; H, 6.65; N, 6.60. Found: C, 78.98; H, 6.70; N, 6.49.

5-(4-Methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (32). Method A gave **32** (372 mg, 34%) as a cream-colored solid, a mixture of two isomers (maj:min = 3.5:1.0): mp 239-240 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.31 (bs, 1H, 1min-H), 7.70 (bs, 1H, 1maj-H), 7.21 (d, *J* = 9.0 Hz, 2H, Ph), 6.98 (d, *J* = 9.0 Hz, 2H, Ph), 6.19 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 5.77 (dd, *J* = 3.3, 1.2 Hz, 1H, 3min-H), 3.94 (dd, *J* = 8.6, 2.0 Hz, 1H, 3b α -H), 3.83 (s, 3H, OCH₃), 3.45 (dd, *J* = 8.6, 5.6 Hz, 1H, 6a α min-H), 3.38 (dd, *J* = 8.4, 5.4 Hz, 1H, 6a α maj-H), 3.11-3.17 (m, 1H, 10a α maj-H), 3.00-3.07 (m, 1H, 10a β min-H), 2.50-2.58 (m, 1H, 6b-H), 2.31-2.32 (dd, *J* = 0.9, 0.9 Hz, 3H, 2-CH₃), 2.10-2.19 (m, 1H, cyclohex.); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.50 (d, *J* = 1.5 Hz, 1H, 1min-H), 10.24 (app. bs, 1H, 1maj-H), 7.13 (d, *J* = 9.0 Hz, 2H, Ph), 7.02 (d, *J* = 9.0 Hz, 2H, Ph), 5.83 (d, *J* = 0.9 Hz, 1H, 3maj-H), 5.59 (d, *J* = 1.5 Hz, 1H, 3min-H), 4.12 (d, *J* = 8.1 Hz, 1H, 3b α min-H), 3.98 (dd, *J* = 8.4, 1.5 Hz, 1H, 3b α maj-H), 3.78 (s, 3H, OCH₃), 3.36 (dd, *J* = 8.4, 5.4 Hz, 1H, 6a α min-H), 3.31 (dd, *J* = 8.4, 5.1 Hz, 1H, 6a α maj-H), 2.98-3.05 (m, 1H, 10a α maj-H), 2.89-2.95 (m, 1H, 10a β min-H), 2.04-2.40 (m, 2H, cyclohex., 6b α -H), 2.18 (s, 3H, 2-CH₃), 0.99-1.64 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.4, 178.3, 177.1, 176.5, 159.4, 127.7, 127.4, 127.1, 114.6, 114.5, 109.4, 103.7, 55.6, 46.0, 38.8, 38.6, 38.4, 37.8, 33.0, 32.9, 29.1, 28.1, 26.1, 25.6, 23.0, 22.7, 21.1, 20.6, 13.3; IR (thin film, cm⁻¹) 3447(bs), 2935(m), 2858(m), 2150(bw), 1772(w), 1697(s), 1651(bs), 1518(m), 1392(m), 1252(m), 1183(m), 1162(m); HRMS

m/z ($M + Na^+$) calcd 387.1680, found 387.1701. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.61; H, 6.84; N, 7.64.

5-(4-Methoxyphenyl)-2,8-dimethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (33). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **33** (1100 mg, 61%) as a colorless solid, a mixture of three isomers (maj:min:min = 2.3:1.0:0.3): mp 265-268 °C; 1H NMR (300 MHz, $DMSO-d_6$, δ) 10.50 (bs, 1H, 1min-H), 10.25 (bs, 1H, 1maj-H), 10.23 (bs, 1H, 1min-H), 7.14 (d, $J = 9.0$ Hz, 2H, Ph min), 7.12 (d, $J = 9.0$ Hz, 2H, Ph maj), 7.04 (d, $J = 8.4$ Hz, 2H, Ph min), 7.02 (d, $J = 8.7$ Hz, 2H, Ph maj), 5.81 (dd, $J = 1.5, 0.6$ Hz, 1H, 3maj-H), 5.60 (app. d, $J = 2.4$ Hz, 1H, 3min-H), 5.58 (app. d, $J = 2.4$ Hz, 1H, 3min-H), 4.12 (app. d, $J = 8.4$ Hz, 1H, 3 α min-H), 3.98 (dd, $J = 8.4, 1.5$ Hz, 1H, 3 β min-H), 3.97 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β maj-H), 3.79 (s, 3H, OCH_3 min), 3.78 (s, 3H, OCH_3 maj), 3.37 (dd, $J = 8.3, 5.0$ Hz, 1H, 6 α min-H), 3.34 (dd, $J = 8.3, 5.6$ Hz, 1H, 6 α min-H), 3.33 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α maj-H), 2.93-3.00 (m, 1H, 10 α maj-H), 2.85-2.90 (m, 1H, 10 β min-H), 1.74-2.56 (m, 4H, cyclohex., 6b-H), 2.17 (s, 3H, 2- CH_3), 0.90-1.66 (m, 4H, cyclohex.), 0.95 (d, $J = 6.9$ Hz, 3H, 8- CH_3 maj), 0.72 (d, $J = 6.6$ Hz, 3H, 8- CH_3 min); ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 178.5, 178.0, 159.3, 128.6, 126.5, 125.7, 114.7, 109.0, 108.9, 105.0, 104.9, 55.9, 45.5, 33.1, 32.2-32.7 (overlapped peaks), 13.4; IR (thin film, cm^{-1}) 3462(m), 3390(bs), 3068(w), 3012(w), 2957(m), 2924(m), 2863(m), 1776(m), 1705(s), 1516(s), 1391(m), 1303(m), 1253(m), 1177(s); HRMS m/z ($M + Na^+$) calcd 401.1836, found 401.1841. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.74; H, 6.66; N, 7.38.

8-Ethyl-5-(4-methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (34). Method A gave **34** (424 mg, 36%) as a white solid, a mixture of three isomers (maj:min:min = 4.3:1.0:0.1): mp 249-251 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.30 (bs, 1H, 1min-H), 7.71 (bs, 1H, 1maj-H), 7.16-7.24 (m, 2H, Ph), 6.96-7.02 (m, 2H, Ph), 6.18 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 5.79 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.75 (d, *J* = 3.3 Hz, 1H, 3min-H), 3.94 (dd, *J* = 8.4, 1.8 Hz, 1H, 3b α -H), 3.83 (s, 3H, OCH₃), 3.44 (dd, *J* = 8.7, 5.7 Hz, 1H, 6a α min-H), 3.41 (dd, *J* = 8.4, 5.4 Hz, 1H, 6a α min-H), 3.37 (dd, *J* = 8.4, 5.4 Hz, 1H, 6a α maj-H), 3.05-3.11 (m, 1H, 10a α maj-H), 2.95-3.01 (m, 1H, 10a β min-H), 2.64-2.74 (m, 1H, 6b α maj-H), 2.53-2.62 (m, 1H, 6b β min-H), 2.30-2.32 (m, 3H, 2-CH₃), 1.81-1.97 (m, 2H, cyclohex.), 1.10-1.60 (m, 7H, cyclohex., CH₂CH₃), 0.86 (t, *J* = 7.4 Hz, 3H, CH₂CH₃); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.51 (bs, 1H, 1min-H), 10.26 (bs, 1H, 1maj-H), 10.23 (bs, 1H, 1min-H), 7.02-7.16 (m, 4H, Ph), 5.82 (dd, *J* = 2.4, 1.5 Hz, 1H, 3maj-H), 5.60 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 5.58 (dd, *J* = 2.7, 1.2 Hz, 1H, 3min-H), 4.11 (app. d, *J* = 8.7 Hz, 1H, 3b α min-H), 3.98 (dd, *J* = 8.4, 1.8 Hz, 1H, 3b α min-H), 3.97 (dd, *J* = 8.4, 1.5 Hz, 1H, 3b α maj-H), 3.791 (s, 3H, OCH₃ min), 3.787 (s, 3H, OCH₃ min), 3.78 (s, 3H, OCH₃ maj), 3.36 (dd, *J* = 8.9, 5.6 Hz, 1H, 6a α min-H), 3.34 (dd, *J* = 8.1, 5.4 Hz, 1H, 6a α min-H), 3.32 (dd, *J* = 8.4, 5.4 Hz, 1H, 6a α maj-H), 2.98-3.02 (m, 1H, 10amin-H), 2.93-2.99 (m, 1H, 10a α maj-H), 2.85-2.90 (m, 1H, 10a β min-H), 2.37-2.50 (m, 1H, 6b α maj-H), 2.26-2.38 (m, 1H, 6bmin-H), 2.17 (s, 3H, 2-CH₃), 1.74-2.17 (m, 1H, cyclohex.), 1.68-1.84 (m, 1H, cyclohex.), 0.98-1.66 (m, 5H, cyclohex.), 1.40 (app. q, *J* = 7.5 Hz, 2H, CH₂CH₃), 0.80 (t, *J* = 7.2 Hz, 3H, CH₂CH₃ maj), 0.78 (t, *J* = 7.8 Hz, 3H, CH₂CH₃ min); ¹³C NMR (75 MHz, CDCl₃, δ) 178.3, 178.2, 177.1, 159.4, 127.7, 127.4,

126.8, 124.8, 114.6, 114.5, 109.6, 105.8, 103.8, 55.5, 45.8, 45.6, 39.1, 38.8, 38.4, 34.5, 34.0, 32.7-33.0 (overlapped peaks), 29.7, 27.9, 27.3, 26.5, 24.4, 23.7, 22.9, 13.3, 12.3; IR (thin film, cm^{-1}) 3393(bs), 2916(m), 2862(m), 2400(w), 2150(bw), 1774(w), 1694(s), 1644(bs), 1518(m), 1388(m), 1256(m), 1178(m), 1160(m); HRMS m/z ($M + \text{Na}^+$) calcd 415.1993, found 415.1986. Anal. Calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.31; H, 7.06; N, 7.03.

8-Isopropyl-5-(4-methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (35). Method B with **3f** (981 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **35** (1450 mg, 74%) as a colorless solid, a mixture of four isomers (maj:min:min:min = 2.9:1.0:0.3:0.3): mp 300-303 °C; ^1H NMR (300 MHz, $\text{DMSO-}d_6$, δ) 10.51 (d, $J = 2.1$ Hz, 1H, 1min-H), 10.47-10.50 (m, overlapped, 1H, 1min-H), 10.27 (d, $J = 2.1$ Hz, 1H, 1maj-H), 10.22 (d, $J = 2.7$ Hz, 1H, 1min-H), 7.10 (d, $J = 9.0$ Hz, 2H, Ph), 7.04 (d, $J = 9.3$ Hz, 2H, Ph), 5.82 (dd, $J = 2.4, 0.6$ Hz, 1H, 3maj-H), 5.79-5.81 (m, overlapped, 1H, 3min-H), 5.61 (dd, $J = 2.1, 0.6$ Hz, 1H, 3min-H), 5.58 (dd, $J = 2.7, 1.5$ Hz, 1H, 3min-H), 4.13 (app. d, $J = 8.4$ Hz, 1H, 3 β amin-H), 4.11 (dd, $J = 9.6, 1.2$ Hz, 1H, 3 β amin-H), 3.99 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β amin-H), 3.96 (dd, $J = 9.6, 1.8$ Hz, 1H, 3 β amaj-H), 3.78 (s, 3H, OCH_3), 3.40 (dd, $J = 8.7, 5.3$ Hz, 1H, 6 α amin-H), 3.36 (dd, $J = 8.7, 5.4$ Hz, 1H, 6 α amin-H), 3.35 (dd, $J = 8.4, 5.1$ Hz, 1H, 6 α amin-H), 3.32 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amaj-H), 2.93-2.99 (m, 1H, 10 α amaj-H), 2.86-2.91 (m, 1H, 10 α β min-H), 2.25-2.50 (m, 1H, 6b-H), 2.17 (s, 3H, 2- CH_3), 0.94-2.17 (m, 8H, cyclohex., $\text{CH}(\text{CH}_3)_2$), 0.854 (d, $J = 6.3$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$ maj), 0.845 (d, $J = 6.6$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$ min), 0.79 (d, $J = 6.3$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$ min), 0.75 (d, $J = 6.6$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$ min), 0.70

(d, $J = 6.6$ Hz, 6H, CH(CH₃)₂ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.8, 177.6, 159.4, 128.9, 128.7, 127.6, 126.8, 126.7, 126.0, 125.6, 114.9, 114.8, 109.2, 104.5, 45.4, 33.1-33.9 (overlapped peaks), 13.5; IR (thin film, cm⁻¹) 3397(bs), 3063(w), 2948(s), 2867(s), 1774(m), 1706(s), 1516(s), 1454(m), 1389(s), 1304(m), 1252(s), 1175(s); HRMS m/z (M + Na⁺) calcd 429.2149, found 429.2138. Anal. Calcd for C₂₅H₃₀N₂O₃: C, 73.86; H, 7.44; N, 6.89. Found: C, 74.01; H, 7.61; N, 6.98.

8-*tert*-Butyl-5-(4-methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-

1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (36). Method A gave **36** (442 mg, 35%) as a light-orange solid, a mixture of three isomers (maj:min:min = 4.4:1.0:0.3): mp 239-240 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.07 (bs, 1H, 1min-H), 7.62 (bs, 1H, 1min-H), 7.58 (bs, 1H, 1maj-H), 7.12-7.24 (m, 2H, Ph), 6.92-7.02 (m, 2H, Ph), 6.03 (dd, $J = 2.6, 1.1$ Hz, 1H, 3maj-H), 5.75 (dd, $J = 2.6, 1.1$ Hz, 1H, 3min-H), 5.73 (dd, $J = 1.2, 2.7$ Hz, 1H, 3min-H), 4.02 (dd, $J = 7.8, 1.5$ Hz, 1H, 3 β amaj-H), 3.94 (dd, $J = 7.8, 1.5$ Hz, 1H, 3 β amin-H), 3.84 (s, 3H, OCH₃ min), 3.81 (s, 3H, OCH₃ maj), 3.41 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α min-H), 3.40 (dd, $J = 7.8, 5.4$ Hz, 1H, 6 α min-H), 3.32 (dd, $J = 7.7, 5.6$ Hz, 1H, 6 α maj-H), 3.08-3.12 (m, 1H, 10 α β min-H), 2.70-2.77 (m, 1H, 6 β amaj-H), 2.59-2.67 (m, 1H, 10 α maj-H), 2.53-2.60 (m, 1H, 6 β amin-H), 2.26 (d, $J = 0.9$ Hz, 3H, 2-CH₃), 1.77-2.06 (m, 3H, cyclohex.), 1.55-1.66 (m, 1H, cyclohex.), 0.83-1.42 (m, 3H, cyclohex.), 0.90 (s, 9H, *t*-Bu maj), 0.74 (s, 9H, *t*-Bu min); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.36 (d, $J = 2.1$ Hz, 1H, 1min-H), 10.32 (d, $J = 2.4$ Hz, 1H, 1maj-H), 10.21 (d, $J = 1.8$ Hz, 1H, 1min-H), 6.97-7.10 (m, 4H, Ph), 5.67 (dd, $J = 2.4, 0.9$ Hz, 1H, 3maj-H), 5.58 (app. d, $J = 2.1$ Hz, 1H, 3min-H), 5.54 (dd, $J = 2.4, 0.9$ Hz, 1H, 3min-H), 4.08 (app. d, $J = 8.4$ Hz, 1H, 3 β amin-H), 3.99 (dd, $J = 7.8, 2.1$ Hz, 1H,

3 β amin-H), 3.88 (dd, $J = 7.7, 1.4$ Hz, 1H, 3 β maj-H), 3.79 (s, 3H, OCH₃ min), 3.78 (s, 3H, OCH₃ min), 3.77 (s, 3H, OCH₃ maj), 3.46 (dd, $J = 8.3, 6.5$ Hz, 1H, 6 α amin-H), 3.43 (dd, $J = 7.5, 5.7$ Hz, 1H, 6 α maj-H), 3.38 (dd, $J = 7.5, 5.1$ Hz, 1H, 6 α maj-H), 2.88-2.91 (m, 1H, 10amin-H), 2.30-2.65 (m, 3H, 6 β -H, 10 α maj-H, 10amin-H), 0.78-2.20 (m, 7H, cyclohex.), 2.18 (s, 3H, 2-CH₃ min), 2.13 (s, 3H, 2-CH₃ min), 2.12 (s, 3H, 2-CH₃ maj), 0.85 (s, 9H, *t*-Bu maj), 0.84 (s, 9H, *t*-Bu min), 0.68 (s, 9H, *t*-Bu min); ¹³C NMR (75 MHz, CDCl₃, δ) 178.8, 178.5, 178.2, 177.3, 159.4, 130.3, 128.0, 127.68, 127.67, 127.2, 127.0, 125.0, 124.9, 114.6, 114.5, 109.7, 109.3, 105.9, 104.7, 55.6, 47.9, 46.1, 45.6, 45.3, 41.6, 40.7, 39.1, 38.9, 34.6, 34.3, 34.2, 32.9, 32.6, 32.5, 30.5, 28.6, 28.4, 27.6, 25.5, 24.3, 22.2, 13.2; ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.7, 177.5, 176.3, 159.4, 159.3, 130.2, 128.7, 128.4, 126.9, 125.7, 125.6, 117.0, 114.8, 114.6, 109.4, 104.0, 55.9, 45.2, 44.8, 41.6, 34.2-34.6 (overlapped peaks), 33.9, 33.2, 33.0, 30.7, 28.2, 28.0, 25.7, 13.4; IR (thin film, cm⁻¹) 3386(bs), 2952(m), 2865(m), 2050(bw), 1774(w), 1702(s), 1654(bs), 1513(s), 1390(m), 1251(s), 1168(m); HRMS *m/z* (M + Na⁺) calcd 443.2306, found 443.2292. Anal. Calcd for C₂₆H₃₂N₂O₃: C, 74.26; H, 7.67; N, 6.66. Found: C, 74.39; H, 7.82; N, 6.49.

5-(4-Methoxyphenyl)-2-methyl-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (37). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **37** (1200 mg, 57%) as a colorless solid, a mixture of three isomers (maj:min:min = 4.7:1.0:0.8): mp 306-309 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.54 (app. bs, 1H, 1min-H), 10.36 (d, $J = 0.9$ Hz, 1H, 1maj-H), 10.33 (app. bs, 1H, 1min-H), 6.98-7.37 (m, 9H, Ph), 5.84-5.87 (m, 1H, 3min-H), 5.77-5.85 (m, 1H, 3maj-H), 5.63-5.66 (m, 1H,

3min-H), 4.15 (d, $J = 8.1$ Hz, 1H, 3b α min-H), 4.03 (dd, $J = 8.1, 2.4$ Hz, 1H, 3b α min-H), 3.98 (d, $J = 8.1$ Hz, 1H, 3b α maj-H), 3.79 (s, 3H, OCH₃ maj), 3.74 (s, 3H, OCH₃ min), 3.48 (dd, $J = 8.1, 5.4$ Hz, 1H, 6a α min-H), 3.43 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α maj-H), 3.07-3.13 (m, 1H, 10amin-H), 2.88-2.96 (m, 1H, 10amaj-H), 2.82-2.88 (m, 1H, 10amin-H), 1.55-2.60 (m, 8H, cyclohex., 6b-H), 2.18(s, 3H, 2-CH₃); IR (thin film, cm⁻¹) 3446(m), 3393(bs), 3056(w), 3023(w), 2935(m), 2868(m), 1773(w), 1705(s), 1514(s), 1389(m), 1302(m), 1252(m), 1189(m), 1172(m); HRMS m/z (M + Na⁺) calcd 463.1993, found 463.2013. Anal. Calcd for C₂₈H₂₈N₂O₃: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.11; H, 6.41; N, 6.16.

2-Methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (38). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **38** (910 mg, 44%) as a colorless solid, a mixture of two isomers (maj:min = 5.0:1.0): mp 282-284 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.52 (bs, 1H, 1maj-H), 10.25 (bs, 1H, 1min-H), 7.41-7.47 (m, 2H, Ph), 7.17-7.31 (m, 3H, Ph), 7.07-7.11 (m, 4H, Ph), 5.84 (d, $J = 1.8$ Hz, 1H, 3min-H), 5.60 (d, $J = 1.8$ Hz, 1H, 3maj-H), 4.15 (app. d, $J = 7.8$ Hz, 1H, 3b α maj-H), 4.01 (dd, $J = 8.4, 1.5$ Hz, 1H, 3b α min-H), 3.38 (dd, $J = 8.3, 5.3$ Hz, 1H, 6a α maj-H), 3.34 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α min-H), 3.00-3.05 (m, 1H, 10a β min-H), 2.90-2.95 (m, 1H, 10a α maj-H), 2.04-2.40 (m, 2H, cyclohex., 6b α -H), 2.18 (s, 3H, 2-CH₃), 1.02-1.64 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.1, 176.3, 157.7, 130.0, 128.9, 127.9, 124.1, 123.9, 120.4, 119.7, 119.6, 118.9, 103.7, 46.0, 38.8, 38.7, 38.4, 37.8, 33.0, 32.9, 29.1, 28.1, 26.1, 23.0, 22.7, 21.1, 20.6, 13.4; IR (thin film, cm⁻¹) 3390(bs), 2925(m), 2855(m), 1777(w), 1701(s), 1590(m), 1508(s), 1489(s), 1392(m),

1244(s), 1180(m), 1165(m); HRMS m/z ($M + Na^+$) calcd for $C_{27}H_{26}N_2O_3$: 449.1836, found 449.1837.

2,8-Dimethyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (39). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **39** (1100 mg, 52%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.2:1.0:0.1): mp 278-280 °C; 1H NMR (300 MHz, $DMSO-d_6$, δ) 10.67 (bs, 1H, 1min-H), 10.52 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 7.38-7.46 (m, 2H, Ph), 7.15-7.26 (m, 3H, Ph), 7.06-7.14 (m, 4H, Ph), 5.82-5.84 (m, 1H, 3maj-H), 5.60 (d, $J = 1.8$ Hz, 1H, 3min-H), 5.58 (d, $J = 2.1$ Hz, 1H, 3min-H), 4.14 (app. d, $J = 8.1$ Hz, 1H, 3 α min-H), 4.01 (dd, $J = 8.3, 2.3$ Hz, 1H, 3 α min-H), 3.99 (dd, $J = 8.4, 1.5$ Hz, 1H, 3 α maj-H), 3.41 (dd, $J = 8.4, 6.0$ Hz, 1H, 6 α min-H), 3.40 (dd, $J = 8.0, 5.6$ Hz, 1H, 6 α min-H), 3.35 (dd, $J = 8.4, 5.7$ Hz, 1H, 6 α maj-H), 2.93-3.00 (m, 1H, 10amaj-H), 2.85-2.92 (m, 1H, 10amin-H), 2.70-2.74 (m, 1H, 10amin-H), 2.44-2.54 (m, 1H, 6bmaj-H), 2.30-2.40 (m, 1H, 6bmin-H), 2.18 (s, 3H, 2- CH_3), 0.98-2.16 (m, 7H, cyclohex.), 0.95 (d, $J = 6.9$ Hz, 3H, 8- CH_3 maj), 0.71 (d, $J = 6.0$ Hz, 3H, 8- CH_3 min); ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 178.4, 177.5, 157.0, 156.6, 130.7, 129.3, 129.1, 127.9, 126.6, 124.5, 119.7, 119.0, 108.9, 105.0, 45.6, 33.0-33.3 (overlapped peaks), 32.2-32.6 (overlapped peaks), 26.7, 13.5; IR (thin film, cm^{-1}) 3461(m), 3394(bs), 3077(w), 2954(m), 2923(m), 2864(m), 1777(w), 1711(s), 1591(m), 1508(s), 1489(s), 1391(m), 1245(s), 1192(m), 1165(m); HRMS m/z ($M + Na^+$) calcd 463.1993, found 463.1993. Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.19; H, 6.21; N, 6.23.

8-Ethyl-2-methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (40). Method B with **3e** (883 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **40** (1000 mg, 46%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.7:1.0:0.3): mp 272-274 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.52 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 10.24 (bs, 1H, 1min-H), 7.40-7.47 (m, 2H, Ph), 7.17-7.25 (m, 3H, Ph), 7.06-7.13 (m, 4H, Ph), 5.83 (dd, *J* = 2.1, 0.6 Hz, 1H, 3maj-H), 5.61 (dd, *J* = 2.4, 0.6 Hz, 1H, 3min-H), 5.58 (dd, *J* = 2.7, 0.9 Hz, 1H, 3min-H), 4.15 (app. d, *J* = 8.7 Hz, 1H, 3bαmin-H), 4.14 (app. d, *J* = 8.1 Hz, 1H, 3bαmin-H), 3.99 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.41 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.38 (dd, *J* = 8.3, 5.3 Hz, 1H, 6aαmin-H), 3.34 (dd, *J* = 8.3, 5.3 Hz, 1H, 6aαmaj-H), 2.99-3.04 (m, 1H, 10amin-H), 2.93-2.99 (m, 1H, 10aαmaj-H), 2.85-2.91 (m, 1H, 10aβmin-H), 2.24-2.50 (m, 1H, 6b-H), 2.27 (s, 3H, 2-CH₃), 0.84-2.16 (m, 7H, cyclohex.), 1.37 (app. q, *J* = 7.8 Hz, 2H, CH₂CH₃), 0.80 (t, *J* = 7.2 Hz, 3H, CH₂CH₃ maj), 0.78 (t, *J* = 7.2 Hz, 3H, CH₂CH₃ min); ¹³C NMR (75 MHz, CDCl₃, δ) 178.1, 178.0, 176.9, 159.8, 157.9, 130.0, 127.9, 127.4, 127.0, 126.8, 123.9, 119.7, 118.9, 109.5, 105.8, 45.7, 38.9, 34.5, 34.0, 32.8-33.1 (overlapped peaks), 13.3, 12.3; IR (thin film, cm⁻¹) 3462(m), 3393(bs), 3073(w), 2958(m), 2922(s), 2868(m), 1776(w), 1702(s), 1590(m), 1508(s), 1489(s), 1390(m), 1243(s), 1190(m), 1164(m); HRMS *m/z* (M + Na⁺) calcd for C₂₉H₃₀N₂O₃: 477.2149, found 477.2153.

8-Isopropyl-2-methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (41). Method B with **3f** (981 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave

41 (950 mg, 42%) as a colorless solid, a mixture of three isomers (maj:min:min = 2.1:1.0:0.3): mp 158-160 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.52 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 10.24 (bs, 1H, 1min-H), 7.40-7.48 (m, 2H, Ph), 7.16-7.26 (m, 3H, Ph), 7.04-7.16 (m, 4H, Ph), 5.80-5.84 (m, 1H, 3maj-H), 5.60-5.63 (m, 1H, 3min-H), 5.57-5.59 (m, 1H, 3min-H), 4.15 (app. d, *J* = 8.4 Hz, 1H, 3βmin-H), 4.14 (d, *J* = 8.1 Hz, 1H, 3βmin-H), 3.99 (dd, *J* = 8.7, 1.5 Hz, 1H, 3βmaj-H), 3.42 (dd, *J* = 8.1, 4.5 Hz, 1H, 6αmin-H), 3.38 (dd, *J* = 8.7, 5.4 Hz, 1H, 6αmin-H), 3.34 (dd, *J* = 8.3, 5.3 Hz, 1H, 6αmaj-H), 2.93-3.10 (m, 1H, 10αmaj-H), 2.86-2.92 (m, 1H, 10βmin-H), 2.22-2.50 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH₃), 0.90-2.12 (m, 8H, cyclohex., CH(CH₃)₂), 0.74-0.88 (m, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃, δ) 178.3, 176.9, 157.5, 156.5, 130.1, 130.0, 127.9, 127.4, 126.8, 124.1, 124.0, 119.8, 119.7, 118.8, 109.6, 109.5, 105.8, 105.0, 103.8, 45.6, 39.7, 38.9, 33.1, 33.07, 32.8-33.2 (overlapped peaks), 23.3, 21.4, 21.3, 29.1, 25.6, 23.1-23.7 (overlapped peaks), 21.3, 20.9, 20.1, 13.3; IR (thin film, cm⁻¹) 3394(bs), 3064(w), 2930(m), 2866(m), 1776(w), 1705(s), 1591(m), 1508(s), 1490(s), 1389(m), 1243(s), 1189(m), 1165(m); HRMS *m/z* (M + Na⁺) calcd 491.2306, found 491.2325. Anal. Calcd for C₃₀H₃₂N₂O₃: C, 76.90; H, 6.88; N, 5.98. Found: C, 76.76; H, 6.79; N, 5.78.

8-*tert*-Butyl-2-methyl-5-(4-phenoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (42). Method B with **3g** (1080 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **42** (700 mg, 30%) as a colorless solid, a mixture of three isomers (maj:min:min = 4.8:1.0:0.9): mp 243-245 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.50 (d, *J* = 1.8 Hz, 1H, 1min-H), 10.36 (d, *J* = 1.5 Hz, 1H, 1maj-H), 10.33 (d, *J* = 2.1 Hz, 1H, 1min-H),

7.38-7.48 (m, 2H, Ph), 7.04-7.27 (m, 7H, Ph), 5.67 (dd, $J = 2.7, 1.5$ Hz, 1H, 3min-H), 5.58 (dd, $J = 2.4, 0.6$ Hz, 1H, 3min-H), 5.54 (dd, $J = 2.4, 0.9$ Hz, 1H, 3maj-H), 4.16 (app. d, $J = 7.5$ Hz, 1H, 3 α min-H), 4.10 (app. d, $J = 8.4$ Hz, 1H, 3 α min-H), 3.85 (dd, $J = 7.5, 1.2$ Hz, 1H, 3 α maj-H), 3.49 (dd, $J = 8.4, 6.3$ Hz, 1H, 6 α min-H), 3.46 (dd, $J = 7.2, 8.7$ Hz, 1H, 6 α min-H), 3.42 (dd, $J = 8.1, 5.1$ Hz, 1H, 6 α maj-H), 2.86-2.92 (m, 1H, 10amin-H), 2.50-2.66 (m, 1H, 10 α maj-H), 2.24-2.50 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH₃ min), 2.13 (s, 3H, 2-CH₃ maj), 2.12 (s, 3H, 2-CH₃ min), 1.38-2.00 (m, 4H, cyclohex.), 0.95-1.24 (m, 3H, cyclohex.), 0.84 (s, 9H, *t*-Bu maj), 0.67 (s, 9H, *t*-Bu min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.7, 176.1, 157.2, 156.5, 130.8, 129.2, 128.8, 128.5, 127.9, 124.6, 120.1, 119.8, 119.6, 119.0, 116.9, 104.2, 102.7, 44.9, 34.3-34.6 (overlapped peaks), 33.2, 32.6, 28.2, 28.0, 27.8, 13.4; IR (thin film, cm⁻¹) 3388(bs), 3070(w), 2952(s), 2866(m), 1777(w), 1705(s), 1591(m), 1507(s), 1489(s), 1392(m), 1244(s), 1180(m), 1165(m); HRMS m/z ($M + Na^+$) calcd 505.2462, found 505.2467. Anal. Calcd for C₃₁H₃₄N₂O₃: C, 77.15; H, 7.10; N, 5.80. Found: C, 76.92; H, 6.98; N, 5.66.

2-Methyl-5-(4-phenoxyphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (43). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **43** (1150 mg, 48%) as a colorless solid, a mixture of four isomers (maj:min:min = 5.4:1.0:1.0:0.7): mp 297-299 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.57 (bs, 1H, 1min-H), 10.55 (bs, 1H, 1min-H), 10.38 (bs, 1H, 1maj-H), 10.34 (bs, 1H, 1min-H), 7.37-7.46 (m, 2H, Ph), 6.97-7.35 (m, 12H, Ph), 5.86-5.88 (m, 1H, 3min-H), 5.78-5.86 (m, 1H, 3maj-H), 5.63-5.66 (m, 1H, 3min-H), 4.17 (app. d, $J = 8.4$ Hz, 1H, 3 α min-H),

4.06 (dd, $J = 8.6, 1.7$ Hz, 1H, 3 β amin-H), 4.01 (d, $J = 7.8$ Hz, 1H, 3 β amaj-H), 3.50 (dd, $J = 8.4, 5.1$ Hz, 1H, 6 α amin-H), 3.45 (dd, $J = 8.1, 5.1$ Hz, 1H, 6 α amaj-H), 3.07-3.13 (m, 1H, 10amin-H), 2.96-3.04 (m, 1H, 10amin-H), 2.86-2.97 (m, 1H, 10 α amaj-H), 2.80-2.89 (m, 1H, 10amin-H), 2.46-2.58 (m, 1H, 6 β -H), 1.20-2.30 (m, 7H, cyclohex.), 2.19 (s, 3H, 2-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.5, 178.3, 177.0, 176.3, 156.5, 130.7, 129.2, 128.9, 127.6, 124.6, 124.5, 119.9, 119.7, 119.1, 45.4, 33.2-33.5 (overlapping peaks), 13.5; IR (thin film, cm⁻¹) 3390(bs), 3060(w), 2932(m), 2866(m), 1774(w), 1702(s), 1590(m), 1507(s), 1490(s), 1391(m), 1243(s), 1191(m), 1165(m); HRMS m/z (M + Na⁺) calcd for C₃₃H₃₀N₂O₃: 525.2149, found 525.2140.

2-Methyl-5-(3-nitrophenyl)-3 β ,6 α ,6 β ,7,8,9,10,10 α -octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (44). Method B with **3c** (600 mg, 6.12 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **44** (700 mg, 40%) as a yellow solid, a mixture of two isomers (maj:min = 2.8:1.0): mp 223-225 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.24-8.31 (m, 3H, Ph, Ph, 1min-H), 7.62-7.77 (m, 3H, Ph, 1maj-H), 6.19 (dd, $J = 2.4, 1.2$ Hz, 1H, 3maj-H), 5.79 (dd, $J = 2.4, 0.6$ Hz, 1H, 3min-H), 4.04 (app. d, $J = 8.7$ Hz, 1H, 3 β amin-H), 4.01 (dd, $J = 8.6, 2.0$ Hz, 1H, 3 β amaj-H), 3.52 (dd, $J = 8.9, 5.6$ Hz, 1H, 6 α amin-H), 3.45 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amaj-H), 3.14-3.20 (m, 1H, 10 α amaj-H), 3.03-3.08 (m, 1H, 10 β min-H), 2.53-2.61 (m, 1H, 6 $\beta\alpha$ -H), 2.33 (s, 3H, 2-CH₃), 2.12-2.28 (m, 1H, cyclohex.), 1.43-1.85 (m, 3H, cyclohex.), 1.17-1.38 (m, 4H, cyclohex.); ¹³C NMR (75 MHz, CDCl₃, δ) 177.4, 176.1, 148.5, 133.5, 133.1, 132.3, 130.1, 130.0, 127.7, 127.1, 123.3, 123.1, 121.6, 120.6, 108.8, 105.8, 103.8, 46.0, 38.9, 38.7, 38.4, 37.9, 33.0, 32.8, 29.1, 28.0, 26.0, 25.6, 23.1, 22.7, 21.0, 20.5, 13.3; IR (thin film, cm⁻¹) 3414(bs),

3081(m), 2928(m), 2858(m), 1779(w), 1707(s), 1532(s), 1384(w), 1350(m), 1164(m);

HRMS m/z ($M + Na^+$) calcd for $C_{21}H_{21}N_3O_4$: 402.1425, found 402.1434.

2,8-Dimethyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (45). Method B with **3d** (750 mg, 6.70

mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether

wash (10 mL) gave **45** (820 mg, 44%) as a colorless solid, a mixture of two isomers

(maj:min = 3.7:1.0): mp 236-238 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.24-8.30 (m, 3H,

Ph, Ph, 1min-H), 7.64-7.76 (m, 3H, Ph, 1maj-H), 6.18 (dd, $J = 2.6, 1.1$ Hz, 1H, 3maj-

H), 5.80 (dd, $J = 2.6, 1.1$ Hz, 1H, 3min-H), 4.04 (app. d, $J = 8.4$ Hz, 1H, 3b α min-H),

4.01 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α maj-H), 3.53 (dd, $J = 8.7, 5.7$ Hz, 1H, 6a α min-H),

3.46 (dd, $J = 8.6, 5.3$ Hz, 1H, 6a α maj-H), 3.08-3.14 (m, 1H, 10a α maj-H), 2.98-3.04 (m,

1H, 10a β min-H), 2.72-2.82 (m, 1H, 6b α maj-H), 2.55-2.67 (m, 1H, 6b α min-H), 2.32 (s,

3H, 2- CH_3), 1.81-2.12 (m, 3H, cyclohex.), 1.45-1.68 (m, 2H, cyclohex.), 1.18-1.34 (m,

1H, cyclohex.), 0.95-1.14 (m, 1H, cyclohex.), 1.03 (s, 3H, 8- CH_3 maj), 1.01 (s, 3H, 8-

CH_3 min); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.3, 176.1, 148.5, 132.2, 129.9, 127.7,

123.1, 121.7, 109.0, 105.7, 45.7, 39.0, 32.9, 32.6, 26.7, 13.3; IR (thin film, cm^{-1})

3430(bs), 2924(m), 2850(m), 1773(w), 1705(s), 1534(m), 1385(m), 1350(m), 1168(m);

HRMS m/z ($M + Na^+$) calcd 416.1582, found 416.1567. Anal. Calcd for $C_{22}H_{23}N_3O_4$:

C, 67.16; H, 5.89; N, 10.68. Found: C, 67.12; H, 5.64; N, 10.53.

8-Ethyl-2-methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (46). Method B with **3e** (820 mg, 6.50 mmol),

1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10

mL) gave **46** (800 mg, 41%) as a yellow solid, a mixture of two isomers (maj:min =

3.3:1.0): mp 213-215 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.24-8.31 (m, 3H, Ph, Ph, 1min-H), 7.64-7.75 (m, 3H, Ph, 1maj-H), 6.18 (dd, *J* = 2.1, 0.9 Hz, 1H, 3maj-H), 5.81 (app. d, *J* = 2.7 Hz, 1H, 3min-H), 4.01 (dd, *J* = 8.4 Hz, 1H, 3β_α-H), 3.52 (dd, *J* = 8.7, 5.7 Hz, 1H, 6α_αmin-H), 3.45 (dd, *J* = 8.6, 5.3 Hz, 1H, 6α_αmaj-H), 3.08-3.14 (m, 1H, 10α_αmaj-H), 2.97-3.04 (m, 1H, 10α_βmin-H), 2.67-2.76 (m, 1H, 6β_α-H), 2.33 (s, 3H, 2-CH₃), 1.80-2.04 (m, 2H, cyclohex.), 1.18-1.66 (m, 6H, cyclohex., 8-CH₂CH₃), 1.10-1.26 (m, 1H, cyclohex.), 0.86 (t, *J* = 7.2 Hz, 3H, 8-CH₂CH₃), 0.85 (t, *J* = 7.2 Hz, 3H, 8-CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 177.3, 176.2, 148.5, 133.1, 132.2, 130.7, 130.0, 127.7, 123.7, 123.1, 121.6, 109.0, 105.7, 45.7, 39.0, 33.9, 32.9, 23.8, 13.3, 12.3; IR (thin film, cm⁻¹) 3401(bs), 2928(m), 2868(m), 1778(w), 1714(s), 1532(s), 1353(m), 1160(m); HRMS *m/z* (M + Na⁺) calcd 430.1738, found 430.1732. Anal. Calcd for C₂₃H₂₅N₃O₄: C, 67.80; H, 6.18; N, 10.31. Found: C, 68.29; H, 6.20; N, 10.51.

8-Isopropyl-2-methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (47). Method B with **3f** (910 mg, 6.50 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **47** (600 mg, 30%) as a yellow solid, a mixture of three isomers (maj:min:min = 2.8:1.0:0.2): mp 205-207 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.24-8.31 (m, 3H, Ph, Ph, 1min-H), 7.63-7.74 (m, 3H, Ph, 1maj-H), 6.18 (dd, *J* = 2.7, 1.5 Hz, 1H, 3maj-H), 5.81 (dd, *J* = 2.7, 0.6 Hz, 1H, 3min-H), 5.77 (dd, *J* = 2.3, 1.1 Hz, 1H, 3min-H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H, 3β_α-H), 3.55 (dd, *J* = 8.4, 5.7 Hz, 1H, 6α_αmin-H), 3.51 (dd, *J* = 8.9, 5.9 Hz, 1H, 6α_αmin-H), 3.44 (dd, *J* = 8.4, 5.4 Hz, 1H, 6α_αmaj-H), 3.07-3.15 (m, 1H, 10α_αmaj-H), 2.98-3.04 (m, 1H, 10α_βmin-H), 2.66-2.75 (m, 1H, 6β_αmaj-H), 2.53-2.62 (m, 1H, 6β_{min}-H), 2.33 (s, 3H, 2-CH₃), 1.78-2.02 (m, 3H, cyclohex.), 1.20-1.65

(m, 5H, cyclohex., $\text{CH}(\text{CH}_3)_2$), 0.90 (d, $J = 6.3$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 0.86 (d, $J = 6.6$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3 , δ) 177.4, 176.1, 148.5, 133.1, 132.2, 130.0, 127.7, 123.1, 121.6, 108.9, 105.7, 45.7, 40.1, 39.6, 39.0, 33.1, 32.9, 26.1, 23.3, 21.3, 20.8, 13.3; IR (thin film, cm^{-1}) 3408(bs), 2937(m), 2850(m), 1778(w), 1708(s), 1531(m), 1381(m), 1353(m), 1195(m), 1164(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 444.1895, found 444.1889. Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.38; H, 6.26; N, 9.75.

8-tert-Butyl-2-methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (48). Method B with **3g** (1000 mg, 6.490 mmol), 3-h reflux, removal of solvent under vacuum, elution through a 5-cm silica gel plug with CH_2Cl_2 , and then reprecipitation twice from diethyl ether/hexanes (2:1, 20 mL) gave **48** (650 mg, 31%) as a yellow solid, a mixture of two isomers (maj:min = 2.1:1.0): mp 203-205 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 8.18-8.26 (m, 3H, Ph, 1maj-H), 7.57-7.71 (m, 3H, Ph, Ph, 1min-H), 7.01 (dd, $J = 2.9, 1.1$ Hz, 1H, 3maj-H), 7.00 (m, overlapped, 1H, 3min-H), 4.14 (dd, $J = 7.5, 2.1$ Hz, 1H, 3 β amin-H), 4.09 (dd, $J = 7.5, 1.5$ Hz, 1H, 3 β amaj-H), 3.39 (dd, $J = 7.4, 5.4$ Hz, 1H, 6 α amaj-H), 3.35 (dd, $J = 7.5, 3.9$ Hz, 1H, 6 α amin-H), 2.70-2.78 (m, 1H, 6b-H), 2.62-2.70 (m, 1H, 10 α β maj-H), 2.44-2.54 (m, 1H, 10 α amin-H), 1.75-2.32 (m, 3H, cyclohex.), 2.27 (d, $J = 0.6$ Hz, 3H, 2- CH_3), 1.63 (ddd, $J = 13.9, 11.5, 7.1$ Hz, 1H, cyclohex.), 1.07-1.40 (m, 3H, cyclohex.), 0.94 (s, 9H, *t*-Bu min), 0.92 (s, 9H, *t*-Bu maj); ^1H NMR (300 MHz, $\text{DMSO}-d_6$, δ) 10.38 (d, $J = 1.8$ Hz, 1H, 1maj-H), 10.32 (d, $J = 2.1$ Hz, 1H, 1min-H), 8.21-8.28 (m, 1H, Ph), 8.06-8.08 (m, 1H, Ph), 7.62-7.80 (m, 2H, Ph), 5.67-5.70 (m, 1H, 3-H), 3.98 (dd, $J = 7.2, 1.8$ Hz, 1H, 3 β amin-H), 3.96 (dd, $J = 7.2, 1.2$ Hz, 1H, 3 β amaj-H), 3.50-3.55 (m,

overlapped, 1H, 6 α amin-H), 3.53 (dd, $J = 7.5, 5.7$ Hz, 1H, 6 α maj-H), 2.55-2.70 (m, 1H, 10 α β maj-H), 2.50 (s, 3H, 2-CH₃), 1.49-2.33 (m, 5H, cyclohex., 6 β α -H), 1.00-1.40 (m, 3H, cyclohex.), 0.89 (s, 9H, *t*-Bu min), 0.86 (s, 9H, *t*-Bu maj); ¹³C NMR (75 MHz, CDCl₃, δ) 177.2, 176.1, 148.5, 133.4, 132.7, 132.3, 130.4, 129.9, 129.7, 128.0, 127.7, 123.0, 122.8, 122.0, 121.7, 109.3, 105.0, 104.1, 49.0, 46.0, 45.9, 42.2, 41.8, 41.1, 40.8, 34.3, 34.2, 34.1, 32.8, 32.7, 30.5, 28.9, 27.7, 27.6, 26.3, 25.6, 13.2; IR (thin film, cm⁻¹) 3393(bs), 3097(m), 2958(s), 2868(s), 2361(m), 2255(m), 1778(m), 1716 (s), 1532(s), 1478(m), 1356(s), 1171(m); HRMS m/z ($M + Na^+$) calcd for C₂₅H₂₉N₃O₄: 458.2051, found 458.2036.

2-Methyl-5-(3-nitrophenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (49). Method B with **3h** (1140 mg, 6.555 mmol), 1-h reflux, reprecipitation twice from ethanol/diethyl ether (4:1, 20 mL), and then a diethyl ether wash (10 mL) gave **49** (900 mg, 40%) as a yellow solid, a mixture of three isomers (maj:min:min = 4.2:1.0:0.6): mp 236-238 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.59 (bs, 1H, 1min-H), 10.41 (bs, 1H, 1maj-H), 8.28-8.33 (m, 2H, 5-Ph), 7.74-7.86 (m, 2H, 5-Ph), 7.27-7.35 (m, 4H, 8-Ph), 7.15-7.21 (m, 1H, 8-Ph), 5.86-5.89 (m, 1H, 3min-H), 5.80-5.86 (m, 1H, 3maj-H), 5.65-5.67 (m, 1H, 3min-H), 4.22 (d, $J = 9.0$ Hz, 1H, 3 β amin-H), 4.13 (d, $J = 9.0$ Hz, 1H, 3 β amin-H), 4.06 (d, $J = 8.1$ Hz, 1H, 3 β α maj-H), 3.28-3.58 (m, obscured by H₂O, 1H, 6 α α -H), 3.08-3.17 (m, 1H, 10amin-H), 2.83-3.00 (m, 1H, 10 α α maj-H), 2.51-2.62 (m, 1H, 6 β -H), 2.19 (s, 3H, 2-CH₃), 1.34-2.09 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.3, 148.4, 134.0, 131.0, 128.8, 127.6, 126.1, 123.6, 122.2, 45.5, 40.9, 39.2, 33.4, 13.5; IR (thin film, cm⁻¹)

3417(bs), 3071(m), 2928(m), 2865(m), 1776(w), 1707(s), 1533(m), 1382(m), 1350(m), 1160(m); HRMS m/z ($M + Na^+$) calcd for $C_{27}H_{25}N_3O_4$: 478.1738, found 478.1757.

4-(2-Methyl-4,6-dioxo-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

cyclopenta[g]pyrrolo[3,4-e]indol-5-yl)benzoic acid (50). Method B with **3c** (600 mg, 6.12 mmol), 1.5-h reflux, reprecipitation from diethyl ether (10 mL), and then a diethyl ether wash (5 mL) gave **50** (550 mg, 31%) as a colorless solid, a mixture of two isomers (maj:min = 1.5:1.0): mp 257-259 °C; 1H NMR (300 MHz, DMSO- d_6 , δ) 13.16 (s, 1H, CO₂H), 10.55 (d, $J = 2.4$ Hz, 1H, 1min-H), 10.27 (d, $J = 2.1$ Hz, 1H, 1maj-H), 8.07 (d, $J = 8.7$ Hz, 2H, Ph min), 8.05 (d, $J = 8.4$ Hz, 2H, Ph maj), 7.41 (d, $J = 8.7$ Hz, 2H, Ph min), 7.40 (d, $J = 8.7$ Hz, 2H, Ph maj), 5.84 (dd, $J = 2.1, 0.6$ Hz, 1H, 3maj-H), 5.60 (dd, $J = 2.1, 0.6$ Hz, 1H, 3min-H), 4.19 (app. d, $J = 8.4$ Hz, 1H, 3b α min-H), 4.05 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α maj-H), 3.37-3.44 (m, 1H, 6a α -H), 3.00-3.06 (m, 1H, 10a α maj-H), 2.90-2.96 (m, 1H, 10a β min-H), 2.27-2.41 (m, 1H, 6b α -H), 2.18 (s, 3H, 2-CH₃), 0.95-1.62 (m, 8H, cyclohex.); ^{13}C NMR (75 MHz, CDCl₃, δ) 178.1, 177.9, 177.2, 167.2, 136.7, 130.9, 130.5, 127.4, 126.9, 126.6, 119.0, 108.6, 105.4, 105.0, 65.5, 46.3, 46.5, 46.0, 38.4, 33.0, 25.7, 21.4, 13.5; IR (thin film, cm^{-1}) 3472(bs), 3409(bs), 2950(m), 2847(m), 2294(w), 1770(w), 1686(s), 1514(w), 1422(m), 1378(m), 1279(m), 1170(m); HRMS m/z ($M + Na^+$) calcd 401.1473, found 401.1490. Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.59; H, 6.20; N, 7.45.

4-(2,8-Dimethyl-4,6-dioxo-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

cyclopenta[g]pyrrolo[3,4-e]indol-5-yl)benzoic acid (51). Method B with **3d** (750 mg, 6.70 mmol), 1.5-h reflux, reprecipitation from ethanol/diethyl ether (1:3, 20 mL), and then a diethyl ether wash (5 mL) gave **51** (550 mg, 31%) as a colorless solid, a mixture

of two isomers (maj:min = 1.6:1.0): mp 258-260 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 13.15 (s, 1H, CO₂H), 10.54 (d, *J* = 2.2 Hz, 1H, 1min-H), 10.28 (d, *J* = 1.6 Hz, 1H, 1maj-H), 8.07 (d, *J* = 8.4 Hz, 2H, Ph min), 8.05 (d, *J* = 8.7 Hz, 2H, Ph maj), 7.41 (d, *J* = 8.4 Hz, 2H, Ph min), 7.39 (d, *J* = 8.4 Hz, 2H, Ph maj), 5.82 (d, *J* = 1.2 Hz, 1H, 3maj-H), 5.61 (d, *J* = 2.1 Hz, 1H, 3min-H), 4.19 (app. d, *J* = 8.7 Hz, 1H, 3bαmin-H), 4.04 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 3.43 (dd, *J* = 8.4, 5.4 Hz, 1H, 6αmin-H), 3.39 (dd, *J* = 8.3, 5.3 Hz, 1H, 6αmaj-H), 2.94-3.00 (m, 1H, 10αmaj-H), 2.86-2.92 (m, 1H, 10αβmin-H), 2.35-2.60 (m, overlapped by DMSO, 1H, 6bα-H), 2.17 (s, 3H, 2-CH₃), 1.74-1.94 (m, 2H, cyclohex.), 1.30-1.46 (m, 2H, cyclohex.), 1.08-1.22 (m, 1H, cyclohex.), 0.88-1.04 (m, 2H, cyclohex.), 0.96 (d, *J* = 7.2 Hz, 3H, 8-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.0, 177.2, 167.2, 136.7, 130.8, 130.5, 127.4, 126.6, 108.8, 105.3, 45.7, 38.3, 34.7, 33.1, 32.6, 27.0, 26.7, 13.5; IR (thin film, cm⁻¹) 3458(bs), 3381(bs), 2919(m), 2285(w), 1780(w), 1700(s), 1515(w), 1425(m), 1382(m), 1285(m), 1161(m); HRMS *m/z* (M + Na⁺) calcd for C₂₃H₂₄N₂O₄: 415.1629, found 415.1628.

4-(8-Ethyl-2-methyl-4,6-dioxo-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-*e*]-5-indolyl)benzoic acid (52). Method B with **3e** (820 mg, 6.50 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **52** (600 mg, 31%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.7:1.0:0.1): mp 233-235 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 13.14 (s, 1H, CO₂H), 10.54 (d, *J* = 2.4 Hz, 1H, 1min-H), 10.29 (d, *J* = 2.1 Hz, 1H, 1maj-H), 10.24-10.28 (app. bs, 1H, 1min-H), 8.06 (d, *J* = 8.7 Hz, 2H, Ph), 7.38 (d, *J* = 8.4 Hz, 2H, Ph), 5.83 (app. s, 1H 3maj-H), 5.62 (d, *J* = 1.8 Hz, 1H, 3min-H), 5.59 (app. s, 1H, 3min-H), 4.18 (d, *J* = 8.1 Hz, 1H, 3bαmin-H), 4.04 (dd, *J* = 8.6, 1.7, 1H, 3bαmaj-

H), 3.42 (dd, $J = 8.4, 5.7$ Hz, 1H, 6 α min-H), 3.38 (dd, $J = 8.7, 5.1$ Hz, 1H, 6 α maj-H), 2.93-3.00 (m, 1H, 10 α maj-H), 2.86-2.92 (m, 1H, 10 α β -H), 2.40-2.54 (m, 1H, 6b-H), 1.86-2.40 (m, 2H, cyclohex.), 2.18 (s, 3H, 2-CH₃), 0.92-1.84 (m, 7H, cyclohex., CH₂CH₃), 0.87 (t, $J = 7.5$ Hz, 3H, CH₂CH₃ min), 0.80 (t, $J = 7.2$ Hz, 3H, CH₂CH₃ maj); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.1, 177.2, 167.2, 136.7, 130.8, 130.6, 127.3, 126.6, 108.7, 105.3, 45.6, 39.2, 35.0, 33.9, 33.3, 33.1, 32.8, 13.5, 12.6; IR (thin film, cm⁻¹) 3396(bs), 2922(m), 2860(m), 2293(w), 1693(s), 1513(w), 1426(m), 1387(m), 1284(m), 1166(m); HRMS m/z (M + Na⁺) calcd 429.1786, found 429.1797. Anal. Calcd for C₂₄H₂₆N₂O₄: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.92; H, 6.37; N, 6.75.

4-(8-Isopropyl-2-methyl-4,6-dioxo-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-*e*]-5-indolyl)benzoic acid (53). Method B with **3f** (910 mg, 6.50 mmol), 1-h reflux, reprecipitation from diethyl ether (20 mL), and then a diethyl ether wash (10 mL) gave **53** (600 mg, 30%) as a colorless solid, a mixture of three isomers (maj:min:min = 5.3:1.0:0.2): mp 260-262 °C; ¹H NMR (300 MHz, CDCl₃, δ) 13.16 (s, 1H, CO₂H), 10.55 (d, $J = 1.8$ Hz, 1H, 1min-H), 10.30 (d, $J = 2.1$ Hz, 1H, 1maj-H), 10.24-10.27 (app. bs, 1H, 1min-H), 8.07 (d, $J = 8.4$ Hz, 2H, Ph), 7.37 (d, $J = 8.7$ Hz, 2H, Ph), 5.83 (app. s, 1H, 3maj-H), 5.62 (d, $J = 1.2$ Hz, 1H, 3min-H), 5.59 (app. s, 1H, 3min-H), 4.18 (app. d, 1H, 3b α min-H), 4.03 (dd, $J = 8.4, 1.5$ Hz, 1H, 3b α maj-H), 3.34-3.48 (m, 1H, 6 α -H), 2.93-3.03 (m, 1H, 10 α maj-H), 2.86-2.92 (m, 1H, 10 α β min-H), 2.39-2.50 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH₃), 1.70-2.12 (m, 2H, cyclohex.), 1.10-1.55 (m, 6H, cyclohex., CH(CH₃)₂), 0.85 (d, $J = 6.6$ Hz, 6H, CH(CH₃)₂ maj), 0.79 (d, $J = 6.6$ Hz, CH(CH₃)₂ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.2, 177.1, 167.2, 136.8, 130.9, 130.6, 127.2, 126.6, 108.7, 105.3, 65.5, 45.6, 39.4, 33.0, 21.7, 21.0, 15.7,

13.5; IR (thin film, cm^{-1}) 3398(bs), 2950(m), 2865(m), 1770(w), 1696(s), 1514(w), 1430(m), 1388(m), 1285(m), 1184(m); HRMS m/z ($M + \text{Na}^+$) calcd 443.1942, found 443.1938. Anal. Calcd for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.16; H, 6.46; N, 6.49.

4-(2-Methyl-4,6-dioxo-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-cyclopenta[g]pyrrolo[3,4-e]-5-indolyl)benzoic acid (54). Method B with **3h** (1140 mg, 6.550 mmol), 1-h reflux, reprecipitation from ethanol/diethyl ether (1:2, 20 mL), and then a diethyl ether wash (10 mL) gave **54** (1000 mg, 46%) as a colorless solid, a mixture of two isomers (maj:min = 4.3:1.0): mp 255-257 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$, δ) 13.16 (s, 1H, CO_2H), 10.57 (bs, 1H, 1min-H), 10.39 (bs, 1H, 1maj-H), 8.06 (d, $J = 8.4$ Hz, 2H, 5-Ph), 7.41 (d, $J = 8.7$ Hz, 2H, 5-Ph), 7.27-7.35 (m, 4H, 8-Ph), 7.15-7.23 (m, 1H, 8-Ph), 5.78-5.86 (m, 1H, 3maj-H), 5.64-5.67 (m, 1H, 3min-H), 4.22 (d, $J = 8.7$ Hz, 1H, 3bamin-H), 4.04 (d, $J = 7.5$ Hz, 1H, 3bamaj-H), 3.25-3.58 (m, obscured by H_2O , 1H, 6a α -H), 2.80-3.00 (m, 1H, 10a α maj-H), 2.40-60 (m, overlapped by DMSO, 1H, 6b α -H), 2.18 (s, 3H, 2- CH_3), 1.45-2.10 (m, 7H, 1H, cyclohex.); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$, δ) 178.2, 177.1, 167.2, 136.8, 130.7, 130.6, 128.8, 127.2, 127.1, 126.6, 108.7, 99.7, 65.5, 45.6, 42.5, 42.1, 39.2, 33.0, 21.8, 15.7, 13.5; IR (thin film, cm^{-1}) 3475(bs), 3399(bs), 2933(m), 2861(m), 1770(w), 1703(s), 1510(w), 1427(m), 1386(m), 1286(m), 1188(m); HRMS m/z ($M + \text{Na}^+$) calcd 477.1786, found 477.1804. Anal. Calcd for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.66; H, 5.42; N, 6.00.

5-(4-Bromophenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (55). Method B with **3c** (687 mg, 7.00 mmol),

3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **55** (820 mg, 41%) as a colorless solid, a mixture of two isomers (maj:min = 1.8:1.0): mp 284-286 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.53 (bs, 1H, 1min-H), 10.26 (bs, 1H, 1maj-H), 7.72 (d, *J* = 8.4 Hz, 2H, Ph min), 7.70 (d, *J* = 8.7 Hz, 2H, Ph maj), 7.23 (d, *J* = 8.7 Hz, 2H, Ph min), 7.22 (d, *J* = 8.7 Hz, 2H, Ph maj), 5.83 (dd, *J* = 1.2, 0.6 Hz, 1H, 3maj-H), 5.59 (dd, *J* = 2.1, 0.6 Hz, 1H, 3min-H), 4.16 (dd, *J* = 8.4, 0.9 Hz, 1H, 3bamin-H), 4.02 (dd, *J* = 8.6, 1.7 Hz, 1H, 3bamaj-H), 3.40 (dd, *J* = 8.1, 5.1 Hz, 1H, 6aamin-H), 3.35 (dd, *J* = 8.6, 5.3 Hz, 1H, 6aamaj-H), 2.99-3.05 (m, 1H, 10aα-H), 2.90-2.95 (m, 1H, 10aβ-H), 2.26-2.40 (m, 2H, cyclohex., 6b-H), 2.25-2.40 (m, 2H, cyclohex.), 2.18 (s, 3H, 2-CH₃), 1.32-1.44 (m, 1H, cyclohex.), 0.96-1.24 (m, 4H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.1, 178.0, 177.2, 176.1, 132.6, 132.55, 132.2, 132.0, 129.5, 128.3, 126.9, 126.6, 121.9, 121.7, 119.0, 116.7, 114.0, 108.6, 105.4, 102.9, 94.5, 46.3, 46.0, 38.8, 38.5, 38.4, 38.2, 33.0, 29.3, 27.6, 26.1, 25.7, 23.2, 22.9, 21.4, 20.8, 13.5, 13.4; IR (thin film, cm⁻¹) 3400(bs), 2923(m), 2855(m), 1776(w), 1701(s), 1492(m), 1386(m), 1179(m), 1159(m); HRMS *m/z* (M + Na⁺) calcd 435.0679, found 435.0696. Anal. Calcd for C₂₁H₂₁BrN₂O₂: C, 61.03; H, 5.12; N, 6.78. Found: C, 61.11; H, 5.03; N, 6.67.

5-(4-Bromophenyl)-2,8-dimethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (56). Method B with **3d** (785 mg, 7.00

mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave

56 (1000 mg, 49%) as a colorless solid, a mixture of three isomers (maj:min:min =

3.6:1.0:0.2): mp 274-276 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.53 (bs, 1H, 1min-H), 10.27 (bs, 1H, 1maj-H), 10.26 (bs, 1H, 1min-H), 7.72 (d, *J* = 9.0 Hz, 2H, Ph min),

7.71 (d, $J = 9.6$ Hz, 2H, Ph min), 7.70 (d, $J = 8.7$ Hz, 2H, Ph maj), 7.23 (d, $J = 8.4$ Hz, 2H, Ph min), 7.21 (d, $J = 8.7$ Hz, 2H, Ph min), 7.20 (d, $J = 8.7$ Hz, 2H, Ph maj), 5.82 (dd, $J = 2.1, 0.6$ Hz, 1H, 3maj-H), 5.60 (dd, $J = 2.1, 0.6$ Hz, 1H, 3min-H), 5.59 (d, $J = 2.1, 0.6$ Hz, 1H, 3min-H), 4.15 (app. d, $J = 8.4$ Hz, 1H, 3b α min-H), 4.02 (dd, $J = 8.6, 1.7$ Hz, 1H, 3b α min-H), 4.01 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α maj-H), 3.41 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α min-H), 3.36 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α maj-H), 2.93-3.02 (m, 1H, 10a α maj-H), 2.85-2.92 (m, 1H, 10a β min-H), 2.30-2.52 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH₃), 1.74-2.16 (m, 2H, cyclohex.), 0.86-1.68 (m, 5H, cyclohex.), 0.95 (d, $J = 7.2$ Hz, 3H, 8-CH₃ maj), 0.72 (d, $J = 6.6$ Hz, 3H, 8-CH₃ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.1, 177.2, 176.0, 132.6, 132.5, 132.2, 132.1, 129.5, 129.4, 128.4, 128.3, 126.6, 121.8, 121.7, 118.5, 116.8, 108.8, 108.6, 105.3, 105.0, 45.6, 39.0, 38.9, 39.8, 33.1, 32.3-32.9 (overlapped peaks), 26.7, 13.4; IR (thin film, cm⁻¹) 3460(m), 3393(bs), 3095(w), 3066(w), 2959(m), 2922(s), 2889(m), 2866(m), 2854(m), 1777(w), 1705(s), 1492(s), 1383(s), 1188(m), 1177(m), 1159(m); HRMS m/z ($M + Na^+$) calcd 449.0836, found 449.0840. Anal. Calcd for C₂₂H₂₃BrN₂O₂: C, 61.83; H, 5.42; N, 6.56. Found: C, 62.02; H, 5.21; N, 6.59.

5-(4-Bromophenyl)-8-ethyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (57). Method B with **3e** (883 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **57** (1000 mg, 47%) as a colorless solid, a mixture of four isomers (maj:min:min:min = 3.0:1.0:0.3:0.3): mp 277-279 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.53 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 10.25 (bs, 1H, 1min-H), 7.73 (d, $J = 8.7$ Hz, 2H, Ph min), 7.71 (d, $J = 9.0$ Hz, 2H, Ph maj), 7.22 (d, $J = 8.4$ Hz, 2H, Ph min), 7.20 (d, $J =$

8.7 Hz, 2H, Ph maj), 5.81-5.83 (m, 1H, 3maj-H), 5.80-5.82 (m, 1H, 3min-H), 5.61 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.58 (app. d, $J = 2.1$ Hz, 1H, 3min-H), 4.16 (app. d, $J = 8.1$ Hz, 1H, 3 β amin-H), 4.15 (d, $J = 8.4$ Hz, 1H, 3 β amin-H), 4.02 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β amin-H), 4.00 (dd, $J = 8.6, 2.0$ Hz, 1H, 3 β amaj-H), 3.43 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.39 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.38 (dd, $J = 7.5, 5.4$ Hz, 1H, 6 α amin-H), 3.35 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amaj-H), 2.99-3.04 (m, 1H, 10amin-H), 2.93-2.99 (m, 1H, 10 α amaj-H), 2.86-2.90 (m, 1H, 10amin-H), 2.10-2.50 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH₃), 0.96-2.17 (m, 9H, cyclohex., CH₂CH₃), 0.79 (t, $J = 7.5$ Hz, 3H, CH₂CH₃ maj), 0.77 (t, $J = 7.2$ Hz, 3H, CH₂CH₃ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.1, 177.9, 177.2, 176.0, 132.7, 132.6, 132.2, 129.4, 129.3, 128.3, 126.9, 126.6, 121.7, 116.8, 108.7, 105.3, 103.0, 45.6, 33.9, 33.0, 32.6-32.9 (overlapped peaks), 13.5, 12.6, 11.8; IR (thin film, cm⁻¹) 3468(m), 3388(bs), 3093(w), 3065(w), 2957(m), 2927(m), 2869(m), 1777(w), 1705(s), 1492(s), 1383(m), 1188(m), 1176(m), 1157(m), ; HRMS *m/z* (M + Na⁺) calcd 463.0992, found 463.0980. Anal. Calcd for C₂₃H₂₅BrN₂O₂: C, 62.59; H, 5.71; N, 6.35. Found: C, 62.62; H, 5.63; N, 6.55.

5-(4-Bromophenyl)-8-isopropyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (58). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **58** (900 mg, 41%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.8:1.0:0.3): mp 291-293 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.53 (bs, 1H, 1min-H), 10.28 (bs, 1H, 1maj-H), 10.24 (bs, 1H, 1min-H), 7.74 (d, $J = 8.4$ Hz, 2H, Ph min), 7.71 (d, $J = 8.1$ Hz, 2H, Ph maj), 7.20 (d, $J = 8.4$ Hz, 2H, Ph min), 7.18 (d, $J = 8.7$ Hz, 2H, Ph maj), 5.79-5.84 (m, 1H, 3maj-H), 5.60-5.63 (m, 1H, 3min-H), 5.58-5.60 (m, 1H, 3min-H),

4.12-4.18 (m, overlapped, 3 β amin-H), 4.14 (d, $J = 7.8$ Hz, 1H, 3 β amin-H), 4.00 (d, $J = 8.4$ Hz, 1H, 3 β amaj-H), 3.31-3.46 (m, 1H, 6a-H), 2.93-3.02 (m, 1H, 10 α amaj-H), 2.86-2.92 (m, 1H, 10 α β min-H), 2.26-2.50 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH₃), 0.90-2.08 (m, 8H, cyclohex., CH(CH₃)₂), 0.67-0.86 (m, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.1, 176.0, 165.3, 132.7, 132.6, 129.3, 128.2, 126.6, 121.9, 119.0, 116.7, 105.2, 103.0, 45.9, 35.0, 32.7-33.2 (overlapped peaks), 28.9, 25.5, 21.1, 21.0, 20.9, 13.5; IR (thin film, cm⁻¹) 3467(m), 3398(s), 3094(w), 3067(w), 2946(m), 2888(m), 2867(m), 1777(w), 1705(s), 1492(s), 1386(m), 1176(m), 1162(m); HRMS m/z (M + Na⁺) calcd 477.1149, found 477.1152. Anal. Calcd for C₂₄H₂₇BrN₂O₂: C, 63.30; H, 5.98; N, 6.15. Found: C, 63.07; H, 5.67; N, 6.16.

5-(4-Bromophenyl)-8-*tert*-butyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (59). Method B with **3g** (1080 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **59** (700 mg, 31%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.3:1.0:0.5): mp 263-265 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.51 (d, $J = 1.8$ Hz, 1H, 1min-H), 10.38 (d, $J = 1.5$ Hz, 1H, 1maj-H), 10.34 (d, $J = 1.8$ Hz, 1H, 1min-H), 7.77 (d, $J = 8.7$ Hz, 2H, Ph min), 7.71 (d, $J = 9.0$ Hz, 2H, Ph maj), 7.66 (d, $J = 9.0$ Hz, 2H, Ph min), 7.17 (d, $J = 9.0$ Hz, 2H, Ph min), 7.15 (d, $J = 8.7$ Hz, 2H, Ph maj), 7.11 (d, $J = 8.7$ Hz, 2H, Ph min), 5.66 (dd, $J = 2.4, 0.9$ Hz, 1H, 3min-H), 5.59 (dd, $J = 2.4, 0.6$ Hz, 1H, 3min-H), 5.54 (dd, $J = 2.4, 0.9$ Hz, 1H, 3maj-H), 4.16 (app. d, $J = 8.4$ Hz, 1H, 3 β amin-H), 4.11 (app. d, $J = 8.1$ Hz, 1H, 3 β amaj-H), 3.90 (dd, $J = 7.5, 1.2$ Hz, 1H, 3 β amin-H), 3.50 (dd, $J = 8.1, 6.3$ Hz, 1H, 6 α amaj-H), 3.47 (dd, $J = 7.5, 5.4$ Hz, 1H, 6 α amin-H), 3.44 (dd, $J = 8.4, 5.1$ Hz, 1H, 6 α amin-H), 2.22-2.68 (m, 2H, 6b-H, 10a-H),

2.18 (s, 3H, 2-CH₃ min), 2.12 (s, 3H, 2-CH₃ maj), 2.11 (s, 3H, 2-CH₃ min), 0.92-2.04 (m, 7H, cyclohex.), 0.85 (s, 9H, *t*-Bu min), 0.84 (s, 9H, *t*-Bu maj), 0.67 (s, 9H, *t*-Bu min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.3, 178.2, 177.0, 175.8, 175.7, 175.1, 132.6, 132.4, 132.3, 129.5, 129.4, 128.6, 121.8, 116.8, 104.5, 104.2, 44.9, 34.3-34.5 (overlapped peaks), 33.2, 28.2, 28.0, 27.9, 13.4; IR (thin film, cm⁻¹) 3403(bs), 2923(m), 2353(w), 1770(w), 1713(s), 1492(m), 1390(m), 1163(m); HRMS *m/z* (M + Na⁺) calcd 491.1305, found 491.1328. Anal. Calcd for C₂₅H₂₉BrN₂O₂: C, 63.97; H, 6.23; N, 5.97. Found: C, 63.94; H, 6.00; N, 5.73.

5-(4-Bromophenyl)-2-methyl-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (60). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **60** (1000 mg, 43%) as a colorless solid, a mixture of four isomers (maj:min:min:min = 2.2:1.0:0.6:0.1): mp 294-296 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.59 (bs, 1H, 1min-H), 10.57 (bs, 1H, 1min-H), 10.38 (bs, 1H, 1maj-H), 10.35 (bs, 1H, 1min-H), 7.64-7.75 (m, 2H, Ph), 7.08-7.35 (m, 7H, Ph), 5.82-5.92 (m, 1H, 3min-H), 5.76-5.88 (m, 1H, 3maj-H), 5.63-5.70 (m, 1H, 3min-H), 5.50-5.55 (d, *J* = 7.2 Hz, 1H, 3min-H), 4.30 (d, *J* = 7.2 Hz, 1H, 3b α min-H), 4.18 (d, *J* = 8.1 Hz, 1H, 3b α min-H), 4.01 (d, *J* = 8.1 Hz, 1H, 3b α maj-H), 3.38-3.54 (m, 1H, 6 α -H), 2.78-2.96 (m, 1H, 10a-H), 2.46-2.58 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH₃), 1.48-1.98 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.4, 177.1, 132.7, 132.6, 132.34, 132.3, 132.3, 132.2, 129.6, 128.9, 127.6, 126.8, 126.7, 126.0, 121.7, 116.9, 105.0, 45.5, 33.1-33.6 (overlapped peaks), 13.5; IR (thin film, cm⁻¹) 3464(m), 3397(s), 3087(m), 3061(m), 3025(m), 2939(s), 2871(m), 1777(m), 1712(s), 1601(m), 1491(s), 1454(m), 1387(s), 1333(m), 1162(s),

1072(m); HRMS m/z ($M + Na^+$) calcd 511.0992, found 511.1012. Anal. Calcd for $C_{27}H_{25}BrN_2O_2$: C, 66.26; H, 5.15; N, 5.72. Found: C, 66.25; H, 5.17; N, 5.63.

5-(4-Fluorophenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (61). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **61** (760 mg, 45%) as a light-brown solid, a mixture of two isomers (maj:min = 1.8:1.0): mp 266-268 °C; 1H NMR (300 MHz, $DMSO-d_6$, δ) 10.53 (d, $J = 1.8$ Hz, 1H, 1maj-H), 10.26 (d, $J = 1.2$ Hz, 1H, 1min-H), 7.25-7.42 (m, 4H, Ph), 5.83 (dd, $J = 2.1, 0.6$ Hz, 1H, 3min-H), 5.60 (dd, $J = 2.4, 0.6$ Hz, 1H, 3maj-H), 4.15 (dd, $J = 8.1, 0.9$ Hz, 1H, 3 β amaj-H), 4.01 (dd, $J = 8.4$ Hz, 1H, 3 β amin-H), 3.40 (dd, $J = 8.4, 5.1$ Hz, 1H, 6 α amaj-H), 3.35 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 2.99-3.05 (m, 1H, 10 α amin-H), 2.90-2.95 (m, 1H, 10 β maj-H), 2.06-2.40 (m, 2H, cyclohex., 6b-H), 2.18 (s, 3H, 2- CH_3), 0.98-1.64 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 178.4, 178.2, 177.4, 176.3, 163.8, 160.0, 129.7, 129.5, 129.3, 129.0, 128.3, 126.9, 126.6, 119.0, 116.8, 116.7, 116.6, 116.4, 116.3, 108.6, 105.4, 102.8, 46.2, 45.9, 38.7, 38.5, 38.4, 38.2, 33.0, 29.3, 27.6, 26.1, 25.7, 23.2, 22.9, 21.4, 20.8, 13.5, 13.4; IR (thin film, cm^{-1}) 3460(m), 3390(s), 3072(w), 2928(m), 2856(m), 1777(w), 1701(s), 1604(w), 1512(s), 1391(m), 1230(m), 1180(m), 1161(m); HRMS m/z ($M + Na^+$) calcd 375.1480, found 375.1488. Anal. Calcd for $C_{21}H_{21}FN_2O_2$: C, 71.57; H, 6.01; N, 7.95. Found: C, 71.66; H, 6.28; N, 7.73.

5-(4-Fluorophenyl)-2,8-dimethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (62). Method B with **3d** (785 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **62** (670 mg, 38%) as a colorless solid, a mixture of three isomers (maj:min:min =

1.6:1.0:0.2): mp 265-267 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.52 (d, *J* = 1.5 Hz, 1H, 1min-H), 10.27 (d, *J* = 2.1 Hz, 1H, 1maj-H), 10.24-10.27 (app. bs, 1H, 1min-H), 7.24-7.40 (m, 4H, Ph), 5.82 (dd, *J* = 2.1, 0.9 Hz, 1H, 3maj-H), 5.60 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 5.59 (dd, *J* = 2.4, 0.9 Hz, 1H, 3min-H), 4.15 (dd, *J* = 8.1, 1.8 Hz, 1H, 3βmin-H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H, 3βmaj-H), 4.00 (dd, *J* = 8.4, 1.8 Hz, 1H, 3βmin-H), 3.41 (dd, *J* = 8.3, 5.3 Hz, 1H, 6αmin-H), 3.37 (dd, *J* = 8.7 Hz, 1H, 6αmin-H), 3.36 (dd, *J* = 8.1, 5.1 Hz, 1H, 6αmaj-H), 2.93-3.00 (m, 1H, 10αmaj-H), 2.87-2.92 (m, 1H, 10βmin-H), 2.30-2.58 (m, 1H, 6b-H), 2.17 (s, 3H, 2-CH₃), 0.85-2.10 (m, 7H, cyclohex.), 0.951 (d, *J* = 7.2 Hz, 3H, 8-CH₃ maj), 0.949 (d, *J* = 7.2 Hz, 3H, 8-CH₃ min), 0.72 (d, *J* = 6.6 Hz, 1H, 8-CH₃ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.3, 178.1, 177.3, 176.2, 163.5, 160.3, 129.7, 129.5, 129.4, 129.2, 129.1, 129.0, 128.2, 126.6, 116.9, 116.7, 116.6, 116.4, 116.3, 108.8, 105.3, 103.0, 45.9, 45.6, 38.5, 38.1, 33.1, 32.6, 32.5, 27.0, 26.7, 18.2, 13.5, 13.4; IR (thin film, cm⁻¹) 3462(m), 3390(bs), 3071(w), 2956(m), 2920(m), 2889(m), 2856(m), 1777(w), 1701(s), 1604(m), 1512(s), 1391(m), 1231(m), 1189(m), 1174(m), 1161(m); HRMS *m/z* (M + Na⁺) calcd 389.1637, found 389.1651. Anal. Calcd for C₂₂H₂₃FN₂O₂: C, 72.11; H, 6.33; N, 7.64. Found: C, 72.11; H, 6.28; N, 7.48.

8-Ethyl-5-(4-fluorophenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (63). Method B with **3e** (883 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **63** (800 mg, 44%) as a colorless solid, a mixture of three isomers (maj:min:min = 2.3:1.0:0.6): mp 283-285 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.53 (d, *J* = 2.1 Hz, 1H, 1maj-H), 10.28 (d, *J* = 1.5 Hz, 1H, 1min-H), 7.23-7.41 (m, 4H, Ph), 5.82 (dd, *J* = 1.8, 0.9 Hz,

1H, 3min-H), 5.61 (dd, $J = 2.4, 1.2$ Hz, 1H, 3maj-H), 5.58 (dd, $J = 2.1, 0.9$ Hz, 1H, 3min-H), 4.15 (dd, $J = 7.8, 1.2$ Hz, 1H, 3 α maj-H), 4.14 (dd, $J = 8.1, 0.6$ Hz, 1H, 3 β amin-H), 4.00 (dd, $J = 8.6, 1.7$ Hz, 1H, 3 β amin-H), 3.43 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.39 (dd, $J = 8.3, 5.3$ Hz, 1H, 6 α maj-H), 3.35 (dd, $J = 8.1, 5.41$ Hz, 1H, 6 α amin-H), 2.94-2.99 (m, 1H, 10 α amin-H), 2.90-2.93 (m, 1H, 10amin-H), 2.85-2.91 (m, 1H, 10 β maj-H), 2.40-2.50 (m, 1H, 6 β maj-H), 2.25-2.40 (m, 1H, 6bmin-H), 2.18 (s, 3H, 2-CH₃), 0.82-2.18 (m, 9H, cyclohex., CH₂CH₃), 0.80 (t, 3H, CH₂CH₃ min), 0.78 (t, 3H, CH₂CH₃ maj); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.2, 177.4, 176.2, 129.6, 129.5, 129.4, 129.0, 128.2, 126.6, 119.0, 118.7, 116.9, 116.8, 116.7, 116.5, 116.3, 108.8, 103.0, 45.9, 38.2, 38.1, 34.3, 33.9, 33.0, 32.9, 32.8, 32.7, 30.0, 23.6-24.0 (overlapped peaks); IR (thin film, cm⁻¹) 3461(m), 3393(bs), 3071(w), 2959(m), 2925(s), 2866(m), 1779(w), 1702(s), 1512(s), 1391(m), 1231(m), 1186(m), 1161(m); HRMS *m/z* (M + Na⁺) calcd for C₂₃H₂₅FN₂O₂: 403.1793, found 403.1809.

5-(4-Fluorophenyl)-8-isopropyl-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (64). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **64** (770 mg, 41%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.9:1.0:0.2): mp 286-288 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.53 (d, $J = 2.4$ Hz, 1H, 1min-H), 10.28 (d, $J = 2.4$ Hz, 1H, 1maj-H), 10.24 (d, $J = 2.4$ Hz, 1H, 1min-H), 7.21-7.43 (m, 4H, Ph), 5.82 (dd, $J = 1.8, 0.6$ Hz, 1H, 3maj-H), 5.61 (dd, $J = 2.4, 0.6$ Hz, 1H, 3min-H), 5.58 (dd, $J = 1.8, 0.9$ Hz, 1H, 3min-H), 4.16 (dd, $J = 9.3, 1.2$ Hz, 1H, 3 β amin-H), 4.14 (dd, $J = 7.8, 0.9$ Hz, 1H, 3 β amin-H), 3.99 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β maj-H), 3.43 (dd, $J = 8.3, 5.3$ Hz, 1H, 6 α amin-H), 3.39 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.35

(dd, $J = 8.4, 5.7$ Hz, 1H, 6 α maj-H), 2.93-3.01 (m, 1H, 10 α maj-H), 2.86-2.92 (m, 1H, 10 β min-H), 2.20-2.50 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH₃), 0.95-2.16 (m, 8H, cyclohex., CH(CH₃)₂), 0.85 (d, $J = 6.3$ Hz, 6H, CH(CH₃)₂ maj), 0.84 (d, $J = 6.3$ Hz, 6H, CH(CH₃)₂ min), 0.79 (d, $J = 6.3$ Hz, 6H, CH(CH₃)₂ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.5, 177.4, 176.2, 129.5, 129.4, 129.2, 129.1, 129.02, 129.0, 128.5, 128.2, 126.5, 118.9, 116.8, 116.7, 116.5, 116.4, 108.8, 105.3, 105.0, 104.5, 102.9, 45.5, 32.7-33.1, 21.8, 21.7, 21.0, 13.6, 13.5; IR (thin film, cm⁻¹) 3402(bs), 2922(m), 1770(w), 1730(s), 1453(m), 1231(m), 1157(m), 1110(m); HRMS m/z (M + Na⁺) calcd 417.1950, found 417.1964. Anal. Calcd for C₂₄H₂₇FN₂O₂: C, 73.07; H, 6.90; N, 7.10. Found: C, 72.91; H, 6.76; N, 6.90.

8-*tert*-Butyl-5-(4-fluorophenyl)-2-methyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (65). Method B with **3g** (1080 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **65** (670 mg, 34%) as a light-yellow solid, a mixture of four isomers (maj:min:min:min = 1.6:1.0:0.3:0.2): mp 223-225 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.51 (d, $J = 1.8$ Hz, 1H, 1min-H), 10.37 (d, $J = 2.4$ Hz, 1H, 1min-H), 10.34 (d, $J = 2.4$ Hz, 1H, 1maj-H), 10.23 (d, $J = 2.7$ Hz, 1H, 1min-H), 7.13-7.46 (m, 4H, Ph), 5.81 (dd, $J = 2.1, 0.6$ Hz, 1H, 3min-H), 5.67 (dd, $J = 2.4, 0.9$ Hz, 1H, 3maj-H), 5.59 (dd, $J = 2.4, 0.9$ Hz, 1H, 3min-H), 5.54 (dd, $J = 2.4, 0.9$ Hz, 1H, 3min-H), 4.16 (dd, $J = 1.8$ Hz, 9.6 Hz, 1H, 3 β min-H), 4.11 (app. d, $J = 8.7$ Hz, 1H, 3 β min-H), 4.02 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β min-H), 3.90 (dd, $J = 7.7, 1.4$ Hz, 1H, 3 β maj-H), 3.50 (dd, $J = 8.3, 6.2$ Hz, 1H, 6 α min-H), 3.46 (dd, $J = 7.8, 5.7$ Hz, 1H, 6 α maj-H), 3.44 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α min-H), 3.38 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α min-H), 2.96-3.02 (m, 1H, 10amin-H),

2.86-2.92 (m, 1H, 10amin-H), 2.24-2.64 (m, 2H, 6b-H, 10a α maj-H), 0.94-2.22 (m, 7H, cyclohex.), 2.18 (s, 3H, 2-CH₃ min), 2.13 (2, 3H, 2-CH₃ min), 2.11 (s, 3H, 2-CH₃ maj), 0.86 (s, 9H, *t*-Bu maj), 0.84 (s, 9H, *t*-Bu min), 0.68 (s, 9H, *t*-Bu min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.6, 178.5, 177.2, 176.0, 130.3, 129.7, 129.6, 129.3, 129.25, 129.2, 129.1, 128.5, 126.9, 126.8, 126.6, 122.3, 119.0, 116.8, 116.7, 116.5, 116.4, 116.2, 109.3, 104.2, 104.0, 46.26, 45.3, 44.9, 41.8, 34.4, 33.9, 33.2, 33.0, 32.6, 30.6-30.9 (overlapped peaks), 28.9-29.3 (overlapped peaks), 28.2, 28.0, 27.8, 27.7, 25.9, 13.4; IR (thin film, cm⁻¹) 3388(bs), 2921(m), 2864(m), 1774(w), 1713(s), 1512(s), 1391(m), 1231(m), 1160(m); HRMS *m/z* (M + Na⁺) calcd for C₂₅H₂₉FN₂O₂: 431.2106, found 431.2109.

5-(4-Fluorophenyl)-2-methyl-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (66). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **66** (1000 mg, 49%) as a colorless solid, a mixture of four isomers (maj:min:min:min = 8.0:1.0:0.5:0.4): mp 310-312 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.58 (app. bs, 1H, 1min-H), 10.56 (app. bs, 1H, 1min-H), 10.38 (d, *J* = 1.2 Hz, 1H, 1maj-H), 10.35 (app. bs, 1H, 1min-H), 7.15-7.39 (m, 9H, Ph), 5.87 (dd, *J* = 2.7, 0.6 Hz, 1H, 3min-H), 5.77-5.85 (app. m, 1H, 3maj-H), 5.65 (dd, *J* = 1.5, 0.6 Hz, 1H, 3min-H), 5.50-5.52 (app. m, 1H, 3min-H), 4.29 (dd, *J* = 6.9, 0.9 Hz, 1H, 3b α min-H), 4.18 (dd, *J* = 8.7, 0.6 Hz, 1H, 3b α min-H), 4.06 (dd, *J* = 8.6, 1.7 Hz, 1H, 3b α min-H), 4.01 (app. d, *J* = 8.1 Hz, 1H, 3b α maj-H), 3.34-3.52 (m, 1H, 6a α -H), 3.06-3.12 (m, 1H, 10amin-H), 2.86-2.96 (m, 1H, 10a α maj-H), 2.80-2.90 (m, 1H, 10a β min-H), 2.46-2.58 (m, 1H, 6b-H), 2.18 (s, 3H, 2-CH₃), 1.40-2.18 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.6, 177.4,

163.5, 160.5, 129.8, 129.7, 129.3, 129.2, 128.9, 127.6, 126.8, 126.1, 116.6, 116.4, 116.3, 75.0, 45.4, 33.1-33.8 (overlapped peaks), 13.5; IR (thin film, cm^{-1}) 3461(m), 3391(bs), 2935(m), 2871(m), 1775(w), 1701(s), 1603(w), 1512(s), 1391(m), 1228(m), 1191(m), 1165(m); HRMS m/z ($M + \text{Na}^+$) calcd 451.1793, found 451.1797. Anal. Calcd for $\text{C}_{27}\text{H}_{25}\text{FN}_2\text{O}_2$: C, 75.68; H, 5.88; N, 6.54. Found: C, 75.53; H, 5.76; N, 6.40.

2-Methyl-5-phenyl-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-

cyclohepta[g]pyrrolo[3,4-*e*]indole-4,6-dione (67). Method B with **3b** (1100 mg, 9.820 mmol), 4-h reflux, and then a diethyl ether wash (10 mL) gave **67** (350 mg, 21%) as a colorless solid, a mixture of two isomers (maj:min = 16.7:1.0): mp 232-233 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 8.20 (bs, 1H, 1min-H), 7.64 (bs, 1H, 1maj-H), 7.31-7.52 (m, 4H, Ph), 7.24-7.31 (m, 1H, Ph), 6.05 (d, $J = 1.5$ Hz, 1H, 3maj-H), 5.77 (d, $J = 2.1$ Hz, 1H, 3min-H), 3.97 (dd, $J = 7.8, 1.8$ Hz, 1H, 3 $\beta\alpha$ -H), 3.45 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α min-H), 3.34 (dd, $J = 8.0, 5.0$ Hz, 1H, 6 α maj-H), 2.98-3.10 (m, 1H, 11a-H), 2.52-2.63 (m, 1H, 6 $\beta\alpha$ -H), 2.05-2.30 (m, 1H, cyclohept.), 2.27 (s, 3H, 2- CH_3), 1.30-1.92 (m, 9H, cyclohept.); ^1H NMR (300 MHz, $\text{DMSO-}d_6$, δ) 10.44 (d, $J = 1.8$ Hz, 1H, 1min-H), 10.34 (d, $J = 2.4$ Hz, 1H, 1maj-H), 7.35-7.51 (m, 4H, Ph), 7.11-7.16 (m, 1H, Ph), 5.67 (dd, $J = 2.1, 0.9$ Hz, 1H, 3maj-H), 5.57 (dd, $J = 2.4, 0.9$ Hz, 1H, 3min-H), 4.09 (dd, $J = 9.0, 1.8$ Hz, 3 $\beta\alpha$ min-H), 3.87 (dd, $J = 7.7, 1.7$ Hz, 1H, 3 $\beta\alpha$ maj-H), 3.44 (dd, $J = 5.1, 4.2$ Hz, 1H, 6 α min-H), 3.42 (dd, $J = 7.5, 4.8$ Hz, 1H, 6 α maj-H), 2.88-2.96 (m, 1H, 11a-H), 2.34-2.43 (m, 1H, 6 $\beta\alpha$ -H), 2.10-2.23 (m, 1H, cyclohept.), 2.13 (s, 3H, 2- CH_3), 1.17-1.91 (m, 9H, cyclohept.); ^{13}C NMR (75 MHz, CDCl_3 , δ) 178.4, 176.7, 132.1, 130.2, 129.1, 128.3, 127.9, 126.5, 109.9, 104.7, 45.3, 40.7, 39.5, 36.8, 31.0, 30.4, 28.0, 26.6, 13.3; IR (thin film, cm^{-1}) 3393(bs), 3059(m), 2937(m), 2907(m), 2854(m), 1775(w),

1704(s), 1505(m), 1498(m), 1455(m), 1383(m), 1190(m), 1166(m), 1112(m); HRMS m/z ($M + Na^+$) calcd 371.1731, found 371.1734. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.66; H, 6.93; N, 7.78.

5-(4-Isopropylphenyl)-2-methyl-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-*e*]indole-4,6-dione (68). Method B with **3b** (1100 mg, 9.820 mmol), 2-h reflux, and then reprecipitation from diethyl ether (5 mL) gave **68** (50 mg, 3%) as a colorless solid, a mixture of three isomers (maj:min:min = 1.2:1.0:0.05): mp 188-192 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.82 (bs, 1H, 1min-H), 8.20 (bs, 1H, 1min-H), 7.62 (bs, 1H, 1min-H), 7.32 (d, $J = 8.4$ Hz, 2H, Ph min), 7.29 (d, $J = 8.7$ Hz, 2H, Ph maj), 7.18 (d, $J = 8.4$ Hz, 2H, Ph min), 7.17 (d, $J = 8.7$ Hz, 1H, Ph maj), 6.05 (dd, $J = 2.1, 0.6$ Hz, 1H, 3maj-H), 5.92 (dd, $J = 2.4, 1.2$ Hz, 1H, 3min-H), 5.77 (dd, $J = 2.7, 0.9$ Hz, 1H, 3min-H), 4.07 (app. d, $J = 8.1$ Hz, 1H, 3b α min-H), 4.00 (d, $J = 8.4$ Hz, 1H, 3b α min-H), 3.96 (dd, $J = 7.8, 1.8$ Hz, 1H, 3b α maj-H), 3.45 (dd, $J = 8.6, 5.6$ Hz, 1H, 6a α min-H), 3.33 (dd, $J = 7.8, 5.1$ Hz, 1H, 6a α maj-H), 2.97-3.09 (m, 1H, 11a-H), 2.93 (septet, $J = 6.8$ Hz, 1H, $CH(CH_3)_2$), 2.52-2.63 (m, 1H, 6b-H), 2.35 (s, 3H, 2- CH_3 min), 2.29 (s, 3H, 2- CH_3 min), 2.27 (s, 3H, 2- CH_3 maj), 2.10-2.26 (m, 1H, cyclohept.), 1.65-1.90 (m, 6H, cyclohept.), 1.32-1.63 (m, 3H, cyclohept.), 1.27 (d, $J = 6.9$ Hz, 6H, $CH(CH_3)_2$ min), 1.25 (d, $J = 6.9$ Hz, 6H, $CH(CH_3)_2$ maj); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.4, 149.1, 127.3, 127.2, 126.2, 104.8, 45.3, 40.6, 36.8, 34.0, 31.0, 30.4, 26.7, 24.0, 13.3; IR (thin film, cm^{-1}) 3395(bs), 3047(m), 2957(m), 2919(m), 2858(m), 2361(w), 1774(w), 1698(s), 1516(m), 1389(m), 1181(m), 1171(m); HRMS m/z ($M + Na^+$) calcd for $C_{25}H_{30}N_2O_2$: 413.2200, found 413.2203.

5-(4-Methoxyphenyl)-2-methyl-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-e]indole-4,6-dione (69). Method B with **3b** (1100 mg, 9.820 mmol), 4-h reflux, removal of solvent under reduced pressure, column chromatography eluting with CH₂Cl₂, and then reprecipitation from diethyl ether (20 mL) gave **69** (400 mg, 11%) as a colorless solid, a mixture of three isomers (maj:min:min = 5.8:1.0:0.3): mp 191-193 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.16 (bs, 1H, 1min-H), 7.61 (bs, 1H, 1maj-H), 7.17 (d, *J* = 9.0 Hz, 2H, Ph), 6.95 (d, *J* = 9.0 Hz, 2H, Ph), 6.05 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.99 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.77 (d, *J* = 2.1 Hz, 1H, 3min-H), 4.06 (dd, *J* = 7.4, 2.0 Hz, 1H, 3bαmin-H), 3.93 (dd, *J* = 7.8, 1.8 Hz, 1H, 3bαmaj-H), 3.84 (s, 3H, OCH₃ min), 3.82 (s, 3H, OCH₃ maj), 3.81 (s, 3H, OCH₃ min), 3.44 (dd, *J* = 8.7, 5.7, 1H, 6aαmin-H), 3.35 (dd, *J* = 7.7, 3.5 Hz, 1H, 6aαmin-H), 3.33 (dd, *J* = 7.8, 4.8 Hz, 1H, 6aαmaj-H), 3.01-3.09 (m, 1H, 11a-H), 2.53-2.62 (m, 1H, 6b-H), 2.10-2.30 (m, 1H, cyclohept.), 2.29 (s, 3H, 2-CH₃ min), 2.27 (s, 3H, 2-CH₃ maj), 2.24 (s, 3H, 2-CH₃ min), 1.70-1.98 (m, 6H, cyclohept.), 1.32-1.55 (m, 3H, cyclohept.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.5, 177.0, 159.3, 130.2, 127.8, 127.7, 124.8, 114.4, 114.2, 109.9, 105.2, 104.7, 55.6, 48.2, 45.3, 43.2, 42.5, 40.6, 39.6, 37.6, 36.8, 31.9, 31.8, 31.0, 30.9, 30.4, 27.9, 27.5, 26.6, 26.4, 24.8, 13.3; IR (thin film, cm⁻¹) 3379(bs), 2925(m), 2858(m), 1773(w), 1705(s), 1513(s), 1387(m), 1252(m), 1169(m); HRMS *m/z* (M + Na⁺) calcd 401.1836, found 401.1837. Anal. Calcd for C₂₃H₂₆N₂O₃: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.80; H, 6.92; N, 7.41.

2-Methyl-5-(3-nitrophenyl)-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-e]indole-4,6-dione (70). Method B with **3b** (1100 mg, 9.820 mmol), 1.5 h-reflux, removal of solvent under reduced pressure, column

chromatography eluting with CH₂Cl₂, and then reprecipitation from diethyl ether (20 mL) gave **70** (450 mg, 24%) as a colorless solid, a mixture of two isomers (maj:min = 9.0:1.0): mp 169-170 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.21-8.29 (m, 2H, Ph), 8.13 (bs, 1H, 1min-H), 7.60-7.72 (m, 3H, Ph, Ph, 1maj-H), 6.02 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 5.78 (dd, *J* = 3.0, 0.9 Hz, 1H, 3min-H), 4.07 (app. d, *J* = 8.4 Hz, 1H, 3βamin-H), 4.02 (dd, *J* = 7.8, 1.8 Hz, 1H, 3βamaj-H), 3.49 (dd, *J* = 8.6, 5.7 Hz, 1H, 6αamin-H), 3.38 (dd, *J* = 7.7, 5.0 Hz, 1H, 6αamaj-H), 3.02-3.10 (m, 1H, 11a-H), 2.54-2.63 (m, 1H, 6βα-H), 2.20-2.38 (m, 1H, cyclohex.), 2.28 (s, 3H, 2-CH₃), 1.57-1.95 (m, 6H, cyclohept.), 1.35-1.58 (m, 3H, cyclohept.); ¹³C NMR (75 MHz, CDCl₃, δ) 177.5, 176.0, 148.4, 133.2, 132.3, 130.4, 129.8, 128.3, 122.9, 121.6, 109.5, 104.5, 45.3, 41.0, 39.2, 36.8, 36.7, 31.1, 31.0, 30.6, 28.5, 28.3, 26.3, 13.3; IR (thin film, cm⁻¹) 3394(bs), 2926(m), 2859(m), 1777(w), 1713(s), 1533(s), 1351(m), 1195(w), 1165(m); HRMS *m/z* (M + Na⁺) calcd 416.1582, found 416.1589. Anal. Calcd for C₂₂H₂₃N₃O₄: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.33; H, 5.86; N, 10.80.

5-(4-Chlorophenyl)-2-methyl-3b,6a,6b,7,8,9,10,11,11a-nonahydro-1H,5H-cyclohepta[g]pyrrolo[3,4-*e*]indole-4,6-dione (71). Method B with **3b** (1100 mg, 9.820 mmol), 4-h reflux, removal of solvent under reduced pressure, column chromatography eluting with CH₂Cl₂, and then reprecipitation from diethyl ether (20 mL) gave **71** (300 mg, 17%) as a colorless solid, a mixture of two isomers (maj:min = 28.0:1.0): mp 219-220 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.15 (bs, 1H, 1min-H), 7.63 (bs, 1H, 1maj-H), 7.41 (d, *J* = 8.7 Hz, 2H, Ph), 7.23 (d, *J* = 9.0 Hz, 2H, Ph), 6.03 (dd, *J* = 2.4, 0.9 Hz, 1H, 3maj-H), 5.77 (dd, *J* = 2.7, 0.9 Hz, 1H, 3min-H), 4.08 (dd, *J* = 7.2, 2.1, 1H, 3βamin-H), 3.96 (dd, *J* = 7.8, 2.1 Hz, 1H, 3βamaj-H), 3.45 (dd, *J* = 8.4, 5.4 Hz, 1H, 6αamin-H),

3.33 ($J = 7.7, 5.0$ Hz, 1H, 6 α maj-H), 3.00-3.08 (m, 1H, 11a-H), 2.52-2.61 (m, 1H, 6b α -H), 2.15-2.25 (m, 1H, cyclohept.), 2.27 (s, 3H, 2-CH₃), 1.68-1.92 (m, 6H, cyclohept.), 1.32-1.55 (m, 3H, cyclohept.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.0, 176.4, 134.0, 130.6, 130.2, 129.2, 128.0, 127.7, 109.7, 104.6, 45.3, 40.7, 39.4, 36.8, 31.0, 30.4, 28.1, 27.8, 26.5, 13.3; IR (thin film, cm⁻¹) 3394(bs), 2925(m), 2858(m), 1775(w), 1709(s), 1494(m), 1381(m), 1195(w), 1166(w), 1092(w); HRMS m/z (M + Na⁺) calcd 405.1341, found 405.1340. Anal. Calcd for C₂₂H₂₃ClN₂O₃: C, 69.01; H, 6.05; N, 7.32. Found: C, 69.21; H, 6.33; N, 7.40.

5-Dimethylamino-2-ethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (72). Method A gave **72** (265 mg, 28%) as a light-brown solid, a mixture of two isomers (maj:min = 8.5:1.0): mp 218-219 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.29 (bs, 1H, 1min-H), 7.68 (bs, 1H, 1maj-H), 6.18 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.76 (d, $J = 2.4$ Hz, 1H, 3min-H), 3.70 (dd, $J = 8.6, 1.6$ Hz, 1H, 3b α -H), 3.23 (dd, $J = 8.7, 5.7$ Hz, 1H, 6 α amin-H), 3.17 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α maj-H), 3.04-3.10 (m, 1H, 10 α maj-H), 2.80-2.92 (m, 1H, 10 α β min-H), 2.92 (s, 6H, N(CH₃)₂), 2.43-2.71 (m, 3H, 6b α -H, CH₂CH₃), 0.87-2.23 (m, 11H, cyclohex., CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 177.6, 176.7, 133.4, 126.8, 108.4, 103.6, 44.0, 43.8, 38.2, 36.8, 32.9, 27.6, 25.7, 23.0, 21.4, 21.0, 14.7; IR (thin film, cm⁻¹) 3371(bs), 2932(m), 2857(m), 2380(w), 1770(w), 1704(s), 1445(m), 1369(m), 1194(m); HRMS m/z (M + Na⁺) calcd 338.1840, found 338.1844. Anal. Calcd for C₁₈H₂₅N₃O₂: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.36; H, 8.06; N, 13.12.

5-Dimethylamino-2,8-diethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (73). Method A gave **73** (319 mg, 31%) as a

white solid, a mixture of two isomers (maj:min = 4.7:1.0): mp 221-222 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.29 (bs, 1H, 1min-H), 7.68 (bs, 1H, 1maj-H), 6.18 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.78 (d, *J* = 3.0 Hz, 1H, 3min-H), 3.73 (dd, *J* = 8.6, 2.0 Hz, 1H, 3βmin-H), 3.70 (dd, *J* = 8.4, 1.8 Hz, 1H, 3βmaj-H), 3.22 (dd, *J* = 8.7, 5.7 Hz, 1H, 6αmin-H), 3.17 (d, *J* = 8.4, 5.4 Hz, 1H, 6αmaj-H), 3.01-3.06 (m, 1H, 10αmaj-H), 2.92-2.96 (m, 1H, 10βmin-H), 2.93 (s, 6H, N(CH₃)₂), 2.56-2.75 (m, 3H, 6β-H, 2-CH₂CH₃), 1.80-1.99 (m, 2H, cyclohex.), 1.07-1.52 (m, 10H, cyclohex., 2-CH₂CH₃, 8-CH₂CH₃), 0.85 (t, *J* = 7.4 Hz, 3H, 8-CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 177.6, 177.4, 176.7, 175.6, 135.0, 133.3, 126.7, 116.9, 112.5, 108.5, 105.0, 103.6, 101.2, 43.8, 43.7, 36.8, 33.9, 33.0, 32.6, 21.1, 14.7, 12.5; IR (thin film, cm⁻¹) 3378(bs), 2931(m), 2857(m), 2342(m), 1770(w), 1703(s), 1447(m), 1362(m), 1194(m); HRMS *m/z* (M + Na⁺) calcd 366.2153, found 366.2161. Anal. Calcd for C₂₀H₂₉N₃O₂: C, 69.94; H, 8.51; N, 12.23. Found: C, 69.78; H, 8.35; N, 12.08.

8-*tert*-Butyl-5-dimethylamino-2-ethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (74). Method A gave **74** (256 mg, 23%) as a light-orange solid, a mixture of two isomers (maj:min = 14.0:1.0): mp 190-191 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.61 (bs, 1H, 1maj-H), 6.13 (d, *J* = 2.7 Hz, 1H, 3min-H), 6.02 (d, *J* = 2.4 Hz, 1H, 3maj-H), 3.79 (dd, *J* = 7.8, 1.5 Hz, 1H, 3β-H), 3.19 (dd, *J* = 12.3, 8.1 Hz, 1H, 6αmin-H), 3.10 (dd, *J* = 5.9, 8.0 Hz, 1H, 6αmaj-H), 2.87 (s, 6H, N(CH₃)₂), 2.52-2.75 (m, 4H, 6β-H, 10a-H, CH₂CH₃), 1.72-2.04 (m, 4H, cyclohex.), 1.51 (ddd, *J* = 13.5, 10.2, 6.6 Hz, 1H, cyclohex.), 1.11-1.33 (m, 2H, cyclohex.), 1.25 (t, *J* = 7.5 Hz, 3H, CH₂CH₃), 0.90 (s, 9H, *t*-Bu); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 177.7, 176.4, 133.4, 129.9, 108.8, 102.4, 43.5, 43.1, 34.3, 34.0, 33.0, 30.6, 28.4, 28.0, 25.6,

21.0, 14.3; IR (thin film, cm^{-1}) 3386(bs), 2961(m), 2359(w), 1774(w), 1712(s), 1448(m), 1365(m), 1203(m), 1148(m); HRMS m/z ($M + \text{Na}^+$) calcd 394.2466, found 394.2473. Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_2$: C, 71.12; H, 8.95; N, 11.31. Found: C, 71.32; H, 8.75; N, 11.31.

2-Ethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (75). Method A gave **75** (502 mg, 48%) as a white solid, a mixture of two isomers (maj:min = 1.4:1.0): mp 219-220 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 8.20 (bs, 1H, 1min-H), 7.83 (bs, 1H, 1maj-H), 7.44-7.54 (m, 3H, Ph), 7.27-7.31 (m, 2H, Ph), 6.14 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.82 (d, $J = 2.4$ Hz, 1H, 3min-H), 4.02 (dd, $J = 8.9, 2.0$ Hz, 1H, 3bamin-H), 3.97 (dd, $J = 8.6, 2.0$ Hz, 1H, 3bamaj-H), 3.78 (dd, $J = 8.6, 5.6$ Hz, 1H, 6aamin-H), 3.40 (dd, $J = 8.4, 5.4$ Hz, 1H, 6aamaj-H), 3.13-3.19 (m, 1H, 10aamaj-H), 3.03-3.13 (m, 1H, 10aamin-H), 2.67 (q, $J = 7.5$ Hz, 2H, 2- CH_2CH_3), 2.47-2.57 (m, 1H, 6b-H), 2.17-2.30 (m, 1H, cyclohex.), 1.10-1.83 (m, 10H, cyclohex., 2- CH_2CH_3); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$, δ) 178.4, 178.2, 177.5, 176.3, 135.2, 133.5, 133.0, 132.8, 129.6, 129.5, 128.9, 128.8, 127.5, 127.4, 126.9, 118.7, 116.8, 108.5, 103.8, 101.1, 46.3, 46.0, 33.1, 33.07, 29.3, 27.6, 26.1, 25.7, 23.3, 22.9, 21.5, 21.0, 20.9, 14.8, 14.7; IR (thin film, cm^{-1}) 3394(bs), 2938(m), 2857(m), 2310(w), 1774(w), 1698(s), 1499(m), 1387(m), 1190(m), 1160(m); HRMS m/z ($M + \text{Na}^+$) calcd 371.1731, found 371.1738. Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.92; H, 7.03; N, 8.11.

2,8-Diethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (76). Method A gave **76** (395 mg, 35%) as a cream-colored solid, a mixture of four isomers (maj:min:min:min = 1.2:1.0:0.2:0.1): mp 243-244 °C; ^1H NMR

(300 MHz, CDCl₃, δ) 8.38 (bs, 1H, 1maj-H), 7.82 (bs, 1H, 1min-H), 7.42-7.55 (m, 3H, Ph), 7.27-7.30 (m, 2H, Ph), 6.13 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.82 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.79 (d, $J = 2.7$ Hz, 1H, 3min-H), 4.02 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H, 3 β amaj-H), 3.97 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β amin-H), 3.51 (dd, $J = 5.6$ Hz, 8.6 Hz, 1H, 6 α amin-H), 3.47 (dd, $J = 8.7, 5.7$ Hz, 1H 6 α maj-H), 3.43 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.39 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.09-3.16 (m, 1H, 10 α amin-H), 2.98-3.06 (m, 1H, 10 β maj-H), 2.50-2.72 (m, 1H, 6b-H), 2.67 (q, $J = 7.5$ Hz, 2H, 2-CH₂CH₃), 1.89-2.30 (m, 2H, cyclohex.), 1.19-1.57 (m, 10H, cyclohex., 2-CH₂CH₃, 8-CH₂CH₃), 0.87 (t, $J = 7.2$ Hz, 3H, 8-CH₂CH₃ min), 0.86 (t, $J = 7.5$ Hz, 1H, 8-CH₂CH₃ maj); IR (thin film, cm⁻¹) 3384(bs), 2953(m), 2923(m), 1773(w), 1694(s), 1497(w), 1456(w), 1447(w), 1389(m), 1192(m); HRMS m/z ($M + Na^+$) calcd 399.2044, found 399.2059. Anal. Calcd for C₂₄H₂₈N₂O₂: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.41; H, 7.73; N, 7.24.

8-tert-Butyl-2-ethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (77). Method A gave **77** (328 mg, 27%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 4.4:1.0:0.3): mp 209-210 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.20 (bs, 1H, 1min-H), 7.76 (bs, 2H, 1maj-H, 1min-H), 7.37-7.56 (m, 3H, Ph), 7.19-7.29 (m, 2H, Ph), 6.12 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.98 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.76 (d, $J = 2.4$ Hz, 1H, 3min-H), 4.03 (dd, $J = 7.8, 1.5$ Hz, 1H, 3 β amaj-H), 3.98 (dd, $J = 8.6, 2.0$ Hz, 1H, 3 β amin-H), 3.442 (dd, $J = 8.3, 5.9$ Hz, 1H, 6 α amin-H), 3.437 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.36 (dd, $J = 7.8, 5.7$ Hz, 1H, 6 α maj-H), 3.10-3.13 (m, 1H, 10 β min-H), 2.74-2.81 (m, 1H, 6 β amaj-H), 2.52-2.71 (m, 3H, 10 α maj-H, CH₂CH₃), 1.76-2.28 (m, 3H, cyclohex.), 1.62 (ddd, J

= 13.7, 11.0, 6.9 Hz, 1H, cyclohex.), 0.84-1.46 (m, 6H, cyclohex., CH₂CH₃), 0.92 (s, 9H, *t*-Bu), 0.75 (s, 9H, *t*-Bu); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.5, 178.46, 177.5, 177.3, 133.7, 133.5, 133.1, 133.0, 130.3, 129.6, 129.4, 128.8, 128.6, 127.5, 127.2, 126.9, 115.5, 109.1, 108.4, 103.8, 102.3, 47.5, 46.0, 45.9, 45.3, 41.8, 34.5, 33.9, 33.0, 32.7, 32.6, 30.6-31.0 (multiple peaks), 28.8-29.3 (multiple peaks), 27.6-28.3 (multiple peaks), 25.8-26.0 (multiple peaks), 22.4, 21.1, 21.0, 14.8, 14.3; IR (thin film, cm⁻¹) 3386(bs), 2961(m), 2923(m), 1771(w), 1708(s), 1496(m), 1372(m), 1314(m), 1176(m), 1163(m); HRMS *m/z* (M + Na⁺) calcd 427.2357, found 427.2340. Anal. Calcd for C₂₆H₃₂N₂O₂: C, 77.19; H, 7.97; N, 6.92. Found: C, 77.34; H, 8.23; N, 7.07.

2-Ethyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (78). Method A gave **78** (466 mg, 41%) as a cream-colored solid, a mixture of two isomers (maj:min = 5.6:1.0): mp 242-243 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.37 (bs, 1H, 1maj-H), 7.70 (bs, 1H, 1min-H), 7.16-7.28 (m, 2H, Ph), 6.95-7.02 (m, 2H, Ph), 6.24 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.80 (d, *J* = 3.0 Hz, 1H, 3maj-H), 3.97 (dd, *J* = 8.9, 2.0 Hz, 1H, 3βmaj-H), 3.96 (dd, *J* = 8.6, 2.0 Hz, 1H, 3βamin-H), 3.843 (s, 3H, OCH₃ maj), 3.841 (s, 3H, OCH₃ min), 3.46 (dd, *J* = 8.7, 5.7 Hz, 1H, 6αmaj-H), 3.39 (dd, *J* = 8.6, 5.3 Hz, 1H, 6αamin-H), 3.12-3.17 (m, 1H, 10αamin-H), 3.02-3.07 (m, 1H, 10αβmaj-H), 2.66 (q, *J* = 7.8 Hz, 2H, CH₂CH₃), 2.49-2.59 (m, 1H, 6β-H), 2.14-2.27 (m, 1H, cyclohex.), 1.20-1.77 (m, 10H, cyclohex., CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.4, 176.5, 159.4, 135.1, 133.5, 128.6, 125.4, 118.7, 116.9, 114.8, 114.7, 108.5, 101.1, 55.9, 46.2, 46.0, 33.1, 29.3, 26.1, 22.9, 21.1, 20.9, 14.7; IR (thin film, cm⁻¹) 3399(bs), 2935(m), 1774(w), 1697(s), 1518(m), 1456(m), 1395(m), 1304(m), 1256(m), 1182(m); HRMS *m/z* (M + Na⁺) calcd 401.1836,

found 401.1851. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.78; H, 6.88; N, 7.32.

2,8-Diethyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (79). Method A gave **79** (439 mg, 36%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 6.5:1.0:0.3): mp 252-253 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.35 (bs, 1H, 1min-H), 7.73 (bs, 1H, 1maj-H), 7.16-7.23 (m, 2H, Ph), 6.97-7.01 (m, 2H, Ph), 6.21 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.81 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.78 (d, $J = 2.4$ Hz, 1H, 3min-H), 3.97 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β min-H), 3.94 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β maj-H), 3.84 (s, 3H, OCH_3), 3.45 (dd, $J = 8.7, 6.0$ Hz, 1H, 6 α min-H), 3.41 (dd, $J = 8.6, 5.3$ Hz, 1H, 6 α min-H), 3.38 (dd, $J = 8.6, 5.6$ Hz, 1H, 6 α maj-H), 3.05-3.16 (m, 1H, 10 α maj-H), 2.98-3.05 (m, 1H, 10 β min-H), 2.59-2.74 (m, 3H, 6b-H, 2- CH_2CH_3), 1.03-2.20 (m, 9H, cyclohex., 8- CH_2CH_3), 1.29 (t, $J = 7.5$ Hz, 3H, 2- CH_2CH_3), 0.86 (t, $J = 7.5$ Hz, 3H, 8- CH_2CH_3); ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 178.6, 177.7, 159.3, 133.4, 128.6, 125.6, 114.9, 114.8, 108.7, 103.8, 103.7, 55.9, 45.5, 34.0, 33.9, 33.1, 32.9, 32.8, 32.75, 32.7, 21.0, 14.7, 12.6; IR (thin film, cm^{-1}) 3383(bs), 2932(m), 2356(w), 1772(w), 1695(s), 1518(m), 1392(m), 1258(m), 1195(m), 1176(m); HRMS m/z ($M + Na^+$) calcd 429.2149, found 429.2167. Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 70.74; H, 6.94; N, 6.62.

8-tert-Butyl-2-ethyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (80). Method A gave **80** (365 mg, 28%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 2.1:1.0:0.1): mp 207-208 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.10 (bs, 1H, 1min-H), 7.64 (bs, 1H, 1min-H),

7.61 (bs, 1H, 1maj-H), 7.19 (d, $J = 8.7$ Hz, 2H, Ph min), 7.14 (d, $J = 8.7$ Hz, 2H, Ph maj), 7.00 (d, $J = 9.3$ Hz, 2H, Ph min), 6.95 (d, $J = 8.7$ Hz, 2H, Ph maj), 6.20 (d, $J = 2.4$ Hz, 1H, 3min-H), 6.06 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.77 (d, $J = 2.4$ Hz, 1H, 3min-H), 4.04 (dd, $J = 7.5, 1.2$ Hz, 1H, 3bmaj-H), 3.96 (dd, $J = 8.6, 2.0$ Hz, 1H, 3bmin-H), 3.84 (s, 3H, OCH₃ min), 3.82 (s, 3H, OCH₃ maj), 3.42 (dd, $J = 8.6, 5.3$ Hz, 1H, 6 α min-H), 3.33 (dd, $J = 7.8, 5.4$ Hz, 1H, 6 α maj-H), 3.05-3.14 (m, 1H, 10 α βmin-H), 2.55-2.76 (m, 4H, 6b-H, 10 α maj-H, CH₂CH₃), 0.91-2.25 (m, 7H, cyclohex.), 1.27 (t, $J = 7.8$ Hz, 3H, CH₂CH₃), 0.91 (s, 9H, *t*-Bu maj), 0.73 (s, 9H, *t*-Bu min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.7, 178.7, 177.7, 177.5, 176.2, 159.4, 159.3, 135.2, 133.6, 133.5, 130.0, 128.7, 128.6, 128.3, 128.2, 126.9, 125.7, 126.6, 126.55, 114.9, 114.8, 114.6, 109.1, 108.4, 103.8, 102.4, 55.9, 47.5, 46.0, 45.1, 44.7, 34.5, 33.9, 33.3, 33.0, 32.7, 32.6, 28.2, 28.0, 27.8, 21.1, 21.0, 14.8, 14.5, 14.3; IR (thin film, cm⁻¹) 3390(bs), 2963(m), 2935(m), 2357(w), 1513, 1770(w), 1705(s), 1640(bm), 1514(s), 1389(m), 1252(m), 1168(m); HRMS m/z (M + Na⁺) calcd 457.2462, found 457.2471. Anal. Calcd for C₂₇H₃₄N₂O₃: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.73; H, 7.83; N, 6.36.

2-Benzyl-5-(dimethylamino)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (81). Method A gave **81** (396 mg, 35%) as a light-brown solid, a mixture of two isomers (maj:min = 3.2:1.0): mp 238-239 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.22 (bs, 1H, 1min-H), 7.57 (bs, 1H, 1maj-H), 7.29-7.36 (m, 2H, Ph), 7.21-7.28 (m, 3H, Ph), 6.25 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.79 (d, $J = 2.7$ Hz, 1H, 3min-H), 4.04 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 4.02 (AA'd, $J = 15.9$ Hz, 1H, Bn min), 3.95 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 3.94 (AA'd, $J = 16.2$ Hz, 1H, Bn min), 3.69 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α -H), 3.21 (dd, $J = 8.6, 5.4$ Hz, 1H, 6 α min-H), 3.16

(dd, $J = 8.6, 5.3$ Hz, 1H, 6 α maj-H), 3.01-3.05 (m, 1H, 10a-H), 2.93 (s, 6H, N(CH₃)₂), 2.42-2.52 (m, 1H, 6b-H), 1.99-2.22 (m, 1H, cyclohex.), 0.99-1.74 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, CDCl₃, δ) 177.6, 177.4, 176.7, 175.6, 141.53, 141.47, 132.3, 130.4, 129.1, 128.7, 127.4, 126.3, 119.0, 117.4, 108.9, 105.7, 102.9, 44.3, 44.0, 43.8, 38.2, 36.7, 36.3, 34.0, 33.0, 29.2, 27.6, 26.0, 25.7, 23.1, 22.7, 21.4, 20.8; IR (thin film, cm⁻¹) 3450(bs), 2923(m), 2100(bw), 1770(w), 1703(s), 1648(bs), 1442(m), 1366(m), 1194(m), 1148(m); HRMS m/z (M + Na⁺) calcd for C₂₃H₂₇N₃O₂: 400.1996, found 400.1992.

2-Benzyl-5-dimethylamino-8-ethyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (82). Method A gave **82** (353 mg, 29%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 5.3:1.0:0.3): mp 239-240 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.54 (bs, 1H, 1min-H), 7.35 (bs, 2H, 1maj-H, 1min-H), 7.23-7.36 (m, 5H, Ph), 6.25 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.81 (d, $J = 2.7$ Hz, 1H, 3min-H), 5.77 (d, $J = 2.7$ Hz, 1H, 3min-H), 4.04 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 4.03 (AA'd, $J = 15.9$ Hz, 1H, Bn min), 3.95 (AA'd, $J = 15.9$ Hz, 1H, Bn maj), 3.94 (AA'd, $J = 15.9$ Hz, 1H, Bn min), 3.69 (dd, $J = 8.4, 2.1$ Hz, 1H, 3b α -H), 3.24 (dd, $J = 6.0$ Hz, 1H, 6 α min-H), 3.20 (dd, $J = 5.9$ Hz, 1H, 6 α min-H), 3.20 (dd, $J = 5.4$ Hz, 1H, 6 α min-H), 3.16 (dd, $J = 5.3$ Hz, 1H, 6 α maj-H), 2.86-3.01 (m, 7H, 10a-H, N(CH₃)₂), 2.58-2.67 (m, 1H, 6b α maj-H), 2.46-2.55 (m, 1H, 6bmin-H), 0.98-2.08 (m, 9H, cyclohex., CH₂CH₃), 0.85 (t, $J = 7.2$ Hz, 3H, CH₂CH₃ maj), 0.77 (t, $J = 7.2$ Hz, 3H, CH₂CH₃ min); ¹³C NMR (75 MHz, CDCl₃, δ) 177.4, 177.3, 176.6, 139.6, 130.4, 128.8, 128.7, 128.7, 127.8, 127.6, 126.5, 120.0, 117.6, 117.5, 109.2, 44.1, 43.9, 39.3, 38.9, 38.5, 38.2, 37.0, 36.0, 34.5, 34.45, 34.37, 33.9, 32.9, 32.8, 32.7, 29.7, 29.6, 29.2, 29.0,

27.7, 27.4, 27.0, 26.1, 24.3, 23.6, 12.2, 11.4; IR (thin film, cm^{-1}) 3452(bs), 2923(m), 2122(bw), 1770(w), 1703(s), 1645(bs), 1446(m), 1367(m), 1190(m), 1151(m); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_2$: 428.2309, found 428.2327.

2-Benzyl-8-tert-butyl-5-(dimethylamino)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,3bH-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (83). Method A gave **83** (325 mg, 25%) as cream-colored crystals, a single isomer: mp 195-196 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.46 (bs, 1H, 1-H), 7.20-7.35 (m, 5H, Ph), 6.11 (d, $J = 2.7$ Hz, 1H, 3-H), 3.98 (AA'd, $J = 16.2$ Hz, 1H, Bn), 3.90 (AA'd, $J = 16.2$ Hz, 1H, Bn), 3.78 (dd, $J = 8.1, 1.5$ Hz, 1H, 3b α -H), 3.08 (dd, $J = 6.0, 8.1$ Hz, 1H, 6a α -H), 2.87 (s, 6H, $\text{N}(\text{CH}_3)_2$), 2.63-2.70 (m, 1H, 10a α -H), 2.51-2.58 (m, 1H, 6b α -H), 1.66-2.08 (m, 4H, cyclohex.), 1.50 (ddd, $J = 13.7, 10.4, 6.8$ Hz, 1H, cyclohex.), 1.04-1.30 (m, 2H, cyclohex.), 0.89 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, CDCl_3 , δ) 177.1, 176.5, 139.5, 130.7, 130.6, 128.8, 128.7, 126.5, 109.3, 105.5, 43.8, 43.3, 40.8, 39.3, 34.3, 34.1, 33.9, 32.9, 30.1, 27.7, 24.8; IR (thin film, cm^{-1}) 3388(bs), 2957(m), 2108(bw), 1774(w), 1709(s), 1604(bs), 1448(m), 1364(m), 1202(m), 1146(m); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_2$: 456.2622, found 456.2631.

2-Benzyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (84). Method A gave **84** (690 mg, 56%) as a cream-colored solid, a mixture of two isomers (maj:min = 3.6:1.0): mp 252-253 °C; ^1H NMR (300 MHz, $\text{DMSO-}d_6$, δ) 10.70 (bs, 1H, 1min-H), 10.41 (bs, 1H, 1maj-H), 7.38-7.53 (m, 4H, Ph), 7.15-7.32 (m, 6H, Ph), 5.85 (d, $J = 2.4$ Hz, 1H, 3maj-H), 5.60 (d, $J = 2.4$ Hz, 1H, 3min-H), 4.19 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α min-H), 4.03 (dd, $J = 8.6, 1.7$ Hz, 1H, 3b α maj-H), 3.90 (AA'd, $J = 15.9$ Hz, 1H, Bn), 3.85 (AA'd, $J = 16.5$ Hz, 1H, Bn), 3.40 (dd, $J = 8.1,$

4.8 Hz, 1H, 6 α min-H), 3.35 (dd, $J = 8.6, 5.3$ Hz, 1H, 6 α maj-H), 3.02-3.08 (m, 1H, 10 α maj-H), 2.91-2.96 (m, 1H, 10 α β min-H), 2.07-2.42 (m, 2H, 6b-H, cyclohex.), 1.04-1.62 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO- d_6 , δ) 178.4, 178.2, 177.4, 176.3, 141.5, 133.0, 132.8, 132.4, 130.5, 129.6, 129.5, 129.1, 128.9, 128.7, 127.5, 127.48, 127.4, 126.3, 119.2, 117.4, 108.9, 105.8, 103.0, 46.2, 45.9, 38.7, 38.5, 38.3, 38.2, 34.1, 34.0, 33.1, 29.3, 27.6, 26.1, 25.7, 23.3, 22.9, 21.4, 20.9; IR (thin film, cm^{-1}) 3390(bs), 2924(m), 2853(m), 2110(bw), 1772(w), 1697(s), 1651(bs), 1496(w), 1455(w), 1444(w), 1382(m), 1187(m), 1157(m), 1004(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 433.1887, found 433.1901. Anal. Calcd for $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.03; H, 6.30; N, 6.87.

2-Benzyl-8-ethyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (85). Method A gave **85** (474 mg, 36%) as a light-orange solid, a mixture of four isomers (maj:min:min:min = 1.7:1.0:0.6:0.4): mp 225-226 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 8.60 (bs, 1H, 1maj-H), 7.61 (bs, 1H, 1min-H), 7.59 (bs, 1H, 1min-H), 7.23-7.52 (m, 10H, Ph), 6.30 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.85 (d, $J = 3.0$ Hz, 1H, 3maj-H), 5.82 (d, $J = 2.7$ Hz, 1H, 3min-H), 4.05 (AA'd, $J = 15.9$ Hz, 1H, Bn min), 4.03 (AA'd, $J = 15.9$ Hz, 1H, Bn maj), 3.97 (dd, $J = 10.5, 1.8$ Hz, 1H, 3 β -H), 3.95 (AA'd, $J = 16.2$ Hz, 2H, Bn min, Bn maj), 3.48 (dd, $J = 9.3, 5.7$ Hz, 1H, 6 α min-H), 3.45 (dd, $J = 8.7, 5.7$ Hz, 1H, 6 α maj-H), 3.42 (dd, $J = 8.6, 5.3$ Hz, 1H, 6 α min-H), 3.39 (dd, $J = 8.6, 5.3$ Hz, 1H, 6 α min-H), 3.08-3.13 (m, 1H, 10amin-H), 3.02-3.07 (m, 1H, 10 α amin-H), 2.98-3.03 (m, 1H, 10 α β maj-H), 2.66-2.75 (m, 1H, 6 β maj-H), 2.53-2.62 (m, 1H, 6bmin-H), 1.00-2.30 (m, 7H, cyclohex.), 1.44 (app. q, $J = 7.5$ Hz, 2H, CH_2CH_3), 0.86 (t, $J = 7.5$ Hz, CH_2CH_3 maj), 0.80 (t, $J = 7.5$ Hz, 3H,

CH₂CH₃ min); ¹³C NMR (75 MHz, CDCl₃, δ); IR (thin film, cm⁻¹) 3422(bs), 2929(m), 2863(m), 2100(bw), 1777(w), 1694(s), 1651(bs), 1500(m), 1454(m), 1388(m), 1188(m), 1166(m); HRMS *m/z* (M + Na⁺) calcd 461.2200, found 461.2205. Anal. Calcd for C₂₉H₃₀N₂O₂: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.19; H, 7.02; N, 6.40.

2-Benzyl-8-isopropyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (86). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **86** (1325 mg, 61%) as a light-pink solid, a mixture of three isomers (maj:min:min = 4.1:1.0:0.7): mp 246-247 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.72 (d, *J* = 2.4 Hz, 1H, 1maj-H), 10.70 (d, *J* = 2.4 Hz, 1H, 1min-H), 10.45 (d, *J* = 1.2 Hz, 1H, 1min-H), 7.40-7.57 (m, 3H, Ph), 7.14-7.33 (m, 7H, Ph), 5.83 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.62 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.60 (d, *J* = 2.4 Hz, 1H, 3min-H), 4.20 (dd, *J* = 7.8, 1.2 Hz, 1H, 3bαmin-H), 4.18 (dd, *J* = 8.4, 1.8 Hz, 1H, 3bαmaj-H), 4.02 (dd, *J* = 8.7, 1.2 Hz, 1H, 3bαmin-H), 3.90 (AA'd, *J* = 15.9 Hz, 1H, Bn), 3.85 (AA'd, *J* = 15.9 Hz, 1H, Bn), 3.44 (dd, *J* = 8.4, 5.4 Hz, 1H, 6ααmin-H), 3.39 (dd, *J* = 8.1, 5.4 Hz, 1H, 6ααmaj-H), 3.35 (dd, *J* = 8.7, 5.7 Hz, 1H, 6ααmin-H), 2.96-3.02 (m, 1H, 10ααmin-H), 2.86-2.93 (m, 1H, 10αβmaj-H), 2.40-2.50 (m, 1H, 6bαmaj-H), 2.28-2.38 (m, 1H, 6bmin-H), 0.94-2.18 (m, 8H, cyclohex., CH(CH₃)₂), 0.84 (d, *J* = 6.3 Hz, 6H, CH(CH₃)₂ maj), 0.77 (d, *J* = 6.3 Hz, 6H, CH(CH₃)₂ min), 0.70 (d, *J* = 6.6 Hz, 6H, CH(CH₃)₂ min); ¹³C NMR (75 MHz, CDCl₃, δ) 178.0, 176.1, 139.6, 132.1, 131.9, 129.4, 129.3, 129.2, 128.8, 128.7, 128.5, 126.5, 126.44, 126.41, 117.7, 117.6, 106.7, 104.3, 104.2, 46.0, 45.6, 43.9, 40.3, 38.9, 37.9, 34.6, 34.5, 34.4, 33.3, 33.2, 33.0, 32.94, 32.88, 32.8, 29.0, 26.3, 24.0, 21.4, 21.0, 20.0, 19.9; IR (KBr, cm⁻¹) 3462(w), 3381(bs), 3061(w), 3029(w), 2928(w), 2864(m),

2359(w), 1777(w), 1699(s), 1598(w), 1498(m), 1453(m), 1387(m), 1173(m); HRMS m/z ($M + Na^+$) calcd 475.2357, found 475.2372. Anal. Calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13; N, 6.19. Found: C, 79.80; H, 7.24; N, 6.33.

2-Benzyl-8-*tert*-butyl-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (87). Method A gave **87** (546 mg, 39%) as a cream-colored solid, a mixture of four isomers (maj:min:min:min = 3.0:1.0:0.5:0.3): mp 184-185 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.26 (bs, 1H, 1min-H), 8.04 (bs, 1H, 1min-H), 7.55 (bs, 1H, 1maj-H), 7.22-7.51 (m, 10H, Ph), 6.28 (d, $J = 2.4$ Hz, 1H, 3maj-H), 6.06 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.85 (d, $J = 2.4$ Hz, 1H, 3min-H), 1.59 (d, $J = 2.7$ Hz, 1H, 3min-H), 4.05 (dd, $J = 7.8, 1.2$ Hz, 1H, 3 α -H), 3.99 (AA'd, $J = 15.9$ Hz, 1H, Bn maj), 3.91 (AA'd, $J = 15.9$ Hz, 1H, Bn maj), 3.41 (dd, $J = 8.1, 5.7$ Hz, 1H, 6 α min-H), 3.34 (dd, $J = 7.4, 5.3$ Hz, 1H, 6 α maj-H), 2.60-2.73 (m, 2H, 6b-H, 10a-H), 2.15-2.22 (m, 1H, cyclohex.), 2.01-2.07 (m, 1H, cyclohex.), 1.73-1.88 (m, 2H, cyclohex.), 1.59 (ddd, $J = 13.8, 11.3, 6.9$ Hz, 1H, cyclohex.), 1.29-1.40 (m, 1H, cyclohex.), 1.06-1.19 (m, 1H, cyclohex.), 0.91 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 178.5, 177.3, 141.1, 133.2, 131.0, 130.9, 129.4, 129.1, 128.8, 128.6, 127.5, 126.4, 109.4, 104.4, 45.3, 41.7, 34.4, 34.2, 33.9, 33.0, 30.4-30.8 (multiple peaks), 28.8-29.1 (multiple peaks), 28.0, 25.6-26.0 (multiple peaks); IR (thin film, cm^{-1}) 3386(bs), 2951(m), 2866(m), 2126(bw), 1774(w), 1708(s), 1648(bs), 1500(m), 1400(m), 1371(m), 1200(m), 1176(m); HRMS m/z ($M + Na^+$) calcd 489.2513, found 489.2517. Anal. Calcd for $C_{31}H_{34}N_2O_2$: C, 79.79; H, 7.34; N, 6.00. Found: C, 79.69; H, 7.20; N, 6.01.

2-Benzyl-5,8-diphenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (88). Method B with **3h** (1220 mg, 7.000

mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **88** (1471 mg, 63%) as a dark-red solid, a mixture of two isomers (maj:min = 2.8:1.0): mp 222-224 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.73-10.77 (app. m, 1H, 1maj-H), 10.54 (d, *J* = 1.5 Hz, 1H, 1min-H), 7.10-7.56 (m, 15H, Ph), 5.81-5.85 (app. m, 1H, 3min-H), 5.65 (d, *J* = 2.1 Hz, 1H, 3maj-H), 4.22 (dd, *J* = 8.4, 1.2 Hz, 1H, 3bαmaj-H), 4.03 (app. d, *J* = 7.5 Hz, 1H, 3bαmin-H), 3.90 (s, 2H, Bn), 3.40-3.58 (m, 1H, 6αα-H), 2.80-3.20 (m, 2H, 6bα-H, 10a-H), 1.40-2.60 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.4, 176.2, 176.1, 141.4, 132.9, 132.6, 129.7, 129.5, 129.3, 129.0, 128.9, 128.8, 128.76, 128.7, 127.6, 127.4, 127.24, 127.20, 126.3, 126.0, 34.1, 33.3-33.6 (overlapped peaks); IR (KBr, cm⁻¹) 3379(bs), 3058(w), 3026(w), 2928(s), 2858(m), 2359(w), 2334(w), 1776(w), 1709(s), 1598(w), 1496(m), 1452(w), 1383(m), 1185(m), 1155(m); HRMS *m/z* (M + Na⁺) calcd 509.2200, found 509.2210. Anal. Calcd for C₃₃H₃₀N₂O₂: C, 81.45; H, 6.21; N, 5.76. Found: C, 81.23; H, 5.99; N, 5.47.

2-Benzyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (89). Method A gave **89** (780 mg, 59%) as a white solid, a mixture of three isomers (maj:min:min = 3.0:1.0:0.3): mp 247-248 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.67 (bs, 1H, 1min-H), 10.40 (bs, 1H, 1maj-H), 10.30 (bs, 1H, 1min-H), 7.10-7.31 (m, 7H, Ph), 6.96-7.05 (m, 2H, Ph), 5.84 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.67 (d, *J* = 2.1 Hz, 1H, 3min-H), 5.60 (d, *J* = 2.4 Hz, 1H, 3min-H), 4.15 (app. d, *J* = 7.5 Hz, 1H, 3bαmin-H), 3.99 (d, *J* = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.87 (s, 2H, Bn), 3.78 (s, 3H, OCH₃), 3.42 (dd, *J* = 7.4, 4.1 Hz, 1H, 6ααmin-H), 3.37 (dd, *J* = 8.4, 5.4 Hz, 1H, 6ααmin-H), 3.32 (dd, *J* = 8.4, 5.4 Hz, 1H, 6ααmaj-H), 3.02-3.08 (m, 1H, 10ααmaj-H), 2.93-2.98 (m, 1H, 10αβmin-H), 2.20-2.42 (m, 2H, cyclohex., 6b-H),

1.02-1.85 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO- d_6 , δ) 178.6, 178.4, 177.6, 176.5, 132.4, 130.5, 129.1, 128.9, 128.7, 128.66, 128.64, 127.5, 126.3, 125.6, 125.4, 119.1, 117.5, 114.8, 114.7, 109.0, 105.8, 103.0, 55.9, 46.2, 45.8, 34.1, 34.0, 33.1, 29.3, 27.6, 26.1, 25.7, 23.3, 22.9, 21.5, 20.9; IR (thin film, cm^{-1}) 3446(bs), 2928(m), 2861(w), 2113(bw), 1770(w), 1697(s), 1646(bs), 1515(m), 1391(m), 1256(m), 1193(m), 1170(m), 1160(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 463.1993, found 463.2008. Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.26; H, 6.59; N, 6.35.

2-Benzyl-8-ethyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (90). Method A gave **90** (506 mg, 36%) as a light-pink solid, a mixture of four isomers (maj:min:min:min = 2.5:1.0:0.3:0.2): mp 231-232 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 8.25 (bs, 1H, 1min-H), 7.59 (bs, 1H, 1maj-H), 7.14-7.36 (m, 7H, Ph), 6.96-7.01 (m, 2H, Ph), 6.29 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.85 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.81 (d, $J = 2.4$ Hz, 1H, 3min-H), 4.05 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 4.03 (AA'd, $J = 16.2$ Hz, 1H, Bn min), 3.96 (AA'd, $J = 15.9$ Hz, 1H, Bn maj), 3.954 (AA'd, $J = 15.6$ Hz, 1H, Bn min), 3.951 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α -H), 3.84 (s, 3H, OCH_3), 3.46 (dd, $J = 8.7, 5.7$ Hz, 1H, 6a α min-H), 3.43 (dd, $J = 8.6, 5.9$ Hz, 1H, 6a α min-H), 3.41 (dd, $J = 8.6, 5.6$ Hz, 1H, 6a α min-H), 3.37 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α maj-H), 3.07-3.12 (m, 1H, 10amin-H), 3.02-3.08 (m, 1H, 10a α maj-H), 2.96-3.02 (m, 1H, 10a β min-H), 2.64-2.73 (m, 1H, 6b α maj-H), 2.52-2.61 (m, 1H, 6bmin-H), 1.04-2.28 (m, 9H, cyclohex., CH_2CH_3), 0.85 (t, $J = 7.4$ Hz, 3H, CH_2CH_3 maj), 0.79 (t, $J = 7.2$ Hz, 3H, CH_2CH_3 min); ^{13}C NMR (75 MHz, DMSO- d_6 , δ) 179.0, 178.6, 178.4, 177.64, 177.6, 176.5, 159.5, 159.4, 159.3, 141.5, 132.3, 130.5, 129.1, 128.9, 128.8, 128.7, 128.6, 127.5, 127.4, 126.3, 125.6, 115.0, 114.9, 114.8, 109.2,

105.9, 105.7, 55.9, 45.5, 34.3, 34.0, 33.9, 33.3, 33.2, 33.1, 33.0, 32.9, 32.8, 32.7, 32.6, 32.0, 28.0, 27.4, 27.36, 23.6, 12.6; IR (thin film, cm^{-1}) 3444(bs), 2930(m), 2100(bw), 1694(s), 1648(bm), 1515(m), 1389(m), 1252(m), 1172(m); HRMS m/z ($M + \text{Na}^+$) calcd 491.2306, found 491.2299. Anal. Calcd for $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_3$: C, 76.90; H, 6.88; N, 5.98. Found: C, 77.09; H, 6.76; N, 5.79.

2-Benzyl-8-isopropyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (91). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **91** (1459 mg, 63%) as a light-pink solid, a mixture of three isomers (maj:min:min = 3.8:1.0:0.8): mp 254-256 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$, δ) 10.84 (d, $J = 2.4$ Hz, 1H, 1maj-H), 10.68 (d, $J = 3.0$ Hz, 1H, 1min-H), 10.44 (d, $J = 3.0$ Hz, 1H, 1min-H), 7.02-7.31 (m, 9H, Ph), 5.82 (d, $J = 2.1$ Hz, 1H, 3min-H), 5.61 (d, $J = 2.4$ Hz, 1H, 3maj-H), 5.60 (d, $J = 2.4$ Hz, 1H, 3min-H), 4.16 (dd, $J = 8.7, 1.5$ Hz, 1H, 3 α min-H), 4.14 (dd, $J = 8.6, 1.7$ Hz, 1H, 3 β maj-H), 3.98 (dd, $J = 8.7, 1.8$ Hz, 1H, 3 α min-H), 3.87 (s, 2H, Bn), 3.79 (s, 3H, OCH_3 maj), 3.78 (s, 3H, OCH_3 min), 3.41 (dd, $J = 9.0, 6.0$ Hz, 1H, 6 α min-H), 3.36 (dd, $J = 8.1, 5.1$ Hz, 1H, 6 α maj-H), 3.32 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α min-H), 2.96-3.02 (m, 1H, 10 α min-H), 2.86-2.92 (m, 1H, 10 β maj-H), 2.38-2.49 (m, 1H, 6 β maj-H), 2.26-2.36 (m, 1H, 6 β min-H), 1.00-2.18 (m, 8H, cyclohex., $\text{CH}(\text{CH}_3)_2$), 0.84 (d, $J = 6.6$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$ maj), 0.77 (d, $J = 6.6$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$ min), 0.70 (d, $J = 6.9$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$ min); IR (KBr, cm^{-1}) 3459(w), 3372(bs), 3060(w), 3029(w), 2932(s), 2864(m), 2361(w), 1776(w), 1698(s), 1611(w), 1593(w), 1514(s), 1453(m), 1390(m), 1305(m), 1256(m), 1169(s), 1107(w), 1032(w); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_3$: 505.2462, found 505.2476.

2-Benzyl-8-*tert*-butyl-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (92). Method A gave **92** (358 mg, 24%) as a light-orange solid, a mixture of four isomers (maj:min:min:min = 24.0:1.0:0.3:0.2): mp 179-180°C; ¹H NMR (300 MHz, CDCl₃, δ) 8.25 (bs, 1H, 1min-H), 8.05 (bs, 1H, 1min-H), 7.55 (bs, 1H, 1min-H), 7.49 (bs, 1H, 1maj-H), 7.10-7.36 (m, 7H, Ph), 6.91-7.02 (m, 2H, Ph), 6.13 (d, *J* = 2.7 Hz, 1H, 3maj-H), 6.10 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.83 (d, *J* = 2.7 Hz, 1H, 3min-H), 4.03 (dd, *J* = 8.0, 1.7 Hz, 1H, 3bα-H), 3.99 (AA'd, *J* = 16.2 Hz, 1H, Bn), 3.90 (AA'd, *J* = 16.2 Hz, 1H, Bn), 3.82 (s, 3H, OCH₃), 3.39 (dd, *J* = 8.1, 5.7 Hz, 1H, 6αamin-H), 3.32 (dd, *J* = 7.8, 5.4 Hz, 1H, 6αmaj-H), 3.03-3.07 (m, 1H, 10amin-H), 2.98-3.02 (m, 1H, 10amin-H), 2.59-2.72 (m, 3H, 6b-H, 10αmaj-H, 10βmin-H), 1.00-2.22 (m, 7H, cyclohex.), 0.89 (s, 9H, *t*-Bu maj), 0.74 (s, 9H, *t*-Bu min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.7, 177.5, 159.3, 141.0, 130.9, 129.1, 128.8, 128.7, 126.4, 125.7, 114.6, 109.4, 105.0, 104.3, 55.9, 45.1, 34.2, 33.9, 33.0, 28.0, 28.0; IR (thin film, cm⁻¹) 3387(bs), 2958(m), 2100(bw), 1776(w), 1705(s), 1645(bm), 1513(s), 1391(m), 1301(m), 1252(m), 1168(m); HRMS *m/z* (M + Na⁺) calcd 519.2619, found 519.2620. Anal. Calcd for C₃₂H₃₆N₂O₃: C, 77.39; H, 7.31; N, 5.64. Found: C, 77.56; H, 7.46; N, 5.57.

2-Benzyl-5-(4-methoxyphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (93). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **93** (1413 mg, 57%) as a pink solid, a mixture of three isomers (maj:min:min = 3.2:1.0:0.5): mp 235-237 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.74 (app. bs, 1H, 1maj-H), 10.53 (d, *J* = 2.1 Hz, 1H, 1min-H), 6.97-7.34 (m, 14 H, Ph), 5.81-5.85 (app.

m, 1H, 3min-H), 5.67 (d, $J = 2.7$ Hz, 1H, 3min-H), 5.64 (d, $J = 1.8$ Hz, 1H, 3min-H), 4.21 (dd, $J = 8.7, 1.5$ Hz, 1H, 3 β min-H), 4.19 (dd, $J = 8.4, 1.2$ Hz, 1H, 3 β maj-H), 4.00 (app. d, $J = 8.1$ Hz, 1H, 3 β min-H), 3.90 (s, 2H, Bn), 3.80 (s, 3H, OCH₃ maj), 3.79 (s, 3H, OCH₃ min), 3.75 (s, 3H, OCH₃ min), 3.48 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α min-H), 3.37-3.46 (m, 2H, 6 α maj-H, 6 α min-H), 2.80-3.10 (m, 2H, 6 β -H, 10 α -H), 1.40-2.00 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.8, 178.6, 176.4, 159.5, 159.3, 141.4, 132.5, 129.1, 129.0, 128.8, 128.7, 127.6, 126.7, 126.3, 125.9, 125.4, 117.7, 114.9, 114.8, 55.9, 34.1, 33.2-33.6 (overlapped peaks); IR (KBr, cm⁻¹) 3452(w), 3380(bs), 3083(w), 3059(w), 3026(w), 2930(s), 2859(m), 2263(w), 1775(w), 1701(s), 1601(w), 1514(s), 1451(m), 1389(m), 1302(w), 1254(m), 1170(m), 1106(w), 1301(w); HRMS m/z (M + Na⁺) calcd 539.2306, found 539.2310. Anal. Calcd for C₃₄H₃₂N₂O₃: C, 79.04; H, 6.24; N, 5.42. Found: C, 79.20; H, 6.10; N, 5.27.

2-(4-Methylbenzyl)-5-phenyl-3 β ,6 α ,6 β ,7,8,9,10,10 α -octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (94). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **94** (1304 mg, 64%) as a pink solid, a mixture of two isomers (maj:min = 1.6:1.0): mp 223-225 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.67 (d, $J = 1.8$ Hz, 1H, 1maj-H), 10.39 (d, $J = 1.8$ Hz, 1H, 1min-H), 7.38-7.54 (m, 3H, Ph), 7.19-7.27 (m, 2H, Ph), 7.07-7.16 (m, 4H, Ph), 5.81 (d, $J = 2.1$ Hz, 1H, 3min-H), 5.56 (d, $J = 2.4$ Hz, 1H, 3maj-H), 4.19 (dd, $J = 8.3, 1.7$ Hz, 1H, 3 β maj-H), 4.02 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β min-H), 3.87 (s, 2H, Bn), 3.39 (dd, $J = 8.4, 5.1$ Hz, 1H, 6 α maj-H), 3.35 (dd, $J = 8.4, 5.1$ Hz, 1H, 6 α min-H), 3.02-3.07 (m, 1H, 10 α min-H), 2.90-2.95 (m, 1H, 10 α β maj-H), 2.51 (s, 3H, PhCH₃), 2.03-2.44 (m, 2H, cyclohex., 6 β -H), 1.00-1.64 (m, 7H, cyclohex.); ¹³C NMR (75 MHz,

DMSO- d_6 , δ) 178.4, 178.2, 177.4, 176.3, 138.4, 138.3, 135.2, 133.0, 132.8, 132.7, 130.8, 129.6, 129.5, 129.3, 129.0, 128.9, 128.8, 128.7, 127.5, 127.4, 119.1, 117.3, 108.9, 105.7, 102.8, 46.2, 45.9, 38.7, 38.5, 38.4, 38.2, 33.7, 33.6, 33.1, 29.3, 28.0, 27.6, 26.1, 25.7, 23.3, 22.9, 21.5, 21.2, 20.9; IR (KBr, cm^{-1}) 3457(w), 3374(bs), 3052(w), 2924(s), 2856(m), 1777(m), 1701(s), 1597(w), 1500(m), 1444(w), 1388(s), 1310(w), 1185(s), 1160(S); HRMS m/z ($M + \text{Na}^+$) calcd 447.2044, found 447.2040. Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.02; H, 6.74; N, 6.37.

8-Isopropyl-2-(4-methylbenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (95). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **95** (1366 mg, 61%) as a pink solid, a mixture of three isomers (maj:min:min = 2.7:1.0:0.8): mp 252-254 °C; ^1H NMR (300 MHz, DMSO- d_6 , δ) 10.67 (d, $J = 2.4$ Hz, 1H, 1maj-H), 10.65 (d, $J = 2.1$ Hz, 1H, 1min-H), 10.42 (d, $J = 2.4$ Hz, 1H, 1min-H), 7.40-7.56 (m, 3H, Ph), 7.05-7.24 (m, 6H, Ph), 5.79 (d, $J = 2.1$ Hz, 1H, 3min-H), 5.58 (d, $J = 2.4$ Hz, 1H, 3maj-H), 5.57 (d, $J = 2.7$ Hz, 1H, 3min-H), 4.19 (dd, $J = 8.3, 1.4$ Hz, 1H, 3 α min-H), 4.18 (dd, $J = 8.4, 1.5$ Hz, 1H, 3 β amaj-H), 4.01 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β amin-H), 3.82 (s, 2H, Bn), 3.43 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α min-H), 3.39 (dd, $J = 8.3, 5.3$ Hz, 1H, 6 α maj-H), 3.35 (dd, $J = 8.1, 5.4$ Hz, 1H, 6 α amin-H), 2.96-3.02 (m, 1H, 10 α amin-H), 2.86-2.92 (m, 1H, 10 α β maj-H), 2.39-2.49 (m, 1H, 6 β amaj-H), 2.28-2.38 (m, 1H, 6 β min-H), 2.26 (s, 3H, PhCH_3), 1.00-1.90 (m, 8H, cyclohex., $\text{CH}(\text{CH}_3)_2$), 0.84 (d, $J = 6.6$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$ maj), 0.77 (d, $J = 6.3$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$ min), 0.70 (d, $J = 6.6$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$ min); ^{13}C NMR (75 MHz, CDCl_3 , δ) 178.0, 176.2, 160.2, 136.6, 132.4, 129.4, 129.2, 128.8, 128.7, 128.6, 126.5, 126.4, 117.6, 106.4, 105.0, 104.1,

104.0, 46.0, 45.7, 43.9, 40.2, 39.0, 38.9, 37.9, 34.1, 34.05, 34.0, 33.2, 33.0, 32.95, 32.9, 29.0, 24.0, 21.2, 21.1, 21.0; IR (KBr, cm^{-1}) 3458(w), 3380(bs), 3054(w), 3027(w), 2926(m), 2863(s), 1776(m), 1703(s), 1595(w), 1500(m), 1452(m), 1387(s), 1315(w), 1187(s), 1172(s), 1150(s); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 489.2513, found 489.2527. Anal. Calcd for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2$: C, 79.79; H, 7.34; N, 6.00. Found: C, 79.61; H, 7.15; N, 5.83.

2-(4-Methylbenzyl)-5,8-diphenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-

benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (96). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **96** (1538 mg, 64%) as a dark-red solid, a mixture of two isomers (maj:min = 5.0:1.0): mp 215-217 °C; ^1H NMR (300 MHz, $\text{DMSO-}d_6$, δ) 10.71 (app. bs, 1H, 1maj-H), 10.51 (d, $J = 1.8$ Hz, 1H, 1min-H), 6.98-7.56 (m, 14H, Ph), 5.65 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.61 (d, $J = 2.4$ Hz, 1H, 3maj-H), 4.22 (dd, $J = 8.7, 1.8$ Hz, 1H, 3 β amaj-H), 4.02 (dd, $J = 8.4, 1.2$ Hz, 1H, 3 β amin-H), 3.84 (s, 2H, Bn), 3.51 (dd, $J = 9.0, 5.7$ Hz, 1H, 6 α amin-H), 3.40-3.50 (m, 2H, 6 α amaj-H, 6 α amin-H), 2.80-3.10 (m, 2H, 6b-H, 10a-H), 2.26 (s, 3H, PhCH_3), 1.10-2.26 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, CDCl_3 , δ) 177.9, 177.8, 176.8, 176.1, 136.4, 136.1, 134.3, 132.7, 131.8, 131.0, 130.2, 129.4, 129.3, 128.8, 128.7, 128.6, 127.4, 127.3, 126.9, 126.7, 126.6, 126.5, 126.1, 125.8, 125.6, 117.6, 104.2, 45.6, 34.1, 34.0, 33.2-33.6 (overlapped peaks), 21.1; IR (KBr, cm^{-1}) 3454(w), 3378(s), 3055(w), 3025(m), 2926(s), 2860(m), 1776(m), 1703(s), 1598(m), 1499(m), 1450(m), 1387(s), 1331(w), 1186(s), 1155(s); HRMS m/z ($\text{M} + \text{Na}^+$) calcd for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{O}_2$: 523.2357, found 523.2382.

5-(4-Methoxyphenyl)-2-(4-methylbenzyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (97). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **97** (1368 mg, 65%) as a light-pink solid, a mixture of two isomers (maj:min = 1.9:1.0): mp 218-220 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.65 (d, *J* = 2.1 Hz, 1H, 1maj-H), 10.38 (d, *J* = 2.4 Hz, 1H, 1min-H), 7.00-7.17 (m, 8H, Ph), 5.80 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.56 (d, *J* = 2.4 Hz, 1H, 3maj-H), 4.15 (dd, *J* = 8.4, 1.5 Hz, 1H, 3bαmaj-H), 3.99 (dd, *J* = 8.6, 1.7 Hz, 1H, 3bαmin-H), 3.82 (s, 2H, Bn), 3.79 (s, 3H, OCH₃ maj), 3.78 (s, 3H, OCH₃ min), 3.37 (dd, *J* = 8.1, 5.3 Hz, 1H, 6aαmaj-H), 3.32 (dd, *J* = 8.4, 5.4 Hz, 1H, 6aαmin-H), 3.01-3.06 (m, 1H, 10aαmin-H), 2.89-2.94 (m, 1H, 10aβmaj-H), 2.03-2.42 (m, 2H, cyclohex., 6bα-H), 2.26 (s, 3H, PhCH₃), 1.02-1.62 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.6, 178.4, 177.6, 159.4, 138.4, 138.3, 135.2, 130.8, 129.3, 129.0, 128.8, 128.6127.4, 125.5, 125.3, 119.1, 117.4, 114.7, 113.8, 108.9, 105.7, 105.0, 55.9, 45.8, 38.6, 38.4, 38.1, 33.6, 33.1, 27.6, 26.1, 25.7, 23.3, 23.0, 21.5, 21.1; IR (KBr, cm⁻¹) 3457(w), 3380(s), 3050(w), 3004(w), 2926(s), 2856(m), 1776(m), 1714(s), 1610(m), 1593(m), 1514(s), 1459(m), 1443(m), 1390(s), 1302(m), 1255(s), 1189(s), 1166(s), 1108(m), 1031(m); HRMS *m/z* (M + Na⁺) calcd 477.2149, found 477.2169. Anal. Calcd for C₂₉H₃₀N₂O₃: C, 76.63; H, 6.65; N, 6.16. Found: C, 76.40; H, 6.61; N, 5.96.

8-Isopropyl-5-(4-methoxyphenyl)-2-(4-methylbenzyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (98). Method B with **3f** (982 mg, 7.00 mmol), 3.5 h-reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **98** (1315 mg, 57%) as a light-pink solid, a mixture of three isomers

(maj:min:min = 3.4:1.0:0.9): mp 244-246 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.66 (d, *J* = 2.4 Hz, 1H, 1maj-H), 10.64 (d, *J* = 1.8 Hz, 1H, 1min-H), 10.41 (d, *J* = 1.5 Hz, 1H, 1min-H), 7.02-7.16 (m, 8H, Ph), 5.79 (d, *J* = 1.8 Hz, 1H, 3min-H), 5.57 (d, *J* = 2.1 Hz, 1H, 3maj-H), 5.56 (d, *J* = 2.0 Hz, 1H, 3min-H), 4.15 (dd, *J* = 8.7, 1.8 Hz, 1H, 3βamin-H), 4.14 (dd, *J* = 8.4, 1.5 Hz, 1H, 3βαmaj-H), 3.97 (dd, *J* = 8.4, 1.5 Hz, 1H, 3βamin-H), 3.82 (s, 2H, Bn), 3.79 (s, 3H, OCH₃ maj), 3.78 (s, 3H, OCH₃ min), 3.40 (dd, *J* = 8.4, 5.4 Hz, 1H, 6αamin-H), 3.36 (dd, *J* = 8.4, 5.4 Hz, 1H, 6αmaj-H), 3.32 (dd, *J* = 8.1, 5.4 Hz, 1H, 6αamin-H), 2.94-3.02 (m, 1H, 10αamin-H), 2.85-2.91 (m, 1H, 10αβmaj-H), 2.38-2.49 (m, 1H, 6βαmaj-H), 2.30-2.36 (m, 1H, 6bmin-H), 2.26 (s, 3H, PhCH₃), 0.95-2.26 (m, 8H, cyclohex., CH(CH₃)₂), 0.84 (d, *J* = 6.6 Hz, 6H, CH(CH₃)₂ maj), 0.77 (d, *J* = 6.3 Hz, 6H, CH(CH₃)₂ min), 0.70 (d, *J* = 6.6 Hz, 6H, CH(CH₃)₂ min); ¹³C NMR (75 MHz, CDCl₃, δ) 178.3, 177.0, 176.4, 159.6, 155.1, 136.5, 136.1, 132.4, 129.4, 128.7, 128.6, 127.6, 124.4, 120.5, 120.1, 117.9, 117.5, 114.7, 14.6, 109.5, 106.5, 104.1, 103.8, 55.6, 45.9, 45.6, 45.5, 43.9, 40.3, 38.9, 38.8, 37.8, 37.7, 34.1, 34.0, 34.9, 33.2, 33.0, 32.9, 32.8, 29.0, 26.3, 24.0, 21.4, 21.1, 21.0, 20.9, 20.0, 19.9; IR (KBr, cm⁻¹) 3463(w), 3380(bs), 3087(w), 3052(w), 3005(w), 2945(bs), 2864(s), 1776(m), 1699(s), 1612(m), 1589(w), 1514(s), 1452(m), 1391(s), 1304(m), 1256(s), 1171(s), 1109(m), 1032(m); HRMS *m/z* (M + Na⁺) calcd for C₃₂H₃₆N₂O₃: 519.2619, found 519.2637.

5-(4-Methoxyphenyl)-2-(4-methylbenzyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1*H*,5*H*-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (99). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **99** (1532 mg, 62%) as a light-brown solid, a mixture of two isomers (maj:min = 3.0:1.0): mp 227-228 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.67-10.71

(app. bs, 1H, 1maj-H), 10.49 (d, $J = 3.0$ Hz, 1H, 1min-H), 6.97-7.34 (m, 13H, Ph), 5.76-5.82 (app. m, 1H, 3min-H), 5.60 (d, $J = 2.4$ Hz, 1H, 3maj-H), 4.18 (dd, $J = 8.4$, 1.5 Hz, 1H, 3 β amaj-H), 3.99 (app. d, $J = 8.4$ Hz, 1H, 3 β amin-H), 3.84 (s, 2H, Bn), 3.80 (d, 3H, OCH₃ maj), 3.79 (d, 3H, OCH₃ min), 3.36-3.51 (m, 1H, 6 α -H), 2.80-3.10 (m, 2H, 10 α -H, 6 β -H), 1.50-2.60 (m, 7H, cyclohex.), 2.26 (s, 3H, PhCH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 178.3, 178.2, 177.0, 176.4, 159.7, 159.5, 136.1, 132.7, 129.4, 128.7, 128.6, 128.5, 128.4, 127.8, 127.7, 127.6, 127.4, 127.3, 126.7, 125.8, 125.6, 124.4, 117.6, 114.7, 114.6, 55.6, 45.5, 34.2, 34.1, 33.1-33.7 (overlapped peaks), 21.1; IR (KBr, cm⁻¹) 3458(w), 3389(s), 3085(w), 3057(w), 3023(w), 2933(s), 2860(m), 2368(w), 1775(w), 1698(s), 1607(w), 1514(s), 1448(m), 1390(m), 1301(m), 1253(s), 1170(s), 1108(w), 1032(m); HRMS m/z ($M + Na^+$) calcd 553.2462, found 553.2488. Anal. Calcd for C₃₅H₃₄N₂O₃: C, 79.22; H, 6.46; N, 5.28. Found: C, 78.91; H, 6.32; N, 5.19.

5-Dimethylamino-2-(4-methoxybenzyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (100). Method A gave **100** (293 mg, 24%) as a cream-colored solid, a mixture of two isomers (maj:min = 3.8:1.0): mp 228-229 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.20 (bs, 1H, 1min-H), 7.51 (bs, 1H, 1maj-H), 7.16 (d, $J = 8.7$ Hz, 2H, Ph), 6.87 (d, $J = 8.4$ Hz, 2H, Ph), 6.23 (d, $J = 2.4$ Hz, 1H, 3maj-H), 5.77 (d, $J = 2.7$ Hz, 1H, 3min-H), 3.97 (AA'd, $J = 15.9$ Hz, 1H, Bn maj), 3.96 (AA'd, $J = 16.2$ Hz, 1H, Bn min), 3.90 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 3.89 (AA'd, $J = 15.9$ Hz, 1H, Bn maj), 3.81 (s, 3H, OCH₃), 3.69 (dd, 1H, 3 β -H), 3.21 (dd, $J = 8.4$, 5.7 Hz, 1H, 6 α min-H), 3.16 (dd, $J = 8.7$, 5.7 Hz, 1H, 6 α maj-H), 3.00-3.06 (m, 1H, 10 α maj-H), 2.93 (s, 6H, N(CH₃)₂), 2.91-2.92 (m, 1H, 10 α β min-H), 2.44-2.52 (m, 1H, 6 β -H), 1.05-2.22 (m, 8H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 177.6, 177.5, 176.7, 159.1,

158.0, 133.4, 131.0, 130.0, 129.9, 127.3, 114.1, 108.8, 105.4, 55.5, 44.3, 44.0, 43.8, 38.2, 36.7, 33.2, 33.1, 32.9, 27.6, 25.6, 23.0, 21.4; IR (thin film, cm^{-1}) 3371(bs), 2924(m), 2852(m), 1770(w), 1703(s), 1515(m), 1444(m), 1360(w), 1252(m), 1193(m); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_3$: 430.2102, found 430.2087.

5-Dimethylamino-8-ethyl-2-(4-methoxybenzyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (101). Method A gave **101** (287 mg, 22%) as a cream-colored solid, a mixture of three isomers (maj:min = 4.0:1.0:0.2): mp 179-180 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 8.22 (bs 1H, 1min-H), 7.55 (bs, 1H, 1maj-H), 7.16 (d, $J = 8.7$ Hz, 2H, Ph), 6.86 (d, $J = 8.7$ Hz, 2H, Ph), 6.22 (d, $J = 2.4$ Hz, 1H, 3maj-H), 5.78 (d, $J = 2.7$ Hz, 1H, 3min-H), 5.74 (d, $J = 2.1$ Hz, 1H, 3min-H), 3.97 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 3.96 (AA'd, $J = 16.2$ Hz, 1H, Bn min), 3.89 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 3.88 (AA'd, $J = 16.2$ Hz, 1H, Bn min), 3.81 (s, 3H, OCH_3), 3.69 (dd, $J = 8.4, 1.8$ Hz, 1H, $3b\alpha\text{-H}$), 3.24 (dd, $J = 5.4, 9.6$ Hz, 1H, $6a\alpha\text{min-H}$), 3.20 (dd, $J = 8.7, 5.7$ Hz, 1H, $6a\alpha\text{min-H}$), 3.19 (dd, $J = 8.7, 5.6$ Hz, 1H, $6a\alpha\text{min-H}$), 3.16 (dd, $J = 8.6, 5.6$ Hz, 1H, $6a\alpha\text{maj-H}$), 2.91-2.94 (m, 7H, 10a-H, $\text{N}(\text{CH}_3)_2$), 2.58-2.67 (m, 1H, $6b\alpha\text{maj-H}$), 2.46-2.55 (m, 1H, $6b\text{min-H}$), 1.00-2.07 (m, 9H, cyclohex., CH_2CH_3), 0.84 (t, $J = 7.4$ Hz, 3H, CH_2CH_3 maj), 0.76 (t, $J = 7.2$ Hz, 3H, CH_2CH_3 maj); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$, δ) 177.6, 177.4, 176.7, 176.6, 158.0, 133.3, 131.0, 130.0, 129.9, 129.8, 127.2, 127.15, 127.1, 117.3, 114.1, 114.0, 108.9, 108.8, 105.4, 105.0, 102.8, 55.5, 43.9, 43.8, 43.6, 36.7, 33.9, 33.0-33.2 (multiple peaks), 32.6, 29.9, ; IR (thin film, cm^{-1}) 3378(bs), 2928(m), 2358(w), 1773(w), 1709(s), 1510(m), 1246(m); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_3$: 458.2415, found 458.2422.

8-tert-Butyl-5-(dimethylamino)-2-(4-methoxybenzyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (102). Method A gave **102** (292 mg, 21%) as orange crystals, a single isomer: mp 95-96 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.43 (bs, 1H, 1-H), 7.13 (d, *J* = 8.4 Hz, 2H, Ph), 6.85 (d, *J* = 8.7 Hz, 2H, Ph), 6.08 (d, *J* = 2.7 Hz, 1H, 3-H), 3.92 (AA'd, *J* = 17.1 Hz, 1H, Bn), 3.83 (AA'd, *J* = 17.1 Hz, 1H, Bn), 3.81 (s, 3H, OCH₃), 3.78 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H, 3bα-H), 3.09 (dd, *J* = 8.0, 5.9 Hz, 1H, 6α-H), 2.87 (s, 6H, N(CH₃)₂), 2.61-2.70 (m, 1H, 6bα), 2.50-2.57 (m, 1H, 10α-H), 1.65-2.06 (m, 4H, cyclohex.), 1.49 (ddd, *J* = 13.8, 10.4, 6.8 Hz, 1H, cyclohex.), 1.07-1.30 (m, 2H, cyclohex.), 0.89 (s, 9H, *t*-Bu); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 177.7, 176.4, 158.0, 133.0, 131.3, 130.5, 130.0, 129.9, 114.1, 109.1, 104.2, 55.5, 43.6, 43.55, 43.1, 33.9, 33.3, 33.0, 32.8, 30.4, 28.0, 27.9; IR (thin film, cm⁻¹) 3364(bs), 2955(m), 1774(w), 1712(s), 1511(s), 1364(m), 1246(m); HRMS *m/z* (M + Na⁺) calcd for C₂₈H₃₇N₃O₃: 486.2728, found 486.2720.

2-(4-Methoxybenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (103). Method B with **3c** (687 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **103** (1270 mg, 60%) as a cream-colored solid, a mixture of two isomers (maj:min = 1.8:1.0): mp 234-235 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.27 (bs, 1H, 1maj-H), 7.58 (bs, 1H, 1min-H), 7.37-7.51 (m, 3H, Ph), 7.24-7.32 (m, 2H, Ph), 7.16-7.21 (m, 2H, Ph), 6.85-6.90 (m, 2H, Ph), 6.27 (d, *J* = 2.4 Hz, 1H, 3min-H), 5.81 (*J* = 2.4 Hz, 1H, 3maj-H), 3.99 (AA'd, *J* = 17.1 Hz, 1H, Bn maj), 3.971 (dd, *J* = 8.6, 2.0 Hz, 1H, 3bα-H), 3.968 (AA'd, *J* = 15.9 Hz, 1H, Bn min), 3.91 (AA'd, *J* = 15.9 Hz, 1H, Bn maj), 3.81 (s, 3H, OCH₃), 3.46 (dd, *J* = 8.7, 5.7 Hz, 1H, 6αmaj-H), 3.39 (dd, *J* = 8.6, 5.3 Hz, 1H,

6 α amin-H), 3.08-3.14 (m, 1H, 10 α amin-H), 3.02-3.07 (m, 1H, 10 α β maj-H), 2.50-2.58 (m, 1H, 6 β α -H), 2.04-2.25 (m, 1H, cyclohex.), 1.18-1.76 (m, 7H, cyclohex.); ^1H NMR (300 MHz, DMSO- d_6 , δ) 10.65 (d, $J = 2.1$ Hz, 1H, 1maj-H), 10.38 (d, $J = 1.8$ Hz, 1H, 1min-H), 7.38-7.54 (m, 3H, Ph), 7.12-7.26 (m, 4H, Ph), 6.81-6.87 (m, 2H, Ph), 5.80 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.56 (d, $J = 2.4$ Hz, 1H, 3maj-H), 4.18 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β α maj-H), 4.02 (dd, $J = 8.4, 1.8$ Hz, 1H, 3 β amin-H), 3.80 (s, 2H, Bn), 3.71 (s, 3H, OCH₃), 3.37 (dd, $J = 8.4, 5.1$ Hz, 1H, 6 α α maj-H), 3.34 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.01-3.07 (m, 1H, 10 α amin-H), 2.90-2.95 (m, 1H, 10 α β maj-H), 2.03-2.42 (m, 2H, cyclohex., 6 β -H), 1.03-1.64 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, DMSO- d_6 , δ) 178.4, 178.2, 177.4, 176.3, 158.0, 133.4, 138.3, 133.0, 131.1, 130.0, 129.9, 129.6, 129.5, 128.9, 128.8, 127.4, 119.1, 117.3, 114.1, 108.9, 105.6, 102.7, 55.5, 46.2, 45.9, 38.7, 38.5, 38.4, 38.2, 33.2, 33.1, 29.3, 27.6, 26.1, 25.7, 23.5, 22.9, 21.5, 20.9; IR (thin film, cm^{-1}) 3372, 2920, 1697, 1515; HRMS m/z ($\text{M} + \text{Na}^+$) calcd 463.1993, found 463.2009. Anal. Calcd for C₂₈H₂₈N₂O₃: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.26; H, 6.59; N, 6.35.

8-Ethyl-2-(4-methoxybenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (104). Method A gave **104** (450 mg, 32%) as a cream-colored solid, a mixture of four isomers (maj:min:min:min = 1.1:1.0:0.3:0.3): mp 214-215 °C; ^1H NMR (300 MHz, CDCl₃, δ) 8.25 (bs, 1H, 1maj-H), 7.58 (bs, 1H, 1min-H), 7.56 (bs, 1H, 1min-H), 7.37-7.51 (m, 3H, Ph), 7.28-7.32 (m, 2H, Ph), 7.15-7.20 (m, 2H, Ph), 6.85-6.90 (m, 2H, Ph), 6.26 (d, $J = 2.7$ Hz, 1H, 3maj-H), 5.82 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.79 (d, $J = 3.0$ Hz, 1H, 3min-H), 3.98 (AA'd, $J = 15.9$ Hz, 1H, Bn min), 3.97 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 3.96 (dd, $J = 8.6, 2.0$ Hz, 1H, 3 β α -H),

3.91 (AA'd, $J = 16.2$ Hz, 1H, Bn min), 3.90 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 3.82 (s, 3H, OCH₃), 3.48 (dd, $J = 9.02, 5.3$ Hz, 1H, 6 α min-H), 3.45 (dd, $J = 8.1, 5.7$ Hz, 1H, 6 α min-H), 3.42 (dd, $J = 7.8, 5.4$ Hz, 1H, 6 α min-H), 3.39 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α maj-H), 2.97-3.08 (m, 1H, 10a-H), 2.65-2.74 (m, 2H, 6 β maj-H, 6 β min-H), 2.53-2.62 (m, 2H, 6 β min-H), 1.07-2.30 (m, 7H, cyclohex.), 1.43 (app. q, $J = 7.5$ Hz, 2H, CH₂CH₃), 0.85 (t, $J = 7.2$ Hz, 3H, CH₂CH₃ maj), 0.79 (t, $J = 7.2$ Hz, 3H, CH₂CH₃ min); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.4, 178.2, 177.4, 176.3, 158.0, 133.4, 133.35, 133.3, 133.0, 132.9, 132.8, 131.1, 131.0, 130.0, 129.9, 129.8, 129.7, 129.6, 129.5, 128.9, 128.7, 127.4, 127.35, 127.3, 119.0, 118.8, 117.4, 114.1, 109.0, 105.5, 105.0, 102.8, 55.5, 45.9, 45.5, 38.9, 38.7, 38.4, 38.2, 38.1, 34.3, 33.9, 32.7-33.3 (multiple peaks), 30.0, 27.4, 23.7, 23.6, 12.6, 11.8; IR (thin film, cm⁻¹) 3389(bs), 2931(m), 1777(w), 1706(s), 1509(m), 1383(m), 1246(m), 1176(m); HRMS m/z (M + Na⁺) calcd 491.2306, found 491.2323. Anal. Calcd for C₃₀H₃₂N₂O₃: C, 76.90; H, 6.88; N, 5.98. Found: C, 76.98; H, 7.19; N, 5.19.

8-Isopropyl-2-(4-methoxybenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (105). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **105** (1181 mg, 51%) as a light-pink solid, a mixture of three isomers (maj:min:min = 4.5:1.0:0.9): mp 235-237 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.65 (d, $J = 2.4$ Hz, 1H, 1maj-H), 10.64 (d, $J = 1.8$ Hz, 1H, 1min-H), 10.40 (d, $J = 1.8$ Hz, 1H, 1min-H), 7.41-7.56 (m, 3H, Ph), 7.13-7.24 (m, 4H, Ph), 6.80-6.86 (m, 2H, Ph), 5.78 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.57 (d, $J = 2.4$ Hz, 1H, 3maj-H), 5.55 (d, $J = 2.1$ Hz, 1H, 3min-H), 4.19 (dd, $J = 8.4, 1.5$ Hz, 1H, 3bamin-H), 4.17 (dd, $J = 7.8, 0.9$ Hz, 1H, 3bamaj-H),

4.00 (dd, $J = 8.4, 2.1$ Hz, 1H, 3b α min-H), 3.80 (s, 2H, Bn), 3.713 (s, 3H, OCH₃ maj), 3.709 (s, 3H, OCH₃ min), 3.70 (s, 3H, OCH₃ min), 3.43 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α min-H), 3.38 (dd, $J = 8.4, 5.1$ Hz, 1H, 6a α maj-H), 3.35 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α min-H), 2.95-3.01 (m, 1H, 10a α min-H), 2.85-2.91 (m, 1H, 10a β maj-H), 2.38-2.50 (m, 1H, 6b α maj-H), 2.20-2.36 (m, 1H, 6bmin-H), 1.20-2.02 (m, 8H, cyclohex, CH(CH₃)₂), 0.84 (d, $J = 6.3$ Hz, 6H, CH(CH₃)₂ maj), 0.77 (d, $J = 6.3$ Hz, 6H, CH(CH₃)₂ min), 0.69 (d, $J = 6.6$ Hz, 6H, CH(CH₃)₂ min); ¹³C NMR (75 MHz, CDCl₃, δ) 178.0, 176.2, 132.6, 131.9, 131.6, 129.8, 129.75, 129.7, 129.4, 129.3, 129.2, 128.8, 128.7, 128.4, 126.5, 126.4, 126.2, 117.6, 114.1, 106.4, 105.0, 104.0, 103.9, 55.4, 45.7, 45.7, 43.9, 40.3, 38.9, 37.8, 32.8-33.7 (overlapped peaks), 26.3, 24.0, 22.5, 21.4, 21.0, 19.9; IR (KBr, cm⁻¹) 3463(w), 3384(bs), 3064(w), 2999(w), 2929(s), 2864(s), 2836(m), 2361(w), 2329(w), 1777(m), 1698(s), 1613(m), 1595(m), 1512(s), 1454(m), 1387(s), 1248(m), 1175(s); HRMS m/z (M + Na⁺) calcd for C₃₁H₃₄N₂O₃: 505.2462, found 505.2483.

8-tert-Butyl-2-(4-methoxybenzyl)-5-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (106). Method A gave **106** (432 mg, 29%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 5.2:1.0:0.6): mp 219-220 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.26 (bs, 1H, 1min-H), 8.06 (bs, 1H, 1maj-H), 7.36-7.53 (m, 3H, Ph), 7.12-7.28 (m, 4H, Ph), 6.84-6.89 (m, 2H, Ph), 6.10 (d, $J = 2.7$ Hz, 1H, 3min-H), 5.81 (d, $J = 2.7$ Hz, 1H, 3min-H), 5.76 (d, $J = 2.7$ Hz, 1H, 3maj-H), 4.06 (dd, $J = 8.1, 1.8$ Hz, 1H, 3b α -H), 3.90-3.97 (m, overlapped, 2H, 2XBn min), 3.92 (AA'd, $J = 14.4$ Hz, 1H, Bn maj), 3.84 (AA'd, $J = 14.4$ Hz, 1H, Bn maj), 3.81 (s, 3H, OCH₃), 3.49 (dd, $J = 8.6, 5.6$ Hz, 1H, 6a α min-H), 3.41 (dd, $J = 8.1, 5.7$ Hz, 1H,

6 α maj-H), 3.34 (dd, $J = 7.8, 5.4$ Hz, 1H, 6 α min-H), 2.53-2.75 (m, 2H, 6b α -H, 10a-H), 1.02-2.32 (m, 7H, cyclohex.), 0.90 (s, 9H, *t*-Bu), 0.74 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, DMSO- d_6 , δ) 178.5, 176.0, 158.0, 158.75, 133.2, 133.16, 130.1, 129.8, 129.7, 129.6, 129.4, 128.8, 128.6, 127.5, 127.1, 117.3, 117.26, 114.1, 104.0, 55.5, 44.9, 34.3-34.5 (multiple peaks), 34.0, 33.8, 33.3, 33.2, 33.1, 33.0, 32.7, 28.2, 27.7; IR (thin film, cm^{-1}) 3455(bs), 2950(m), 2360(w), 1770(w), 1702(s), 1648(bm), 1511(m), 1388(m), 1247(m), 1176(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 519.2619, found 519.2627. Anal. Calcd for $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_3$: C, 77.39; H, 7.31; N, 5.64. Found: C, 77.44; H, 7.68; N, 5.67.

2-(4-Methoxybenzyl)-5,8-diphenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[*g*]pyrrolo[3,4-*e*]indole-4,6-dione (107). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **107** (1513 mg, 61%) as a brown solid, a mixture of two isomers (maj:min = 5.2:1.0): mp 223-225 $^\circ\text{C}$; ^1H NMR (300 MHz, DMSO- d_6 , δ) 10.69 (bs, 1H, 1maj-H), 10.50 (bs, 1H, 1min-H), 7.15-7.56 (m, 12H, Ph), 6.83-6.88 (m, 2H, Ph), 5.79 (d, $J = 2.1$ Hz, 1H, 3min-H), 5.61 (d, $J = 2.7$ Hz, 1H, 3maj-H), 4.21 (dd, $J = 8.7, 0.9$ Hz, 1H, 3b α maj-H), 4.02 (dd, $J = 6.6, 2.7$ Hz, 1H, 3b α min-H), 3.82 (s, 2H, Bn), 3.72 (s, 3H, OCH $_3$), 3.41-3.55 (m, 1H, 6 α -H), 2.70-3.10 (m, 2H, 6b-H, 10a-H), 1.40-2.10 (m, 7H, cyclohex.); ^{13}C NMR (75 MHz, CDCl $_3$, δ) 178.0, 176.0, 158.4, 136.1, 132.9, 131.8, 131.4, 129.8, 129.4, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 127.4, 127.3, 126.5, 126.4, 125.6, 114.1, 55.4, 45.6, 33.4-33.8 (overlapped peaks); IR (KBr, cm^{-1}) 3458(w), 3381(bs), 3061(w), 3026(w), 3003(w), 2930(s), 2861(m), 2836(m), 2360(w), 2335(w), 1777(m), 1703(s), 1599(m), 1510(s), 1452(m), 1387(s), 1249(m), 1176(s); HRMS m/z ($\text{M} + \text{Na}^+$) calcd for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{O}_3$: 539.2306, found 539.2308.

2-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (108). Method A gave **108** (593 mg, 42%) as a cream-colored solid, a mixture of two isomers (maj:min = 1.2:1.0): mp 234-235 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.26 (bs, 1H, 1min-H), 7.56 (bs, 1H, 1maj-H), 7.15-7.24 (m, 4H, Ph), 6.96-7.01 (m, 2H, Ph), 6.85-6.87 (m, 2H, Ph), 6.27 (d, *J* = 2.7 Hz, 1H, 3maj-H), 5.81 (d, *J* = 2.7 Hz, 1H, 3min-H), 3.99 (AA'd, *J* = 15.9 Hz, 1H, Bn maj), 3.97 (AA'd, *J* = 16.2 Hz, 1H, Bn min), 3.90-3.97 (m, overlapped, 1H, 3b α -H), 3.90 (AA'd, *J* = 16.5 Hz, 1H, Bn maj), 3.89 (AA'd, *J* = 15.6 Hz, 1H, Bn min), 3.84 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.44 (dd, *J* = 8.9, 5.6 Hz, 1H, 6a α min-H), 3.38 (dd, *J* = 8.4, 5.4 Hz, 1H, 6a α maj-H), 3.08-3.12 (m, 1H, 10a α maj-H), 3.02-3.06 (m, 1H, 10a β min-H), 2.49-2.57 (m, 1H, 6b α -H), 2.04-2.24 (m, 1H, cyclohex.), 1.08-1.76 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.4, 176.5, 159.5, 158.0, 133.3, 132.9, 130.0, 129.9, 128.6, 125.3, 119.0, 117.4, 114.8, 114.7, 114.1, 105.6, 102.7, 74.9, 58.9, 55.9, 55.5, 46.2, 38.4, 38.1, 33.2, 33.12, 33.07, 33.04, 29.3, 26.1, 22.9, 20.9; IR (thin film, cm⁻¹) 3386(bs), 2920(m), 2360(w), 1769(w), 1697(s), 1516(m), 1392(m), 1257(m), 1178(m); HRMS *m/z* (M + Na⁺) calcd for C₂₉H₃₀N₂O₄: 493.2099, found 493.2116.

8-Ethyl-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-e]indole-4,6-dione (109). Method A gave **109** (434 mg, 29%) as a cream-colored solid, a mixture of three isomers (maj:min:min = 1.9:1.0:0.2): mp 228-229 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.25 (bs, 1H, 1min-H), 7.57 (bs, 1H, 1maj-H), 7.14-7.23 (m, 4H, Ph), 6.96-7.02 (m, 2H, Ph), 6.85-6.90 (m, 2H, Ph), 6.26 (d, *J* = 2.4 Hz, 1H, 3maj-H), 5.82 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.78 (d, *J* =

2.7 Hz, 1H, 3min-H), 4.99 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 4.97 (AA'd, $J = 16.8$ Hz, 1H, Bn min), 3.91-3.96 (m, overlapped, 1H, 3b α -H), 3.90 (AA'd, $J = 16.2$ Hz, 1H, Bn maj), 3.89 (AA'd, $J = 16.5$ Hz, 1H, Bn min), 3.84 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.43 (dd, $J = 8.7, 5.7$ Hz, 1H, 6a α min-H), 3.37 (dd, $J = 8.4, 5.4$ Hz, 1H, 6a α maj-H), 3.02-3.07 (m, 1H, 10a α maj-H), 2.96-3.01 (m, 1H, 10a β min-H), 2.64-2.73 (m, 1H, 6b α maj-H), 2.53-2.60 (m, 1H, 6bmin-H), 1.07-1.92 (m, 9H, cyclohex., CH₂CH₃), 0.85 (t, $J = 7.2$ Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.5, 178.45, 178.4, 177.6, 176.5, 159.5, 159.4, 159.2, 158.0, 133.3, 132.9, 132.8, 131.0, 131.95, 130.1, 129.9, 129.8, 128.6, 128.5, 127.2, 125.6, 125.4, 118.7, 117.4, 114.9, 114.8, 114.1, 109.1, 105.5, 102.8, 55.9, 55.5, 45.8, 45.5, 34.3, 34.0, 33.0-33.3 (multiple peaks), 33.9, 32.6-32.8 (multiple peaks), 23.6, 23.5, 12.6; IR (thin film, cm⁻¹) 3441(bs), 2934(m), 2100(bw), 1777(w), 1694(s), 1651(bm), 1515(s), 1388(m), 1252(m), 1174(m); HRMS m/z (M + Na⁺) calcd 521.2412, found 521.2416. Anal. Calcd for C₃₁H₃₄N₂O₄: C, 74.67; H, 6.87; N, 5.62. Found: C, 72.72; H, 6.59; N, 5.45.

8-Isopropyl-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (110). Method B with **3f** (982 mg, 7.00 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **110** (1304 mg, 53%) as a colorless solid, a mixture of three isomers (maj:min:min = 3.8:1.0:0.6): mp 252-254 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.64 (d, $J = 2.4$ Hz, 1H, 1maj-H), 10.63 (d, $J = 2.7$ Hz, 1H, 1min-H), 10.39 (d, $J = 2.4$, 1H, 1min-H), 7.01-7.21 (m, 6H, Ph), 6.80-6.86 (m, 2H, Ph), 5.78 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.57 (d, $J = 2.4$ Hz, 1H, 3maj-H), 5.55 (d, $J = 2.1$ Hz, 1H, 3min-H), 4.15 (dd, $J = 8.4, 1.8$ Hz, 1H, 3b α min-H), 4.13 (dd, $J = 8.4, 1.5$ Hz, 1H, 3b α maj-H), 3.97 (dd, $J =$

8.7, 2.1 Hz, 1H, 3 β amin-H), 3.80 (s, 2H, Bn), 3.79 (s, 3H, PhOCH₃ min), 3.79 (s, 3H, PhOCH₃ maj), 3.78 (s, 3H, PhOCH₃ min), 3.712 (s, 3H, BnOCH₃ min), 3.710 (s, 3H, BnOCH₃ maj), 3.70 (s, 3H, BnOCH₃ min), 3.40 (dd, $J = 8.7, 5.4$ Hz, 1H, 6 α amin-H), 3.35 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α maj-H), 3.31 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 2.94-3.01 (m, 1H, 10 α amin-H), 2.84-2.91 (m, 1H, 10 $\alpha\beta$ maj-H), 2.37-2.48 (m, 1H, 6 β maj-H), 2.26-2.36 (m, 1H, 6 β min-H), 0.88-2.18 (m, 8H, cyclohex., CH(CH₃)₂), 0.84 (d, $J = 6.0$ Hz, 6H, CH(CH₃)₂ maj), 0.76 (d, $J = 6.6$ Hz, 6H, CH(CH₃)₂ min), 0.69 (d, $J = 6.9$ Hz, 1H, CH(CH₃)₂ min); IR (KBr, cm⁻¹) 3462(w), 3377(bs), 3064(w), 2996(w), 2931(bs), 2864(m), 2837(m), 1776(m), 1695(s), 1612(m), 1589(m), 1514(s), 1452(m), 1391(m), 1303(m), 1250(s), 1169(s), 1106(m), 1033(m); HRMS m/z (M + Na⁺) calcd 535.2568, found 535.2589. Anal. Calcd for C₃₂H₃₆N₂O₄: C, 74.97; H, 7.08; N, 5.46. Found: C, 74.77; H, 6.82; N, 5.28.

8-tert-Butyl-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (111). Method A gave **111** (348 mg, 22%) as a cream-colored solid, a mixture of four isomers (maj:min:min:min = 2.7:1.0:0.7:0.3): mp 224-225 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.25 (bs, 1H, 1min-H), 8.05 (bs, 1H, 1maj-H), 7.50 (bs, 1H, 1min-H), 7.47 (bs, 1H, 1min-H), 7.09-7.18 (m, 4H, Ph), 6.94-7.03 (m, 2H, Ph), 6.83-6.89 (m, 2H, Ph), 6.29 (d, $J = 2.4$ Hz, 1H, 3min-H), 6.10 (d, $J = 2.4$ Hz, 1H, 3min-H), 5.80 (d, $J = 2.7$ Hz, 1H, 3min-H), 5.75 (d, $J = 2.7$ Hz, 1H, 3maj-H), 4.04 (d, $J = 8.1$ Hz, 1H, 3 $\beta\alpha$ -H), 3.80-3.95 (m, 2H, Bn), 3.81 (s, 6H, 2XOCH₃), 3.47 (dd, $J = 8.7, 5.4$ Hz, 1H, 6 α amin-H), 3.42 (dd, $J = 8.4, 5.4$ Hz, 1H, 6 α amin-H), 3.38 (dd, $J = 8.1, 5.7$ Hz, 1H, 6 α maj-H), 3.32 (dd, $J = 7.5, 5.4$ Hz, 1H, 6 α amin-H), 3.03-3.07 (m, 1H, 10amin-H), 2.98-3.02 (m, 1H, 10amin-H), 2.54-2.70 (m,

3H, 6b-H, 10 α maj-H, 10amin-H), 1.05-2.27 (m, 7H, cyclohex.), 0.89 (s, 9H, *t*-Bu maj), 0.74 (s, 9H, *t*-Bu min); IR (thin film, cm⁻¹) 3440(bs), 2952(m), 2358(m), 1770(w), 1698(s), 1514(s), 1393(m), 1303(m), 1250(m), 1174(m); HRMS *m/z* (M + Na⁺) calcd for C₃₂H₃₈N₂O₄: 549.2725, found 549.2694.

2-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-8-phenyl-3b,6a,6b,7,8,9,10,10a-octahydro-1H,5H-benzo[g]pyrrolo[3,4-*e*]indole-4,6-dione (112). Method B with **3h** (1220 mg, 7.000 mmol), 3.5-h reflux, ethanol wash (4 mL), and then a diethyl ether wash (10 mL) gave **112** (1548 mg, 59%) as a light-brown solid, a mixture of two isomers (maj:min = 8.1:1.0): mp 226-227 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.67 (app. bs, 1H, 1maj-H), 10.48 (d, *J* = 2.4 Hz, 1H, 1min-H), 6.97-7.39 (m, 11H, Ph), 6.82-6.90 (m, 2H, Ph), 5.62 (d, *J* = 2.7 Hz, 1H, 3min-H), 5.60 (d, *J* = 2.4 Hz, 1H, 3maj-H), 4.20 (dd, *J* = 8.7, 1.8 Hz, 1H, 3 β amin-H), 4.18 (dd, *J* = 8.4, 1.5 Hz, 1H, 3 β maj-H), 3.82 (s, 2H, Bn), 3.79 (s, 3H, PhCH₃ maj), 3.78 (s, 3H, PhCH₃ min), 3.73 (s, 3H, BnCH₃ min), 3.72 (s, 3H, BnCH₃ maj), 3.36-3.48 (m, 1H, 6 α -H), 2.80-3.20 (m, 2H, 6b-H, 10 α -H), 1.20-2.30 (m, 7H, cyclohex.); ¹³C NMR (75 MHz, CDCl₃, δ) 178.2, 176.4, 159.7, 158.3, 132.9, 131.5, 130.4, 129.8, 128.5, 127.8, 127.4, 127.3, 126.8, 125.6, 124.4, 117.6, 114.7, 114.3, 114.1, 104.1, 57.4, 55.6, 55.4, 45.5, 33.6, 33.2-33.6 (overlapped peaks), 32.3; IR (KBr, cm⁻¹) 3479(w), 3458(w), 3388(bs), 3059(w), 3025(w), 3002(w), 2933(s), 2860(m), 2837(m), 2360(w), 2340(w), 1776(m), 1699(s), 1610(m), 1513(s), 1451(m), 1390(m), 1302(m), 1251(s), 1174(s), 1031(s); HRMS *m/z* (M + Na⁺) calcd 569.2412, found 569.2406. Anal. Calcd for C₃₅H₃₄N₂O₄: C, 76.90; H, 6.27; N, 5.12. Found: C, 76.84; H, 6.27; N, 4.89.

6.2 Experimental for Part II

General Methods for the Preparation of Vinylpyrroles.

Method I.^{38,39} Sodium ethoxide (0.125 mol, 2.5 equiv, made freshly from sodium (2.87 g, 0.125 mol, 2.5 equiv) and EtOH followed by evaporation using a rotating evaporator) was suspended with the appropriate alkyltriphenylphosphonium bromide (0.1 mol, 2 equiv) in THF (50 mL). The mixture was stirred at rt under nitrogen for 3 h. Then a solution of the appropriate pyrrole-2-carboxaldehyde **114a** or **114b** or 2-acetylpyrrole **114c** or **114d** (0.05 mol) in THF (20 mL) was added over 1 min, and the mixture was stirred under reflux for 15 h. The solvent was removed using a rotating evaporator, the residue was suspended in dichloromethane and filtered, and the filter cake was washed with dichloromethane (3 x 50 mL). The filtrate was washed with saturated NaHSO₃ (50 mL), saturated Na₂CO₃ (50 mL), and brine (50 mL), and dried over Na₂SO₄. The solvent was removed using a rotating evaporator and the crude product was vacuum-distilled, giving the appropriate pure 2-vinylpyrrole (with the exception of **116**, see below) at comparable 60% yield.^{38,39} When Method I was used to generate vinylpyrrole **116**, **119** was found to be an unwanted byproduct in an approximately 1:1 molar ratio to the desired product. This mixture was used without further purification in subsequent Diels-Alder reactions.

Method II. Potassium *t*-butoxide (14.76 g, 0.132 mol, 1.25 equiv) was added slowly to methyltriphenylphosphonium bromide (46.98 g, 0.132 mol, 1.25 equiv) in THF (100 mL) at 0 °C. Formation of the bright yellow color characteristic of the ylide was observed immediately. The mixture was stirred at rt under nitrogen for 30 min and then cooled to 0 °C. A solution of the pyrrole **114a** (10.00 g, 0.105 mmol) in THF (20 mL)

was added over 5 min, with stirring, and refluxed for 30 min until TLC analysis indicated the reaction was complete. The mixture was allowed to cool to rt and filtered. The filter cake was washed with diethyl ether (4 x 25 mL). The filtrate was washed with saturated NaHSO₃ (50 mL), saturated Na₂CO₃ (50 mL), and brine (50 mL), and dried over anhydrous Na₂SO₄. The solvents were removed using a rotating evaporator and the residue was vacuum-distilled, giving **116** as a colorless liquid (7.66 g, 78%). The ¹H and ¹³C NMR data matched the values in the literature.^{38,39}

For Diels-Alder reactions, vinylpyrroles **117a** and **117b** were synthesized using Corey's procedure for the Wittig reaction⁴¹ and method I was used to synthesize vinylpyrroles **115a-g**. However, for purposes of characterization **115a-c**, **115e-f** and **117a** were synthesized using method II.

2-(2-Propenyl)-1H-pyrrole (115a).^{37a} Method II with **114c** (3.16 g, 0.029 mol) and distillation at 37 °C/0.04 mm Hg gave **115a** (436 mg, 14%) as a white waxy solid: mp 71-73 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.32 (bs, 1H, 1-H), 6.82 (ddd, *J* = 2.8, 2.8, 1.4 Hz, 1H, 5-H), 6.37 (dddd, *J* = 3.1, 3.1, 1.7, 1.3 Hz, 1H, 3-H), 6.32 (dddd, *J* = 3.3, 2.6, 2.6, 0.9 Hz, 1H, 4-H), 5.09-5.11 (m, 1H, 1'-H *cis* to pyrrole), 4.91-4.93 (m, 1H, 1'-H *trans* to pyrrole), 2.17 (ddd, *J* = 1.6, 0.8, 0.8 Hz, 3H, 3'-H); ¹³C NMR (75 MHz, CDCl₃, δ) 135.1, 133.2, 118.8, 109.5, 107.0, 105.7, 20.8; IR (thin film, cm⁻¹) 3450(bs), 3400(s), 2969(s), 2925(m), 2840(w), 1634(m), 1597(m), 1557(w), 1499(w), 1470(m), 1403(m), 1235(m), 1110(w), 1035(m); HRMS *m/z* (M + H⁺) calcd for C₇H₉N: 108.0808, found 108.0815.

2-(1-Propenyl)-1H-pyrrole (115b).^{37b,38a} Method II with **114a** (2.66 g, 0.028 mol) and distillation at 35.5 °C/0.05 mm Hg gave **115b** (2.32 g, 77%) as a white solid:

1.0:3.9 *E:Z*; mp 27-28 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.10 (bs, 1H, 1-H), 6.82 (ddd, *J* = 2.6, 2.6, 1.4 Hz, 1H, 5maj-H), 6.74 (ddd, *J* = 2.7, 2.7, 1.4 Hz, 1H, 5min-H), 6.22-6.42 (m, 3H, 3-H, 4-H, 1'-H), 5.80-5.93 (m, 1H, 2'min-H), 5.61-5.74 (m, 1H, 2'maj-H), 2.03-2.07 (m, 3H, 3'maj-H), 1.93-1.97 (m, 3H, 3'min-H); ¹³C NMR (75 MHz, CDCl₃, δ) 130.4, 122.2, 121.8, 120.9, 120.4, 118.0, 117.8, 109.6, 109.4, 109.0, 106.6, 18.5, 15.2; IR (thin film, cm⁻¹) 3469(s), 3396(bs), 3107(w), 3024(m), 2963(m), 2950(m), 2935(m), 2857(w), 1642(m), 1603(w), 1546(w), 1459(m), 1409(w), 1366(m), 1294(w), 1278(w), 1216(w), 1118(m), 1098(m), 1032(m), 957(w), 800(s); HRMS *m/z* (M + H⁺) calcd 108.0808, found 108.0802. Anal. Calcd for C₇H₉N: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.28; H, 8.66; N, 12.94.

2-(2-But-2-enyl)-1H-pyrrole (115c). Method II with **114c** (3.16 g, 0.029 mol) and distillation at 43 °C/0.04 mm Hg gave **115c** (922 mg, 26%) as a colorless liquid: 2.8:1.0 *E:Z*; ¹H NMR (300 MHz, CDCl₃, δ) 8.32 (bs, 1H, 1-H), 6.87 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1H, 5maj-H), 6.77 (ddd, *J* = 2.2, 2.2, 2.2 Hz, 1H, 5min-H), 6.36-6.40 (m, 2H, 3maj-H, 4maj-H), 6.27-6.31 (m, 2H, 3min-H, 4min-H), 5.67-5.76 (m, 1H, 3'min-H), 5.50-5.59 (m, 1H, 3'maj-H), 2.12-2.15 (m, 3H, 1'maj-H), 2.05-2.07 (m, 3H, 1'min-H), 1.97-2.01 (m, 3H, 4'maj-H), 1.86-1.90 (m, 3H, 4'min-H); ¹³C NMR (75 MHz, CDCl₃, δ) 134.9, 132.4, 127.6, 126.9, 119.5, 117.8, 117.5, 116.0, 109.1, 109.0, 108.4, 105.2, 23.1, 15.4, 14.4, 13.7; IR (thin film, cm⁻¹) 3481(s), 3419(bm), 2973(m), 2922(m), 2862(m), 1643(w), 1551(w), 1452(m), 1403(m), 1378(m), 1353(w), 1119(m), 1090(m), 1068(w), 1036(m), 806(m), 791(m); HRMS *m/z* (M + H⁺) calcd 122.0964, found 122.0965. Anal. Calcd for C₈H₁₁N: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.22; H, 8.96; N, 11.33.

***N*-Methyl-2-(2-propenyl)-1*H*-pyrrole (115e).**^{16a,37c,37e,37f} Method II with **114d** (3.57 g, 0.029 mol) and distillation at 31.5 °C/0.04 mm Hg gave **115e** (1.62 g, 46%) as a colorless liquid: ¹H NMR (300 MHz, CDCl₃, δ) 6.77 (ddd, *J* = 2.7, 1.4, 1.4 Hz, 1H, 5-H), 6.37 (ddd, *J* = 3.7, 1.9, 1.9 Hz, 1H, 3-H), 6.30 (ddd, *J* = 3.8, 2.7, 1.8 Hz, 1H, 4-H), 5.26 (dq, *J* = 3.0, 1.5 Hz, 1H, 1'-H *cis* to pyrrole), 5.17 (dq, *J* = 3.0, 1.5 Hz, 1H, 1'-H *trans* to pyrrole), 3.85 (d, *J* = 1.2 Hz, 3H, 1-CH₃), 2.28 (dddd, *J* = 1.7, 1.7, 1.0, 0.9 Hz, 3H, 3'-H); ¹³C NMR (75 MHz, CDCl₃, δ) 135.9, 134.7, 124.7, 111.6, 108.8, 107.3, 36.3, 24.1; IR (thin film, cm⁻¹) 3104(m), 2974(s), 2952(s), 2921(s), 2881(m), 2806(w), 2726(w), 1794(w), 1701(w), 1626(s), 1478(s), 1449(m), 1434(s), 1413(m), 1374(m), 1363(m), 1313(s), 1260(m), 1224(w), 1094(m), 1062(w), 997(w), 789(m), 605(m); HRMS *m/z* (M + H⁺) calcd 122.0964, found 122.0959. Anal. Calcd for C₈H₁₁N: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.54; H, 8.92; N, 11.54.

***N*-Methyl-2-(1-propenyl)-1*H*-pyrrole (115f).**^{37d,37g,37i} Method II with **114b** (3.50 g, 0.032 mol) and distillation at 32.5 °C/0.04 mm Hg gave **115f** (2.66 g, 68%) as a colorless liquid: 1.0:1.8 *E:Z*; ¹H NMR (300 MHz, CDCl₃, δ) 6.72 (ddd, *J* = 2.9, 1.5, 1.5 Hz, 1H, 5maj-H), 6.66 (ddd, *J* = 2.4, 2.0, 2.0 Hz, 1H, 5min-H), 6.36-6.44 (m, 2H, 3-H, 4-H), 6.29-6.32 (m, 1H, 1'maj-H), 6.20-6.23 (m, 1H, 5'min-H), 6.06-6.19 (m, 1H, 2'min-H), 5.76-5.88 (m, 1H, 2'maj-H), 3.69 (s, 3H, 1min-CH₃), 3.69 (s, 3H, 1maj-CH₃), 2.04-2.08 (m, 3H, 3'maj-H), 1.98-2.02 (m, 3H, 2'maj-H); ¹³C NMR (75 MHz, CDCl₃, δ) 132.4, 130.4, 124.3, 124.1, 122.24, 122.16, 120.1, 118.6, 109.6, 107.8, 107.6, 105.3, 34.1, 18.9, 15.3; IR (thin film, cm⁻¹) 3103(m), 3018(m), 2967(s), 2937(s), 2917(s), 2860(m), 1698(w), 1640(w), 1479(s), 1450(m), 1412(m), 1376(m), 1356(w), 1342(w), 1302(m), 1292(s), 1241(w), 1228(w), 1089(m), 1064(w), 1033(w), 998(w), 832(w),

781(m), 649(s), 608(s); HRMS m/z ($M + H^+$) calcd 122.0964, found 122.0956. Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.50; H, 8.93; N, 11.80.

2-(2-But-2-enyl)-*N*-methyl-1*H*-pyrrole (115g). Method II with **114d** (3.50 g, 0.032 mol) and distillation at 31.5 °C/0.04 mm Hg gave **115g** (1.01 g, 23%) as a colorless liquid: 1.0:1.5 *E:Z*; 1H NMR (300 MHz, $CDCl_3$, δ) 6.70 (ddd, $J = 2.7, 1.8, 1.8$ Hz, 1H, 5maj-H), 6.64 (ddd, $J = 2.7, 2.0, 2.0$ Hz, 1H, 5min-H), 6.24 (ddd, $J = 3.5, 2.4, 2.4$ Hz, 1H, 3maj-H), 6.18 (ddd, $J = 3.6, 2.4, 2.4$ Hz, 1H, 3min-H), 6.10 (dddd, $J = 3.9, 3.9, 2.0, 2.0$ Hz, 1H, 4min-H), 6.02 (dddd, $J = 3.8, 3.8, 2.0, 2.0$ Hz, 1H, 4maj-H), 5.74-5.84 (m, 1H, 3' maj-H), 5.60-5.69 (m, 1H, 3' min-H), 3.68 (d, $J = 2.1$ Hz, 3H, 1min- CH_3), 3.57 (d, $J = 1.8$ Hz, 3H, 1maj- CH_3), 2.04-2.06 (m, 3H, 1'-H), 1.85-1.90 (m, 3H, 4' min-H), 1.59-1.64 (m, 3H, 4' maj-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 137.7, 133.6, 129.1, 128.1, 126.3, 124.1, 122.7, 121.4, 107.4, 107.1, 106.8, 33.3, 34.0, 25.5, 17.3, 15.5, 14.2; IR (thin film, cm^{-1}) 3106(m), 3026(m), 2943(m), 2918(m), 2884(m), 2857(w), 2810(w), 1703(w), 1638(m), 1484(s), 1451(m), 1367(w), 1305(s), 1261(w), 1228(w), 1091(m), 1058(w), 1009(w), 954(m), 789(m), 648(s), 605(m); HRMS m/z ($M + H^+$) calcd for $C_9H_{13}N$: 136.1121, found 136.1124.

2-Ethenyl-1*H*-pyrrole (116).^{38,39} Method II with **114a** (10.00 g, 0.105 mol) and distillation at 30 °C/0.04 mm Hg gave **116** (7.66 g, 78%) as a colorless liquid; the 1H and ^{13}C NMR data matched the literature values.^{38,39} Anal. Calcd for C_6H_7N : C, 77.38; H, 7.58; N, 15.04. Found: C, 77.17; H, 7.67; N, 14.83.

2-(1-Heptenyl)-1*H*-pyrrole (117b). Method II with **114a** (2.91 g, 0.031 mol) and distillation at 68 °C/0.04 mm Hg gave **117b** (4.40 g, 81%) as a colorless liquid: 1.0:9.0 *E:Z*; 1H NMR (300 MHz, $CDCl_3$, δ) 8.10 (bs, 1H, 1-H), 6.81 (ddd, $J = 2.3, 2.3, 1.7$ Hz,

1H, 5maj-H), 6.74 (ddd, $J = 2.6, 2.6, 1.4$ Hz, 1H, 5min-H), 6.21-6.37 (m, 3H, 3-H, 4-H, 1'-H), 5.85 (ddd, $J = 16.1, 7.0, 7.0$ Hz, 1H, 2'min-H), 5.53 (ddd, $J = 12.8, 6.8, 5.8$ Hz, 1H, 2'maj-H), 2.45 (ddt, $J = 7.3, 7.2, 1.8$ Hz, 2H, 3'maj-H), 2.25 (dt, $J = 7.2, 7.1, 1.5$ Hz, 2H, 3'min-H), 1.34-1.65 (m, 6H, 4'-H, 5'-H, 6'-H), 1.01 (t, $J = 7.2$ Hz, 3H, 7'-H); ^{13}C NMR (75 MHz, CDCl_3 , δ) 134.0, 133.7, 130.3, 128.9, 128.8, 128.7, 128.6, 126.3, 120.5, 119.0, 117.8, 117.7, 109.6, 109.4, 108.9, 106.7, 32.9, 31.8, 31.5, 29.4, 29.4, 22.7, 14.2; IR (thin film, cm^{-1}) 3469(s), 3392(bs), 3105(m), 3014(m), 2957(s), 2926(s), 2857(s), 1712(w), 1639(m), 1545(w), 1460(m), 1434(m), 1412(m), 1379(m), 1293(w), 1280(w), 1212(w), 1182(w), 1118(m), 1095(m), 1033(m), 955(m), 799(m), 949(m); HRMS m/z ($\text{M} + \text{H}^+$) calcd 164.1434, found 164.1434. Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{N}$: C, 80.93; H, 10.50; N, 8.58. Found: C, 81.07; H, 10.32; N, 8.74.

2-(1-Ethoxyethyl)-N-methyl-1H-pyrrole (119). A 1:1 molar mixture of **116** and **119**, prepared using Method I, was left in a refrigerator for 6 months, giving large colorless crystals of **119**. The crystals were removed and the liquid **116** was washed off using ice-cold petroleum ether, giving colorless crystals: mp 26.5-28.5 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 8.39 (bs, 1H, 1-H), 6.78 (ddd, $J = 2.6, 2.6, 1.6$ Hz, 1H, 5-H), 6.16 (ddd, $J = 3.3, 2.7, 2.5$ Hz, 1H, 4-H), 6.08 (ddd, $J = 3.5, 2.6, 1.5$ Hz, 1H, 3-H), 4.55 (q, $J = 6.6$ Hz, 1H, 1'-H), 3.44 (dq, $J = 12.0, 7.0$ Hz, 1H, OCH_2CH_3), 3.40 (dq, overlapped, $J = 11.7, 7.0$ Hz, 1H, OCH_2CH_3), 1.51 (d, $J = 6.6$ Hz, 3H, 2'-H), 1.19 (dd, $J = 6.9, 7.2$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3 , δ) 133.7 (C2), 117.5 (C5), 107.9 (C4), 106.0 (C3), 71.1 (C1'), 63.4 (OCH_2CH_3), 21.7 (C2'), 15.5 (OCH_2CH_3); IR (film, cm^{-1}) 3464(m), 3322(w), 3054(m), 2980(m), 2933(w), 2873(w), 1446(w), 1422(w), 1373(w),

1325(w), 1266(s), 1151(w), 1086(m), 1028(w), 1006(w), 896(w), 796(w), 739(s), 707(s). X-ray data for **7** in CIF format is available in the Supporting Information.

General Method for the Synthesis of Chiral Maleimides.⁴³ The primary amine (0.070 mol) dissolved in a large excess of diethyl ether (100 mL) was added over 20 min using a dropping funnel to a 2 L flask containing maleic anhydride (6.85 g, 0.070 mol, 1 equiv) dissolved in diethyl ether (500 mL). Throughout the addition the mixture turned into a thick off-white suspension. The suspension was concentrated to half-volume, cooled in the freezer, and vacuum-filtered, giving the crude acid as a thick paste. Acetic anhydride (300 mL) and sodium acetate (2.87 g, 0.035 mol, 0.5 equiv) were added to the crude acid and the mixture was heated to 100 °C in a boiling water bath for 2 h. The mixture was then cooled to rt, diluted with water (200 mL), and portions of NaHCO₃ were added slowly with vigorous stirring until the acetic acid was nearly neutralized. The solution was extracted with ether (3 x 200 mL), and the organic extracts were washed with saturated NaHCO₃ until neutral, and then washed with water (100 mL) and brine (100 mL), and dried over anhydrous Na₂SO₄. The solvent was removed using a rotating evaporator and the product was purified using flash chromatography on silica gel using ethyl acetate/hexanes to give the pure chiral maleimide in moderate yield (~50%).

(+)-(R)-2-(2,5-Dioxo-1H-pyrrol-1-yl)-2-phenylethyl acetate (4p). The general method gave **4p** (8.167 g, 45%) as a light-red oil: $[\alpha]_{\text{D}}^{23} +1.7$ (*c* 10.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃, δ) 7.43-7.46 (m, 2H, Ph), 7.33-7.40 (m, 3H, Ph), 6.71 (s, 2H, vinyl-H), 5.43 (dd, *J* = 10.5, 5.4 Hz, 1H, 2'-H), 4.99 (dd, *J* = 11.1, 10.5 Hz, 1H, 1'-H), 4.71 (dd, *J* = 11.1, 5.4 Hz, 1H, 1'-H), 2.04 (s, 3H, OAc); ¹³C NMR (75 MHz, CDCl₃, δ)

170.7, 170.6, 135.9, 134.3, 128.9, 128.6, 128.0, 62.4, 53.6, 20.8; IR (film, cm^{-1}) 3465(m), 3101(m), 2950(w), 1743(s), 1713(s), 1399(s), 1370(s), 1232(s), 1163(m), 1043(m), 828(m), 696(s); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_4$: 282.0738, found 282.0740.

(+)-(R)-1-(2-Methoxy-1-phenylethyl)-1H-pyrrole-2,5-dione (4q). The general method gave **4q** (7.608 g, 47%) as white crystals: mp 55-56 °C; $[\alpha]_{\text{D}}^{23} +22.5$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , δ) 7.41-7.45 (m, 2H, Ph), 7.30-7.38 (m, 3H, Ph), 6.68 (s, 2H, vinyl-H), 5.38 (dd, $J = 10.5, 5.4$ Hz, 1H, 1'-H), 4.46 (dd, $J = 11.2, 11.2$ Hz, 1H, 2'-H), 3.82 (dd, $J = 10.9, 5.4$ Hz, 1H, 2'-H), 3.39 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, CDCl_3 , δ) 171.0, 137.0, 134.2, 128.8, 128.3, 128.0, 70.8, 58.8, 54.3; IR (film, cm^{-1}) 3460(bm), 3095(m), 2915(m), 2810(w), 1706(s), 1400(m), 1368(m), 1154(w), 1110(m), 826(m), 696(s); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_3$: 254.0783, found 254.0783.

General Method for Diels-Alder Reactions. A mixture of the vinylpyrrole (0.0050 mol, 1.1 equiv) and the maleimide (0.0045 mol) (1) in chloroform (20 mL) was stirred at rt for 24 h and, if TLC analysis indicated maleimide remaining, the mixture was also refluxed for 24 h (method A) or (2) in toluene (20 mL) was refluxed for 24 h (method B). The solvent was removed using a rotating evaporator. The crude adduct was purified with flash chromatography or MPLC with ethyl acetate/hexanes as eluent, except in the case of chiral adducts, which were used without further purification in the next step.

General Method for the Dehydrogenation of Diels-Alder Adducts. A mixture of the adduct (3.76 mmol) and activated MnO_2 ⁴⁸ (18.8 mmol, 5 equiv) in toluene (30 mL) was

refluxed for 2-3 h until the reaction was complete, as indicated by TLC (method C), or refluxed for 24 h (method D). For dehydrogenation of chiral adducts, the crude Diels-Alder reaction product was placed in toluene (30 mL) along with activated MnO₂ (5 equiv) and refluxed for 24 h (method E). The mixture was cooled to rt and filtered through a fine glass frit. The insoluble manganese salts were washed with several portions of dichloromethane until the washings ran clear (5 x 20 mL), and the combined organic filtrate and washings were evaporated to dryness using a rotating evaporator. Flash chromatography or MPLC with ethyl acetate/hexanes as eluent provided the desired product in good yields.

Compounds 122-149, 163-208.

2-Dimethylamino-3 α ,4,5,8 β -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (122). Method A with vinylpyrrole **116** and maleimide **4a** gave **122** (597 mg, 64% crude yield, including contamination from double-addition type products, detected by TLC; the crude adduct was recrystallized from methylene chloride/petroleum ether, giving the pure compound, but the isolated yield is not available) as a light-brown powder: mp 56-57 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.02 (bs, 1H, 6-H), 6.68 (dd, *J* = 2.7, 2.7 Hz, 1H, 7-H), 6.37 (dd, *J* = 2.9, 2.9 Hz, 1H, 8-H), 3.89 (ddd, *J* = 8.1, 1.4, 1.4 Hz, 1H, 8 β -H), 3.18 (ddd, *J* = 7.8, 5.4, 5.4 Hz, 1H, 3 α -H), 2.84 (s, 6H, N(CH₃)₂), 2.57-2.65 (m, 2H, 5 α -H and 5 β -H), 2.34 (dddd, *J* = 13.6, 5.1, 5.1, 5.1 Hz, 1H, 4 β -H), 2.00 (dddd, *J* = 13.7, 8.6, 6.3, 5.1 Hz, 1H, 4 α -H); ¹³C NMR (75 MHz, CDCl₃, δ) 177.6, 176.7, 127.1, 117.2, 109.9, 107.7, 44.0, 38.8, 38.7, 22.2, 19.5; IR (film, cm⁻¹) 3361(bs), 2930(m), 1777(w), 1711(s), 1448(w), 1369(m), 1200(m), 1147(m), 719(w); HRMS *m/z*

(M + Na⁺) calcd 256.1057, found 256.1057. Anal. Calcd for C₁₂H₁₅N₃O₂: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.59; H, 6.32; N, 17.90.

2-Benzyl-3 α ,4,5,8 β α -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (123).

Method A with vinylpyrrole **116** and maleimide **4k** gave **123** (258 mg, 23%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃, δ) 7.98 (bs, 1H, 6-H), 7.24-7.29 (m, 5H, Ph), 6.68 (dd, *J* = 2.7, 2.7 Hz, 1H, 7-H), 6.37 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.64 (AA' d, *J* = 14.4 Hz, 1H, Bn), 4.58 (AA' d, *J* = 14.1 Hz, 1H, Bn), 3.98 (ddd, *J* = 8.1, 1.2, 1.2 Hz, 1H, 8 β α -H), 3.24 (ddd, *J* = 7.8, 5.1, 5.1 Hz, 1H, 3 α α -H), 2.61 (dddd, *J* = 16.0, 5.3, 5.3, 0.9 Hz, 1H, 5 β -H), 2.51 (dddd, *J* = 15.4, 9.9, 5.4, 0.9 Hz, 1H, 5 α -H), 2.37 (dddd, *J* = 13.5, 4.8, 4.8, 4.8, 1H, 4 β -H), 1.99 (dddd, *J* = 13.7, 9.8, 5.5, 5.3 Hz, 1H, 4 α -H); ¹³C NMR (75 MHz, CDCl₃, δ) 179.0, 178.0, 136.0, 128.7, 128.4, 127.8, 127.2, 117.2, 110.4, 107.6, 42.3, 40.4, 40.1, 22.2, 19.6; IR (KBr, cm⁻¹) 3450s, 3100w, 2924m, 2980w, 1701s; HRMS *m/z* (M + Na⁺) calcd for C₁₇H₁₆N₂O₂: 303.1105, found 303.1093.

2-Phenyl-3 α ,4,5,8 β α -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (124).

Method A with vinylpyrrole **116** and maleimide **4b** gave **124** (980 mg, 92% crude yield, including contamination from double-addition type products, detected by TLC; the crude adduct was recrystallized from methylene chloride/petroleum ether, giving the pure compound, but the isolated yield is not available) as a light-brown powder: mp 155-156 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.95 (bs, 1H, 6-H), 7.41-7.47 (m, 2H, Ph), 7.33-7.39 (m, 1H, Ph), 7.23-7.28 (m, 2H, Ph), 6.70 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 6.41 (dd, *J* = 2.6, 2.6 Hz, 1H, 8-H), 4.15 (ddd, *J* = 8.1, 1.4, 1.4 Hz, 1H, 8 β α -H), 3.45 (ddd, *J* = 8.1, 5.0, 5.0 Hz, 1H, 3 α α -H), 2.63-2.67 (m, 2H, 5 α -H and 5 β -H), 2.53 (dddd, *J* = 13.6, 4.5, 4.5, 4.5 Hz, 1H, 4 β -H), 2.06 (dddd, *J* = 13.4, 8.3, 7.6, 5.2 Hz, 1H, 4 α -H); ¹³C

NMR (75 MHz, CDCl₃, δ) 178.3, 177.3, 132.1, 129.1, 128.4, 127.3, 126.4, 117.3, 110.2, 107.7, 40.5, 40.4, 22.0, 19.4; IR (film, cm⁻¹) 3374(bs), 2857(m), 1775(w), 1707(s), 1596(w), 1498(m), 1383(m), 1177(m), 1064(m), 793(m), 723(m); HRMS m/z (M + Na⁺) calcd 289.0948, found 289.0947. Anal. Calcd for C₁₆H₁₄N₂O₂: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.96; H, 5.43; N, 10.57.

2-(4-Ethylphenyl)-3 α ,4,5,8 β α -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (125). Method A with vinylpyrrole **116** and maleimide **4l** gave **125** (577 mg, 49%) as a white powder: mp 144-146 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.93 (bs, 1H, 6-H), 7.26 (d, J = 8.9, 2H, Ph), 7.15 (d, J = 8.4 Hz, 2H, Ph), 6.70 (dd, J = 2.6, 2.6 Hz, 1H, 7-H), 6.41 (dd, J = 2.7, 2.7 Hz, 1H, 8-H), 4.13 (ddd, J = 7.8, 1.4, 1.4 Hz, 1H, 8 β α -H), 3.43 (ddd, J = 8.1, 5.0, 5.0 Hz, 1H, 3 α α -H), 2.63-2.71 (m, 2H, 5 α -H and 5 β -H), 2.66 (q, overlapped, J = 7.6 Hz, 2H, CH₂CH₃), 2.52 (dddd, J = 13.7, 4.6, 4.6, 4.6 Hz, 1H, 4 β -H), 2.06 (dddd, J = 13.4, 8.4, 7.3, 5.1 Hz, 1H, 4 α -H), 1.23 (t, J = 7.7 Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 178.7, 177.7, 144.7, 129.6, 128.6, 127.3, 126.4, 117.3, 110.1, 107.4, 40.6, 40.4, 28.7, 22.1, 19.4, 15.6; IR (KBr, cm⁻¹) 3340(bs), 3030(w), 2970(m), 2940(m), 2860(w), 1780(m), 1700(s), 1600(w), 1510(m), 1445(w), 1395(s), 1360(w), 1310(w), 1295(w), 1205(m), 1195(m), 1170(m), 850(w), 815(w), 785(m), 720(m), 695(m); HRMS m/z (M + Na⁺) calcd 317.1261, found 317.1262. Anal. Calcd for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.60; H, 6.26; N, 9.36.

2-(4-Isopropylphenyl)-3 α ,4,5,8 β α -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (126). Method A with vinylpyrrole **116** and maleimide **14m** gave **126** (395 mg, 32%) as a light-orange powder: mp 188-190 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.93 (bs, 1H, 6-H), 7.29 (d, J = 8.4 Hz, 2H, Ph), 7.16 (d, J = 8.7 Hz, 2H, Ph), 6.70 (dd, J =

2.6, 2.6 Hz, 1H, 7-H), 6.41 (dd, $J = 2.6, 2.6$ Hz, 1H, 8-H), 4.13 (ddd, $J = 8.1, 1.4, 1.4$ Hz, 1H, 8 β -H), 3.44 (ddd, $J = 8.1, 5.0, 5.0$ Hz, 1H, 3 α -H), 2.92 (septet, $J = 6.9$ Hz, 1H, CH(CH₃)₂), 2.65 (m, 2H, 5 α -H and 5 β -H), 2.52 (dddd, $J = 13.7, 4.6, 4.6, 4.6$ Hz, 1H, 4 β -H), 2.06 (dddd, $J = 13.5, 8.3, 7.4, 5.1$ Hz, 1H, 4 α -H), 1.24 (d, $J = 6.9$ Hz, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃, δ) 178.6, 177.5, 149.2, 129.6, 127.2 (2 peaks overlapped), 117.2, 110.2, 107.6, 40.5, 40.4, 34.0, 24.0, 22.0, 19.4; ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 179.0, 177.8, 148.9, 130.7, 127.2 (3 peaks overlapped), 117.1, 110.0, 106.8, ~40 (2 peaks obscured by DMSO), 33.7, 24.3, 22.5, 19.5; IR (KBr, cm⁻¹) 3444(m), 3353(bs), 3105(w), 2959(m), 2931(m), 2863(w), 1773(w), 1704(s), 1513(m), 1463(w), 1428(w), 1381(m), 1347(w), 1280(w), 1194(m), 1177(m), 1152(m), 1093(w), 1067(w), 1051(w), 721(m); HRMS m/z (M + Na⁺) calcd 331.1418, found 331.1410. Anal. Calcd for C₁₉H₂₀N₂O₃: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.00; H, 6.51; N, 9.16.

2-(4-Methoxyphenyl)-3 $\alpha\alpha$,4,5,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (127). Method A with vinylpyrrole **116** and maleimide **4d** gave **127** (1.067 g, 90% crude yield, including contamination from double-addition type products, detected by TLC; the crude adduct was recrystallized from methylene chloride/petroleum ether, giving the pure compound, but the isolated yield is not available) as a white powder: mp 187-188 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.94 (bs, 1H, 6-H), 7.17 (d, $J = 9.0$ Hz, 2H, Ph), 6.94 (d, $J = 9.0$ Hz, 2H, Ph), 6.70 (dd, $J = 2.7, 2.7$ Hz, 1H, 7-H), 6.41 (dd, $J = 2.9, 2.9$ Hz, 1H, 8-H), 4.15 (ddd, $J = 8.1, 1.4, 1.4$ Hz, 1H, 8 $\beta\alpha$ -H), 3.82 (s, 3H, OCH₃), 3.45 (ddd, $J = 7.8, 5.0, 5.0$ Hz, 1H, 3 $\alpha\alpha$ -H), 2.63-2.67 (m, 2H, 5 α -H and 5 β -H), 2.53 (dddd, $J = 13.5, 4.5, 4.5, 4.5$ Hz, 1H, 4 β -H), 2.06 (dddd, $J = 13.7, 8.0, 7.7, 5.2$ Hz, 1H, 4 α -H);

^{13}C NMR (75 MHz, CDCl_3 , δ) 178.5, 177.5, 159.3, 127.7, 127.2, 124.8, 117.2, 114.4, 110.4, 107.7, 55.6, 40.5, 40.3, 22.0, 19.4; IR (film, cm^{-1}) 3378(bm), 2931(w), 2842(w), 1776(w), 1704(s), 1608(w), 1513(s), 1466(w), 1441(w), 1389(m), 1300(w), 1251(m), 1168(m), 1030(w), 729(w); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 319.1054, found 319.1056. Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.86; H, 5.61; N, 9.28.

2-(4-Phenoxyphenyl)-3 $\alpha\alpha$,4,5,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (128). Method A with vinylpyrrole **116** and maleimide **4e** gave **128** (473 mg, 33%) as a light-yellow powder: mp 200-202 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.93 (bs, 1H, 6-H), 7.33-7.39 (m, 2H, Ph), 7.21 (d, $J = 9.0$ Hz, 2H, Ph), 7.12-7.17 (m, 1H, Ph), 7.01-7.06 (m, 2H, Ph), 7.03 (d, overlapped, $J = 9.0$ Hz, 2H, Ph), 6.70 (dd, $J = 2.7, 2.7$ Hz, 1H, 7-H), 6.41 (dd, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.14 (ddd, $J = 8.1, 1.4, 1.4$ Hz, 1H, 8 $\beta\alpha$ -H), 3.44 (ddd, $J = 7.8, 4.9, 4.9$ Hz, 1H, 3 $\alpha\alpha$ -H), 2.63-2.67 (m, 2H, 5 α -H and 5 β -H), 2.53 (dddd, $J = 13.4, 4.6, 4.6, 4.6$ Hz, 1H, 4 β -H), 2.06 (dddd, $J = 13.6, 8.5, 7.3, 5.1$ Hz, 1H, 4 α -H); ^1H NMR (300 MHz, $\text{DMSO-}d_6$) 10.60 (bs, 1H, 6-H), 7.39-7.44 (m, 2H, Ph), 7.15-7.20 (m, 1H, Ph), 7.19 (d, overlapped, $J = 8.7$ Hz, 2H, Ph), 7.03-7.07 (m, 2H, Ph), 7.05 (d, overlapped, $J = 8.7$ Hz, 2H, Ph), 6.59 (dd, $J = 2.6, 2.6$ Hz, 1H, 7-H), 6.04 (dd, $J = 2.4, 2.4$ Hz, 1H, 8-H), 4.02 (d, $J = 8.1$ Hz, 1H, 8 $\beta\alpha$ -H), 3.51 (ddd, $J = 8.1, 5.2, 5.2$ Hz, 1H, 3 $\alpha\alpha$ -H), 2.58 (ddd, $J = 15.5, 4.7, 4.7$ Hz, 1H, 5 β -H), 2.43 (ddd, 15.2, 10.0, 4.9 Hz, 1H, 5 α -H), 2.23 (dddd, $J = 13.5, 4.8, 4.8, 4.8$ Hz, 1H, 4 β -H), 1.88 (dddd, $J = 13.6, 10.1, 5.2, 5.2$ Hz, 1H, 4 α -H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$, δ) 178.9, 177.8, 156.9, 156.6, 130.8, 129.1, 127.9, 127.3, 124.5, 119.7, 118.9, 117.1, 110.0, 106.8, 22.5, 21.3, 19.5, 18.2; IR (KBr, cm^{-1}) 3387(bs), 3104(w), 2960(w), 2934(w), 2854(w),

1771(w), 1702(s), 1588(m), 1506(m), 1487(m), 1430(w), 1390(m), 1352(w), 1285(w), 1244(s), 1199(m), 1179(m), 1155(m), 1093(w), 1069(w), 876(w), 723(m); HRMS m/z ($M + Na^+$) calcd 381.1210, found 381.1202. Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.95; H, 5.03; N, 7.71.

2-Dimethylamino-6-methyl-3 α ,4,5,8 β -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (129). Method A with vinylpyrrole **115d** and maleimide **4a** gave **129** (880 mg, 89%) as a dark-brown oil: 1H NMR (300 MHz, $CDCl_3$, δ) 6.54 (d, $J = 2.7$ Hz, 1H, 7-H), 6.28 (d, $J = 2.7$ Hz, 1H, 8-H), 3.87 (ddd, $J = 8.1, 1.4, 1.4$ Hz, 1H, 8 β -H), 3.50 (s, 3H, 6- CH_3), 3.15 (ddd, $J = 8.1, 5.3, 5.3$ Hz, 1H, 3 α -H), 2.85 (s, 6H, $N(CH_3)_2$), 2.58 (dddd, $J = 16.1, 5.6, 5.6, 1.2$ Hz, 1H, 5 β -H), 2.48 (dddd, $J = 15.5, 9.5, 5.6, 1.2$ Hz, 1H, 5 α -H), 2.34 (dddd, $J = 13.4, 5.3, 5.3, 5.3$ Hz, 1H, 4 β -H), 1.99 (dddd, $J = 13.5, 9.1, 5.5, 5.5$ Hz, 1H, 4 α -H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 177.5, 176.6, 128.1, 121.5, 110.1, 106.5, 44.0, 38.9, 38.6, 33.2, 22.1, 18.2; IR (film, cm^{-1}) 3105(w), 3054(w), 2931(m), 2891(m), 1777(m), 1716(s), 1497(m), 1446(m), 1364(s), 1270(w), 1248(w), 1181(m), 1145(m), 1053(w), 714(m); HRMS m/z ($M + Na^+$) calcd 270.1214, found 270.1221. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 62.94; H, 7.07; N, 16.76.

6-Methyl-2-phenyl-3 α ,4,5,8 β -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (130). Method A with vinylpyrrole **115d** and maleimide **4b** gave **130** (1.054 g, 94%) as a light-brown powder: mp 169-170 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 7.38-7.47 (m, 2H, Ph), 7.32-7.38 (m, 1H, Ph), 7.24-7.29 (m, 2H, Ph), 6.57 (d, $J = 2.7, 2.7$ Hz, 1H, 7-H), 6.33 (d, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.13 (ddd, $J = 8.4, 1.4, 1.4$ Hz, 1H, 8 β -H), 3.52 (s, 3H, 6- CH_3), 3.43 (ddd, $J = 8.1, 4.5, 4.4$ Hz, 1H, 3 α -H), 2.50-2.68 (m, 3H, 4 β -H, 5 α -

H and 5 β -H), 2.05 (dddd, $J = 15.4, 12.5, 6.2, 5.0$ Hz, 1H, 4 α -H); ^{13}C NMR (75 MHz, CDCl_3 , δ) 178.2, 177.2, 132.2, 129.0, 128.3, 128.2, 126.4, 121.6, 110.6, 106.5, 40.6, 40.4, 33.2, 21.7, 18.2; IR (film, cm^{-1}) 3060(w), 2931(m), 2849(w), 1777(w), 1711(s), 1596(w), 1498(m), 1455(w), 1380(m), 1290(w), 1269(w), 1173(m), 1150(m), 718(m), 692(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 303.1105, found 303.1109. Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.60; H, 5.67; N, 9.81.

2-(4-Methoxyphenyl)-6-methyl-3 α ,4,5,8 β a-tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (131). Method A with vinylpyrrole **115d** and maleimide **4d** gave **131** (1.154 g, 93%) as a cream-colored powder: mp 161-162 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3 , δ) 7.17 (d, $J = 9.0$ Hz, 2H, Ph), 6.94 (d, $J = 9.0$ Hz, 2H, Ph), 6.57 (d, $J = 2.7$ Hz, 1H, 7-H), 6.33 (d, $J = 2.7$ Hz, 1H, 8-H), 4.11 (ddd, $J = 8.4, 2.0, 2.0$ Hz, 1H, 8 β α -H), 3.82 (s, 3H, OCH_3), 3.52 (s, 3H, 6- CH_3), 3.40 (ddd, $J = 7.8, 4.7, 4.7$ Hz, 1H, 3 α α -H), 2.49-2.68 (m, 3H, 4 β -H, 5 α -H and 5 β -H), 2.05 (dddd, $J = 16.5, 7.6, 6.0, 4.5$ Hz, 1H, 4 α -H); ^{13}C NMR (75 MHz, CDCl_3 , δ) 178.5, 177.5, 159.3, 128.2, 127.6, 124.9, 121.5, 114.3, 110.6, 106.5, 55.6, 40.5, 40.4, 33.2, 21.8, 18.2; IR (film, cm^{-1}) 2934(w), 2841(w), 1776(w), 1709(s), 1609(w), 1513(s), 1442(w), 1386(m), 1300(w), 1250(m), 1171(m), 1151(w), 1030(w); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 333.1210, found 333.1222. Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.89; H, 6.00; N, 8.90.

2-Dimethylamino-5 β ,6-dimethyl-3 α ,4,5 α ,8 β a-tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (132). Method A with vinylpyrrole **115e** and maleimide **4a** with reflux gave **132** (899 mg, 86%) as a light-orange powder: mp 100-101 $^\circ\text{C}$; maj:min = 13:1; ^1H NMR (300 MHz, CDCl_3 , δ) 6.55 (d, $J = 2.7$ Hz, 1H, 7-H), 6.28 (d, $J = 2.7$ Hz,

1H, 8-H), 3.92 (dd, $J = 9.0, 0.6$ Hz, 1H, 8 β -H), 3.53 (s, 3H, 6-CH₃), 3.14 (ddd, $J = 8.9, 7.0, 2.3$ Hz, 1H, 3 α -H), 3.02 (dddq, $J = 7.2, 5.7, 2.1, 0.6$ Hz, 1H, 5 α -H), 2.87 (s, 6H, N(CH₃)₂), 2.50 (ddd, $J = 14.1, 2.1, 2.1$ Hz, 1H, 4 β -H), 2.04 (ddd, $J = 14.1, 7.2, 5.7$ Hz, 1H, 4 α -H), 1.11 (d, $J = 7.2$ Hz, 3H, 5 β -CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 178.7, 176.6, 132.5, 121.9, 109.2, 106.5, 43.7, 38.3, 36.8, 33.0, 28.8, 25.3, 22.0; IR (film, cm⁻¹) 2962(s), 1777(m), 1711(s), 1500(w), 1446(w), 1369(m), 1293(w), 1189(m), 1149(m), 1046(w); HRMS m/z (M + Na⁺) calcd 284.1370, found 284.1373. Anal. Calcd for C₁₄H₁₉N₃O₂: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.15; H, 7.12; N, 16.18.

5 β ,6-Dimethyl-2-phenyl-3 $\alpha\alpha$,4,5 α ,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (133). Method A with vinylpyrrole **115e** and maleimide **4b** with reflux gave **133** (1.071 g, 91%) as a light-yellow cream-colored powder: mp 239-240 °C; maj:min = 54:1; ¹H NMR (300 MHz, CDCl₃, δ) 7.42-7.48 (m, 2H, Ph), 7.33-7.39 (m, 1H, Ph), 7.25-7.29 (m, 2H, Ph), 6.58 (d, $J = 3.0$ Hz, 1H, 7-H), 6.32 (d, $J = 2.7$ Hz, 1H, 8-H), 4.16 (d, $J = 8.7$ Hz, 1H, 8 $\beta\alpha$ -H), 3.55 (s, 3H, 6-CH₃), 3.39 (ddd, $J = 8.8, 6.7, 2.2$ Hz, 1H, 3 $\alpha\alpha$ -H), 3.08 (ddq, $J = 6.6, 6.6, 2.4$ Hz, 1H, 5 α -H), 2.62 (ddd, $J = 14.1, 2.1, 2.1$ Hz, 1H, 4 β -H), 2.16 (ddd, $J = 14.0, 6.3, 6.3$ Hz, 1H, 4 α -H), 1.19 (d, $J = 6.9$ Hz, 3H, 5 β -CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 179.5, 177.3, 132.6, 132.3, 129.1, 128.4, 126.4, 122.0, 109.5, 106.5, 40.0, 38.6, 33.1, 29.0, 25.4, 22.2; IR (film, cm⁻¹) 2960(m), 2956(m), 1775(w), 1711(s), 1595(w), 1499(m), 1453(w), 1380(m), 1348(m), 1293(w), 1270(w), 1175(m), 1157(m), 1062(w), 741(w), 728(w), 717(w), 691(m); HRMS m/z (M + Na⁺) calcd 317.1261, found 317.1253. Anal. Calcd for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.55; H, 6.31; N, 9.51.

2-(4-Methoxyphenyl)-5 β ,6-dimethyl-3 $\alpha\alpha$,4,5 α ,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (134). Method A with vinylpyrrole **115e** and maleimide **4d** with reflux gave **134** (1.207 g, 93%) as a white powder: mp 190-191 °C; maj:min = 37:1; ¹H NMR (300 MHz, CDCl₃, δ) 7.18 (d, *J* = 9.3 Hz, 2H, Ph), 6.95 (d, *J* = 9.3 Hz, 2H, Ph), 6.57 (d, *J* = 3.0 Hz, 1H, 7-H), 6.32 (d, *J* = 2.7 Hz, 1H, 8-H), 4.15 (dd, *J* = 8.7, 0.6 Hz, 1H, 8 $\beta\alpha$ -H), 3.82 (s, 3H, OCH₃), 3.55 (s, 3H, 6-CH₃), 3.37 (ddd, *J* = 8.9, 6.8, 2.3 Hz, 1H, 3 $\alpha\alpha$ -H), 3.07 (dddq, *J* = 6.9, 5.7, 2.1, 0.6 Hz, 1H, 5 α -H), 2.61 (ddd, *J* = 14.1, 2.1, 2.1 Hz, 1H, 4 β -H), 2.15 (ddd, *J* = 14.1, 6.9, 5.7 Hz, 1H, 4 α -H), 1.17 (d, *J* = 6.9 Hz, 3H, 5 β -CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 179.7, 177.5, 159.4, 132.6, 127.7, 125.0, 122.0, 114.5, 109.6, 106.5, 55.6, 39.9, 38.5, 33.1, 29.0, 25.4, 22.2; IR (film, cm⁻¹) 2964(m), 1777(w), 1709(s), 1610(w), 1513(s), 1386(m), 1299(w), 1250(m), 1196(m), 1030(w); HRMS *m/z* (M + Na⁺) calcd 347.1367, found 347.1367. Anal. Calcd for C₁₉H₂₀N₂O₃: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.20; H, 6.37; N, 8.44.

2-Dimethylamino-4-methyl-3 $\alpha\alpha$,4,5,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (135). Method A with vinylpyrrole **115b** and maleimide **4a** with reflux gave **135** (564 mg, 57%) as a brown powder: mp 117-118 °C; maj:min = 1.4:1.0; ¹H NMR (300 MHz, CDCl₃, δ) 7.94 (bs, 1H, 6-H), 6.66-6.69 (m, 1H, 7-H), 6.35-6.66 (m, 1H, 8-H), 3.83-3.87 (m, 1H, 8 $\beta\alpha$ -H), 3.12 (ddd, *J* = 7.8, 4.4, 0.9 Hz, 1H, 3 $\alpha\alpha$ min-H), 2.83-2.88 (m, 1H, 3 $\alpha\alpha$ maj-H), 2.85 (s, overlapped by 3 $\alpha\alpha$ maj-H, 6H, N(CH₃)₂maj), 2.84 (s, overlapped by 3 $\alpha\alpha$ maj-H, 6H, N(CH₃)₂min), 2.32-2.78 (m, 3H, 4-H and 5-H x 2), 1.34 (d, *J* = 6.9 Hz, 3H, 4 β min-CH₃), 1.56 (d, *J* = 6.9 Hz, 3H, 4 α maj-CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 177.2, 176.6, 125.7, 117.2, 109.0, 107.5, 45.1, 44.0, 37.9, 28.2, 27.4, 19.5; IR (film, cm⁻¹) 3321(bm), 2960(m), 1776(w), 1710(s), 1448(w), 1367(m),

1199(m), 1145(m), 1063(w), 719(w); HRMS m/z ($M + Na^+$) calcd 270.1214, found 270.1217. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.40; H, 7.10; N, 16.88.

4-Methyl-2-phenyl-3 α ,4,5,8 β -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (136). Method A with vinylpyrrole **115b** and maleimide **4b** with reflux gave **136** (1.043 g, 93%) as a cream-colored powder: mp 208-209 °C; maj:min = 2.0:1.0; 1H NMR (300 MHz, $CDCl_3$, δ) 7.90 (bs, 1H, 6-H), 7.21-7.46 (m, 5H, Ph), 6.68-6.71 (m, 1H, 7-H), 6.39-6.41 (m, 1H, 8-H), 4.11 (d, $J = 7.8$ Hz, 1H, 8 β amin-H), 4.10 (d, overlapped by 8 β amin-H, $J = 7.5$ Hz, 1H, 8 β maj-H), 3.38 (dd, $J = 7.7, 4.1$ Hz, 1H, 3 α amin-H), 3.14 (ddd, $J = 8.0, 5.0, 0.9$ Hz, 1H, 3 α maj-H), 2.39-2.86 (m, 3H, 4-H and 5-H x 2), 1.47 (d, $J = 6.9$ Hz, 3H, 4 β min- CH_3), 1.21 (d, $J = 6.9$ Hz, 3H, 4 α maj- CH_3); ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 178.3, 177.5, 133.0, 129.4, 128.6, 127.4, 125.8, 117.2, 109.0, 106.8, 46.7, 41.3, 28.6, 27.5, 19.9; IR (film, cm^{-1}) 3367(bs), 3050(m), 2990(m), 2900(m), 1776(w), 1693(s), 1591(w), 1495(w), 1453(w), 1386(m), 1177(m), 1164(m), 1065(w), 786(w), 769(w), 741(w); HRMS m/z ($M + Na^+$) calcd 303.1105, found 303.1103. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.61; H, 5.59; N, 9.96.

2-(4-Methoxyphenyl)-4-methyl-3 α ,4,5,8 β -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (137). Method A with vinylpyrrole **115b** and maleimide **4d** with reflux gave **137** (1.117 g, 90%) as a cream-colored powder: mp 163-164 °C; maj:min = 1.3:1.0; 1H NMR (300 MHz, $CDCl_3$, δ) 7.91 (bs, 1H, 6-H), 7.10-7.19 (m, 4H, Ph), 6.68-6.71 (m, 1H, 7-H), 6.38-6.41 (m, 1H, 8-H), 4.05-4.11 (m, 1H, 8 β α -H), 3.82 (s, 3H, OCH_3), 3.36 (ddd, $J = 7.5, 4.2, 0.6$ Hz, 1H, 3 α amin-H), 3.11 (ddd, $J = 8.0, 4.5, 0.9$ Hz, 1H, 3 α maj-H), 2.37-2.86 (m, 3H, 4-H and 5-H x 2), 1.45 (d, $J = 6.9$ Hz, 1H, 4 β min-

CH₃), 1.21 (d, $J = 7.2$ Hz, 1H, 4 α maj-CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 178.1, 177.5, 159.3, 127.7, 125.7, 124.7, 117.3, 114.4, 109.3, 107.5, 55.6, 46.8, 39.4, 28.0, 27.2, 19.6; IR (film, cm⁻¹) 3370(bs), 2930(m), 2870(m), 1767(w), 1703(s), 1609(w), 1513(s), 1442(w), 1389(m), 1300(w), 1251(m), 1192(m), 1166(m), 1028(w), 721(w); HRMS m/z (M + Na⁺) calcd 333.1210, found 333.1216. Anal. Calcd for C₁₈H₁₈N₂O₃: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.45; H, 6.00; N, 8.83.

2-Dimethylamino-4,6-dimethyl-3 α ,4,5,8 β a-tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (138). Method A with vinylpyrrole **115f** and maleimide **4a** with reflux gave **138** (700 mg, 67%) as a cream-colored powder: mp 85-86 °C; maj:min = 1.2:1.0; ¹H NMR (300 MHz, CDCl₃, δ) 6.55 (d, $J = 2.7$ Hz, 1H, 7min-H), 6.52 (d, $J = 2.7$ Hz, 1H, 7maj-H), 6.28 (d, $J = 2.7$ Hz, 1H, 8min-H), 6.26 (d, $J = 2.7$ Hz, 1H, 8maj-H), 3.85 (ddd, $J = 7.5, 1.4, 1.4$ Hz, 1H, 8 β maj-H), 3.80-3.84 (m, overlapped by 8 β maj-H, 1H, 8 β amin-H), 3.09 (ddd, $J = 7.6, 4.1, 0.6$ Hz, 1H, 3 α maj-H), 2.81-2.86 (m, 1H, 3 α amin-H), 2.85 (s, overlapped by 3 α amin-H, 6H, N(CH₃)₂min), 2.83 (s, overlapped by 3 α amin-H, 6H, N(CH₃)₂maj), 2.27-2.70 (m, 3H, 4-H and 5-H x 2), 1.40 (d, $J = 6.6$ Hz, 3H, 4 β maj-CH₃), 1.18 (d, $J = 6.6$ Hz, 4 α maj-CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 176.8, 176.5, 128.0, 121.4, 110.2, 106.3, 44.0, 43.5, 39.9, 33.1, 29.9, 26.5, 18.2; IR (film, cm⁻¹) 2956(m), 2893(m), 1776(m), 1713(s), 1500(w), 1448(m), 1365(m), 1196(m), 1181(m), 1144(m), 706(w), 662(w); HRMS m/z (M + Na⁺) calcd 284.1370, found 284.1370. Anal. Calcd for C₁₄H₁₉N₃O₂: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.30; H, 7.51; N, 16.11.

4,6-Dimethyl-2-phenyl-3 α ,4,5,8 β a-tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (139). Method A with vinylpyrrole **115f** and maleimide **4b** with reflux gave **139**

(1.048 g, 89%) as a light-brown powder: mp 178-179 °C; maj:min = 2.4:1.0; ¹H NMR (300 MHz, CDCl₃, δ) 7.20-7.46 (m, 5H, Ph), 6.57 (d, *J* = 2.7 Hz, 1H, 7min-H), 6.55 (d, *J* = 2.7 Hz, 1H, 7maj-H), 6.32 (d, *J* = 2.7 Hz, 1H, 8min-H), 6.30 (d, *J* = 2.7 Hz, 1H, 8maj-H), 4.07-4.13 (m, 1H, 8bα-H), 3.51 (s, 3H, 6-CH₃), 3.36 (ddd, *J* = 7.4, 3.8, 1.0 Hz, 1H, 3αmaj-H), 3.12 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H, 3αmin-H), 2.32-2.83 (m, 3H, 4-H and 5-H x 2), 1.52 (d, *J* = 6.9 Hz, 3H, 4αmaj-CH₃), 1.23 (d, *J* = 6.9 Hz, 3H, 4βmin-CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 177.3, 177.0, 132.1, 129.0, 128.4, 128.2, 126.4, 121.6, 110.7, 106.4, 45.5, 42.0, 33.2, 30.0, 26.4, 18.7; IR (film, cm⁻¹) 3060(m), 3030(m), 2929(m), 1775(w), 1710(s), 1597(w), 1498(m), 1453(w), 1377(m), 1174(m), 1142(m), 691(w); HRMS *m/z* (M + Na⁺) calcd 317.1261, found 317.1268. Anal. Calcd for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.51; H, 5.98; N, 9.54.

2-(4-Methoxyphenyl)-4,6-dimethyl-3α,4,5,8bα-tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (140). Method A with vinylpyrrole **115f** and maleimide **4d** with reflux gave **140** (1.090 g, 84%) as a light-brown powder: mp 126-127 °C; maj:min = 2.4:1.0; ¹H NMR (300 MHz, CDCl₃, δ) 7.10-7.19 (m, 2H, Ph), 6.90-7.00 (m, 2H, Ph), 6.57 (d, *J* = 2.7 Hz, 1H, 7min-H), 6.55 (d, *J* = 3.0, 1H, 7maj-H), 6.32 (d, *J* = 3.0 Hz, 1H, 8min-H), 6.30 (d, *J* = 3.0 Hz, 1H, 8maj-H), 4.05-4.10 (m, 1H, 8bα-H), 3.82 (s, 3H, OCH₃), 3.51 (s, 3H 6-CH₃), 3.33 (ddd, *J* = 7.6, 3.8, 1.1 Hz, 1H, 3αmaj-H), 3.09 (ddd, *J* = 7.9, 4.6, 0.8, 1H, 3αmin-H), 2.32-2.81 (m, 3H, 4-H and 5-H x 2), 1.51 (d, *J* = 6.9 Hz, 3H, 4αmaj-CH₃), 1.22 (d, *J* = 7.2 Hz, 1H, 4βmin-CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 177.6, 177.3, 159.2, 128.4, 127.7, 124.8, 121.5, 114.3, 110.8, 106.4, 55.6, 45.4, 41.8, 33.2, 30.0, 26.5, 18.6; IR (film, cm⁻¹) 2950(m), 2931(m), 2839(m), 1770(w), 1708(s), 1610(w), 1513(s), 1442(w), 1384(m), 1300(w), 1250(m), 1168(m), 1143(w), 1031(w),

704(w); HRMS m/z ($M + Na^+$) calcd 347.1367, found 347.1362. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.51; H, 6.40; N, 8.79.

4 α -Ethyl-2-phenyl-3 α ,4 β ,5,8 β -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (141). Method B with vinylpyrrole **117a** and maleimide **4b** gave **141** (424 mg, 36%) as a white powder: mp 203-204 °C; 1H NMR (500 MHz, $CDCl_3$, δ) 7.93 (bs, 1H, 6-H), 7.40-7.44 (m, 2H, Ph), 7.32-7.36 (m, 1H, Ph), 7.22-7.27 (m, 2H, Ph), 6.66 (dd, $J = 2.8, 2.8$ Hz, 1H, 7-H), 6.35 (dd, $J = 2.5, 2.5$ Hz, 1H, 8-H), 4.05 (ddd, $J = 7.5, 1.4, 1.4$ Hz, 1H, 8 β -H), 3.28 (ddd, $J = 7.5, 4.0, 0.9$ Hz, 1H, 3 α -H), 2.77 (ddd, $J = 15.8, 5.3, 1.7$ Hz, 1H, 5 β -H), 2.61 (m, 1H, 4 β -H), 2.51 (dd, $J = 15.8, 2.5$ Hz, 1H, 5 α -H, see 3 α -H and 8 β -H), 1.56 (ddq, $J = 14.1, 8.0, 7.3$ Hz, 1H, 4 α - CH_2CH_3), 1.44 (ddq, $J = 14.4, 7.5, 7.3$ Hz, 1H, 4 α - CH_2CH_3), 1.00 (dd, $J = 7.3, 7.3$ Hz, 3H, 4 α - CH_2CH_3); 1H NMR (300 MHz, $DMSO-d_6$, δ) 10.57 (bs, 1H, 6-H), 7.35-7.48 (m, 3H, Ph), 7.17-7.18 (m, 2H, Ph), 6.59 (dd, $J = 2.6, 2.6$ Hz, 1H, 7-H), 6.02 (dd, $J = 2.6, 2.6$ Hz, 1H, 8-H), 3.98 (d, $J = 7.8$ Hz, 1H, 8 β -H), 3.41 (ddd, $J = 8.1, 4.2, 0.9$ Hz, 1H, 3 α -H), 2.60 (dd, $J = 15.9, 5.1$ Hz, 1H, 5 β -H), 2.45 (dd, $J = 15.6, 3.6$ Hz, 1H, 5 α -H), 2.32-2.40 (m, 1H, 4 β -H), 1.47 (ddq, $J = 14.2, 7.5, 6.8$ Hz, 1H, 4 α - CH_2CH_3), 1.32 (ddq, $J = 14.3, 7.7, 7.5$ Hz, 1H, 4 α - CH_2CH_3), 0.93 (dd, $J = 7.5, 7.5$ Hz, 3H, 4 α - CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.1, 177.3, 132.1, 129.0, 128.3, 126.4, 125.6, 117.2, 109.6, 107.6, 45.2, 39.3, 33.9, 25.6, 23.8, 12.1; ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 178.6, 177.7, 132.9, 129.4, 128.6, 127.3, 125.5, 117.2, 109.2, 106.7, 44.8, ~40 (obscured by DMSO), 34.4, 25.6, 24.1, 12.3; IR (KBr, cm^{-1}) 3346(bs), 3064(w), 2962(m), 2962(m), 2925(m), 2875(m), 2859(m), 1771(m), 1699(s), 1599(w), 1499(m), 1459(w), 1390(m), 1308(w), 1287(w), 1187(s), 1150(m), 1083(w), 1065(w), 743(m), 731(m), 689(m); HRMS m/z ($M + Na^+$)

calcd 317.1261, found 317.1263. Anal. Calcd for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.60; H, 6.08; N, 9.71.

4 α -Ethyl-2-(4-ethylphenyl)-3 $\alpha\alpha$,4 β ,5,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (142). Method A with vinylpyrrole **117a** and maleimide **4l** gave **142** (903 mg, 70%), method B with vinylpyrrole **117a** and maleimide **4l** gave **142** (529 mg, 41%), as a light orange powder: mp 247-248 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.93 (bs, 1H, 6-H), 7.25 (d, *J* = 8.1 Hz, 2H, Ph), 7.14 (d, *J* = 8.4 Hz, 2H, Ph), 6.67 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.36 (dd, *J* = 2.7, 2.7, 1H, 8-H), 4.05 (ddd, *J* = 7.8, 1.2, 1.2 Hz, 1H, 8 $\beta\alpha$ -H), 3.28 (ddd, *J* = 7.8, 3.9, 0.9 Hz, 1H, 3 $\alpha\alpha$ -H), 2.78 (ddd, *J* = 15.3, 5.4, 0.9 Hz, 1H, 5 β -H), 2.66 (q, *J* = 7.6 Hz, 2H, PhCH₂CH₃), 2.58-2.64 (m, overlapped by PhCH₂CH₃, 1H, 4 β -H), 2.52 (dd, *J* = 15.6, 3.0 Hz, 1H, 5 α -H, see 3 $\alpha\alpha$ -H and 8 $\beta\alpha$ -H), 1.56 (ddq, *J* = 13.8, 7.5, 6.9 Hz, 1H, 4 α -CH₂CH₃), 1.44 (ddq, *J* = 14.3, 7.4, 7.2 Hz, 1H, 4 α -CH₂CH₃), 1.23 (t, *J* = 7.7 Hz, 3H, PhCH₂CH₃), 1.00 (dd, *J* = 7.7 Hz, 3H, 4 α -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 178.3, 177.5, 144.6, 129.6, 128.5, 126.3, 125.6, 117.1, 109.7, 107.6, 45.2, 39.3, 34.0, 28.6, 25.6, 23.8, 15.5, 12.1; IR (KBr, cm⁻¹) 3342(bs), 2960(m), 2929(w), 2872(w), 1768(m), 1697(s), 1514(m), 1461(w), 1444(w), 1392(m), 1306(w), 1289(w), 1190(s), 1151(m), 834(w), 772(m), 723(m), 702(m); HRMS *m/z* (M + Na⁺) calcd 345.1574, found 345.1575. Anal. Calcd for C₂₀H₂₂N₂O₂: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.48; H, 6.96; N, 8.68.

4-(4 α -Ethyl-1,3-dioxo-3 $\alpha\alpha$,4 β ,5,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indol-2-yl)phenyl acetate (143). Method B with vinylpyrrole **117a** and maleimide **4n** gave **143** (437 mg, 31%) as a cream-colored powder: mp 218-219 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.93 (bs, 1H, 6-H), 7.29 (d, *J* = 9.3 Hz, 2H, Ph), 7.16 (d, *J* = 9.0 Hz, 2H, Ph),

6.67 (dd, $J = 2.7, 2.7$ Hz, 1H, 7-H), 6.35 (dd, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.06 (ddd, $J = 7.8, 1.4, 1.4$ Hz, 1H, 8b α -H), 3.29 (ddd, $J = 7.7, 3.9, 0.9$ Hz, 1H, 3a α -H), 2.78 (ddd, $J = 14.4, 5.4, 1.2$ Hz, 1H, 5 β -H), 2.58-2.65 (m, 1H, 4 β -H), 2.52 (dd, $J = 15.8, 3.2$ Hz, 1H, 5 α -H, see 3a α -H and 8b α -H), 2.29 (s, 3H, Ac), 1.56 (ddq, $J = 14.4, 7.5, 7.4$ Hz, 1H, 4 α -CH₂CH₃), 1.47 (ddq, $J = 14.7, 7.4, 7.2$ Hz, 1H, 4 α -CH₂CH₃), 1.01 (dd, $J = 7.4, 7.4$ Hz, 3H, 4 α -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 177.9, 177.1, 169.2, 150.1, 129.5, 127.4, 125.6, 122.2, 117.2, 109.5, 107.5, 45.1, 39.3, 33.9, 25.6, 23.8, 21.2, 12.1; IR (KBr, cm⁻¹) 3359(bs), 3114(w), 3081(w), 2964(m), 2926(m), 2876(m), 2855(w), 1767(m), 1699(s), 1601(w), 1510(m), 1464(w), 1441(w), 1392(s), 1372(m), 1199(s), 1150(m), 1105(w), 1084(w), 1016(w), 938(w), 911(w), 849(w), 773(m), 719(m), 706(m); HRMS m/z (M + Na⁺) calcd 375.1316, found 375.1317. Anal. Calcd for C₂₀H₂₀N₂O₄: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.89; H, 5.53; N, 7.90.

4 α -Ethyl-2-(4-hydroxyphenyl)-3a α ,4 β ,5,8b α -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (144). Method B with vinylpyrrole **117a** and maleimide **4o** gave **144** (670 mg, 54%) as a cream-colored powder: mp 238-239 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 10.54 (bs, 1H, 6-H), 9.70 (s, 1H, OH), 6.92 (d, $J = 9.0$ Hz, 2H, Ph), 6.78 (d, $J = 8.7$ Hz, 2H, Ph), 6.57 (dd, $J = 2.6, 2.6$ Hz, 1H, 7-H), 6.01 (dd, $J = 2.4, 2.4$ Hz, 1H, 8-H), 3.93 (d, $J = 7.8$ Hz, 1H, 8b α -H), 3.35 (dd, overlapped by H₂O, $J = 4.2, 7.8$ Hz, 1H, 3a α -H), 2.57 (dd, $J = 16.2, 4.8$ Hz, 1H, 5 β -H), 2.44 (dd, $J = 15.6, 3.3$ Hz, 1H, 5 α -H), 2.33-2.39 (m, 1H, 4 β -H), 1.45 (ddq, $J = 13.8, 7.5, 7.2$ Hz, 1H, 4 α -CH₂CH₃), 1.27 (ddq, $J = 14.1, 7.7, 7.5$ Hz, 1H, 4 α -CH₂CH₃), 0.91 (dd, $J = 7.5, 7.5$ Hz, 3H, 4 α -CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 178.9, 178.0, 157.6, 128.6, 125.5, 124.0, 117.1, 115.8, 109.4, 106.7, 44.6, ~40 (obscured by DMSO), 34.4, 25.6, 24.1, 12.3; IR

(KBr, cm^{-1}) 3467(m), 3374(bm), 2965(w), 2927(w), 2877(w), 1767(w), 1696(s), 1601(w), 1518(m), 1447(w), 1398(m), 1274(w), 1198(m), 1165(m), 1105(w), 1065(w), 1021(w), 837(w), 776(w), 725(m), 708(m); HRMS m/z ($M + \text{Na}^+$) calcd 333.1210, found 333.1205. Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.49; H, 6.05; N, 9.20.

2-(4-Chlorophenyl)-4 α -ethyl-3 $\alpha\alpha$,4 β ,5,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (145). Method B with vinylpyrrole **117a** and maleimide **4i** gave **145** (421 mg, 32%) as a white powder: mp 197-198 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.88 (bs, 1H, 6-H), 7.40 (d, $J = 9.0$ Hz, 2H, Ph), 7.22 (d, $J = 9.0$ Hz, 2H, Ph), 6.69 (dd, $J = 2.9, 2.9$ Hz, 1H, 7-H), 6.36 (d, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.06 (ddd, $J = 8.1, 1.4, 1.4$ Hz, 1H, 8 $\beta\alpha$ -H), 3.29 (ddd, $J = 7.8, 3.6, 1.0$ Hz, 1H, 3 $\alpha\alpha$ -H), 2.78 (ddd, $J = 15.3, 5.4, 1.5$ Hz, 1H, 5 β -H), 2.58-2.65 (m, 1H, 4 β -H), 2.53 (dd, $J = 16.0, 2.6$ Hz, 1H, 5 α -H, see 3 $\alpha\alpha$ -H and 8 $\beta\alpha$ -H), 1.54 (ddq, overlapped by H_2O , $J = 14.5, 1.2, 7.2$ Hz, 1H, 4 α - CH_2CH_3), 1.44 (ddq, $J = 14.5, 7.2, 7.2$ Hz, 1H, 4 α - CH_2CH_3), 1.28 (dd, $J = 7.2, 7.2$ Hz, 3H, 4 α - CH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3 , δ) 177.8, 177.0, 134.0, 130.6, 129.2, 127.6, 125.6, 117.3, 109.4, 107.6, 45.1, 39.3, 33.9, 25.6, 23.8, 12.1; IR (KBr, cm^{-1}) 3370(s), 3342(s), 3095(w), 2969(m), 2925(m), 2877(m), 2856(m), 1769(m), 1698(s), 1600(w), 1495(m), 1463(w), 1445(w), 1390(m), 1358(m), 1308(w), 1274(w), 1183(s), 1149(m), 1090(m), 1066(w), 1017(w), 768(m), 715(m); HRMS m/z ($M + \text{Na}^+$) calcd 351.0872, found 351.0871. Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 65.58; H, 5.09; N, 8.69.

2-(4-Bromophenyl)-4 α -ethyl-3 $\alpha\alpha$,4 β ,5,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (146). Method B with vinylpyrrole **117a** and maleimide **4h** gave

146 (523 mg, 35%) as a cream-colored powder: mp 193-194 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.88 (bs, 1H, 6-H), 7.55 (d, *J* = 8.7 Hz, 2H, Ph), 7.16 (d, *J* = 8.7 Hz, 2H, Ph), 6.69 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.35 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.06 (ddd, *J* = 7.5, 1.2, 1.2 Hz, 1H, 8β-*H*), 3.29 (ddd, *J* = 7.8, 3.6, 0.9 Hz, 1H, 3α-*H*), 2.78 (ddd, *J* = 15.6, 5.4, 1.8 Hz, 1H, 5β-*H*), 2.59-2.65 (m, 1H, 4β-*H*), 2.53 (dd, *J* = 16.5, 2.1 Hz, 1H, 5α-*H*, see 3α-*H* and 8β-*H*), 1.53 (ddq, overlapped by H₂O, *J* = 14.0, 7.5, 7.5 Hz, 1H, 4α-CH₂CH₃), 1.44 (ddq, *J* = 14.0, 7.5, 7.5 Hz, 1H, 4α-CH₂CH₃), 1.01 (dd, *J* = 7.4, 7.4 Hz, 3H, 4α-CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 177.8, 176.9, 132.2, 131.1, 127.9, 125.6, 122.0, 117.3, 109.4, 107.6, 45.2, 39.3, 33.9, 25.6, 23.8, 12.1; IR (KBr, cm⁻¹) 3364(s), 3341(s), 3092(w), 2963(m), 2924(m), 2875(m), 2860(m), 1771(w), 1699(s), 1599(w), 1492(m), 1463(w), 1444(w), 1389(m), 1358(w), 1307(w), 1274(w), 1184(s), 1148(m), 1069(m), 1015(m), 935(w), 829(w), 783(w), 767(m), 714(m); HRMS *m/z* (M + Na⁺) calcd 395.0366, found 395.0363. Anal. Calcd for C₁₈H₁₇BrN₂O₂: C, 57.92; H, 4.59; N, 7.51. Found: C, 57.71; H, 4.54; N, 7.59.

4α-Ethyl-2-(4-nitrophenyl)-3α,4β,5,8β-tetrahydro-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (147). Method B with vinylpyrrole **117a** and maleimide **4f** gave **147** (611 mg, 45%) as a cream-colored powder: mp 145-146 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.29 (d, *J* = 9.0 Hz, 2H, Ph), 7.92 (bs, 1H, 6-H), 7.57 (d, *J* = 9.3 Hz, 2H, Ph), 6.71 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 6.35 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.11 (ddd, *J* = 7.9, 1.4, 1.4 Hz, 1H, 8β-*H*), 3.34 (ddd, *J* = 7.7, 3.8, 0.9 Hz, 1H, 3α-*H*), 2.80 (ddd, *J* = 15.6, 5.3, 1.7 Hz, 1H, 5β-*H*), 2.61-2.70 (m, 1H, 4β-*H*), 2.56 (dd, *J* = 15.8, 2.9 Hz, 1H, 5α-*H*, see 3α-*H* and 8β-*H*), 1.39-1.63 (m, 2H, 4-CH₂CH₃), 1.02 (dd, *J* = 7.2, 7.2 Hz, 3H, 4-CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 177.3, 176.4, 146.7, 137.8, 126.7, 125.6,

124.3, 117.5, 109.1, 107.5, 45.2, 39.3, 33.8, 25.5, 23.8, 12.1; IR (KBr, cm^{-1}) 3375(bm), 3115(w), 2960(m), 2929(w), 2873(w), 1771(w), 1704(s), 1611(w), 1598(w), 1519(m), 1499(m), 1460(w), 1384(m), 1348(m), 1297(w), 1193(m), 1170(m), 1147(m), 1105(w), 1067(w), 1019(w), 851(w), 782(w), 743(m), 717(m); HRMS m/z ($M + \text{Na}^+$) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$: 362.1112, found 362.1114.

4 α -*n*-Pentyl-2-phenyl-3 $\alpha\alpha$,4 β ,5,8 $\beta\alpha$ -tetrahydro-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (148). Method B with vinylpyrrole **117b** and maleimide **4b** gave **148** (404 mg, 30%) as a light-brown powder: mp 208-209 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.90 (bs, 1H, 6-H), 7.40-7.46 (m, 2H, Ph), 7.32-7.37 (m, 1H, Ph), 7.22-7.27 (m, 2H, Ph), 6.68 (dd, $J = 2.7, 2.7$ Hz, 1H, 7-H), 6.37 (dd, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.07 (d, $J = 7.8$ Hz, 1H, 8 $\beta\alpha$ -H), 3.28 (ddd, $J = 8.0, 3.0, 0.9$ Hz, 1H, 3 $\alpha\alpha$ -H), 2.79 (ddd, $J = 15.5, 5.2, 1.1$ Hz, 1H, 5 β -H), 2.67-2.75 (m, 1H, 4 β -H), 2.50 (dd, $J = 15.3, 2.0$ Hz, 1H, 5 α -H, see 3 $\alpha\alpha$ -H), 1.25-1.52 (m, 8H, 4 α -(CH_2) $_4$ CH $_3$), 0.90 (t, $J = 6.9$ Hz, 3H, 4 α -(CH_2) $_4$ CH $_3$); ^{13}C NMR (75 MHz, CDCl_3 , δ) 178.0, 177.3, 132.1, 129.0, 128.3, 126.4, 125.6, 117.2, 109.6, 107.6, 45.4, 39.3, 32.7, 32.2, 31.8, 27.3, 24.3, 22.7, 14.1; IR (KBr, cm^{-1}) 3361(bs), 3066(w), 2953(m), 2926(s), 2855(m), 1766(w), 1708(s), 1598(w), 1497(m), 1457(w), 1380(s), 1291(w), 1187(m), 1150(w), 1090(w), 1072(w), 742(w); HRMS m/z ($M + \text{Na}^+$) calcd 359.1731, found 359.1734. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.72; H, 6.93; N, 8.22.

4 β -Ethyl-2-phenyl-3 $\alpha\alpha$,4 α ,5,8 $\beta\alpha$ -tetrahydro-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (149). Method B with vinylpyrrole **118** and maleimide **4b** gave **149** (483 mg, 41%) as a cream-colored powder: mp 182-183 °C; maj:min = 12:1; ^1H NMR (300 MHz, CDCl_3 , δ) 7.89 (bs, 1H, 6-H), 7.41 (dd, $J = 7.8, 7.8$ Hz, 2H, Ph), 7.32-7.38 (m, 1H, Ph),

7.20 (d, $J = 7.5$ Hz, 2H, Ph), 6.67 (dd, $J = 2.5, 2.5$ Hz, 1H, 7-H), 6.36 (dd, $J = 2.8, 2.8$ Hz, 1H, 8-H), 4.11 (ddd, $J = 7.5, 1.3, 1.3$ Hz, 1H, 8 β -H), 3.46 (ddd, $J = 7.3, 3.8, 0.9$ Hz, 1H, 3 α -H), 2.74 (dd, $J = 15.8, 4.3$ Hz, 1H, 5 α -H, see 3 α -H and 8 β -H), 2.51 (ddd, $J = 15.0, 11.0, 1.5$ Hz, 1H, 5 β -H), 2.08-2.15 (m, 1H, 4 α -H), 2.05 (ddq, overlapped by 4 α -H, $J = 13.1, 7.5, 7.5$ Hz, 1H, 4 β -CH₂CH₃), 1.95 (ddq, $J = 13.1, 7.5, 7.5$ Hz, 1H, 4 β -CH₂CH₃), 1.07 (dd, $J = 7.5, 7.5$ Hz, 3H, 4 β -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 177.25, 177.20, 132.0, 129.0, 128.3, 127.5, 126.5, 117.4, 111.0, 107.4, 44.1, 42.0, 37.3, 25.5, 25.2, 12.6; IR (KBr, cm⁻¹) 3369(bs), 3112(w), 3053(m), 2958(m), 2925(m), 2895(m), 2871(m), 2840(w), 1768(m), 1706(w), 1595(m), 1553(w), 1497(m), 1455(m), 1384(s), 1316(w), 1294(m), 1268(w), 1194(s), 1153(m), 1137(m), 1089(w), 1059(m), 1026(w), 994(w), 910(w), 817(w), 719(s); HRMS m/z (M + Na⁺) calcd 317.1261, found 317.1262. Anal. Calcd for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.21; H, 6.13; N, 9.72.

2-Benzyl-5 β -(1-benzyl-2,5-dioxopyrrolidin-3-yl)-3 $\alpha\alpha$,4,5 α ,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (163). Method A with vinylpyrrole **116** and maleimide **4k** gave **163** (421 mg, 45%) as a light-brown powder: mp 212-213 °C; ¹H NMR (300 MHz, CDCl₃, δ) 10.58 (bs, 1H, 6-H), 7.32-7.42 (m, 5H, Ph), 7.18-7.26 (m, 5H, Ph), 6.76 (dd, $J = 2.6, 2.6$ Hz, 1H, 7-H), 6.34 (dd, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.74 (AA' d, $J = 14.1$ Hz, 1H, Bn), 4.69 (AA' d, $J = 13.8$ Hz, 1H, Bn), 4.59 (AA' d, $J = 14.4$ Hz, 1H, Bn), 4.52 (AA' d, $J = 14.4$ Hz, 1H, Bn), 4.02 (dd, $J = 7.8, 1.2$ Hz, 1H, 8 $\beta\alpha$ -H), 3.32 (ddd, $J = 7.9, 4.7, 3.5$ Hz, 1H, 3 $\alpha\alpha$ -H), 3.01 (ddd, $J = 9.4, 9.4, 6.1$ Hz, 1H, 1'-H), 2.93 (dd, overlapped by 1'-H, $J = 17.3, 9.6$ Hz, 1H, 2'-H), 2.83-2.95 (m, overlapped by 2'-H, 1H, 5 α -H), 2.77 (dd, overlapped by 5 α -H, $J = 17.0, 5.6$ Hz, 1H, 2'-H), 2.54 (ddd, $J =$

13.3, 3.8, 3.8 Hz, 1H, 4 β -H), 1.58 (ddd, J = 13.3, 11.5, 4.9 Hz, 1H, 4 α -H); ^{13}C NMR (75 MHz, CDCl_3 , δ) 180.0, 178.2, 177.7, 174.7, 135.8, 135.3, 129.0, 128.9, 128.7, 128.4, 128.3, 127.9, 127.3, 118.3, 111.8, 107.2, 44.6, 42.9, 42.3, 40.1, 40.0, 33.0, 31.5, 26.6; IR (KBr, cm^{-1}) 3446(w), 3329(bs), 3062(w), 3033(w), 2924(m), 2854(w), 1772(m), 1702(s), 1586(w), 1495(w), 1453(w), 1433(m), 1398(s), 1341(m), 1314(m), 1292(w), 1167(s), 1119(w), 1083(w), 714(m), 696(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 490.1738, found 490.1745. Anal. Calcd for $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O}_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 71.97; H, 5.44; N, 8.70.

2-(4-Ethylphenyl)-5 β -(1-(4-ethylphenyl)-2,5-dioxopyrrolidin-3-yl)-3 $\alpha\alpha$,4,5 α ,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (164). Method A with vinylpyrrole **116** and maleimide **4l** gave **164** (228 mg, 23%) as a light-brown powder: mp 173-174 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3 , δ) 10.52 (bs, 1H, 6-H), 7.35 (d, J = 8.4 Hz, 2H, Ph), 7.25 (d, J = 8.4 Hz, 2H, Ph), 7.20 (d, J = 8.4 Hz, 2H, Ph), 7.12 (d, J = 8.4 Hz, 2H, Ph), 6.75 (dd, J = 2.9, 2.9 Hz, 1H, 7-H), 6.39 (dd, J = 2.7, 2.7 Hz, 1H, 8-H), 4.19 (dd, J = 8.1, 1.2 Hz, 1H, 8 $\beta\alpha$ -H), 3.57 (ddd, J = 8.0, 4.7, 3.4 Hz, 1H, 3 $\alpha\alpha$ -H), 3.24 (ddd, J = 9.1, 9.1, 6.2 Hz, 1H, 1'-H), 3.13-3.23 (m, overlapped by 1'-H, 1H, 5 α -H), 3.11 (dd, overlapped by 5 α -H, J = 17.7, 8.7 Hz, 1H, 2'-H), 2.98 (dd, J = 17.7, 6.6 Hz, 1H, 2'-H), 2.73 (ddd, J = 12.9, 3.6, 3.6 Hz, 1H, 4 β -H), 2.72 (q, overlapped by 4 β -H, J = 7.6 Hz, 2H, CH_2CH_3), 2.66 (q, overlapped by CH_2CH_3 , J = 7.7 Hz, 2H, CH_2CH_3), 1.75 (ddd, J = 13.2, 10.8, 4.8 Hz, 1H, 4 α -H), 1.28 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.23 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3 , δ) 179.7, 177.7, 177.1, 174.2, 145.6, 144.8, 129.4, 129.0, 128.9, 128.6, 127.3, 126.4, 126.2, 118.4, 111.8, 107.3, 44.8, 40.4, 40.2, 33.2, 31.6, 28.7, 28.6, 26.6, 15.5, 15.4; IR (KBr, cm^{-1}) 3353(bs), 3122(w), 3103(w),

3038(w), 2964(m), 2930(m), 2872(w), 1777(m), 1711(s), 1580(w), 1514(m), 1485(w), 1459(w), 1440(w), 1390(s), 1294(w), 1282(w), 1179(s), 1117(m), 1064(w), 832(m), 797(w), 768(w), 731(m); HRMS m/z ($M + Na^+$) calcd 518.2051, found 518.2069. Anal. Calcd for $C_{30}H_{29}N_3O_4$: C, 72.71; H, 5.90; N, 8.48. Found: C, 73.00; H, 6.19; N, 8.34.

2-(4-Isopropylphenyl)-5 β -(1-(4-isopropylphenyl)-2,5-dioxopyrrolidin-3-yl)-3 $\alpha\alpha$,4,5 α ,8 $\beta\alpha$ -tetrahydro-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (165). Method A with vinylpyrrole **116** and maleimide **4m** gave **165** (304 mg, 29%) as a light-brown powder: mp 148-150 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 10.45 (bs, 1H, 6-H), 7.37 (d, $J = 8.4$ Hz, 2H, Ph), 7.27 (d, $J = 8.7$ Hz, 2H, Ph), 7.20 (d, $J = 8.4$ Hz, 2H, Ph), 7.13 (d, $J = 8.4$ Hz, 2H, Ph), 6.70 (dd, $J = 2.4, 2.4$ Hz, 1H, 7-H), 6.38 (dd, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.17 (d, $J = 7.8$ Hz, 1H, 8 $\beta\alpha$), 3.56 (ddd, $J = 7.7, 4.0, 4.0$ Hz, 1H, 3 $\alpha\alpha$), 3.24 (ddd, $J = 8.8, 8.8, 6.1$ Hz, 1H, 1'-H), 2.85-3.25 (m, overlapped by 1'-H, 5H, 2'-H x 2 and 5 α -H and $CH(CH_3)_2$ x 2), 2.69 (ddd, $J = 13.4, 3.8, 3.8$ Hz, 1H, 4 β -H), 1.72 (ddd, $J = 13.0, 10.7, 4.3$ Hz, 1H, 4 α -H), 1.29 (d, $J = 6.9$ Hz, 6H, $CH(CH_3)_2$), 1.24 (d, $J = 6.9$ Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 179.7, 177.8, 177.2, 174.4, 150.1, 149.3, 129.4, 129.0, 127.6, 127.3, 127.2, 126.4, 126.1, 118.4, 111.8, 107.3, 44.6, 40.4, 40.2, 35.04, 34.97, 33.1, 31.5, 26.4, 24.0; IR (KBr, cm^{-1}) 3354(bs), 3039(w), 2960(s), 2928(m), 2871(m), 1779(m), 1708(s), 1574(w), 1514(m), 1461(m), 1385(s), 1281(w), 1168(s), 1114(m), 1059(m), 831(m), 732(m), 693(m), 659(m); HRMS m/z ($M + Na^+$) calcd 546.2364, found 546.2377. Anal. Calcd for $C_{32}H_{33}N_3O_4$: C, 73.40; H, 6.35; N, 8.02. Found: C, 73.18; H, 6.52; N, 8.04.

2-(4-Phenoxyphenyl)-5 β -(1-(4-phenoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-3 $\alpha\alpha$,4,5 α ,8 $\beta\alpha$ -tetrahydro-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (166). Method A

with vinylpyrrole **116** and maleimide **4e** gave **166** (474 mg, 38%) as a cream-colored powder: mp 133-135 °C; ¹H NMR (300 MHz, CDCl₃, δ) 10.51 (bs, 1H, 6-H), 7.33-7.42 (m, 4H, Ph), 7.01-7.26 (m, 14H, Ph), 6.76 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.39 (dd, *J* = 2.6, 2.6 Hz, 1H, 8-H), 4.20 (dd, *J* = 7.8, 1.4 Hz, 1H, 8β_α-H), 3.58 (ddd, *J* = 8.0, 4.7, 3.3 Hz, 1H, 3α_α-H), 3.13-3.26 (m, 1H, 5α-H), 3.25 (ddd, overlapped by 5α-H, *J* = 9.2, 9.2, 6.2 Hz, 1H, 1'-H), 3.14 (dd, overlapped by 5α-H, *J* = 17.7, 8.7 Hz, 1H, 2'-H), 3.00 (dd, *J* = 17.9, 6.5 Hz, 1H, 2'-H), 2.74 (ddd, *J* = 13.3, 4.3, 3.5 Hz, 1H, 4β-H), 1.76 (ddd, *J* = 13.1, 11.0, 4.9 Hz, 1H, 4α-H); ¹³C NMR (75 MHz, CDCl₃, δ) 179.7, 177.7, 177.1, 174.2, 158.2, 157.3, 156.5, 156.2, 130.1, 130.0, 128.0, 127.8, 127.3, 126.6, 125.9, 124.3, 124.0, 119.9, 119.5, 118.8, 118.5, 111.8, 107.4, 44.7, 40.4, 40.2, 33.2, 31.6, 26.5; IR (KBr, cm⁻¹) 3346(bs), 3061(m), 2922(m), 1778(m), 1718(s), 1588(m), 1506(s), 1487(s), 1388(m), 1286(m), 1244(s), 1196(m), 1113(m), 1067(m), 1017(w), 875(m), 845(m), 770(m), 695(m); HRMS *m/z* (M + Na⁺) calcd 646.1949, found 646.1951. Anal. Calcd for C₃₈H₂₉N₃O₆: C, 73.18; H, 4.69; N, 6.74. Found: C, 73.40; H, 4.87; N, 6.61.

2-Benzyl-5α-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-3α,4,5β,8βα-tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (167) and 2-Benzyl-5β-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-3α,4,5α,8βα-tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (163). Method A with vinylpyrrole **116** and maleimide **4k** followed by fractional recrystallizations from CH₂Cl₂/petroleum ether gave **167** (168 mg, 18%) as a light-brown powder, with a maximum purity of **167:163** in a 5:1 molar ratio, mass calculated from ¹H NMR, spectroscopic data for **167** only reported: mp 86-91 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.36-7.41 (m, 4H, Ph), 7.27-7.28 (m, 6H, Ph), 7.02 (bs, 1H, 6-H), 6.24 (dd, *J* = 2.6, 2.6 Hz, 1H, 7-H), 6.15 (dd, *J* = 2.7, 2.7 Hz, 1H, 8-H), 4.79 (AA' d, *J* =

13.8 Hz, 1H, Bn), 4.62 (AA' d, $J = 13.8$ Hz, 1H, Bn), 4.61 (AA' d, overlapped, $J = 14.1$ Hz, 1H, Bn), 4.54 (AA' d, $J = 14.1$ Hz, 1H, Bn), 3.89 (dd, $J = 7.8, 0.6$ Hz, 1H, 8b α -H), 3.63 (dddd, $J = 7.5, 5.4, 3.3, 0.8$ Hz, 1H, 5 β -H), 3.17 (ddd, $J = 8.0, 8.0, 5.6$ Hz, 1H, 3a α -H), 3.13 (ddd, overlapped by 5 β -H, $J = 8.9, 5.8, 3.1$ Hz, 1H, 1'-H), 2.74 (dd, $J = 18.0, 9.3$ Hz, 1H, 2'-H *syn* to 1'-H), 2.26 (ddd, $J = 13.5, 7.8, 5.7$ Hz, 1H, 4 β -H), 2.22 (dd, overlapped by 4 β -H, $J = 18.0, 5.7$ Hz, 1H, 2'-H *anti* to 1'-H), 1.88 (ddd, $J = 13.6, 7.7, 5.8$ Hz, 1H, 4 α -H); IR (KBr, cm⁻¹) 3382(bm), 3063(w), 3033(m), 2922(s), 2853(m), 1773(m), 1702(s), 1585(w), 1495(w), 1455(w), 1432(m), 1397(m), 1341(m), 1314(w), 1166(m), 1083(w), 1065(w), 723(w), 699(m); HRMS m/z ($M + Na^+$) calcd 490.1738, found 490.1739. Anal. Calcd for C₂₈H₂₅N₃O₄: C, 71.93; H, 5.39; N, 8.99. Found: C, 71.87; H, 5.52; N, 8.73.

2-(4-Ethylphenyl)-5 α -(1-(4-ethylphenyl)-2,5-dioxopyrrolidin-3-yl)-3a α ,4,5 β ,8b α -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (168). Method A with vinylpyrrole **116** and maleimide **41** gave **168** (50 mg, 5%) as a cream-colored powder: mp 252-254 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.96 (bs, 1H, 6-H), 7.34 (d, $J = 8.4$ Hz, 2H, Ph), 7.29 (d, $J = 8.7$ Hz, 2H, Ph), 7.16 (d, $J = 8.4$ Hz, 2H, Ph), 7.15 (d, overlapped, $J = 8.4$ Hz, 2H, Ph), 6.71 (dd, $J = 2.7, 2.7$ Hz, 1H, 7-H), 6.48 (dd, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.14 (d, $J = 8.1$ Hz, 1H, 8b α -H), 3.92 (ddd, $J = 5.9, 5.9, 3.3$ Hz, 1H, 5 β -H), 3.40 (ddd, $J = 9.2, 6.8, 3.3$ Hz, 1H, 1'-H), 3.39 (ddd, overlapped by 1'-H, $J = 9.6, 7.9, 5.3$ Hz, 1H, 3a α -H), 2.95 (dd, $J = 17.6, 9.2$ Hz, 1H, 2'-H *syn* to 1'-H), 2.71 (q, $J = 7.7$ Hz, 2H, CH₂CH₃), 2.68 (q, overlapped by CH₂CH₃, $J = 7.5$ Hz, 2H, CH₂CH₃), 2.52 (dd, $J = 17.6, 6.8$ Hz, 1H, 2'-H *anti* to 1'-H), 2.42 (ddd, $J = 13.9, 9.2, 5.9$ Hz, 1H, 4 β -H), 2.21 (ddd, $J = 13.7, 5.7, 5.7$ Hz, 1H, 4 α -H), 1.27 (t, $J = 7.6$ Hz, 3H, CH₂CH₃), 1.25 (t,

overlapped by CH_2CH_3 , $J = 7.6$ Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3 , δ) 179.1, 177.9, 176.1, 174.9, 145.5, 144.9, 129.3, 129.1, 129.0, 128.7, 126.23, 126.18, 124.6, 119.4, 113.5, 108.4, 45.4, 39.8, 38.9, 31.3, 30.3, 28.7, 28.4, 15.5; IR (KBr, cm^{-1}) 3462(w), 3364(bs), 3037(w), 2965(m), 2929(m), 2871(w), 1776(m), 1705(s), 1514(m), 1488(w), 1458(w), 1386(s), 1354(m), 1313(w), 1301(w), 1223(w), 1163(s), 1190(s), 1110(w), 1100(w), 1083(w), 770(m), 720(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 518.2051, found 518.2059. Anal. Calcd for $\text{C}_{30}\text{H}_{29}\text{N}_3\text{O}_4$: C, 72.71; H, 5.90; N, 8.48. Found: C, 72.99; H, 5.93; N, 8.70.

2-(4-Isopropylphenyl)-5 α -(1-(4-isopropylphenyl)-2,5-dioxopyrrolidin-3-yl)-3 $\alpha\alpha$,4,5 β ,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (169). Method A with vinylpyrrole **116** and maleimide **4m** gave **169** (84 mg, 8%) as a cream-colored powder: mp 280-282 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.94 (bs, 1H, 6-H), 7.37 (d, $J = 8.1$ Hz, 2H, Ph), 7.31 (d, $J = 8.4$ Hz, 2H, Ph), 7.17 (d, $J = 8.7$ Hz, 2H, Ph), 7.16 (d, $J = 8.4$ Hz, 2H, Ph), 6.71 (dd, $J = 2.9, 2.9$ Hz, 1H, 7-H), 6.48 (dd, $J = 2.6, 2.6$ Hz, 1H, 8-H), 4.14 (d, $J = 8.4$ Hz, 1H, 8 $\beta\alpha$ -H), 3.93 (ddd, $J = 5.6, 5.6, 3.2$ Hz, 1H, 5 β -H), 3.40 (ddd, $J = 9.2, 6.6, 3.3$ Hz, 1H, 1'-H), 3.40 (ddd, overlapped, $J = 9.3, 8.0, 5.6$ Hz, 1H, 3 α -H), 2.97 (septet, $J = 7.0$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 2.95 (dd, overlapped by $\text{CH}(\text{CH}_3)_2 \times 2$, $J = 17.6, 9.2$ Hz, 1H, 2'-H *syn* to 1'-H), 2.94 (dd, overlapped by $\text{CH}(\text{CH}_3)_2$ and 2'-H, $J = 6.9$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 2.53 (dd, $J = 17.9, 6.8$ Hz, 1H, 2'-H *anti* to 1'-H), 2.43 (ddd, $J = 14.0, 9.0, 5.9$ Hz, 1H, 4 β -H), 2.21 (ddd, $J = 14.0, 5.8, 5.8$ Hz, 1H, 4 α -H), 1.28 (d, $J = 7.2$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.26 (d, overlapped by $\text{CH}(\text{CH}_3)_2$, $J = 7.2$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3 , δ) 179.1, 177.9, 176.1, 175.0, 150.0, 149.5, 129.3, 129.1, 127.6, 127.3, 126.2, 126.1, 124.6, 119.4, 113.5, 108.4, 45.4, 39.8, 38.9,

34.0, 31.3, 30.3, 28.4, 24.0; IR (KBr, cm^{-1}) 3365(bs), 3038(w), 2961(s), 2927(m), 2899(m), 1776(m), 1708(s), 1514(m), 1460(w), 1387(s), 1355(m), 1306(w), 1187(s), 1160(s), 1105(m), 1085(w), 1055(m), 832(m), 727(m); HRMS m/z ($M + \text{Na}^+$) calcd 546.2364, found 546.2373. Anal. Calcd for $\text{C}_{32}\text{H}_{33}\text{N}_3\text{O}_4$: C, 73.40; H, 6.35; N, 8.02. Found: C, 73.22; H, 6.51; N, 7.96.

2-(4-Phenoxyphenyl)-5 α -(1-(4-phenoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-3 $\alpha\alpha$,4,5 β ,8 $\beta\alpha$ -tetrahydro-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (170). Method A with vinylpyrrole **116** and maleimide **4e** gave **170** (100 mg, 8%) as a white powder: mp 267-268 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.94 (bs, 1H, 6-H), 7.34-7.43 (m, 4H, Ph), 7.03-7.24 (m, 14H, Ph), 6.72 (dd, $J = 2.9, 2.9$ Hz, 1H, 7-H), 6.48 (dd, $J = 2.7, 2.7$ Hz, 1H, 8-H), 4.15 (d, $J = 8.1$ Hz, 1H, 8 $\beta\alpha$ -H), 3.93 (ddd, $J = 5.6, 5.6, 3.4$ Hz, 1H, 5 β -H), 3.41 (ddd, $J = 9.0, 6.6, 3.3$ Hz, 1H, 1'-H), 3.41 (ddd, overlapped by 1'-H, $J = 9.1, 7.8, 5.9$ Hz, 1H, 3 $\alpha\alpha$ -H), 2.96 (dd, $J = 17.7, 9.0$ Hz, 1H, 2'-H *syn* to 1'-H), 2.53 (dd, 17.7, 6.6 Hz, 1H, 2'-H *anti* to 1'-H), 2.43 (ddd, $J = 14.2, 8.6, 5.6$ Hz, 1H, 4 β -H), 2.21 (ddd, $J = 14.0, 5.9, 5.9$ Hz, 1H, 4 α -H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$, δ) 179.0, 178.2, 177.2, 176.1, 157.1, 156.60, 156.59, 130.8, 129.4, 128.0, 127.9, 127.2, 124.6, 119.75, 119.69, 118.9, 118.4, 111.5, 107.2, 43.4, ~40 (obscured by DMSO), 38.4, 33.2, 32.7, 28.5; ^{13}C NMR (75 MHz, CDCl_3 , δ) 179.01, 178.95, 177.8, 174.8, 157.6, 154.6, 152.8, 130.1, 130.0, 127.82, 127.78, 126.2, 126.0, 124.6, 124.3, 124.0, 119.8, 119.6, 119.4, 118.8, 113.5, 108.4, 45.4, 39.7, 38.9, 31.3, 30.3, 28.3; IR (KBr, cm^{-1}) 3358(bs), 3053(w), 2994(W), 2950(w), 2915(m), 2856(w), 1770(m), 1711(s), 1589(m), 1506(m), 1489(m), 1456(w), 1386(m), 1350(w), 1294(w), 1244(s), 1193(m), 1155(m), 1102(m), 1072(m), 1019(w), 880(w), 800(w), 760(m), 730(m), 699(m); HRMS m/z ($M + \text{Na}^+$) calcd

646.1949, found 646.1958. Anal. Calcd for C₃₈H₂₉N₃O₆: C, 73.18; H, 4.69; N, 6.74.

Found: C, 72.96; H, 4.80; N, 6.58.

2-Dimethylamino-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (171). Method D with adduct **122** gave **171** (55 mg, 64%) as orange crystals: mp 237-238 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 11.89 (bs, 1H, 6-H), 7.79 (m, 2H, 4-H and 5-H), 7.49 (dd, *J* = 8.1, 1.2 Hz, 1H, 7-H), 6.79 (ddd, *J* = 2.1, 2.1, 0.9 Hz, 1H, 8-H), 2.89 (s, 6H, N(CH₃)₂); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.6, 168.4, 141.3, 132.5, 122.8, 122.5, 121.3, 117.3, 115.4, 100.2, 45.0; IR (film, cm⁻¹) 3251(bs), 2940(m), 2870(m), 1756(m), 1704(s), 1448(m), 1440(w), 1357(m), 1274(w), 1142(w), 1104(m), 740(m); HRMS *m/z* (M + Na⁺) calcd 252.0744, found 252.0748. Anal. Calcd for C₁₂H₁₁N₃O₂: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.68; H, 4.81; N, 18.17.

2-Benzyl-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (172). Method C with adduct **123** gave **172** (47 mg, 45%) as a yellow powder: mp 195-196 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 11.99 (bs, 1H, 6-H), 7.81 (dd, *J* = 8.1, 1.1 Hz, 1H, 5-H), 7.79-7.81 (m, overlapped by 4-H, 1H, 7-H), 7.56 (d, *J* = 8.1 Hz, 1H, 4-H), 7.23-7.37 (m, 5H, Ph), 6.81 (ddd, *J* = 3.0, 2.0, 0.9 Hz, 1H, 8-H), 4.76 (s, 2H, Bn); ¹³C NMR (75 MHz, CDCl₃, δ) 169.7, 169.4, 140.4, 137.2, 129.7, 128.7, 128.6, 127.7, 125.2, 124.0, 123.2, 116.4, 115.8, 102.1, 41.4; ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.7, 169.4, 141.3, 137.8, 132.6, 129.1, 127.8 (2 peaks overlapped), 124.3, 123.0, 115.2, 113.8, 100.3, ~40 (obscured by DMSO); IR (KBr, cm⁻¹) 3275(bs), 3108(w), 3057(w), 3035(w), 2941(w), 1756(m), 1687(s), 1590(w), 1508(w), 1492(w), 1455(w), 1433(m), 1398(m), 1368(m), 1340(m), 1272(w), 1062(m), 764(w), 745(m), 675(m); HRMS *m/z* (M + Na⁺) calcd 299.0792,

found 299.0794. Anal. Calcd for C₁₇H₁₂N₂O₂: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.63; H, 4.28; N, 9.90.

2-Phenyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (173). Method D with adduct **124** gave **173** (66 mg, 67%) as bright-yellow crystals: mp 265-266 °C; ¹H NMR (300 MHz, acetone-*d*₆, δ) 11.16 (bs, 1H, 6-H), 7.94 (dd, *J* = 8.4, 0.9 Hz, 1H, 5-H), 7.82 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 7.68 (d, *J* = 8.4 Hz, 1H, 4-H), 7.55-7.60 (m, 4H, Ph), 7.40-7.44 (m, 1H, Ph), 7.01 (ddd, *J* = 3.2, 2.1, 0.9 Hz, 1H, 8-H); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.9, 168.6, 141.3, 132.9, 132.5, 129.3, 128.1, 127.8, 124.1, 123.1, 123.0, 117.5, 115.8, 100.5; IR (film, cm⁻¹) 3288(bs), 2953(m), 2870(m), 1753(m), 1696(s), 1620(w), 1590(w), 1495(w), 1490(w), 1365(m), 1265(w), 1227(w), 1153(w), 1061(w), 753(m); HRMS *m/z* (M + Na⁺) calcd 285.0635, found 285.0641. Anal. Calcd for C₁₆H₁₀N₂O₂: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.00; H, 3.73; N, 10.82.

2-(4-Ethylphenyl)-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (174). Method C with adduct **125** gave **174** (51 mg, 47%) as a yellow powder: mp 172-173 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.82 (bs, 1H, 6-H), 7.76 (d, *J* = 8.4 Hz, 1H, 4-H), 7.71 (dd, *J* = 8.1, 0.9 Hz, 1H, 5-H), 7.52 (dd, *J* = 3.3, 2.4 Hz, 1H, 7-H), 7.40 (d, *J* = 8.7 Hz, 2H, Ph), 7.34 (d, *J* = 8.7 Hz, 2H, Ph), 7.13 (ddd, *J* = 3.1, 2.0, 0.8 Hz, 1H, 8-H), 2.72 (q, *J* = 7.7 Hz, 2H, CH₂CH₃), 1.29 (t, *J* = 7.7 Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.1, 168.7, 143.9, 141.3, 132.6, 130.4, 128.7, 127.8, 124.2, 123.1, 123.0, 117.5, 115.8, 100.4, 28.4, 16.2; IR (KBr, cm⁻¹) 3417(bs), 3319(w), 2963(w), 2929(w), 1760(m), 1706(s), 1629(w), 1592(w), 1517(m), 1460(w), 1426(w), 1380(s), 1366(s), 1274(w), 1228(w), 1088(m), 1068(w), 823(w), 800(w), 759(m), 745(m); HRMS *m/z* (M + Na⁺)

calcd 313.0948, found 313.0942. Anal. Calcd for C₁₈H₁₄N₂O₂: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.35; H, 4.94; N, 9.51.

2-(4-Isopropylphenyl)-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (175). Method C with adduct **126** gave **175** (70 mg, 61%) as yellow needle-like crystals: mp 178-179 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.68 (bs, 1H, 6-H), 7.78 (d, *J* = 8.4 Hz, 1H, 4-H), 7.73 (dd, *J* = 8.1, 0.9 Hz, 1H, 5-H), 7.55 (dd, *J* = 2.4, 0.9 Hz, 1H, 7-H), 7.41 (d, *J* = 8.4 Hz, 2H, Ph), 7.37 (d, *J* = 8.4 Hz, 2H, Ph), 7.15 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H, 8-H), 2.98 (septet, *J* = 6.9 Hz, 1H, CH(CH₃)₂), 1.30 (d, *J* = 6.9 Hz, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.1, 168.7, 148.4, 141.3, 132.6, 130.5, 127.8, 127.2, 124.2, 123.1, 123.0, 117.6, 115.8, 108.5, 100.5, 39.2, 24.4; IR (KBr, cm⁻¹) 3419(s), 2960(m), 2925(s), 2855(m), 1758(m), 1711(s), 1516(w), 1457(w), 1427(w), 1378(m), 1367(m), 1315(w), 1274(m), 1227(w), 1155(w), 1120(m), 1070(w), 714(w); HRMS *m/z* (M + Na⁺) calcd 327.1105, found 327.1113. Anal. Calcd for C₁₉H₁₆N₂O₂: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.71; H, 5.12; N, 9.07.

2-(4-Methoxyphenyl)-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (176). Method D with adduct **127** gave **176** (70 mg, 64%) as brown crystals: mp 220-221 °C; ¹H NMR (300 MHz, acetone-*d*₆, δ) 11.12 (bs, 1H, 6-H), 7.93 (dd, *J* = 8.1, 0.9 Hz, 1H, 5-H), 7.81 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 7.66 (d, *J* = 8.1 Hz, 1H, 4-H), 7.44 (d, *J* = 9.0 Hz, 2H, Ph), 7.09 (d, *J* = 9.0 Hz, 2H, Ph), 6.98-7.02 (m, 1H, 8-H), 3.89 (s, 3H, OCH₃); ¹³C NMR (75 MHz, acetone-*d*₆, δ) 168.7, 168.4, 159.0, 141.2, 131.2, 128.5, 125.6, 124.6, 123.4, 123.2, 116.8, 115.4, 114.0, 100.7, 55.0; IR (film, cm⁻¹) 3300(bs), 2920(m), 2810(m), 1758(w), 1706(s), 1517(m), 1441(w), 1369(m), 1250(m), 1155(w), 1117(w), 743(m);

HRMS m/z ($M + Na^+$) calcd 315.0741, found 315.0743. Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.67; H, 4.10; N, 9.39.

2-(4-Phenoxyphenyl)-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (177). Method C with adduct **128** gave **177** (51 mg, 38%) as bright yellow crystals: mp 193-194 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.72 (bs, 1H, 6-H), 7.78 (d, $J = 8.4$ Hz, 1H, 4-H), 7.73 (dd, $J = 8.4, 0.8$ Hz, 1H, 5-H), 7.56 (dd, $J = 3.2, 2.6$ Hz, 1H, 7-H), 7.36-7.48 (m, 4H, Ph), 7.08-7.19 (m, 6H, 8-H, Ph); ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 169.0, 168.7, 156.8, 156.6, 141.3, 132.6, 130.7, 129.6, 127.9, 124.4, 124.2, 123.1, 123.0, 119.6, 119.0, 117.6, 115.8, 100.5; IR (KBr, cm^{-1}) 3316(bm), 3065(w), 1764(m), 1703(s), 1629(w), 1588(w), 1506(m), 1487(m), 1460(w), 1433(w), 1383(m), 1370(m), 1241(s), 1151(m), 1105(m), 1089(m), 1070(m), 1005(w), 870(w), 822(w), 744(m), 691(m); HRMS m/z ($M + Na^+$) calcd 377.0897, found 377.0883. Anal. Calcd for $C_{22}H_{14}N_2O_3$: C, 74.57; H, 3.98; N, 7.91. Found: C, 74.44; H, 3.93; N, 7.54.

2-Dimethylamino-6-methyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (178). Method D with adduct **129** gave **178** (60 mg, 66%) as yellow crystals: mp 201-202 °C; 1H NMR (300 MHz, $acetone-d_6$, δ) 7.84 (d, $J = 8.4$ Hz, 1H, 4-H), 7.67 (d, $J = 3.3$ Hz, 1H, 7-H), 7.57 (dd, $J = 8.1, 0.6$ Hz, 1H, 5-H), 6.88 (dd, $J = 3.0, 0.6$ Hz, 1H, 8-H), 3.99 (s, 3H, 6- CH_3), 2.99 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 168.8, 168.5, 141.2, 134.6, 123.5, 122.7, 122.0, 115.8, 114.2, 100.7, 45.2, 33.4; IR (film, cm^{-1}) 3102(m), 2969(m), 2877(m), 2854(w), 1763(m), 1706(s), 1509(w), 1498(w), 1375(w), 1357(m), 1296(w), 1168(w), 1092(w), 1023(w); HRMS m/z ($M + Na^+$) calcd 266.0901, found 266.0892. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.46; H, 5.30; N, 17.27.

6-Methyl-2-phenyl-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (179). Method D with adduct **130** gave **179** (74 mg, 71%) as bright orange-yellow crystals: mp 214-215 °C; ¹H NMR (300 MHz, CD₂Cl₂, δ) 7.76 (d, *J* = 8.4 Hz, 1H, 4-H), 7.71 (dd, *J* = 8.4, 0.6 Hz, 1H, 5-H), 7.41-7.58 (m, 6H, 7-H and Ph), 7.03 (dd, *J* = 3.9, 0.7 Hz, 1H, 8-H), 3.93 (s, 3H, 6-CH₃); ¹³C NMR (75 MHz, CD₂Cl₂, δ) 168.8, 168.3, 141.3, 134.9, 132.6, 129.0, 127.8, 127.6, 126.9, 124.3, 123.6, 115.7, 114.6, 100.4, 33.5; IR (film, cm⁻¹) 3125(m), 2900(w), 1759(m), 1710(s), 1595(m), 1512(m), 1490(m), 1453(w), 1377(s), 1361(s), 1294(m), 1223(w), 1171(w), 1094(w), 1063(w), 744(m); HRMS *m/z* (M + Na⁺) calcd 299.0792, found 299.0792. Anal. Calcd for C₁₇H₁₂N₂O₂: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.71; H, 4.28; N, 10.14.

2-(4-Methoxyphenyl)-6-methyl-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (180). Method D with adduct **131** gave **180** (76 mg, 66%) as bright-yellow crystals: mp 236-237 °C; ¹H NMR (300 MHz, CD₂Cl₂, δ) 7.75 (d, *J* = 8.4 Hz, 1H, 4-H), 7.70 (dd, *J* = 8.4, 0.6 Hz, 1H, 5-H), 7.44 (d, *J* = 3.3 Hz, 1H, 7-H), 7.38 (d, *J* = 9.0 Hz, 2H, Ph), 7.06 (d, *J* = 9.0 Hz, 2H, Ph), 7.01 (dd, *J* = 3.3, 0.7 Hz, 1H, 8-H), 3.93 (s, 3H, OCH₃), 3.89 (s, 3H, 6-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.1, 168.7, 159.1, 141.4, 136.6, 129.2, 125.4, 124.2, 123.3, 123.2, 115.9, 115.6, 114.6, 99.8, 55.9, 33.6; IR (film, cm⁻¹) 3125(w), 2988(m), 2870(w), 1753(m), 1709(s), 1509(s), 1388(m), 1366(w), 1352(w), 1299(m), 1249(s), 1170(w), 1092(w), 806(w), 704(m); HRMS *m/z* (M + Na⁺) calcd 329.0897, found 329.0908. Anal. Calcd for C₁₈H₁₄N₂O₃: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.40; H, 4.59; N, 9.01.

2-Dimethylamino-5,6-dimethyl-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (181). Method D with adduct **132** gave **181** (68 mg, 70%) as bright-yellow crystals: mp 226-

227 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.33 (s, 1H, 4-H), 7.21 (d, *J* = 3.3 Hz, 1H, 7-H), 6.95 (d, *J* = 3.0 Hz, 1H, 8-H), 4.13 (s, 3H, 6-CH₃), 3.05 (s, 6H, N(CH₃)₂), 2.87 (s, 3H, 5-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.5, 168.3, 139.6, 137.8, 129.0, 124.1, 122.8, 119.6, 117.4, 99.2, 45.0, 37.3, 20.1; IR (film, cm⁻¹) 3120(m), 2998(m), 2963(m), 2875(m), 2815(m), 1757(s), 1709(s), 1596(w), 1517(m), 1477(w), 1448(m), 1348(s), 1321(m), 1188(w), 1172(m), 1105(w), 1015(w), 760(m), 740(m); HRMS *m/z* (M + Na⁺) calcd 280.1057, found 280.1055. Anal. Calcd for C₁₄H₁₅N₃O₂: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.55; H, 5.99; N, 16.50.

5,6-Dimethyl-2-phenyl-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (182). Method D with adduct **133** gave **182** (79 mg, 72%) as bright orange-yellow crystals: mp 225-226 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.48-7.53 (m, 4H, Ph), 7.45 (s, 1H, 4-H), 7.38-7.41 (m, 1H, Ph), 7.24 (d, *J* = 3.0 Hz, 1H, 7-H), 7.01 (d, *J* = 3.0 Hz, 1H, 8-H), 4.16 (s, 3H, 6-CH₃), 2.91 (s, 3H, 5-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.8, 168.4, 139.7, 138.0, 132.9, 129.4, 129.3, 128.0, 127.7, 124.6, 124.4, 121.3, 117.9, 99.5, 37.3, 20.1; IR (film, cm⁻¹) 3120(m), 2940(m), 1752(m), 1706(s), 1596(w), 1517(w), 1501(m), 1453(w), 1405(w), 1376(m), 1356(m), 1321(w), 1226(w), 1102(w), 753(m); HRMS *m/z* (M + Na⁺) calcd 313.0948, found 313.0945. Anal. Calcd for C₁₈H₁₄N₂O₂: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.70; H, 4.63; N, 9.80.

2-(4-Methoxyphenyl)-5,6-dimethyl-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (183). Method D with adduct **134** gave **183** (79 mg, 66%) as bright-red crystals: mp 229-230 °C; ¹H NMR (300 MHz, CD₂Cl₂, δ) 7.43 (s, 1H, 4-H), 7.36 (d, *J* = 9.0 Hz, 2H, Ph), 7.31 (d, *J* = 3.0 Hz, 1H, 7-H), 7.05 (d, *J* = 9.0 Hz, 2H, Ph), 6.97 (d, *J* = 3.0 Hz, 1H, 8-H), 4.17 (s, 3H, 6-CH₃), 3.88 (s, 3H, OCH₃), 2.94 (s, 3H, 5-CH₃); ¹³C NMR (75 MHz,

DMSO-*d*₆, δ) 169.1, 168.7, 159.0, 139.6, 137.92, 137.87, 129.2, 125.4, 124.6, 124.4, 121.1, 117.8, 114.6, 99.5, 55.9, 37.3, 20.1; IR (film, cm⁻¹) 3104(m), 2938(m), 2844(m), 1751(m), 1698(s), 1512(s), 1461(m), 1384(m), 1356(m), 1327(w), 1299(w), 1249(m), 1171(m), 1090(w), 1074(w), 1031(w), 802(w); HRMS *m/z* (M + Na⁺) calcd 343.1054, found 343.1069. Anal. Calcd for C₁₉H₁₆N₂O₃: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.62; H, 5.10; N, 8.55.

2-Dimethylamino-4-methyl-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (184). Method D with adduct **135** gave **184** (52 mg, 57%) as yellow crystals: mp 255-256 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.70 (bs, 1H, 6-H), 7.41-7.45 (m, 2H, 5-H and 7-H), 7.03 (ddd, *J* = 3.2, 2.0, 1.1 Hz, 1H, 8-H), 3.07 (s, 6H, N(CH₃)₂), 2.77 (d, *J* = 0.9 Hz, 3H, 4-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.2, 168.1, 141.3, 131.8, 129.3, 121.6, 121.5, 119.5, 118.3, 100.0, 44.9, 18.2; IR (film, cm⁻¹) 3250(bs), 2995(m), 2880(m), 2871(m), 1748(m), 1697(s), 1446(m), 1402(w), 1390(w), 1350(m), 1101(w), 762(m); HRMS *m/z* (M + Na⁺) calcd 266.0901, found 266.0907. Anal. Calcd for C₁₃H₁₃N₃O₂: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.96; H, 5.34; N, 17.08.

4-Methyl-2-phenyl-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (185). Method D with adduct **136** gave **185** (63 mg, 61%) as yellow crystals: mp 305-306 °C; ¹H NMR (300 MHz, acetone-*d*₆, δ) 10.93 (bs, 1H, 6-H), 7.72 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 7.67 (dq, *J* = 0.9, 0.9 Hz, 1H, 5-H), 7.50-7.60 (m, 4H, Ph), 7.40-7.50 (m, 1H, Ph), 6.94 (ddd, *J* = 3.6, 2.1, 0.9 Hz, 1H, 8-H), 2.77 (d, *J* = 0.6 Hz, 3H, 4-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.0, 168.4, 141.4, 132.9, 131.9, 129.7, 129.3, 128.0, 127.9, 123.2, 121.9, 121.2, 118.5, 100.3, 18.4; IR (film, cm⁻¹) 3288(bs), 2900(m), 2880(m), 1764(w), 1752(m), 1693(s), 1640(w), 1496(m), 1392(m), 1368(m), 1167(w), 763(m); HRMS *m/z*

(M + Na⁺) calcd 299.0792, found 299.0785. Anal. Calcd for C₁₇H₁₂N₂O₂: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.71; H, 4.54; N, 9.86.

2-(4-Methoxyphenyl)-4-methyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (186).

Method D with adduct **137** gave **186** (68 mg, 59%) as yellow crystals: mp 207-208 °C; ¹H NMR (300 MHz, acetone-*d*₆, δ) 10.91 (bs, 1H, 6-H), 7.71 (dd, *J* = 3.0, 2.6 Hz, 1H, 7-H), 7.66 (dq, *J* = 0.9, 0.9 Hz, 1H, 5-H), 7.43 (d, *J* = 9.3 Hz, 2H, Ph), 7.08 (d, *J* = 9.0 Hz, 2H, Ph), 6.94 (ddd, *J* = 3.2, 2.0, 0.9 Hz, 1H, 8-H), 3.89 (s, 3H, OCH₃), 2.76 (d, *J* = 0.9 Hz, 3H, 4-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.6, 168.6, 159.0, 141.4, 131.7, 129.6, 129.3, 125.5, 123.2, 121.9, 121.2, 118.4, 114.5, 100.3, 55.8, 18.4; IR (film, cm⁻¹) 3331(bs), 2989(m), 2810(m), 1756(m), 1702(s), 1518(m), 1400(m), 1301(w), 1256(m), 1168(w), 1117(w), 760(m); HRMS *m/z* (M + Na⁺) calcd 329.0897, found 329.0905. Anal. Calcd for C₁₈H₁₄N₂O₃: C, 70.58; H, 4.86; N, 8.98. Found: C, 70.77; H, 4.86; N, 8.98.

2-Dimethylamino-4,6-dimethyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (187).

Method D with adduct **138** gave **187** (54 mg, 56%) as light-yellow crystals: mp 179-180 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.31 (dq, *J* = 1.0, 0.9 Hz, 1H, 5-H), 7.25 (d, *J* = 3.3 Hz, 1H, 7-H), 6.95 (dd, *J* = 3.3, 0.9 Hz, 1H, 8-H), 3.84 (s, 3H, 6-CH₃), 3.07 (s, 6H, N(CH₃)₂), 2.78 (d, *J* = 0.9 Hz, 3H, 4-CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 169.4, 168.3, 141.3, 134.0, 130.3, 122.3, 122.2, 119.8, 115.6, 100.5, 45.1, 33.3, 18.5; IR (film, cm⁻¹) 3125(m), 3100(m), 2945(m), 3877(m), 3851(m), 1759(m), 1704(s), 1632(w), 1513(m), 1470(w), 1446(w), 1403(w), 1375(m), 1353(m), 1294(w), 1099(m), 758(w); HRMS *m/z* (M + Na⁺) calcd 280.1057, found 280.1057. Anal. Calcd for C₁₄H₁₅N₃O₂: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.11; H, 5.71; N, 16.38.

4,6-Dimethyl-2-phenyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (188). Method D with adduct **139** gave **188** (68 mg, 62%) as bright orange-yellow crystals: mp 181-182 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.45-7.55 (m, 4H, Ph), 7.35-7.41 (m, 2H, 5-H and Ph), 7.28 (d, *J* = 3.0 Hz, 1H, 7-H), 6.99 (d, *J* = 2.7, 0.9 Hz, 1H, 8-H), 3.85 (s, 3H, 6-CH₃), 2.84 (d, *J* = 0.9 Hz, 3H, 4-CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 169.3, 168.3, 141.4, 134.1, 132.4, 130.6, 129.0, 127.5, 126.7, 123.9, 122.5, 121.4, 115.8, 100.7, 33.3, 18.6; IR (film, cm⁻¹) 3120(m), 2900(m), 2860(m), 1754(m), 1710(S), 1595(w), 1492(m), 1375(s), 1357(s), 1294(w), 1168(w); HRMS *m/z* (M + Na⁺) calcd 313.0948, found 313.0951. Anal. Calcd for C₁₈H₁₄N₂O₂: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.28; H, 4.61; N, 9.60.

2-(4-Methoxyphenyl)-4,6-dimethyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (189). Method D with adduct **140** gave **189** (73 mg, 61%) as bright-yellow crystals: mp 243-244 °C; ¹H NMR (300 MHz, CD₂Cl₂, δ) 7.43 (dq, *J* = 0.9, 0.9 Hz, 1H, 5-H), 7.37-7.40 (m, 3H, 7-H and Ph), 7.06 (d, *J* = 9.0 Hz, 2H, Ph), 6.95 (dd, *J* = 3.0, 0.9 Hz, 1H, 8-H), 3.89 (s, 3H, 6-CH₃ or OCH₃), 3.87 (s, 3H, 6-CH₃ or OCH₃), 2.83 (d, *J* = 0.9 Hz, 3H, 4-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.6, 168.5, 159.1, 141.5, 136.0, 129.6, 129.3, 125.4, 123.5, 122.1, 121.3, 117.0, 114.6, 99.6, 55.9, 33.5, 18.5; IR (film, cm⁻¹) 3120(m), 2999(m), 2940(w), 2860(w), 1751(m), 1706(s), 1632(w), 1612(w), 1510(s), 1480(w), 1438(w), 1402(m), 1382(m), 1362(w), 1345(m), 1290(m), 1244(s), 1167(m), 1113(w), 1089(w), 1028(w); HRMS *m/z* (M + Na⁺) calcd 343.1054, found 343.1064. Anal. Calcd for C₁₉H₁₆N₂O₃: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.41; H, 4.87; N, 8.54.

4-Ethyl-2-phenyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (190). Method D with adduct **141** gave **190** (48 mg, 44%) as light-brown crystals: mp 261-262 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 11.85 (bs, 1H, 6-H), 7.81 (ddd, *J* = 2.0, 1.0, 1.0 Hz, 1H, 8-H), 7.75 (dd, *J* = 3.0, 3.0 Hz, 1H, 7-H), 7.64 (d, *J* = 0.9 Hz, 1H, 5-H), 7.39-7.55 (m, 5H, Ph), 3.15 (q, *J* = 7.5 Hz, 2H, 4-CH₂CH₃), 1.28 (t, *J* = 7.4 Hz, 3H, 4-CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.1, 168.4, 141.6, 136.5, 132.9, 132.1, 129.3, 128.1, 128.0, 123.5, 122.0, 120.7, 117.2, 100.3, 24.9, 16.1; IR (KBr, cm⁻¹) 3300(bs), 2970(m), 1763(m), 1683(s), 1637(m), 1592(w), 1496(m), 1456(w), 1368(s), 1163(w), 1101(w), 1062(w), 848(w), 760(m); HRMS *m/z* (M + Na⁺) calcd 313.0948, found 313.0945. Anal. Calcd for C₁₈H₁₄N₂O₂: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.61; H, 4.88; N, 9.48.

4-Ethyl-2-(4-ethylphenyl)-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (191). Method C with adduct **142** gave **191** (63 mg, 53%) as orange crystals: mp 238-239 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 11.83 (bs, 1H, 6-H), 7.73 (dd, *J* = 2.4, 0.9 Hz, 1H, 7-H), 7.63 (d, *J* = 0.6 Hz, 1H, 5-H), 7.36-7.39 (m, 4H, Ph), 6.80 (ddd, *J* = 2.9, 1.7, 1.0 Hz, 1H, 8-H), 3.14 (q, *J* = 7.4 Hz, 2H, 4-CH₂CH₃), 2.67 (q, *J* = 7.6 Hz, 2H, PhCH₂CH₃), 1.27 (t, *J* = 7.5 Hz, 3H, 4-CH₂CH₃), 1.23 (t, *J* = 7.7, 3H, PhCH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.3, 168.5, 143.7, 141.5, 136.4, 132.1, 130.4, 128.6, 127.9, 123.5, 121.9, 120.7, 117.1, 100.3, 28.4, 24.9, 16.2, 16.1; IR (KBr, cm⁻¹) 3307(bs), 2964(m), 2929(w), 2871(w), 1757(m), 1696(s), 1633(w), 1514(m), 1458(m), 1368(s), 1294(m), 1167(m), 1117(w), 1095(m), 1066(w), 832(w), 764(m), 726(w); HRMS *m/z* (M + Na⁺) calcd 341.1261, found 341.1260. Anal. Calcd for C₂₀H₁₈N₂O₂: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.70; H, 5.58; N, 8.20.

4-Ethyl-2-(4-hydroxyphenyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (192).

Method D with adduct **143** gave **192** (17 mg, 15%) as yellow crystals: mp 265-267 °C; ¹H NMR (500 MHz, DMSO-*d*₆, δ) 11.80 (bs, 1H, 6-H), 9.69 (bs, 1H, Ph-OH), 7.69-7.74 (m, 1H, 5-H), 7.58-7.62 (m, 1H, 7-H), 7.18 (d, *J* = 7.5 Hz, 2H, Ph), 6.85 (d, *J* = 8.0 Hz, 2H, Ph), 6.75-6.79 (m, 1H, 8-H), 3.11 (q, *J* = 7.3 Hz, 2H, 4-CH₂CH₃), 1.25 (t, *J* = 7.3 Hz, 3H, 4-CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.6, 168.8, 157.4, 141.5, 136.3, 132.0, 129.5, 123.8, 123.5, 121.9, 120.7, 117.0, 115.8, 100.2, 24.9, 16.1; IR (KBr, cm⁻¹) 3464(m), 3311(bs), 3115(w), 2966(m), 2926(m), 1751(m), 1683(s), 1636(w), 1597(w), 1515(s), 1455(w), 1379(s), 1295(w), 1269(m), 1206(m), 1162(m), 1114(m), 1087(w), 834(w), 765(w); HRMS *m/z* (M + Na⁺) calcd for C₁₈H₁₄N₂O₃: 329.0897, found 329.0906.

2-(4-Chlorophenyl)-4-ethyl-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (193). Method D with adduct **145** gave **193** (40 mg, 33%) as yellow crystals: mp 219-220 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.56 (bs, 1H, 6-H), 7.53 (app. s, 1H, 5-H), 7.47-7.49 (m, 5H, 7-H and Ph), 7.09 (app. dd, *J* = 2.3, 2.3 Hz, 1H, 8-H), 3.25 (q, *J* = 7.6 Hz, 2H, 4-CH₂CH₃), 1.36 (t, *J* = 7.7 Hz, 3H, 4-CH₂CH₃); ¹H NMR (300 MHz, DMSO-*d*₆, δ) 11.86 (bs, 1H, 6-H), 7.64 (d, *J* = 0.9 Hz, 1H, 5-H), 7.59 (d, *J* = 9.0 Hz, 2H, Ph), 7.50 (d, *J* = 9.0 Hz, 2H, Ph), 7.49 (dd, *J* = 3.1, 2.6 Hz, 1H, 7-H), 6.80 (ddd, *J* = 3.0, 1.8, 1.1 Hz, 1H, 8-H), 3.14 (q, *J* = 7.4 Hz, 2H, 4-CH₂CH₃), 1.27 (t, *J* = 7.5 Hz, 3H, 4-CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.9, 168.1, 141.6, 136.5, 132.4, 132.2, 131.8, 129.6, 129.3, 123.4, 122.0, 120.7, 117.2, 100.3, 24.9, 16.0; IR (KBr, cm⁻¹) 3308(bs), 3105(w), 2968(m), 2933(w), 2880(w), 1762(m), 1707(s), 1635(w), 1495(m), 1459(w), 1409(m), 1376(s), 1313(w), 1295(m), 1241(w), 1209(w), 1167(w), 1109(w), 1092(m), 1066(w),

1016(w), 852(w), 830(m), 807(m), 781(m), 753(m), 717(w); HRMS m/z ($M + Na^+$) calcd for $C_{18}H_{13}ClN_2O_2$: 347.0559, found 347.0557.

2-(4-Bromophenyl)-4-ethyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (194). Method D with adduct **146** gave **194** (50 mg, 36%) as yellow crystals: mp 246-247 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.53 (bs, 1H, 6-H), 7.63 (d, $J = 9.0$ Hz, 2H, Ph), 7.53 (d, $J = 0.9$ Hz, 1H, 5-H), 7.48 (dd, $J = 3.3, 2.4$ Hz, 1H, 7-H), 7.42 (d, $J = 9.0$ Hz, 2H, Ph), 7.10 (ddd, $J = 3.2, 2.2, 0.9$ Hz, 1H, 8-H), 3.25 (q, $J = 7.4$ Hz, 2H, 4- CH_2CH_3), 1.37 (t, $J = 7.7$ Hz, 3H, 4- CH_2CH_3); 1H NMR (300 MHz, $DMSO-d_6$, δ) 11.86 (bs, 1H, 6-H), 7.75 (dd, $J = 2.7$ Hz, 1H, 7-H), 7.72 (d, $J = 8.7$ Hz, 2H, Ph), 7.65 (d, $J = 0.9$ Hz, 1H, 5-H), 7.44 (d, $J = 8.7$ Hz, 2H, Ph), 6.80 (ddd, $J = 3.0, 2.0, 0.9$ Hz, 1H, 8-H), 3.14 (q, $J = 7.5$ Hz, 2H, 4- CH_2CH_3), 1.27 (t, $J = 7.5$ Hz, 3H, 4- CH_2CH_3); ^{13}C NMR (75 MHz, $DMSO-d_6$, δ) 168.8, 168.1, 141.6, 136.5, 132.2, 129.9, 123.4, 122.0, 120.9, 120.69, 120.65, 117.2, 105.0, 100.3, 24.9, 16.1; IR (KBr, cm^{-1}) 3307(bs), 3100(w), 3082(w), 2966(m), 2878(w), 1763(m), 1707(s), 1637(m), 1493(m), 1460(w), 1367(s), 1314(w), 1298(w), 1243(w), 1209(w), 1167(w), 1122(w), 1108(w), 1090(w), 1074(m), 1012(w), 980(w), 820(m), 790(m), 740(m); HRMS m/z ($M + Na^+$) calcd 391.0053, found 391.0044. Anal. Calcd for $C_{18}H_{13}BrN_2O_2$: C, 58.56; H, 3.55; N, 7.59. Found: C, 58.59; H, 3.41; N, 7.46.

4-Ethyl-2-(4-nitrophenyl)-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (195). Method D with adduct **147** gave **195** (35 mg, 28%) as light-orange crystals: mp 296-297 °C; 1H NMR (300 MHz, $DMSO-d_6$, δ) 11.90 (bs, 1H, 6-H), 8.39 (d, $J = 9.3$ Hz, 1H, Ph), 7.83 (d, $J = 9.3$ Hz, 2H, Ph), 7.77 (dd, $J = 2.9, 2.9$ Hz, 1H, 7-H), 7.68 (d, $J = 0.6$ Hz, 1H, 5-H), 6.84 (ddd, $J = 3.2, 2.0, 1.1$ Hz, 1H, 8-H), 3.16 (q, $J = 7.4$ Hz, 2H, 4- CH_2CH_3), 1.29

(t, $J = 7.5$ Hz, 3H, 4-CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.4, 167.7, 146.1, 141.7, 138.9, 136.7, 132.4, 127.9, 124.6, 123.4, 122.1, 120.6, 117.6, 100.4, 25.0, 16.1; IR (KBr, cm⁻¹) 3378(bs), 3120(w), 2970(w), 2933(w), 2879(w), 1765(m), 1718(s), 1631(w), 1591(m), 1516(m), 1498(m), 1471(w), 1411(w), 1376(m), 1318(s), 1213(m), 1185(m), 1165(w), 1718(s), 1631(w), 1591(m), 1516(m), 1498(m), 1471(m), 1411(w), 1376(m), 1318(s), 1213(m), 1185(m), 1165(m), 1110(m), 1086(m), 1051(m), 851(m), 781(m), 750(m); HRMS m/z (M + Na⁺) calcd 358.0799, found 358.0800. Anal. Calcd for C₁₈H₁₃N₃O₄: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.10; H, 4.25; N, 12.16.

(+)-(R)-2-(1,3-Dioxo-2H,6H-pyrrolo[3,4-*e*]indol-2-yl)-2-phenylethyl acetate

(196). Method A with vinylpyrrole **116** and maleimide **4p** gave adduct **150**, which with Method E gave **196** (641 mg, 46%) as dark-yellow crystals: mp 62-63 °C; [α]_D²³ +2.1 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CD₂Cl₂, δ) 8.88 (bs, 1H, 6-H), 7.74 (dd, $J = 8.1, 0.9$ Hz, 1H, 5-H), 7.64 (d, $J = 8.1$ Hz, 1H, 4-H), 7.56-7.61 (m, 3H, 7-H and Ph), 7.31-7.42 (m, 3H, Ph), 7.04 (ddd, $J = 3.2, 2.0, 1.1$ Hz, 1H, 8-H), 5.63 (dd, $J = 9.9, 5.7$ Hz, 1H, 2'-H), 5.13 (dd, $J = 11.1, 9.9$ Hz, 1H, 1'-H), 4.83 (dd, $J = 11.1, 5.7$ Hz, 1H, 1'-H), 2.02 (s, 3H, Ac); ¹³C NMR (75 MHz, CDCl₃, δ) 171.2, 170.2, 169.8, 140.9, 136.7, 130.5, 128.9, 128.5, 128.1, 124.5, 123.4, 123.2, 116.4, 116.1, 101.5, 63.0, 53.2, 21.0; IR (film, cm⁻¹) 3360(bs), 1749(m), 1698(s), 1629(w), 1458(w), 1350(s), 1236(m), 1041(w), 750(m), 699(m); HRMS m/z (M + Na⁺) calcd 371.1003, found 371.1009. Anal. Calcd for C₂₀H₁₆N₂O₄: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.80; H, 4.62; N, 8.00.

(R)-2-(4-Methyl-1,3-dioxo-2H,6H-pyrrolo[3,4-*e*]indol-2-yl)-2-phenylethyl acetate

(197). Method A with vinylpyrrole **115b** and maleimide **4p** gave adduct **151**, which with method E gave **197** (391 mg, 27%) as light-yellow crystals: mp 158-159 °C; ¹H

NMR (300 MHz, CD₂Cl₂, δ) 8.85 (bs, 1H, 6-H), 7.55-7.59 (m, 2H, Ph), 7.33-7.46 (m, 5H, 5-H, 7-H and Ph), 6.95 (ddd, *J* = 3.1, 2.1, 1.0 Hz, 1H, 8-H), 5.65 (dd, *J* = 9.6, 6.0 Hz, 1H, 2'-H), 5.16 (dd, *J* = 11.1, 9.6 Hz, 1H, 1'-H), 4.86 (dd, *J* = 6.0, 11.1 Hz, 1H, 1'-H), 2.73 (d, *J* = 0.9 Hz, 3H, 4-CH₃), 2.01 (s, 3H, Ac); ¹³C NMR (75 MHz, CDCl₃, δ) 171.2, 170.4, 169.6, 140.8, 137.0, 130.7, 129.7, 128.9, 128.4, 128.2, 123.6, 121.9, 121.7, 117.6, 101.5, 63.1, 53.0, 21.0, 18.3; IR (film, cm⁻¹) 3370(bs), 1747(m), 1696(s), 1637(m), 1457(w), 1391(m), 1350(m), 1238(m), 1043(w), 767(m), 738(w), 700(m); HRMS *m/z* (M + Na⁺) calcd 385.1160, found 385.1161. Anal. Calcd for C₂₁H₁₈N₂O₄: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.51; H, 4.98; N, 7.52.

(+)-(R)-2-(6-Methyl-1,3-dioxo-2H,6H-pyrrolo[3,4-*e*]indol-2-yl)-2-phenylethyl acetate (198). Method A with vinylpyrrole **115d** and maleimide **4p** gave adduct **152**, which with method E gave **198** (638 mg, 44%) as light-brown crystals: mp 52-53 °C; [α]_D²³ +3.6 (*c* 2.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃, δ) 7.66 (dd, *J* = 8.4, 0.6 Hz, 1H, 5-H), 7.57-7.61 (m, 2H, Ph), 7.58 (d, overlapped, *J* = 8.4 Hz, 1H, 4-H), 7.28-7.40 (m, 4H, 7-H, Ph), 6.98 (d, *J* = 3.0 Hz, 1H, 8-H), 5.65 (dd, *J* = 10.2, 5.7 Hz, 1H, 2'-H), 5.16 (dd, *J* = 10.5, 10.5 Hz, 1H, 1'-H), 4.87 (dd, *J* = 10.7, 5.7 Hz, 1H, 1'-H), 3.89 (s, 3H, 6-CH₃), 2.01 (s, 3H, Ac); ¹³C NMR (75 MHz, CDCl₃, δ) 170.8, 169.9, 169.5, 141.1, 136.8, 134.6, 128.8, 128.4, 128.2, 124.2, 123.6, 123.5, 115.7, 114.1, 100.1, 62.8, 53.3, 33.4, 20.9; IR (film, cm⁻¹) 3447(bs), 3108(w), 3063(w), 2950(w), 1741(s), 1703(s), 1626(w), 1511(m), 1457(m), 1352(s), 1295(m), 1232(s), 1042(m), 749(s), 701(s); HRMS *m/z* (M + Na⁺) calcd 385.1160, found 385.1166. Anal. Calcd for C₂₁H₁₈N₂O₄: C, 69.60; H, 5.01; N, 7.93. Found: C, 69.75; H, 4.89; N, 7.93.

(+)-(R)-2-(5,6-Dimethyl-1,3-dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (199). Method A with vinylpyrrole **115c** and maleimide **4p** gave adduct **153**, which with method E gave **199** (437 mg, 29%) as yellow crystals: mp 125-126 °C; $[\alpha]_D^{23} +3.9$ (*c* 2.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃, δ) 7.56-7.59 (m, 2H, Ph), 7.27-7.41 (m, 4H, 4-H and Ph), 7.20 (d, *J* = 3.3 Hz, 1H, 7-H), 6.94 (d, *J* = 3.0 Hz, 1H, 8-H), 5.60 (dd, *J* = 9.9, 5.4 Hz, 1H, 2'-H), 5.14 (dd, *J* = 11.1, 10.2 Hz, 1H, 1'-H), 4.85 (dd, *J* = 11.1, 5.4 Hz, 1H, 1'-H), 4.13 (s, 3H, 6-CH₃), 2.87 (s, 3H, 5-CH₃), 2.00 (s, 3H, Ac); ¹³C NMR (75 MHz, CDCl₃, δ) 170.8, 169.9, 169.6, 139.6, 136.9, 136.0, 128.8, 128.3, 128.2, 127.6, 124.8, 124.7, 121.9, 118.2, 100.5, 62.9, 53.2, 37.3, 20.9, 20.4; IR (film, cm⁻¹) 3440(bs), 1742(m), 1701(s), 1518(w), 1496(w), 1367(m), 1347(s), 1232(m), 1089(w), 762(w), 750(w), 731(w), 701(w); HRMS *m/z* (M + Na⁺) calcd 399.1316, found 399.1328. Anal. Calcd for C₂₂H₂₀N₂O₄: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.08; H, 5.39; N, 7.29.

(+)-(R)-2-(4,6-Dimethyl-1,3-dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (200). Method A with vinylpyrrole **115f** and maleimide **4p** gave adduct **154**, which with method E gave **200** (391 mg, 26%) as brownish-orange crystals: mp 163-164 °C; $[\alpha]_D^{23} +5.9$ (*c* 5.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃, δ) 7.57-7.60 (m, 2H, Ph), 7.27-7.40 (m, 4H, 5-H and Ph), 7.25 (d, *J* = 3.0 Hz, 1H, 7-H), 6.98 (d, *J* = 3.0 Hz, 1H, 8-H), 5.63 (dd, *J* = 10.2, 5.7 Hz, 1H, 2'-H), 5.15 (dd, *J* = 11.1, 10.2 Hz, 1H, 1'-H), 4.88 (dd, *J* = 11.1, 5.7 Hz, 1H, 1'-H), 3.81 (s, 3H, 6-CH₃), 2.77 (s, 3H, 4-CH₃), 2.02 (s, 3H, Ac); ¹³C NMR (75 MHz, CDCl₃, δ) 170.8, 170.4, 169.4, 141.2, 137.0, 134.0, 130.2, 128.8, 128.6, 128.3, 123.8, 122.2, 121.4, 115.5, 100.3, 62.9, 53.0, 33.2, 21.0, 18.4; IR (film, cm⁻¹) 3440(bm), 2925(w), 1746(s), 1698(s), 1510(w), 1381(m), 1350(s), 1291(w),

1233(m), 1041(w), 763(w), 701(w); HRMS m/z ($M + Na^+$) calcd 399.1316, found 399.1301. Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.31; H, 5.49; N, 7.36.

(+)-(R)-2-(4,5,6-Trimethyl-1,3-dioxo-2H,6H-pyrrolo[3,4-e]indol-2-yl)-2-phenylethyl acetate (201). Method A with vinylpyrrole **115g** and maleimide **4p** gave adduct **155**, which with method E gave **201** (328 mg, 21%) as yellow crystals: mp 197-198 °C; $[\alpha]_D^{23} +4.1$ (c 2.5, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, δ) 7.55-7.59 (m, 2H, Ph), 7.28-7.40 (m, 3H, Ph), 7.14 (d, $J = 2.7$ Hz, 1H, 7-H), 6.92 (d, $J = 3.0$ Hz, 1H, 8-H), 5.62 (dd, $J = 9.9, 5.7$ Hz, 1H, 2'-H), 5.14 (dd, $J = 10.7, 9.9$ Hz, 1H, 1'-H), 4.88 (dd, $J = 11.1, 5.7$ Hz, 1H, 1'-H), 4.12 (s, 3H, 6- CH_3), 2.75 (s, 3H, 4- CH_3 or 5- CH_3), 2.74 (s, 3H, 4- CH_3 or 5- CH_3), 2.01 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.8, 169.3, 140.0, 137.1, 136.4, 129.4, 128.8, 128.3, 128.2, 126.8, 123.4, 122.0, 121.3, 116.5, 100.0, 62.9, 53.2, 38.0, 25.8, 14.5, 13.8; IR (film, cm^{-1}) 3451(bs), 1746(m), 1697(s), 1498(w), 1455(w), 1387(m), 1344(m), 1309(w), 1231(m), 1039(w), 806(w), 766(m), 730(w); HRMS m/z ($M + Na^+$) calcd 413.1473, found 413.1456. Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.82; H, 5.65; N, 6.96.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-2H,6H-pyrrolo[3,4-e]indole-1,3-dione (202). Method A with vinylpyrrole **116** and maleimide **4q** gave adduct **156**, which with method E gave **202** (500 mg, 39%) as light-yellow crystals: mp 63-64 °C; $[\alpha]_D^{23} +27.0$ (c 5.0, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, δ) 8.75 (bs, 1H, 6-H), 7.55-7.60 (m, 4H, 4-H and 5-H and Ph), 7.28-7.43 (m, 4H, 7-H and Ph), 6.98 (dd, $J = 3.3, 1.8$ Hz, 1H, 8-H), 5.63 (dd, $J = 10.2, 5.7$ Hz, 1H, 1'-H), 4.69 (dd, $J = 10.2, 10.2$ Hz, 1H, 2'-H), 4.01 (dd, $J = 10.2, 5.7$ Hz, 1H, 2'-H), 3.47 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 170.4,

169.9, 140.6, 137.5, 130.3, 128.9, 128.4, 128.2, 124.0, 123.1, 122.8, 115.9, 115.8, 101.5, 71.4, 58.9, 53.8; IR (film, cm^{-1}) 3402(bs), 1754(m), 1699(s), 1610(m), 1458(w), 1393(w), 1353(s), 1109(w), 750(m), 700(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd 343.1054, found 343.1045. Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.46; H, 5.14; N, 8.82.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-4-methyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (203). Method A with vinylpyrrole **115b** and maleimide **4q** gave adduct **157**, which with method E gave **203** (401 mg, 30%) as dark-yellow crystals: mp 139-140 °C; $[\alpha]_{\text{D}}^{23} +14.9$ (c 2.3, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , δ) 8.68 (bs, 1H, 6-H), 7.57-7.60 (m, 2H, Ph), 7.28-7.40 (m, 5H, 5-H and 7-H and Ph), 6.79-6.81 (m, 1H, 8-H), 5.62 (dd, $J = 10.2, 5.7$ Hz, 1H, 1'-H), 4.77 (dd, $J = 10.2, 10.2$ Hz, 1H, 2'-H), 4.00 (dd, $J = 10.2, 5.4$ Hz, 1H, 2'-H), 3.52 (s, 3H, OCH_3), 2.65 (d, $J = 0.9$ Hz, 3H, 4- CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2 , δ) 170.4, 169.6, 140.5, 137.9, 130.3, 129.5, 128.7, 128.6, 128.2, 128.1, 123.3, 121.3, 117.2, 101.1, 71.4, 58.7, 53.3, 18.0; IR (film, cm^{-1}) 3413(bs), 1749(w), 1694(s), 1636(m), 1456(w), 1394(w), 1350(m), 766(w), 699(w); HRMS m/z ($\text{M} + \text{Na}^+$) calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3$: 357.1210, found 357.1211.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-4,5-dimethyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (204). Method A with vinylpyrrole **115e** and maleimide **4q** gave adduct **158**, which with method E gave **204** (362 mg, 26%) as light-yellow crystals: mp 177-178 °C; $[\alpha]_{\text{D}}^{23} +17.6$ (c 0.8, CHCl_3); ^1H NMR (300 MHz, CD_2Cl_2 , δ) 8.67 (bs, 1H, 6-H), 7.53-7.60 (m, 2H, Ph), 7.28-7.41 (m, 4H, 7-H, Ph), 6.87 (d, $J = 3.0, 1.8$ Hz, 1H, 8-H), 5.59 (dd, $J = 9.9, 5.7$ Hz, 1H, 1'-H), 4.60 (dd, $J = 9.9, 9.9$ Hz, 1H, 2'-H), 4.02 (dd, 9.9, 5.5 Hz, 1H, 2'-H), 3.47 (s, 3H, OCH_3), 2.67 (s, 3H, 4- CH_3), 2.45 (s, 3H, 5- CH_3); ^{13}C NMR

(75 MHz, CD₂Cl₂, δ) 170.9, 169.3, 139.9, 138.0, 129.0, 128.6, 128.1, 128.0, 127.9, 125.4, 121.9, 120.9, 120.5, 101.6, 71.5, 58.8, 53.9, 13.2, 13.1; IR (film, cm⁻¹) 3430(bs), 2900(w), 1747(m), 1693(s), 1650(m), 1394(m), 1352(m), 1092(w), 767(m), 732(m), 699(m); HRMS *m/z* (M + Na⁺) calcd 371.1367, found 371.1351. Anal. Calcd for C₂₁H₂₀N₂O₃: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.22; H, 5.74; N, 7.88.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-6-methyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (205). Method A with vinylpyrrole **115d** and maleimide **4q** gave adduct **159**, which with method E gave **205** (535 mg, 40%) as light-yellow crystals: mp 123-124 °C; [α]_D²³ +30.4 (*c* 5.0, CHCl₃); ¹H NMR (300 MHz, CD₂Cl₂, δ) 7.59-7.62 (m, 2H, 4-H, 5-H), 7.54-7.58 (m, 2H, Ph), 7.28-7.52 (m, 4H, 7-H and Ph), 6.94 (dd, *J* = 3.3, 0.9 Hz, 1H, 8-H), 5.58 (dd, *J* = 9.9, 6.3 Hz, 1H, 1'-H), 4.52 (dd, *J* = 9.6, 9.6 Hz, 1H, 2'-H), 4.02 (dd, *J* = 9.9, 6.0 Hz, 1H, 2'-H), 3.89 (s, 3H, 6-CH₃), 3.41 (s, 3H, OCH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 170.2, 169.8, 141.0, 137.7, 134.4, 128.7, 128.3, 128.1, 124.5, 123.9, 123.5, 115.7, 113.9, 100.6, 71.4, 58.9, 53.9, 33.4; IR (film, cm⁻¹) 3443(bs), 2905(m), 2800(w), 1755(m), 1702(s), 1511(m), 1458(w), 1385(m), 1353(s), 1295(w), 1114(m), 1090(w), 748(s), 700(m); HRMS *m/z* (M + Na⁺) calcd 357.1210, found 357.1200. Anal. Calcd for C₂₀H₁₈N₂O₃: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.61; H, 5.32; N, 8.41.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-5,6-dimethyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (206). Method A with vinylpyrrole **115c** and maleimide **4q** gave adduct **160**, which with method E gave **206** (446 mg, 32%) as orangish-yellow crystals: mp 157-158°C; [α]_D²³ +30.2 (*c* 5.0, CHCl₃); ¹H NMR (300 MHz, CD₂Cl₂, δ) 7.53-7.58 (m, 2H, Ph), 7.27-7.39 (m, 4H, 4-H, Ph), 7.25 (d, *J* = 3.3 Hz, 1H, 7-H), 6.89 (d, *J* = 3.3 Hz, 1H,

8-H), 5.54 (dd, $J = 9.6, 5.7$ Hz, 1H, 1'-H), 4.49 (dd, $J = 9.6, 9.6$ Hz, 1H, 2'-H), 4.12 (s, 3H, 6-CH₃), 4.02 (dd, $J = 9.6, 6.0$ Hz, 1H, 2'-H), 3.40 (s, 3H, OCH₃), 2.88 (s, 3H, 5-CH₃); ¹³C NMR (75 MHz, CD₂Cl₂, δ) 170.0, 169.6, 139.4, 138.1, 136.0, 128.6, 128.2, 127.9, 127.7, 124.8, 124.4, 121.8, 117.6, 99.9, 71.3, 58.6, 53.6, 37.1, 20.0; IR (film, cm⁻¹) 3440(bs), 2999(w), 2933(w), 2805(w), 1750(m), 1696(s), 1518(w), 1495(w), 1404(w), 1347(s), 1116(m), 1092(w), 760(w), 750(w), 730(w), 701(m), 661(m); HRMS m/z (M + Na⁺) calcd 371.1367, found 371.1372. Anal. Calcd for C₂₁H₂₀N₂O₃: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.56; H, 5.93; N, 7.96.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-4,6-dimethyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (207). Method A with vinylpyrrole **115f** and maleimide **4q** gave adduct **161**, which with method E gave **207** (404 mg, 29%) as yellow crystals: mp 132-133 °C; $[\alpha]_D^{23} +30.2$ (*c* 5.0, CHCl₃); ¹H NMR (300 MHz, CD₂Cl₂, δ) 7.54-7.58 (m, 2H, Ph), 7.30-7.40 (m, 5H, 5-H and 7-H and Ph), 6.88 (dd, $J = 3.0, 0.9$ Hz, 1H, 8-H), 5.57 (dd, $J = 9.3, 6.0$ Hz, 1H, 1'-H), 4.53 (dd, $J = 9.9, 9.9$ Hz, 1H, 2'-H), 4.04 (dd, $J = 9.9, 6.3$ Hz, 1H, 2'-H), 3.82 (s, 3H, 6-CH₃), 3.42 (s, 3H, OCH₃), 2.77 (d, $J = 0.9$ Hz, 3H, 4-CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 170.6, 169.6, 141.0, 138.0, 133.7, 129.8, 128.8, 128.4, 128.1, 123.7, 122.0, 121.3, 115.2, 100.1, 71.4, 58.9, 53.7, 33.0, 18.3; IR (film, cm⁻¹) 3442(bs), 2915(w), 2790(w), 1749(m), 1697(s), 1636(m), 1508(w), 1350(m), 1291(w), 1104(w), 762(m), 700(m); HRMS m/z (M + Na⁺) calcd 371.1367, found 371.1381. Anal. Calcd for C₂₁H₂₀N₂O₃: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.30; H, 5.81; N, 7.84.

(+)-(R)-2-(2-Methoxy-1-phenylethyl)-4,5,6-trimethyl-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (208). Method A with vinylpyrrole **115g** and maleimide **4q** gave adduct **162**,

which with method E gave **208** (333 mg, 23%) as dark-orange crystals: mp 164-165 °C; $[\alpha]_D^{23} +26.5$ (c 0.4, CHCl_3); ^1H NMR (300 MHz, CD_2Cl_2 , δ) 7.52-7.58 (m, 2H, Ph), 7.28-7.40 (m, 3H, Ph), 7.17 (d, $J = 3.0$ Hz, 1H, 7-H), 6.86 (d, $J = 3.3$ Hz, 1H, 8-H), 5.56 (dd, $J = 9.6, 6.0$ Hz, 1H, 1'-H), 4.50 (dd, $J = 9.6, 9.6$ Hz, 1H, 2'-H), 4.10 (s, 3H, 6- CH_3), 4.04 (dd, $J = 9.9, 6.0$ Hz, 1H, 2'-H), 3.42 (s, 3H, OCH_3), 2.73 (s, 3H, 4- CH_3 or 5- CH_3), 2.72 (s, 3H, 4- CH_3 or 5- CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2 , δ) 170.9, 169.4, 139.9, 138.2, 136.4, 129.2, 128.5, 128.1, 127.8, 126.9, 123.2, 122.0, 121.3, 99.5, 71.4, 58.6, 53.3, 37.9, 14.3, 13.4; IR (film, cm^{-1}) 3450(bs), 2932(w), 1748(m), 1695(s), 1519(w), 1496(w), 1395(m), 1345(m), 1309(w), 1112(w), 765(m), 731(m), 700(m); HRMS m/z ($\text{M} + \text{Na}^+$) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_3$: 385.1523, found 385.1518.

6.3 Experimental for Part III

General Method for Diels-Alder Reactions. A mixture of *N-p*-toluenesulfonyl-3-vinylpyrrole **211** (1.237 g, 0.005 mol) and the dienophile (0.0045 mol, 1.1 equiv) in chloroform (20 mL) was stirred at rt for 24 h and, if TLC analysis indicated insignificant consumption of the dienophile, was refluxed until the reaction was complete. The solvent was removed using a rotating evaporator. The crude adduct was purified by MPLC using ethyl acetate/hexanes as eluent, followed by recrystallization from dichloromethane/petroleum ether, giving the desired product in good yields.

General Method for Dehydrogenation of Diels-Alder Adducts. A mixture of the adduct (0.003 mol) and activated MnO_2 ⁴⁸ (0.015 mol, 5 equiv) in toluene (30 mL) was stirred under reflux until the reaction was complete, as indicated by TLC analysis. The mixture was cooled to rt and vacuum-filtered through a fine glass fritted funnel. The

insoluble manganese salts were washed with several portions of dichloromethane until the washings ran clear (5 x 20 mL). The combined organic filtrate and washings were evaporated to dryness using a rotating evaporator. MPLC with ethyl acetate/hexanes as eluent, followed by recrystallization from dichloromethane/petroleum ether, gave the desired product in fair to good yields.

Compounds 214-219, 223-229, 231.

1-*p*-Toluenesulfonyl-4,5,5 α ,9 α -tetrahydro-1*H*-benzo[*g*]indole-6,9-dione (214).

The general method with quinone **212** and reflux for 48 h gave **214** (1.325 g, 82%) as light-yellow crystals: mp 172-174 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.74 (d, *J* = 8.4 Hz, 2H, Ts), 7.33 (d, *J* = 8.1 Hz, 2H, Ts), 7.20 (d, *J* = 3.5 Hz, 1H, 2-H), 6.88 (d, *J* = 10.2 Hz, 1H, 8-H), 6.70 (dd, *J* = 10.4, 1.4 Hz, 1H, 7-H), 6.17 (d, *J* = 3.6 Hz, 1H, 3-H), 4.84 (d, *J* = 5.7 Hz, 1H, 9 α -H), 3.06 (dddd, *J* = 13.2, 5.5, 2.7, 1.4, 0.9 Hz, 1H, 5 α -H), 2.54-2.70 (m, 2H, 4 α -H, 4 β -H), 2.43 (s, 3H, Ts-CH₃), 2.07 (dddd, *J* = 13.6, 5.0, 2.5, 2.5 Hz, 1H, 5 β -H), 1.68 (dddd, *J* = 13.2, 13.2, 10.4, 7.4 Hz, 1H, 5 α -H); ¹³C NMR (75 MHz, CDCl₃, δ) 200.6, 196.5, 145.0, 141.5, 138.9, 136.5, 129.9, 127.2, 124.2, 123.9, 123.3, 112.6, 49.8, 47.3, 26.3, 22.8, 21.8; IR (KBr, cm⁻¹) 3382(w), 3137(w), 3101(w), 3051(m), 2946(m), 2853(m), 1702(s), 1673(s), 1595(m), 1486(w), 1433(w), 1379(s), 1276(m), 1260(m), 1228(m), 1209(w), 1173(s), 1137(m), 1121(s), 1089(s), 1061(m), 1033(m), 986(m), 923(w), 902(w), 850(m), 813(m), 775(w), 734(w), 704(m), 673(s); HRMS *m/z* (M + Na⁺) calcd 378.0771, found 378.0782. Anal. Calcd for C₁₉H₁₇NO₄S: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.35; H, 4.73; N, 3.88.

1-*p*-Toluenesulfonyl-4,5,5 α ,11 α -tetrahydro-1*H*-naphtho[2,3-*g*]indole-6,11-dione (215). The general method with naphthoquinone **213** and reflux for 5 d gave **215**

(1.235 g, 67%) as a dark-orange powder: mp 114-116 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.11-8.17 (m, 1H, 10-H), 7.97-8.03 (m, 1H, 7-H), 7.74-7.83 (m, 4H, 8-H, 9-H, Ts), 7.34 (d, *J* = 8.4 Hz, 2H, Ts), 7.40 (d, *J* = 3.3 Hz, 1H, 2-H), 6.20 (d, *J* = 3.3 Hz, 1H, 3-H), 4.99 (d, *J* = 5.4 Hz, 1H, 11α-H), 3.25 (ddd, *J* = 13.4, 5.3, 2.7 Hz, 1H, 5α-H), 2.64-2.69 (m, 2H, 4α-H, 4β-H), 2.46 (s, 3H, Ts-CH₃), 2.13 (dddd, *J* = 12.7, 4.1, 2.6, 1.4 Hz, 1H, 5β-H), 1.71 (dddd, *J* = 12.7, 12.7, 8.8, 7.4 Hz, 1H, 5α-H); ¹³C NMR (75 MHz, CDCl₃, δ) 198.5, 195.5, 144.9, 136.6, 135.9, 134.8, 134.4, 133.3, 129.9, 127.3, 127.2, 127.0, 124.9, 123.8, 123.1, 112.6, 50.1, 47.4, 26.0, 23.0, 21.8; IR (KBr, cm⁻¹) 3140(w), 3067(w), 2920(m), 2853(w), 1702(s), 1687(s), 1594(m), 1485(w), 1434(w), 1400(w), 1364(s), 1291(m), 1272(m), 1243(m), 1208(m), 1175(s), 1142(m), 1127(s), 1106(m), 1089(m), 1058(w), 1043(w), 1027(w), 986(w), 903(w), 812(w), 759(w), 716(m), 703(m), 669(s), 611(w); HRMS *m/z* (*M* + Na⁺) calcd 428.0928, found 428.0943. Anal. Calcd for C₂₃H₁₉NO₄S: C, 68.13; H, 4.72; N, 3.45. Found: C, 67.86; H, 4.71; N, 3.36.

7-(4-Isopropylphenyl)-1-*p*-toluenesulfonyl-5,5α,8α,8βα-tetrahydropyrrolo-1*H*,7*H*-benzo[*g*]indole-6,8-dione (216). The general method with maleimide **4m** and **5d** at rt gave **216** (1.472 g, 70%) as light-orange crystals: mp 96-98 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.81 (d, *J* = 8.4 Hz, 2H, Ts), 7.35 (d, *J* = 8.4 Hz, 2H, Ts), 7.27 (d, *J* = 8.4 Hz, 2H, *i*PrPh), 7.08 (d, *J* = 8.4 Hz, 2H, *i*PrPh), 6.83 (d, *J* = 4.2 Hz, 1H, 2-H), 5.69 (d, *J* = 3.9 Hz, 1H, 3-H), 5.56 (ddd, *J* = 7.4, 3.8, 3.8 Hz, 1H, 4-H), 4.23 (ddd, *J* = 6.9, 3.3, 3.4 Hz, 1H, 8βα-H), 3.97 (dd, *J* = 9.0, 7.2 Hz, 1H, 8αα-H), 3.23 (ddd, *J* = 9.0, 7.2, 1.8 Hz, 1H, 5αα-H), 3.01 (ddd, *J* = 15.5, 7.4, 1.9 Hz, 1H, 5β-H), 2.91 (septet, *J* = 6.9 Hz, 1H, -CH(CH₃)₂), 2.45 (s, 3H, Ts-CH₃), 2.05 (dddd, *J* = 15.3, 7.2, 4.1, 3.0 Hz, 1H, 5α-H), 1.23 (d, *J* = 7.2 Hz, 6H, -CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃, δ) 178.1,

173.1, 149.4, 144.5, 142.5, 137.7, 133.8, 130.1, 129.3, 127.7, 127.2, 126.2, 110.8, 110.6, 59.5, 42.3, 36.3, 34.0, 26.1, 24.0, 21.7; IR (KBr, cm^{-1}) 3472(w), 3138(w), 3104(w), 3049(w), 2960(m), 2929(m), 2870(m), 1781(w), 1714(s), 1596(m), 1565(w), 1514(m), 1491(w), 1449(m), 1371(s), 1306(m), 1294(m), 1170(s), 1123(s), 1091(m), 1056(m), 1018(m), 991(m), 900(w), 874(w), 832(m), 812(m), 767(w), 704(m), 669(s); HRMS m/z ($M + \text{Na}^+$) calcd 485.1506, found 485.1523. Anal. Calcd for $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$: C, 67.51; H, 5.67; N, 6.06. Found: C, 67.46; H, 5.61; N, 6.17.

7-(4-Phenoxyphenyl)-1-*p*-toluenesulfonyl-5,5 $\alpha\alpha$,8 $\alpha\alpha$,8 $\beta\alpha$ -tetrahydropyrrolo-1*H*,7*H*-benzo[*g*]indole-6,8-dione (217). The general method with maleimide **4e** and **5d** at rt gave **217** (1.794 g, 77%) as white crystals: mp 217-218 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.80 (d, $J = 8.1$ Hz, 2H, Ts), 7.32-7.40 (m, 4H, Ts, PhOPh), 7.14-7.17 (m, 3H, PhOPh), 6.99-7.05 (m, 4H, PhOPh), 6.85 (d, $J = 3.9$ Hz, 1H, 2-H), 5.69 (d, $J = 3.9$ Hz, 1H, 3-H), 5.56 (ddd, $J = 7.3, 3.7, 3.6$ Hz, 1H, 4-H), 4.23 (ddd, $J = 6.8, 3.2, 3.2$ Hz, 1H, 8 $\beta\alpha$ -H), 3.99 (dd, $J = 9.0, 7.2$ Hz, 1H, 8 $\alpha\alpha$ -H), 3.24 (ddd, $J = 8.9, 7.1, 1.7$ Hz, 1H, 5 $\alpha\alpha$ -H), 3.02 (ddd, $J = 15.5, 7.4, 1.4$ Hz, 1H, 5 β -H), 2.45 (s, 3H, Ts- CH_3), 2.06 (dddd, $J = 15.9, 6.9, 4.0, 2.7$ Hz, 1H, 5 α -H); ^1H NMR (300 MHz, $\text{DMSO}-d_6$, δ) 7.80 (d, $J = 8.1$ Hz, 2H, Ts), 7.38-7.46 (m, 4H, PhOPh), 7.15-7.21 (m, 1H, PhOPh), 7.03-7.07 (m, 6H, PhOPh), 6.76 (d, $J = 3.9$ Hz, 1H, 2-H), 5.80 (d, $J = 4.2$ Hz, 1H, 3-H), 5.53 (ddd, $J = 7.1, 3.7, 3.7$ Hz, 1H, 4-H), 4.29 (ddd, $J = 7.1, 3.3, 3.3$ Hz, 1H, 8 $\beta\alpha$ -H), 3.89 (dd, $J = 8.7, 7.2$ Hz, 1H, 8 $\alpha\alpha$ -H), 3.28 (ddd, $J = 8.9, 7.1, 1.4$ Hz, 1H, 5 $\alpha\alpha$ -H), 2.66 (ddd, $J = 15.2, 7.1, 1.7$ Hz, 1H, 5 β -H), 2.40 (s, 3H, Ts- CH_3), 2.12 (dddd, $J = 15.2, 7.1, 3.7, 3.3$ Hz, 1H, 5 α -H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$, δ) 178.9, 174.1, 157.0, 156.6, 144.8, 142.3, 138.0, 133.5, 130.7, 130.5, 129.0, 127.9, 127.8, 124.5, 119.6, 119.1, 111.9,

111.4, 59.8, 43.3, 36.9, 25.7, 21.6; IR (KBr, cm^{-1}) 3458(w), 3103(m), 3064(m), 2929(w), 2903(w), 2853(w), 1772(w), 1702(s), 1651(w), 1586(m), 1564(w), 1504(m), 1483(m), 1360(m), 1342(m), 1294(w), 1235(s), 1195(s), 1165(s), 1107(m), 1094(m), 1063(m), 1018(w), 991(w), 963(w), 912(w), 874(w), 845(m), 801(m), 730(m), 615(m); HRMS m/z ($M + \text{Na}^+$) calcd 535.1299, found 535.1311. Anal. Calcd for $\text{C}_{29}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$: C, 67.95; H, 4.72; N, 5.47. Found: C, 68.13; H, 4.59; N, 5.16.

7-(4-Isopropylphenyl)-1-*p*-toluenesulfonyl-4,5,5 α ,8 α -tetrahydropyrrolo-1*H*,7*H*-benzo[*g*]indole-6,8-dione (218). Diels-Alder adduct **216** (1.000 g, 2.162 mmol) was dissolved in chloroform (30 mL) and refluxed for 4 d. The solvent was removed with a rotating evaporator, giving **218** (1.000 g, quant.) as a white powder: mp 96-98 °C; ^1H NMR (300 MHz, CDCl_3 , δ) 7.99 (d, $J = 8.4$ Hz, 2H, Ts), 7.28-7.34 (m, 4H, Ts, *iPrPh*), 7.18 (d, $J = 8.7$ Hz, 2H, *iPrPh*), 7.12 (d, $J = 3.6$ Hz, 1H, 2-H), 6.16 (d, $J = 3.3$ Hz, 1H, 3-H), 5.02 (d, $J = 8.4$ Hz, 1H, 8 α -H), 3.42 (ddd, $J = 8.6, 5.9, 5.9$ Hz, 1H, 5 α -H), 2.94 (septet, $J = 7.1$ Hz, 1H, $-\text{CH}(\text{CH}_3)_2$), 2.59 (ddd, $J = 16.0, 5.5, 5.5$ Hz, 1H, 4 α -H), 2.43 (ddd, $J = 16.3, 8.6, 4.6$ Hz, 1H, 4 β -H), 2.42 (s, 3H, Ts- CH_3), 2.29 (dddd, $J = 13.3, 6.1, 6.1, 4.4$ Hz, 1H, 5 β -H), 1.99 (dddd, $J = 14.0, 8.3, 5.2, 4.8$ Hz, 1H, 5 α -H), 1.26 (d, $J = 6.9$ Hz, 6H, $-\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3 , δ) 178.1, 173.8, 149.4, 145.0, 136.5, 129.8, 129.5, 127.8, 127.3, 126.4, 125.6, 123.6, 123.0, 112.6, 41.2, 39.5, 34.0, 25.1, 24.0, 21.8, 21.2; IR (KBr, cm^{-1}) 3478(w), 3137(w), 3103(w), 3037(w), 2959(s), 2929(m), 2868(m), 1783(m), 1718(s), 1595(m), 1514(m), 1484(m), 1451(m), 1370(s), 1306(w), 1295(w), 1226(m), 1171(s), 1123(s), 1090(m), 1017(w), 990(m), 898(w), 873(w), 835(w), 812(m), 766(w), 702(m), 668(s); HRMS

m/z ($M + Na^+$) calcd 485.1506, found 485.1527. Anal. Calcd for $C_{26}H_{26}N_2O_4S$: C, 67.51; H, 5.67; N, 6.06. Found: C, 67.24; H, 5.68; N, 6.16.

7-(4-Phenoxyphenyl)-1-*p*-toluenesulfonyl-4,5,5 α ,8 α -tetrahydropyrrolo-1*H*,7*H*-benzo[*g*]indole-6,8-dione (219). Diels-Alder adduct **217** (1.000 g, 1.951 mmol) was dissolved in chloroform (30 mL) and refluxed for 4 d. The solvent was removed with a rotating evaporator, giving **219** (1.000 g, quant.) as an orange powder: mp 217-218 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 7.97 (d, $J = 8.4$ Hz, 2H, Ts), 7.30-7.41 (m, 4H, Ts, PhOPh), 7.13-7.25 (m, 4H, PhOPh), 7.02-7.08 (m, 4H, PhOPh, 2-H), 6.16 (d, $J = 3.3$ Hz, 1H, 3-H), 5.02 (d, $J = 8.4$ Hz, 1H, 8 α -H), 3.43 (ddd, $J = 8.6, 5.9, 5.9$ Hz, 1H, 5 α -H), 2.59 (ddd, $J = 16.1, 5.4, 5.4$ Hz, 1H, 4 α -H), 2.43 (ddd, $J = 16.2, 8.6, 4.7$ Hz, 1H, 4 β -H), 2.42 (s, 3H, Ts- CH_3), 2.29 (dddd, $J = 13.4, 6.0, 6.0, 4.3$ Hz, 1H, 5 β -H), 1.99 (dddd, $J = 13.6, 8.5, 5.4, 4.7$ Hz, 1H, 5 α -H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 178.0, 173.8, 157.6, 156.5, 145.0, 136.5, 130.0, 129.9, 128.0, 127.7, 126.6, 125.7, 124.0, 123.7, 122.8, 119.6, 118.8, 112.6, 41.2, 39.5, 25.0, 21.8, 21.2; IR (KBr, cm^{-1}) 3464(w), 3146(w), 3111(m), 3065(m), 2943(m), 2850(w), 1773(w), 1707(s), 1586(m), 1505(m), 1484(m), 1445(w), 1397(m), 1372(m), 1335(m), 1293(w), 1232(s), 1203(m), 1187(s), 1167(s), 1120(m), 1091(m), 1017(w), 989(w), 916(w), 901(w), 885(m), 811(m), 782(m), 743(w), 703(m), 646(m); HRMS m/z ($M + Na^+$) calcd 535.1299, found 535.1318. Anal. Calcd for $C_{29}H_{24}N_2O_5S$: C, 67.95; H, 4.72; N, 5.47. Found: C, 67.93; H, 4.64; N, 5.26.

1-*p*-Toluenesulfonyl-7 α -(1-*p*-toluenesulfonyl-1*H*-pyrrol-3-yl)-4,5,6,7 β -tetrahydro-1*H*-indole (223). A mixture of *N-p*-toluenesulfonyl-3-vinylpyrrole **211** (1.237 g, 0.005 mol) and vinylboronic acid 2-methyl-2,4-pentanediol ester **220** (693 mg,

0.0045 mol, 1.1 equiv) in chloroform (20 mL) was stirred for 3 d under reflux, at which point TLC analysis indicated a new spot had formed and no starting materials were being consumed. The solvent was removed using a rotating evaporator. The crude mixture was purified by MPLC with ethyl acetate/hexanes as eluent, followed by recrystallization from dichloromethane/petroleum ether, giving **223** (210 mg, 9%) as a white powder: mp 157-158 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.61 (d, *J* = 8.4 Hz, 2H, 1'-Ts), 7.31 (d, *J* = 8.4 Hz, 2H, 1-Ts), 7.26 (d, *J* = 8.4 Hz, 2H, 1'-Ts), 7.26 (d, *J* = 3.3 Hz, 1H, 2-H), 7.12 (d, *J* = 8.1 Hz, 2H, 1-Ts), 6.87 (dd, *J* = 3.3, 2.4 Hz, 1H, 5'-H), 6.20 (dd, *J* = 2.4, 2.1 Hz, 1H, 2'-H), 6.12 (d, *J* = 3.3 Hz, 1H, 3-H), 6.02 (dd, *J* = 3.2, 1.7 Hz, 1H, 4'-H), 4.41 (dd, *J* = 5.1, 2.4 Hz, 1H, 7β-H), 2.31-2.54 (m, 2H, 4-H), 2.41 (s, 3H, Ts-CH₃), 2.39 (s, 3H, Ts-CH₃), 1.84 (dddd, *J* = 13.1, 13.1, 5.2, 3.1 Hz, 1H, 6β-H), 1.69 (dddd, *J* = 12.8, 3.8, 2.8, 2.8 Hz, 1H, 6α-H), 1.44-1.60 (m, 1H, 5β-H), 1.24-1.48 (m, 1H, 5α-H); ¹³C NMR (75 MHz, CDCl₃, δ) 144.8, 144.6, 136.4, 135.8, 132.8, 130.1, 130.0, 129.6, 126.6, 124.0, 121.9, 120.3, 118.9, 114.4, 111.9, 31.1, 31.0, 22.9, 21.72, 21.69, 17.0; IR (KBr, cm⁻¹) 3144(m), 3113(m), 3065(w), 3031(w), 2944(s), 2925(s), 2856(m), 1596(m), 1490(m), 1473(w), 1442(w), 1424(w), 1401(w), 1365(s), 1243(m), 1232(m), 1175(s), 1146(m), 1124(s), 1094(s), 1056(s), 1019(w), 996(m), 953(w), 905(w), 874(w), 855(w), 799(m), 780(m), 775(m), 748(m), 722(m), 673(s), 630(w); HRMS *m/z* (M + Na⁺) calcd 517.1227, found 517.1241. Anal. Calcd for C₂₆H₂₆N₂O₄S₂: C, 63.13; H, 5.30; N, 5.66. Found: C, 62.91; H, 5.25; N, 5.71.

7-(4-Isopropylphenyl)-1-*p*-toluenesulfonyl-1*H*,7*H*-benzo[*g*]indole-6,8-dione (224). The general method with tetrahydroindole **218** and reflux for 3 h gave **224** (977 mg, 71%) as a white powder: mp 106-108 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.10 (d, *J*

= 3.9 Hz, 1H, 2-H), 8.00 (d, $J = 8.1$ Hz, 1H, 4-H), 7.94 (d, $J = 8.4$ Hz, 2H, Ts), 7.88 (d, $J = 7.8$ Hz, 1H, 5-H), 7.35 (d, $J = 8.4$ Hz, 2H, *i*PrPh), 7.29 (d, $J = 8.7$ Hz, 4H, *i*PrPh, Ts), 6.91 (d, $J = 3.9$ Hz, 1H, 3-H), 2.97 (septet, $J = 6.9$ Hz, 1H, -CH(CH₃)₂), 2.43 (s, 3H, Ts-CH₃), 1.29 (d, $J = 6.9$ Hz, 6H, -CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃, δ) 167.5, 164.6, 148.7, 144.8, 138.4, 136.5, 133.6, 129.73, 129.68, 129.5, 128.2, 127.7, 127.6, 127.1, 126.7, 118.4, 117.3, 108.0, 34.0, 24.0, 21.8; IR (KBr, cm⁻¹) 3648(w), 3475(w), 3154(w), 3123(w), 3070(w), 2959(s), 2901(m), 2871(m), 1776(m), 1722(s), 1619(w), 1595(m), 1537(w), 1515(m), 1453(w), 1424(m), 1402(s), 1374(s), 1309(w), 1266(m), 1247(m), 1226(w), 1190(m), 1173(s), 1150(s), 1124(m), 1093(s), 1056(w), 1016(m), 991(m), 880(w), 839(m), 811(m), 750(m), 739(m), 711(m), 666(s), 608(m); HRMS *m/z* (M + Na⁺) calcd 481.1193, found 481.1206. Anal. Calcd for C₂₆H₂₂N₂O₄S: C, 68.10; H, 4.84; N, 6.11. Found: C, 68.02; H, 5.03; N, 6.19.

7-(4-Phenoxyphenyl)-1-*p*-toluenesulfonyl-1*H*,7*H*-benzo[*g*]indole-6,8-dione (225).

The general method with tetrahydroindole **219** and reflux for 3 d gave **225** (1.144 g, 75%) as yellow crystals: mp 216-217 °C; ¹H NMR (300 MHz, CDCl₃, δ) 8.12 (d, $J = 3.6$ Hz, 1H, 2-H), 8.00 (d, $J = 7.8$ Hz, 1H, 4-H), 7.94 (d, $J = 8.1$ Hz, 2H, Ts), 7.88 (d, $J = 7.8$ Hz, 1H, 5-H), 7.31-7.45 (m, 6H, Ts, PhOPh), 7.06-7.20 (m, 5H, PhOPh), 6.91 (d, $J = 3.9$ Hz, 1H, 3-H), 2.43 (s, 3H, Ts-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 167.4, 164.7, 157.1, 156.6, 145.3, 138.6, 136.5, 134.7, 130.8, 130.3, 130.0, 129.9, 128.8, 128.1, 127.6, 127.4, 124.6, 119.8, 118.9, 118.8, 117.4, 109.4, 21.6; IR (KBr, cm⁻¹) 3159(m), 3114(m), 1773(w), 1716(s), 1587(w), 1536(w), 1506(s), 1487(m), 1454(w), 1428(m), 1398(m), 1365(s), 1320(w), 1266(m), 1233(s), 1178(m), 1147(m), 1121(m), 1093(m), 1017(m), 990(m), 938(w), 909(w), 864(w), 830(m), 806(m), 777(w), 740(m),

665(m); HRMS m/z ($M + Na^+$) calcd 531.0986, found 531.1006. Anal. Calcd for $C_{29}H_{20}N_2O_5S$: C, 68.49; H, 3.96; N, 5.51. Found: C, 68.57; H, 4.03; N, 5.33.

1-*p*-Toluenesulfonyl-1*H*-benzo[*g*]indole-6,9-dione (226). The general method with tetrahydroindole **214** and reflux for 24 h gave **226** (822 mg, 78%) as light-orange crystals: mp 186-187 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.08 (d, $J = 8.08$ Hz, 1H, 4-H), 7.91 (d, $J = 3.9$ Hz, 1H, 2-H), 7.89 (d, $J = 8.4$ Hz, 1H, 5-H), 7.89 ($J = 8.7$ Hz, 2H, Ts), 7.41 (d, $J = 8.4$ Hz, 2H, Ts), 6.97 (d, $J = 10.2$ Hz, 1H, 8-H), 6.90 (d, $J = 10.2$ Hz, 1H, 7-H), 6.83 (d, $J = 3.9$ Hz, 1H, 3-H), 2.49 (s, 3H, Ts- CH_3); 1H NMR (300 MHz, acetone- d_6 , δ) 8.11 (d, $J = 3.9$ Hz, 1H, 2-H), 8.08 (d, $J = 8.4$ Hz, 1H, 4-H), 8.04 (d, $J = 8.1$ Hz, 1H, 5-H), 7.94 (d, $J = 8.4$ Hz, 2H, Ts), 7.50 (d, $J = 8.1$ Hz, 2H, Ts), 7.09 (d, $J = 10.2$ Hz, 1H, 8-H), 7.04 (d, $J = 3.6$ Hz, 1H, 3-H), 7.01 (d, $J = 10.5$ Hz, 1H, 7-H), 2.45 (s, 3H, Ts- CH_3); ^{13}C NMR (75 MHz, DMSO- d_6 , δ) 185.3, 184.8, 145.3, 139.4, 138.0, 137.8, 136.9, 136.7, 131.6, 130.1, 129.5, 127.4, 127.3, 123.2, 122.5, 110.8, 21.6; IR (KBr, cm^{-1}) 3311(m), 3153(m), 3116(w), 3065(m), 1718(w), 1660(s), 1609(m), 1594(m), 1533(m), 1494(w), 1459(w), 1415(w), 1380(m), 1354(s), 1301(s), 1282(m), 1252(m), 1241(w), 1189(m), 1163(s), 1119(m), 1088(m), 1070(s), 997(m), 967(w), 956(w), 882(w), 860(w), 831(m), 810(m), 756(w), 720(m), 666(s), 622(w); HRMS m/z ($M + Na^+$) calcd 374.0458, found 374.0464. Anal. Calcd for $C_{19}H_{13}NO_4S$: C, 64.95; H, 3.73; N, 3.99. Found: C, 64.82; H, 4.10; N, 4.10.

1-*p*-Toluenesulfonyl-1*H*-naphtho[2,3-*g*]indole-6,11-dione (227).⁷⁶ The general method with tetrahydroindole **215** and reflux for 24 h gave **227** (867 mg, 72%) as light-orange crystals: mp 139-140 °C; 1H NMR (300 MHz, $CDCl_3$, δ) 8.31 (d, $J = 8.1$ Hz, 1H, 4-H), 8.26-8.28 (m, 1H, 8-H), 8.14-8.17 (m, 1H, 9-H), 7.91-7.95 (m, 4H, Ts, 2-H,

5-H), 7.77-7.81 (m, 2H, 7-H, 10-H), 7.43 (d, $J = 7.8$ Hz, 2H, Ts), 6.84 (d, $J = 3.6$ Hz, 1H, 3-H), 2.51 (s, 3H, Ts-CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 184.1, 182.6, 145.4, 137.8, 136.8, 135.1, 134.8, 134.7, 133.0, 132.1, 130.7, 130.1, 127.7, 127.6, 127.4, 127.0, 126.9, 125.2, 123.1, 110.8, 21.7; IR (KBr, cm⁻¹) 3180(m), 3066(m), 2915(w), 1668(s), 1593(m), 1529(w), 1458(w), 1412(w), 1379(w), 1352(m), 1324(m), 1286(s), 1258(m), 1195(w), 1172(m), 1130(w), 1095(m), 1044(w), 1014(m), 955(w), 884(w), 851(w), 811(w), 737(w), 715(m), 705(w), 669(m), 636(w); HRMS *m/z* (M + Na⁺) calcd 424.0615, found 424.0622. Anal. Calcd for C₂₃H₁₅NO₄S: C, 68.81; H, 3.77; N, 3.49. Found: C, 68.70; H, 3.79; N, 3.51.

7-(4-Isopropylphenyl)-1*H*,7*H*-benzo[*g*]indole-6,8-dione (228). 40 Mesh magnesium metal powder (245 mg, 10.1 mmol, 20 equiv) was ground with a mortar and pestle by hand for 1 min, then placed immediately in anhydrous methanol (20 mL, ≤ 0.100 % water). The indole **224** (231 mg, 0.504 mmol) was added, and the mixture was stirred under reflux for 5 h, at which time TLC analysis indicated the starting materials were completely converted. The mixture was cooled to rt, vacuum-filtered on a fritted-glass funnel, and the remaining solids were washed several times with dichloromethane (3 x 20 mL). The filtrate and washings were diluted with water (100 mL), and extracted with dichloromethane (3 x 20 mL). The dichloromethane was washed with saturated aqueous sodium bicarbonate (20 mL), water (20 mL), and brine (20 mL), and dried over anhydrous sodium sulfate. The solvent was removed using a rotating evaporator. The crude product was purified using MPLC with ethyl acetate/hexanes as eluent, and recrystallized from dichloromethane/petroleum ether giving **228** (90 mg, 59%) as bright-yellow crystals: mp 185-186 °C; ¹H NMR (300 MHz, CDCl₃, δ) 9.48 (s, 1H, 1-

H), 7.99 (d, $J = 8.1$ Hz, 1H, 4-H), 7.69 (d, $J = 8.1$ Hz, 1H, 5-H), 7.49 (dd, $J = 3.0, 2.4$ Hz, 1H, 2-H), 7.41 (d, $J = 8.1$ Hz, 2H, *iPrPh*), 7.38 (d, $J = 8.1$ Hz, 2H, *iPrPh*), 6.74 (dd, $J = 3.3, 1.8$ Hz, 1H, 3-H), 2.99 (septet, $J = 7.1$ Hz, 1H, $-CH(CH_3)_2$), 1.31 (d, $J = 7.2$ Hz, 6H, $-CH(CH_3)_2$); 1H NMR (300 MHz, DMSO- d_6 , δ) 2.19 (s, 1H, 1-H), 8.04 (d, $J = 7.8$ Hz, 1H, 4-H), 7.69 (dd, $J = 2.9, 2.9$ Hz, 1H, 2-H), 7.54 (d, $J = 7.8$ Hz, 1H, 5-H), 7.40 (d, $J = 9.0$ Hz, 2H, *iPrPh*), 7.37 (d, $J = 9.0$ Hz, 2H, *iPrPh*), 6.75 (dd, $J = 3.2, 1.7$ Hz, 1H, 3-H), 2.96 (septet, $J = 6.9$ Hz, 1H, $-CH(CH_3)_2$), 1.25 (d, $J = 6.9$ Hz, 6H, $-CH(CH_3)_2$); 1H NMR (300 MHz, acetone- d_6 , δ) 11.22 (s, 1H, 1-H), 8.10 (d, $J = 7.8$ Hz, 1H, 4-H), 7.77 (d, $J = 2.7, 2.7$ Hz, 1H, 2-H), 7.60 (d, $J = 7.8$ Hz, 1H, 5-H), 7.46 (d, $J = 9.0$ Hz, 2H, *iPrPh*), 7.42 (d, $J = 8.7$ Hz, 2H, *iPrPh*), 6.82 (dd, $J = 3.2, 2.0$ Hz, 1H, 3-H), 3.02 (septet, $J = 7.1$ Hz, 1H, $-CH(CH_3)_2$), 1.31 (d, $J = 6.9$ Hz, 6H, $-CH(CH_3)_2$); ^{13}C NMR (75 MHz, DMSO- d_6 , δ) 169.0, 168.0, 148.5, 135.5, 132.3, 130.4, 129.3, 127.9, 127.3, 126.8, 125.6, 115.0, 114.0, 103.7, 33.8, 24.4; IR (KBr, cm^{-1}) 3392(bs), 3115(w), 3041(w), 2965(m), 2873(m), 1764(m), 1702(s), 1603(w), 1579(w), 1511(s), 1481(m), 1447(m), 1414(m), 1390(s), 1366(s), 1330(m), 1294(m), 1241(m), 1229(m), 1160(w), 1128(w), 1098(s), 1082(m), 971(w), 944(w), 888(w), 851(m), 825(m), 796(w), 762(m), 730(m), 670(m); HRMS m/z ($M + Na^+$) calcd 327.1105, found 327.1102. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.78; H, 5.16; N, 9.21.

7-(4-Phenoxyphenyl)-1*H*,7*H*-benzo[*g*]indole-6,8-dione (229). 40 Mesh magnesium metal powder (96 mg, 3.93 mmol, 20 eq) was ground with a mortar and pestle by hand for 1 min, then placed immediately in anhydrous methanol (10 mL, \leq 0.100 % water). The indole **225** (100 mg, 0.196 mmol) was added, and the mixture was stirred under reflux for 5 h, at which time TLC analysis indicated complete conversion

of the starting materials. The mixture was cooled to rt, vacuum-filtered on a fritted-glass funnel, and the remaining solids were washed with dichloromethane (3 x 10 mL). The filtrate and washings were diluted with water (50 mL), and extracted with dichloromethane (3 x 10 mL). The dichloromethane was washed with saturated aqueous sodium bicarbonate (10 mL), water (10 mL), and brine (10 mL), and dried over anhydrous sodium sulfate. The solvent was removed using a rotating evaporator. The crude product was purified by MPLC with ethyl acetate/hexanes as eluent, and recrystallized from dichloromethane/petroleum ether, giving **229** (38 mg, 55%) as yellow crystals: mp 206-207 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 12.19 (s, 1H, 1-H), 8.05 (d, *J* = 7.8 Hz, 1H, 4-H), 7.70 (dd, *J* = 2.9, 2.9 Hz, 1H, 2-H), 7.56 (d, *J* = 8.1 Hz, 1H, 5-H), 7.42-7.51 (m, 4H, PhOPh), 7.09-7.23 (m, 5H, PhOPh), 6.76 (dd, *J* = 3.0, 1.8 Hz, 1H, 3-H); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 169.0, 167.9, 156.7, 135.5, 132.3, 130.8, 129.7, 129.4, 127.8, 126.8, 125.6, 124.5, 119.7, 119.0, 114.0, 105.0, 104.3, 103.7; IR (KBr, cm⁻¹) 3346(bs), 2960(m), 2922(s), 2853(m), 1761(m), 1698(s), 1590(w), 1509(m), 1486(m), 1447(m), 1392(m), 1368(m), 1332(w), 1291(w), 1245(m), 1159(w), 1109(m), 1074(m), 1009(w), 871(w), 828(w), 803(w), 756(w), 722(w); HRMS *m/z* (M + Na⁺) calcd for C₂₂H₁₄N₂O₃: 377.0897, found 377.0891.

1H-Naphtho[2,3-*g*]indole-6,11-dione (231). A mixture of indole **217** (105 mg, 0.262 mmol), saturated aqueous sodium carbonate (10 mL), and methanol (10 mL) were stirred under reflux for 6 h, at which time TLC analysis indicated starting materials were completely converted. The mixture was cooled to rt, diluted with water (100 mL), and extracted with dichloromethane (3 x 20 mL). The dichloromethane was washed with saturated aqueous ammonium chloride (20 mL), and brine (20 mL), and dried over

anhydrous sodium sulfate. The solvent was removed using a rotating evaporator, and the product was recrystallized from dichloromethane/petroleum ether, giving **231** (51 mg, 79%) as light-orange crystals: mp 205-206 °C; ¹H NMR (300 MHz, CDCl₃, δ) 10.66 (s, 1H, 1-H), 8.07 (d, *J* = 8.4 Hz, 1H, 4-H), 8.00 (d, *J* = 8.1 Hz, 1H, 5-H), 8.23-8.34 (m, 2H, 8-H, 9-H), 7.75-7.81 (m, 2H, 7-H, 10-H), 7.57 (dd, *J* = 3.0, 2.4 Hz, 1H, 2-H), 6.68 (dd, *J* = 3.3, 1.8 Hz, 1H, 3-H); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 185.0, 183.5, 135.0, 134.8, 134.70, 134.65, 133.8, 133.3, 132.8, 128.0, 127.6, 127.2, 126.7, 118.0, 117.8, 103.2; IR (KBr, cm⁻¹) 3095(w), 2960(m), 2923(m), 2852(w), 1719(w), 1668(s), 1660(m), 1590(m), 1572(w), 1545(w), 1487(m), 1445(w), 1405(w), 1329(m), 1289(s), 1235(w), 1199(w), 1158(m), 1090(s), 1048(m), 1008(m), 898(w), 844(w), 816(m), 724(s), 716(s), 638(w); HRMS *m/z* (M + Na⁺) calcd 270.0526, found 270.0538. Anal. Calcd for C₁₆H₉NO₂: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.74; H, 3.80; N, 5.49.

6.4 Experimental for Part IV

2-Thiocyanato-1H-pyrrole (232).¹⁰⁴ In a 1 L round-bottom flask, Oxone[®] (184.434 g, 0.3 mol, 1.5 equiv) was added to a mixture of ammonium thiocyanate (22.836 g, 0.3 mol, 1.5 equiv), pyrrole (13.89 mL, 13.418 g, 0.2 mol), in methanol (150 mL). The thick mixture was stirred vigorously at rt for 30 minutes. The round-bottom flask was immersed in an ice bath, and with vigorous stirring ice was added slowly until heat was no longer generated, then water was added (100 mL). The mixture was vacuum-filtered on a fritted glass funnel, the filter cake was washed with dichloromethane (3 X 25 mL), the washings and filtrate were placed in a separatory funnel, the water layer was removed, and the organics were set aside. The water layer was extracted with

dichloromethane (5 X 25 mL), and the combined organics were washed with brine, dried over anhydrous sodium sulfate, and the solvents were removed using a rotating evaporator, to give **232** as a dark burnt-rubber-smelling liquid, used immediately as is in the next step. **CAUTION!** If 2-thiocyanatopyrrole is allowed to contact the skin, even in small amounts, dark red splotches appear underneath the skin over the next 24 h and, while painless, they do not disappear for up to a month.¹²²

2-Methylthio-1H-pyrrole (239).¹⁰⁵ Methyl iodide (37.43 mL, 85.164 g, 0.6 mol, 3 equiv) was added to the freshly prepared 2-thiocyanatopyrrole **232**. Carefully, using an ice bath to maintain temperature at rt, 2 N NaOH (300 mL, 0.6 mol, 3 equiv) was added, and the mixture was stirred at rt for 2.5 h. The mixture was acidified to neutrality using 1 N HCl, and extracted with dichloromethane (3 X 75 mL). The dichloromethane was washed with water (50 mL), brine (50 mL), and dried over sodium sulfate, and the solvent was evaporated using a rotating evaporator to give **239** (34.52 g, 76% over two steps) as a dark slightly viscous liquid. ¹H NMR data matched those found in the literature.¹²³ The material was used without further purification in the next step.

5-Methylthio-1H-pyrrole-2-carboxaldehyde (240)¹²⁴. The literature procedure,²⁸ using pyrrole **239** (34.5 g, 0.305 mol), followed by vacuum distillation at about 40-60 °C/0.15 mm Hg (it was difficult to record an accurate boiling point during distillation because the compound crystallized on the thermometer and needed to be melted with a heat gun) then using trituration with hexanes (5 X 30 mL) to remove any codistilled 5-methylthio-*N*-methyl-1*H*-pyrrole-2-carboxaldehyde and recrystallization from dichloromethane/petroleum ether gave **240** (39.16 g, 91%) as white crystals: mp 101.5-102.5 °C; ¹H NMR (300 MHz, CDCl₃, δ) 9.50 (bs, 1H, 1-H), 9.41 (s, 1H, formyl-H),

6.96 (dd, $J = 3.8, 2.6$ Hz, 1H, 3-H), 6.31 (dd, $J = 3.6, 2.4$ Hz, 1H, 4-H), 2.52 (s, 3H, SCH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 178.5, 137.1, 134.3, 123.9, 113.4, 18.4.

2-Methylthio-5-vinyl-1H-pyrrole (241). Potassium *t*-butoxide (14.000 g, 0.125 mol, 2.0 equiv) was added slowly to methyltriphenylphosphonium bromide (33.581 g, 0.094 mol, 1.5 equiv) in THF (100 mL) at 0 °C. Formation of the bright yellow color characteristic of the ylide was observed immediately. The mixture was stirred at rt under nitrogen for 30 min and then cooled to 0 °C. A solution of the aldehyde **240** (7.054 g, 0.062 mmol) in THF (20 mL) was added over 5 min, with stirring, and the mixture was refluxed for 30 min until TLC analysis indicated the reaction was complete. The mixture was allowed to cool to rt and filtered. The filter cake was washed with diethyl ether (4 x 25 mL). The filtrate was washed with saturated NaHSO₃ (50 mL), saturated Na₂CO₃ (50 mL), and brine (50 mL), and dried over anhydrous Na₂SO₄. The solvents were removed using a rotating evaporator and the residue was vacuum-distilled at 39.0 °C/0.02 mm Hg, giving **241** as a colorless liquid (5.99 g, 69%): ¹H NMR (300 MHz, CDCl₃, δ) 8.47 (bs, 1H, 1-H), 6.53 (dd, $J = 18.0, 11.4$ Hz, 1H, 1'-H), 6.36 (dd, $J = 3.6, 2.4$, 1H, pyrrole-β-H), 6.24 (dd, $J = 3.0, 3.0$ Hz, 1H, pyrrole-β-H), 5.34 (d, $J = 18.0$ Hz, 1H, 2'-H *cis* to pyrrole), 5.07 (d, $J = 11.1$ Hz, 1H, 2'-H *trans* to pyrrole), 2.40 (s, 3H, SCH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 133.7, 127.5, 123.4, 116.7, 110.7, 109.8, 22.3; IR (CH₂Cl₂ thin film, cm⁻¹) 3445(bs), 3053(s), 2987(w), 2925(w), 1633(m), 1538(w), 1453(m), 1424(m), 1374(w), 1314(w), 1266(s), 1135(m), 1036(m), 982(m), 893(m), 781(s), 739(s), 705(s), 638(m). Anal. Calcd for C₇H₉NS: C, 60.39; H, 6.52; N, 10.06. Found: C, 60.13; H, 6.32; N, 9.84.

2-(4-Ethylphenyl)-7-methylthio-3 α ,4,8 α ,8 β α -tetrahydro-2H,3 α H-pyrrolo[3,4-*e*]indole-1,3-dione (242). A mixture of the vinylpyrrole **241** (2.68 g, 19.3 mmol, 1.1 equiv) and the maleimide **41** (3.53 g, 17.5 mmol, 1.0 equiv) in chloroform (30 mL) was stirred at rt for 24 h, at which point TLC analysis indicated reaction completion. The solvent was removed using a rotating evaporator. The crude adduct was purified with MPLC using ethyl acetate/hexanes as eluent, followed by recrystallization from dichloromethane/petroleum ether, giving **242** (4.230 g, 71%) as a cream-colored powder: mp 140-142 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.27 (d, *J* = 7.8 Hz, 2H, Ph), 7.09 (d, *J* = 8.4 Hz, 2H, Ph), 5.81 (ddd, *J* = 7.5, 3.6, 2.7 Hz, 1H, 5-H), 3.83 (dd, *J* = 17.3, 4.4 Hz, 1H, 8-H), 3.47 (dd, *J* = 8.9, 7.4 Hz, 1H, 8 β α -H), 3.29 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H, 3 α α -H), 3.08 (dddd, *J* = 9.7, 7.4, 4.6, 2.6, 2.0 Hz, 1H, 8 α α -H), 3.00 (ddd, *J* = 15.5, 7.5, 1.8 Hz, 1H, 4 β -H), 2.99 (dd, *J* = 17.4, 9.9 Hz, 1H, 8-H), 2.67 (q, *J* = 7.7 Hz, 2H, CH₂CH₃), 2.52 (s, 3H, SCH₃), 2.36 (dddd, *J* = 15.5, 6.7, 3.5, 2.2 Hz, 1H, 4 α -H), 1.24 (t, *J* = 7.7 Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 181.9, 178.8, 176.8, 159.2, 145.0, 129.3, 128.7, 126.4, 106.7, 41.3, 40.5, 39.6, 37.1, 28.7, 25.4, 15.5, 14.0; IR (KBr, cm⁻¹) 3053(m), 2967(s), 2927(s), 2848(m), 2595(w), 1771(w), 1702(s), 1528(s), 1514(s), 1459(w), 1397(s), 1337(m), 1313(m), 1283(m), 1251(w), 1205(s), 1092(m), 1077(m), 1052(w), 1020(w), 996(w), 958(w), 897(w), 862(w), 839(m), 799(m), 657(w); HRMS *m/z* (M + Na⁺) calcd 363.1138, found 363.1136. Anal. Calcd for C₁₉H₂₀N₂O₂S: C, 67.03; H, 5.92; N, 8.23. Found: C, 66.99; H, 6.00; N, 8.18.

2-(3-Methoxyphenyl)-7-methylthio-3 α ,4,8 α ,8 β α -tetrahydro-2H,3 α H-pyrrolo[3,4-*e*]indole-1,3-dione (243). A mixture of the vinylpyrrole **241** (2.023 g, 14.5

mmol, 1.1 equiv) and the maleimide **4s** (2.684 g, 13.2 mmol, 1.0 equiv) in chloroform (30 mL) was stirred at rt for 24 h, at which point TLC analysis indicated reaction completion. The solvent was removed using a rotating evaporator. The crude adduct was purified with MPLC using ethyl acetate/hexanes as eluent, followed by recrystallization from dichloromethane/petroleum ether, giving **243** (2.744 g, 61%) as an orange powder: mp 151-152 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.34 (dd, *J* = 8.3, 8.3 Hz, 1H, 5'-H), 6.92 (ddd, *J* = 8.4, 2.7, 0.9 Hz, 1H, 4'-H), 6.77 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H, 6'-H), 6.71 (dd, *J* = 2.1, 2.1 Hz, 1H, 2'-H), 5.81 (ddd, *J* = 7.5, 3.6, 2.7 Hz, 1H, 5-H), 3.82 (dd, *J* = 17.1, 4.2 Hz, 1H, 8-H), 3.80 (s, 3H, OCH₃), 3.47 (dd, *J* = 8.9, 7.4 Hz, 1H, 8β-H), 3.29 (ddd, *J* = 8.8, 7.1, 1.6 Hz, 1H, 3α-H), 3.08 (dddd, *J* = 10.4, 7.4, 4.2, 2.7, 2.1 Hz, 1H, 8α-H), 3.00 (ddd, *J* = 15.6, 7.5, 1.5 Hz, 1H, 4β-H), 2.99 (dd, *J* = 17.0, 10.4 Hz, 1H, 8-H), 2.52 (s, 3H, SCH₃), 2.36 (dddd, *J* = 15.6, 7.0, 3.5, 2.1 Hz, 1H, 4α-H); ¹³C NMR (75 MHz, CDCl₃, δ) 182.0, 178.6, 176.6, 160.1, 159.2, 132.8, 129.9, 118.9, 114.6, 112.5, 106.7, 55.5, 41.3, 40.5, 39.6, 37.1, 25.4, 14.0; IR (KBr, cm⁻¹) 3068(m), 3003(m), 2957(s), 2923(s), 2834(m), 2571(w), 1775(w), 1703(s), 1607(m), 1590(m), 1522(m), 1490(m), 1457(m), 1427(m), 1383(s), 1337(m), 1313(m), 1286(s), 1255(s), 1227(m), 1190(s), 1166(s), 1135(m), 1094(m), 1083(m), 1048(m), 1023(w), 960(w), 865(w), 843(w), 810(m), 783(w), 690(m); HRMS *m/z* (M + Na⁺) calcd 365.0931, found 365.0919. Anal. Calcd for C₁₈H₁₈N₂O₃S: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.82; H, 5.18; N, 7.98.

1-Methyl-2-methylthio-1H-pyrrole (246).^{104,105} In each of 2 1-L round-bottom flasks, Oxone[®] (184.434 g, 0.3 mol, 1.5 equiv) was added to a mixture of ammonium thiocyanate (22.836 g, 0.3 mol, 1.5 equiv) and 1-methylpyrrole (17.8 mL, 16.223 g, 0.2

mol), in methanol (150 mL). The thick mixture was stirred vigorously at rt for 12 h. The round-bottom flask was immersed in an ice bath, and with vigorous stirring ice was added slowly until heat was no longer generated, then water was added (100 mL). The mixture was vacuum-filtered on a fritted glass funnel, the filter cake was washed with dichloromethane (5 X 25 mL), the washings and filtrate were placed in a separatory funnel, the water layer was removed, and the organics were set aside. The water layer was extracted with dichloromethane (3 X 50 mL), and the combined organics were washed with brine, dried over anhydrous sodium sulfate, and the solvents were removed using a rotating evaporator, and the crude products from each of the two reactions were combined to give the crude 1-methyl-2-thiocyanato-1*H*-pyrrole as a dark foul-smelling liquid, used immediately as is in the next step.¹²⁵ Methyl iodide (74.86 mL, 170.33 g, 1.2 mol, 3 equiv) was added to the freshly prepared 2-thiocyanatopyrrole. Carefully, using an ice bath to maintain temperature at rt, 2N NaOH (600 mL, 1.2 mol, 3 equiv) was added, and the mixture was stirred at rt for 2.5 h. The mixture was acidified to neutrality using 1 N HCl, and extracted with dichloromethane (3 X 150 mL). The dichloromethane was washed with water (100 mL), brine (100 mL), and dried over sodium sulfate, and the solvent was removed using a rotating evaporator to give **246** (38.33 g, 75% over two steps) as a dark slightly viscous liquid. ¹H NMR data matched those found in the literature.^{125,126} The material was used without further purification in the next step.

2-Methylthio-5-thioacetyl-1*H*-pyrrole (249).^{51,102} 2-Methylthio-5-acetylpyrrole **247**^{91,109} (8.657g, 55.773 mmol) was dissolved in THF (250 mL). Lawesson's reagent (27.07 g, 66.928 mmol, 1.2 equiv) was added, and the mixture was stirred at rt for 3 h,

at which time TLC indicated complete consumption of the starting material. The solvent was removed using a rotating evaporator, and the crude product was run through a short silica gel column, using 1:2 ethyl acetate:hexanes. The solvent was removed using a rotating evaporator, to give **249** (7.735 g, 81%) as brown plates: mp 75-76 °C; ¹H NMR (300 MHz, CDCl₃, δ) 9.50 (bs, 1H, 1-H), 6.94 (dd, *J* = 3.9, 2.4 Hz, 1H, 3-H), 6.27 (dd, *J* = 4.2, 2.7 Hz, 1H, 4-H), 2.84 (s, 3H, thioacetyl), 2.52 (s, 3H, thioacetyl); ¹³C NMR (75 MHz, CDCl₃, δ) 143.2, 140.8, 116.0, 114.0, 34.1, 17.7; IR (KBr, cm⁻¹) 3291(bs), 2977(m), 1709(w), 1524(m), 1459(m), 1432(m), 1379(s), 1341(m), 1319(m), 1227(m), 1190(m), 1142(m), 1078(w), 1059(m), 990(w), 970(w), 969(w), 931(w), 865(w), 832(s), 760(s). Anal. Calcd for C₇H₉N₁S₂: C, 49.09; H, 5.30; N, 8.18. Found: C, 48.98; H, 5.46; N, 7.99.

1-Methyl-2-methylthio-5-thioacetyl-1H-pyrrole (250).^{51,102} Crude 1-methyl-2-methylthio-5-acetylpyrrole **248**^{91,109} (9.15 g, 54.064 mmol, included approximately 13% 2- and 3-acetyl-1-methylpyrrole by mass) was dissolved in THF (250 mL). Lawesson's reagent (26.24 g, 64.877 mmol, 1.2 equiv) was added, and the mixture was stirred at rt for 3 h, at which time TLC indicated complete consumption of the starting materials. The solvent was removed using a rotating evaporator, and the crude product was run through a short silica gel column, using 1:2 ethyl acetate:hexanes. The solvent was removed using a rotating evaporator, to give **250** (5.207 g, 52%) as a dark foul-smelling liquid which included approximately 15% impurities by mass: ¹H NMR (300 MHz, CDCl₃, δ, only peaks from **250** reported) 7.17 (d, *J* = 4.5 Hz, 1H, 3-H), 6.17 (d, *J* = 4.8 Hz, 1H, 4-H), 4.07 (s, 3H, 1-CH₃), 2.95 (s, 3H, thioacetyl), 2.48 (s, 3H, SCH₃); HRMS *m/z* (M + H⁺) calcd 186.0412, found 186.0402.

2-(4-Ethylphenyl)-5 β ,7-bis(methylthio)-3 $\alpha\alpha$,4,5 α ,8 $\beta\alpha$ -tetrahydro-2H,8H-pyrrolo[3,4-*e*]indole-1,3-dione (253). A mixture of the vinylpyrroles **251** and **252** (2.919 mmol, 1 equiv, generated freshly from 500 mg 2-Methylthio-5-thioacetyl-1H-pyrrole **249**, approximately 2:1 **252:251** by mass) and the maleimide **4l** (1.1 equiv) in chloroform was stirred at rt for 24 h and, if TLC analysis indicated insignificant consumption of the dienophile, was refluxed until reaction completion. The solvent was removed using a rotating evaporator. The crude adduct was purified with MPLC using ethyl acetate/hexanes as eluent, followed by recrystallization from methylene chloride/petroleum ether, giving **253** (405 mg, 38%) as a white powder: mp 136-137 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.25 (d, *J* = 8.7 Hz, 2H, Ph), 7.19 (d, *J* = 8.7 Hz, 2H, Ph), 6.50 (s, 1H, 7-H), 4.13 (d, *J* = 9.3 Hz, 1H, 8 $\beta\alpha$ -H), 4.07 (dd, *J* = 3.9, 2.4 Hz, 1H, 5 α -H), 3.65 (s, 3H, 6-Me), 3.33 (ddd, *J* = 9.2, 7.1, 2.0 Hz, 1H, 3 $\alpha\alpha$ -H), 3.03 (ddd, *J* = 14.6, 2.0, 2.0 Hz, 1H, 4 β -H), 2.65 (q, *J* = 7.6 Hz, 2H, -CH₂CH₃), 2.27 (s, 3H, MeS), 2.18 (s, 3H, MeS), 2.16 (ddd, *J* = 14.7, 6.9, 3.9 Hz, 1H, 4 α -H), 1.22 (t, *J* = 7.7 Hz, 3H, -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 179.5, 177.3, 145.2, 130.7, 129.9, 129.2, 127.0, 125.9, 114.6, 112.7, 39.6, 38.4, 38.2, 30.5, 29.3, 26.4, 21.4, 16.13, 16.11; IR (KBr, cm⁻¹) 2965(m), 2916(m), 1775(w), 1705(s), 1514(m), 1444(m), 1432(m), 1395(m), 1347(w), 1309(w), 1296(w), 1258(w), 1216(m), 1191(m), 1139(w), 1109(w), 960(w), 870(w), 837(w), 817(m), 789(w), 761(w); HRMS *m/z* (M + Na⁺) calcd 423.1172, found 423.1187. Anal. Calcd for C₂₁H₂₄N₂O₂S₂: C, 62.97; H, 6.04; N, 6.99. Found: C, 62.77; H, 5.95; N, 6.77.

2-(4-Ethylphenyl)-8-(1-(4-ethylphenyl)-2,5-dioxopyrrolidin-3-yl)- 5 β ,7-bis(methylthio)-3 $\alpha\alpha$,4,5 α ,8 $\beta\alpha$ -tetrahydro-2H,8H-pyrrolo[3,4-*e*]indole-1,3-dione

(254). From the above procedure for **253**, also isolated by MPLC from the crude product, following recrystallization from methylene chloride/petroleum ether, to give **254** (54 mg, 7%) as white crystals: mp 207-208 °C; ¹H NMR (300 MHz, CDCl₃, δ) 7.32 (d, *J* = 8.7 Hz, 2H, Ph), 7.24-7.27 (m, 4H, Ph), 7.16 (d, *J* = 8.4 Hz, 2H, Ph), 4.80 (dd, *J* = 9.8, 6.8 Hz, 1H, 3'-H), 4.26 (d, *J* = 9.3 Hz, 1H, 8β-H), 4.10 (dd, *J* = 3.8, 2.3 Hz, 1H, 5α-H), 3.72 (s, 3H, 6-Me), 3.28 (ddd, *J* = 9.0, 7.4, 1.5 Hz, 1H, 3α-H), 3.24 (dd, *J* = 9.6, 17.7 Hz, 1H, 4'-H), 3.0 (dd, *J* = 18.0, 6.6 Hz, 1H, 4'-H), 3.01 (ddd, *J* = 14.6, 2.0, 2.0 Hz, 1H, 4β-H), 2.69 (q, *J* = 7.6 Hz, 2H, -CH₂CH₃), 2.66 (q, *J* = 7.6 Hz, 2H, -CH₂CH₃), 2.20 (s, 3H, MeS), 2.19 (s, 3H, MeS), 2.13 (ddd, *J* = 14.5, 7.1, 3.9 Hz, 1H, 4α-H), 1.26 (t, *J* = 7.5 Hz, 3H, -CH₂CH₃), 1.23 (t, *J* = 7.5 Hz, 3H, -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃, δ) 179.4, 179.1, 177.5, 176.8, 145.4, 145.3, 130.80, 130.76, 130.5, 129.4, 129.2, 127.4, 126.9, 39.2, 38.6, 38.5, 38.2, 30.8, 29.33, 29.31, 26.2, 16.2, 16.1; IR (KBr, cm⁻¹) 2960(m), 2923(m), 1776(w), 1709(s), 1514(m), 1457(w), 1419(w), 1388(m), 1353(w), 1177(s), 986(w), 970(w), 877(w), 829(m), 753(m), 732(w); HRMS *m/z* (M + Na⁺) calcd 624.1962, found 624.1984. Anal. Calcd for C₃₃H₃₅N₃O₄S₂: C, 65.86; H, 5.86; N, 6.98. Found: C, 65.98; H, 6.01; N, 6.84.

2-(4-Ethylphenyl)-7-methylthio-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (257). A mixture of the adduct **242** (5.31 g, 15.6 mmol, 1 equiv) and activated MnO₂⁴⁸ (6.78 g, 78.0 mmol, 5 equiv) in toluene (30 mL) was stirred with reflux for 3 h, at which time TLC analysis indicated reaction completion. The mixture was cooled to rt and vacuum-filtered through a fine glass fritted funnel. The insoluble manganese salts were washed with several portions of dichloromethane until the washings ran clear (5 x 20 mL), and the combined organic filtrate and washings were evaporated to dryness using a rotating

evaporator. MPLC with ethyl acetate/hexanes as eluent followed by recrystallization from dichloromethane/petroleum ether gave **257** (3.016 g, 58%) as yellow crystals: mp 280-282 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 12.30 (bs, 1H, 6-H), 7.67 (dd, *J* = 8.3, 0.8 Hz, 1H, 5-H), 7.56 (d, *J* = 8.1 Hz, 1H, 4-H), 7.36 (d, *J* = 8.7 Hz, 2H, Ph), 7.33 (d, *J* = 8.4 Hz, 2H, Ph), 6.71 (dd, *J* = 1.8, 0.6 Hz, 1H, 8-H), 2.67 (q, *J* = 7.6 Hz, 2H, CH₂CH₃), 2.67 (s, 3H, SCH₃), 1.23 (t, *J* = 7.7 Hz, 3H, CH₂CH₃); ¹H NMR (300 MHz, Acetone-*d*₆, δ) 11.28 (bs, 1H, 6-H), 7.76 (dd, *J* = 8.1, 0.9 Hz, 1H, 5-H), 7.61 (d, *J* = 8.4 Hz, 1H, 4-H), 7.44 (d, *J* = 8.7 Hz, 2H, Ph), 7.38 (d, *J* = 8.7 Hz, 2H, Ph), 6.85 (d, *J* = 2.1, 0.9 Hz, 1H, 8-H), 2.74 (q, *J* = 7.6 Hz, 2H, -CH₂-CH₃), 2.74 (s, 3H, -SCH₃), 1.29 (t, *J* = 7.5 Hz, 3H, -CH₂CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.9, 168.5, 143.8, 143.0, 142.5, 130.4, 128.7, 127.8, 124.2, 124.1, 120.6, 115.7, 115.5, 98.4, 28.4, 16.2, 16.0; IR (KBr, cm⁻¹) 3352(bs), 3041(w), 2971(m), 2927(m), 2856(w), 1753(m), 1695(s), 1516(m), 1491(m), 1464(m), 1456(m), 1419(w), 1386(s), 1365(s), 1318(w), 1277(m), 1232(m), 1180(w), 1154(m), 1117(w), 1097(m), 1061(w), 1016(w), 949(w), 810(w), 801(w), 760(m), 750(m); HRMS *m/z* (M + Na⁺) calcd 359.0825, found 359.0836. Anal. Calcd for C₁₉H₁₆N₂O₂S: C, 67.84; H, 4.79; N, 8.33. Found: C, 67.60; H, 5.20; N, 8.44.

2-(3-Methoxyphenyl)-7-methylthio-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (258).

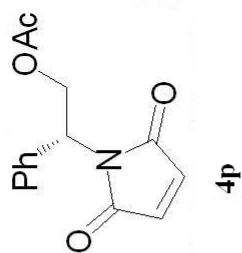
A mixture of the adduct **243** (2.26g, 6.6 mmol, 1 equiv) and activated MnO₂⁴⁸ (2.87g, 33 mmol, 5 equiv) in toluene (20 mL) was stirred with reflux for 3 h, at which time TLC analysis indicated reaction completion. The mixture was cooled to rt and vacuum-filtered through a fine glass fritted funnel. The insoluble manganese salts were washed with several portions of dichloromethane until the washings ran clear (5 x 20 mL), and

the combined organic filtrate and washings were evaporated to dryness using a rotating evaporator. MPLC with ethyl acetate/hexanes as eluent followed by recrystallization from dichloromethane/petroleum ether gave **258** (1.879 g, 84%) as yellow crystals: mp 232-233 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 12.31 (bs, 1H, 6-H), 7.66 (d, *J* = 8.4 Hz, 1H, 5-H), 7.55 (d, *J* = 8.1 Hz, 1H, 4-H), 7.43 (dd, *J* = 8.1, 8.1 Hz, 1H, 5'-H), 6.98-7.06 (m, 3H, 2'-H, 4'-H, 6'-H), 6.70 (d, *J* = 0.9 Hz, 1H, 8-H), 3.79 (s, 3H, OCH₃), 2.67 (s, 3H, SCH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.7, 168.3, 160.0, 143.0, 142.5, 134.0, 130.0, 124.2, 124.0, 120.5, 120.0, 115.8, 115.5, 113.7, 98.5, 55.8, 16.0; IR (KBr, cm⁻¹) 3316(bs), 2957(w), 2922(w), 1753(m), 1703(s), 1607(m), 1495(m), 1459(m), 1387(m), 1371(m), 1316(w), 1288(w), 1264(m), 1217(m), 1181(w), 1152(w), 1098(m), 1034(w), 1022(w), 977(w), 946(w), 902(w), 852(w), 800(w), 768(m), 715(m), 680(w); HRMS *m/z* (M + Na⁺) calcd for C₁₈H₁₄N₂O₃S 361.0638, found 361.0643.

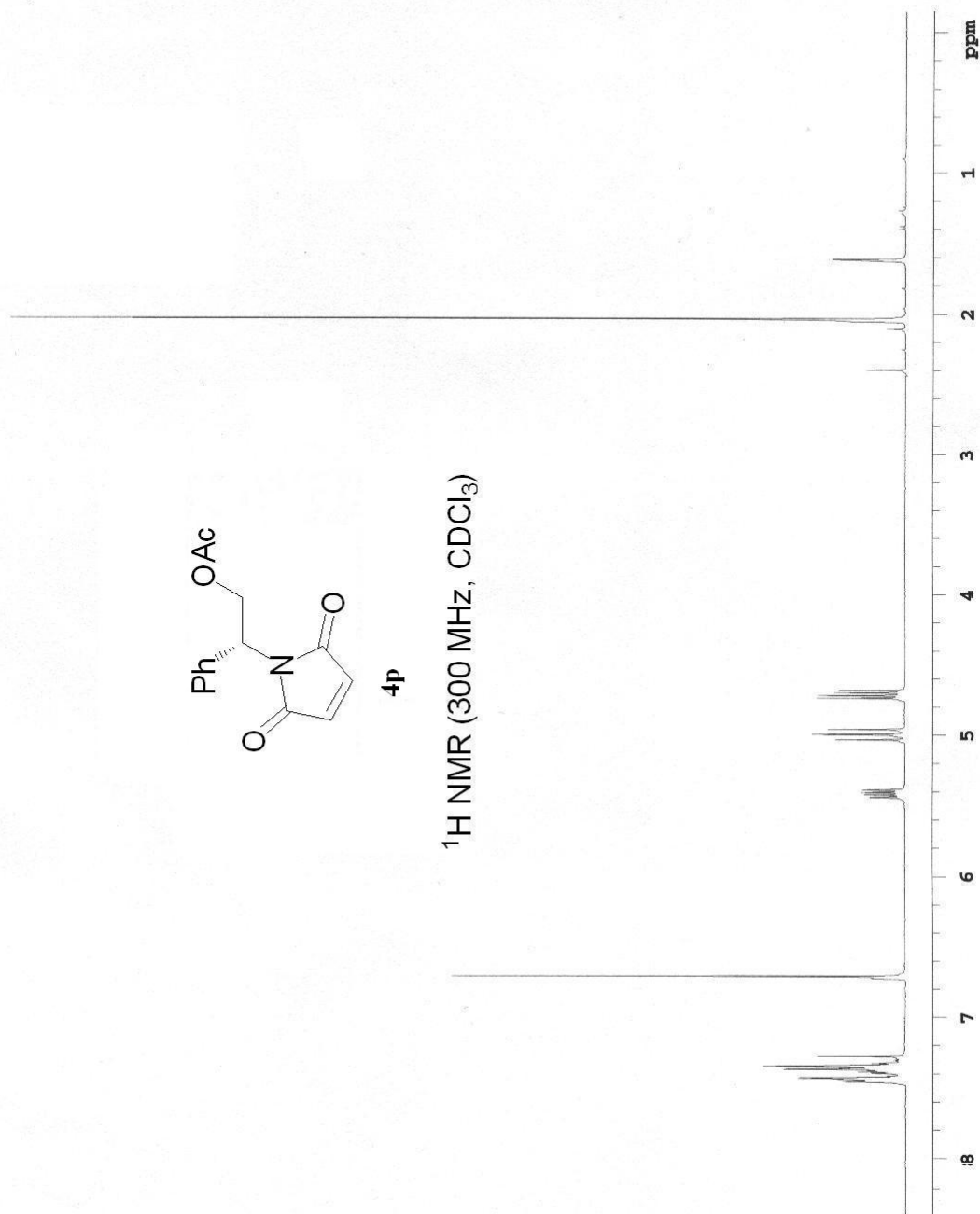
2-(4-Ethylphenyl)-2H,6H-pyrrolo[3,4-*e*]indole-1,3-dione (259).^{92,111} The indole **257** (68 mg, 0.202 mmol) was dissolved in acetone (5 mL), and Raney nickel (300 mg, 5.11 mmol) was added in excess. The reaction was stirred at rt and monitored by TLC, the starting material was observed to be completely consumed after 2 h. The solvent was removed using a rotating evaporator, and the crude product was subjected to MPLC, giving **259** (46 mg, 78%) as light-yellow crystals: mp 172-173 °C; ¹H NMR spectra matched those in the literature;¹² ¹³C NMR (75 MHz, CDCl₃, δ) 169.4, 168.9, 144.1, 140.8, 130.1, 129.7, 128.7, 126.8, 124.8, 123.6, 123.4, 116.5, 102.0, 28.7, 15.6; HRMS *m/z* (M + Na⁺) calcd 313.0948, found 313.0948. Note that this compound is identical to compound **174**, but was prepared via a different method.¹²

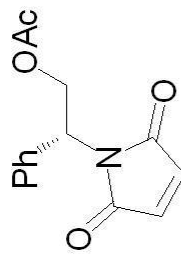
2-(3-Methoxyphenyl)-2*H*,6*H*-pyrrolo[3,4-*e*]indole-1,3-dione (260).^{92,111} The indole **258** (66 mg, 0.195 mmol) was dissolved in acetone (5 mL), and Raney nickel (300 mg, 5.11 mmol) was added in excess. The reaction was stirred at rt and monitored by TLC, the starting material was observed to be completely consumed after 2 hours. The solvent was removed using a rotating evaporator, and the crude product was recrystallized from methylene chloride/petroleum ether, giving **260** (57 mg, 100%) as light-yellow crystals: mp 202-203 °C; ¹H NMR (300 MHz, DMSO-*d*₆, δ) 12.02 (bs, 1H, 6-H), 7.87 (dd, *J* = 8.3, 0.8 Hz, 1H, 5-H), 7.82 (dd, *J* = 2.9, 2.9 Hz, 1H, 5'-H), 7.63 (d, *J* = 8.1 Hz, 1H, 4-H), 7.43 (dd, *J* = 8.1, 8.1 Hz, 1H, 4'-H), 6.98-7.07 (m, 3H, 7-H, 2'-H, 6'-H), 6.85-6.88 (m, 1H, 8-H), 3.79 (s, 3H, OCH₃); ¹H NMR (300 MHz, acetone-*d*₆) 11.2 (bs, 1H, 6-H), 7.95 (dd, *J* = 8.1, 0.9 Hz, 1H, 5-H), 7.82 (dd, *J* = 2.9, 2.9 Hz, 1H, 7-H), 7.68 (d, *J* = 8.4 Hz, 1H, 4-H), 7.45 (dd, *J* = 8.3, 8.3 Hz, 1H, 5'-H), 7.14-7.16 (m, 1H, 4'-H or 6'-H), 7.12 (dd, *J* = 1.8, 0.9 Hz, 1H, 2'-H), 7.01 (ddd, *J* = 3.3, 2.3, 1.1 Hz, 1H, 8-H), 6.98-7.01 (m, 1H, 4'-H or 6'-H), 3.79 (s, 3H, OCH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, δ) 168.8, 168.5, 160.0, 141.4, 134.0, 132.6, 130.0, 124.2, 123.1, 123.0, 120.1, 117.6, 115.9, 113.8, 100.5, 55.9; IR (KBr, cm⁻¹) 3362(m), 3304(m), 2922(w), 1762(m), 1703(s), 1606(m), 1496(m), 1461(m), 1387(m), 1370(m), 1343(w), 1319(w), 1262(m), 1217(w), 1154(w), 1097(w), 1072(w), 1039(w), 1009(w), 972(w), 906(w), 852(w), 740(w), 715(w); HRMS *m/z* (M + Na⁺) calcd 315.0741, found 315.0733. Anal. Calcd for C₁₇H₁₂N₂O₃: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.61; H, 4.32; N, 9.36.

Appendix 1. ^1H and ^{13}C NMR Spectra



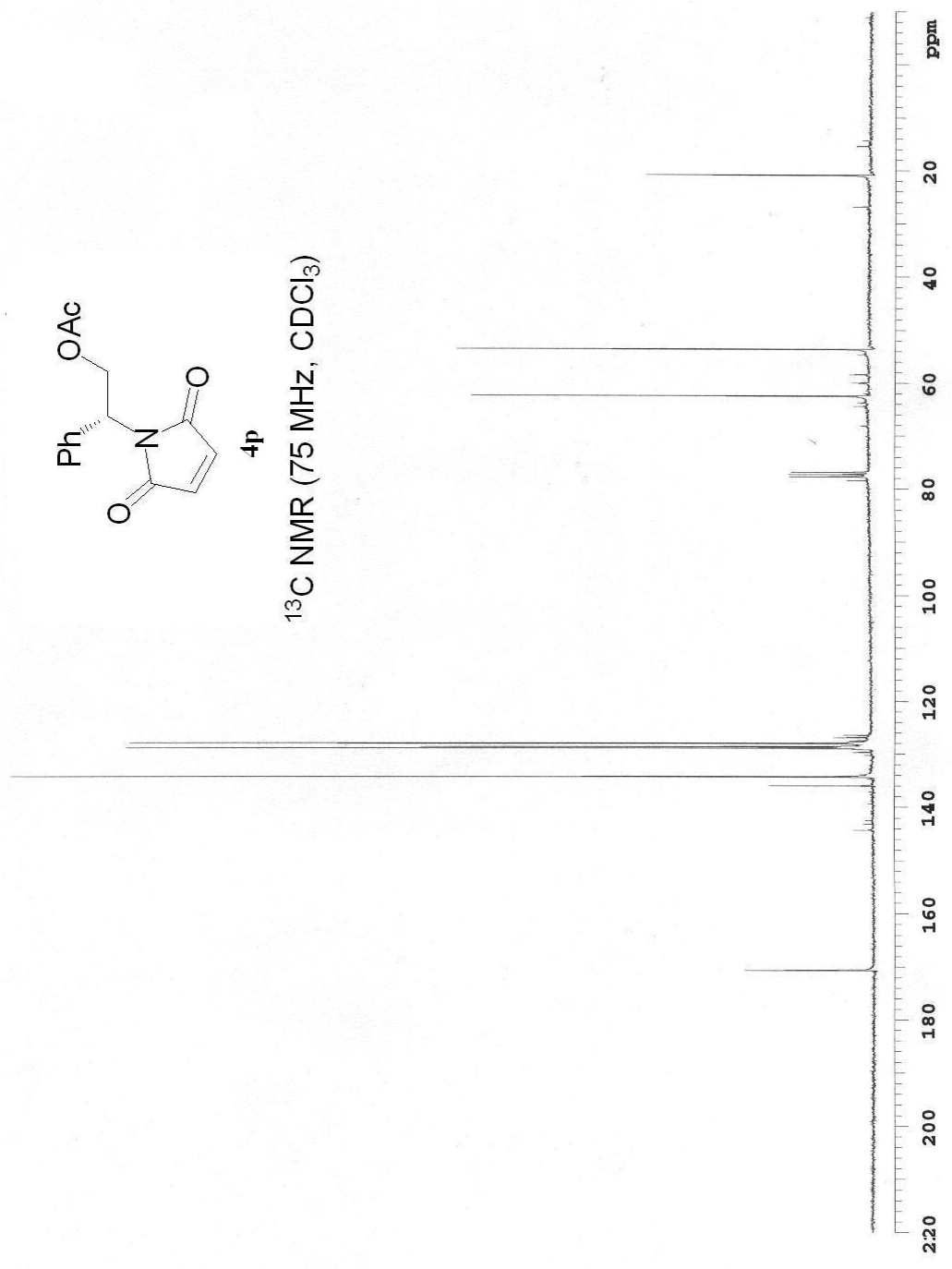
^1H NMR (300 MHz, CDCl_3)

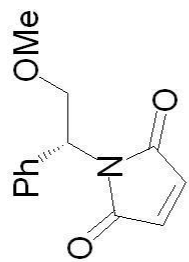




4p

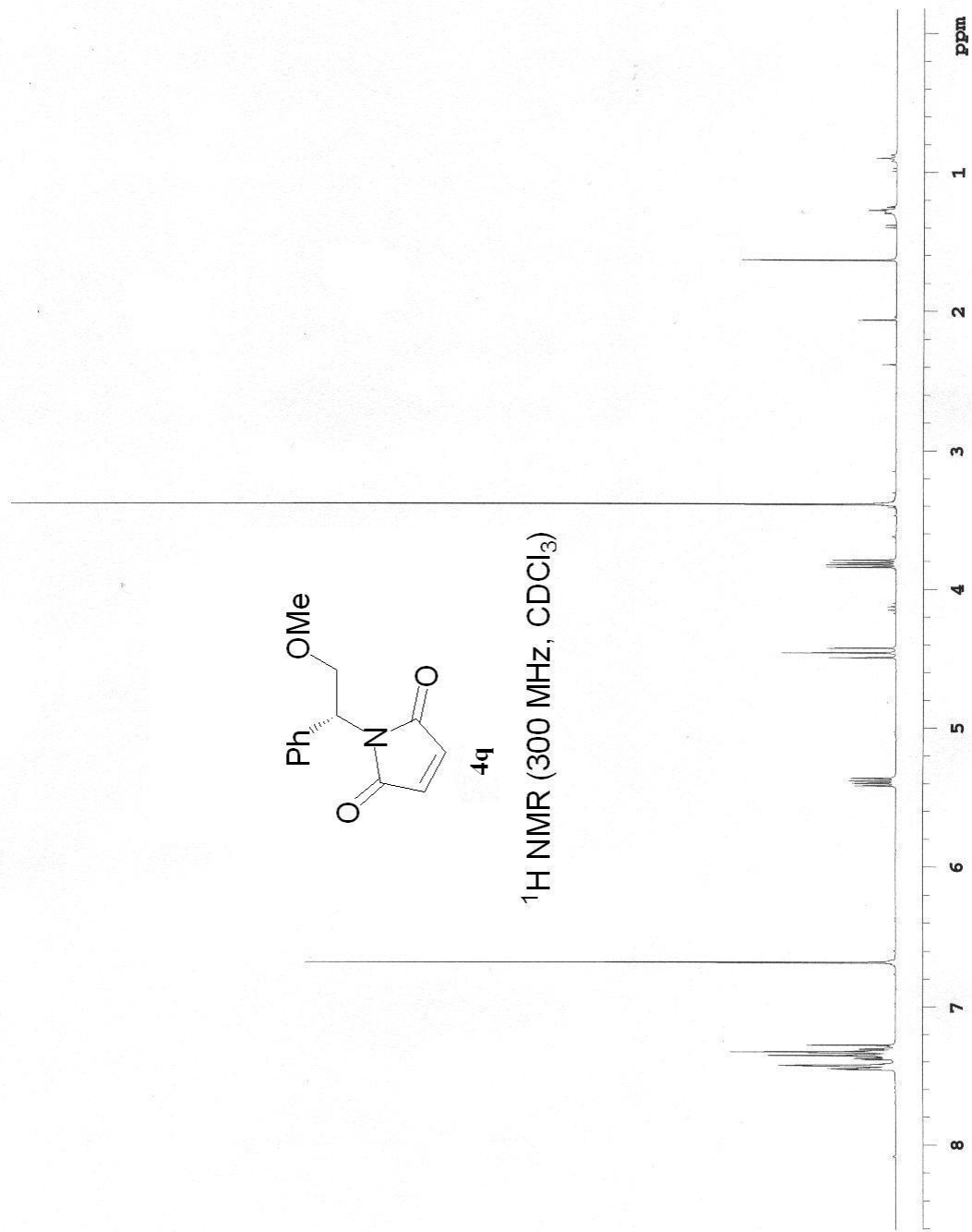
¹³C NMR (75 MHz, CDCl₃)

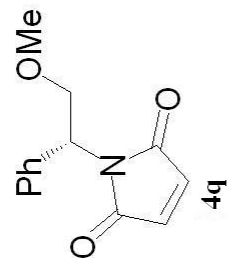




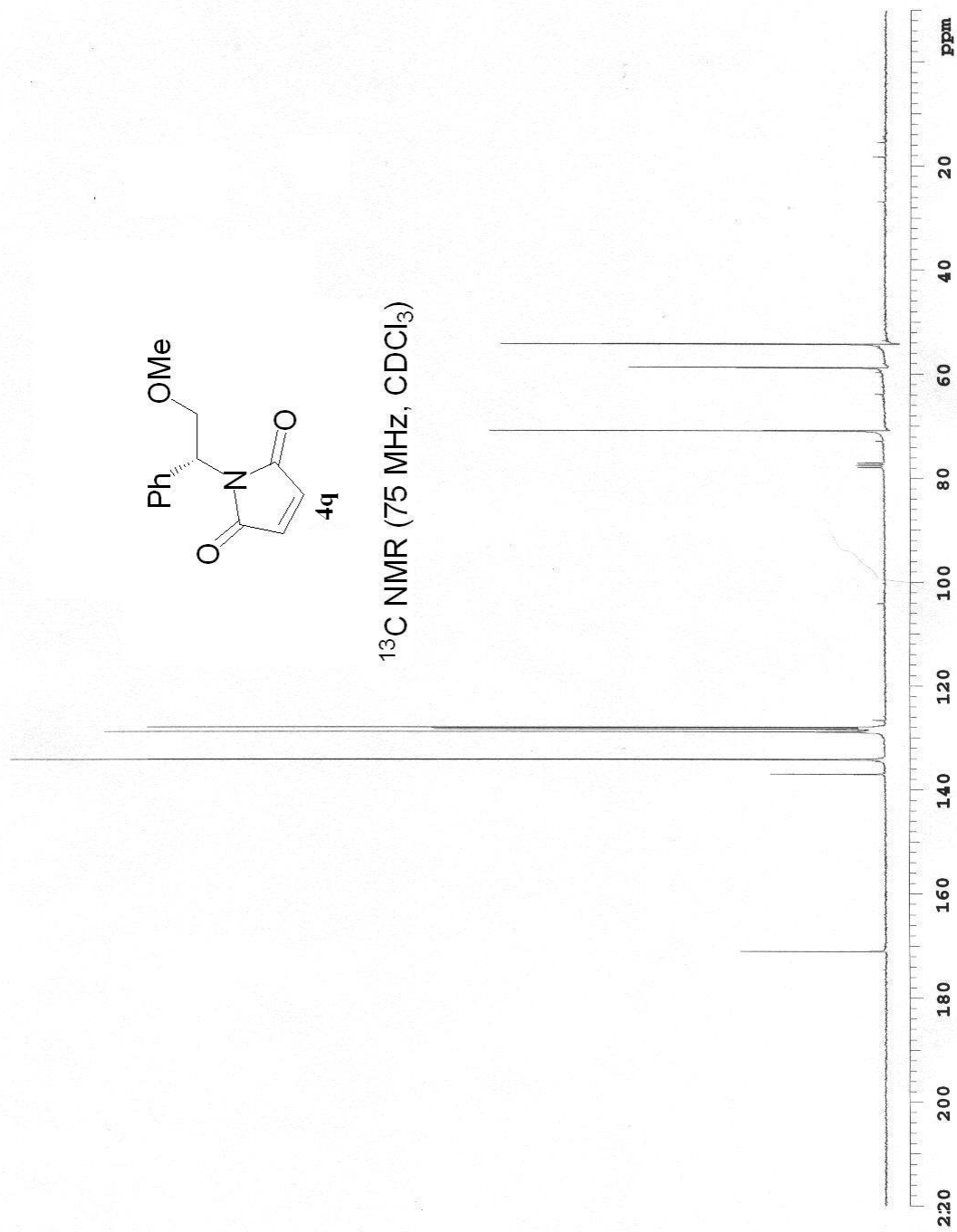
4q

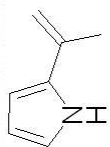
$^1\text{H NMR}$ (300 MHz, CDCl_3)





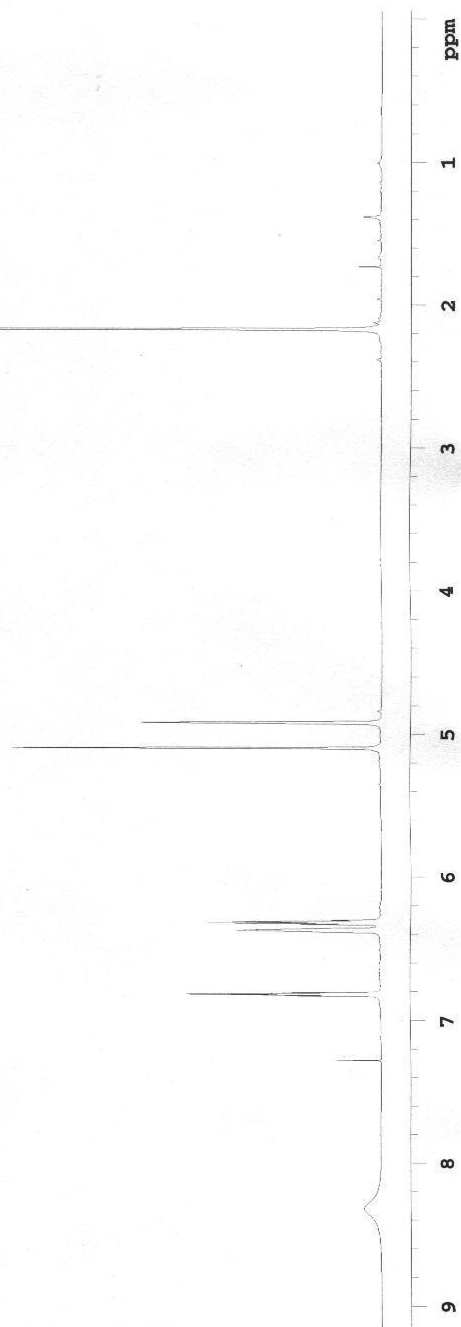
^{13}C NMR (75 MHz, CDCl_3)

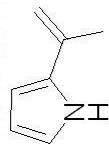




115a

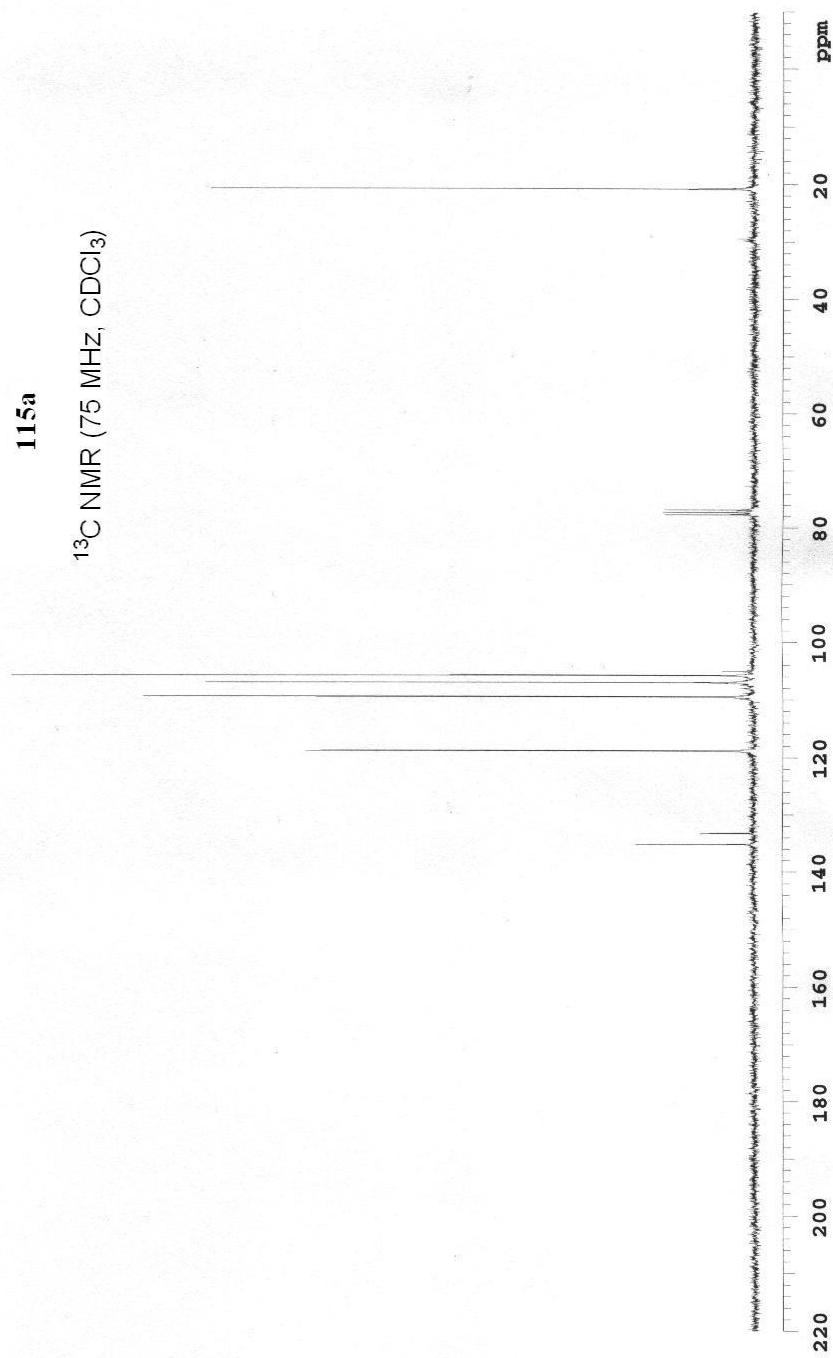
^1H NMR (300 MHz, CDCl_3)

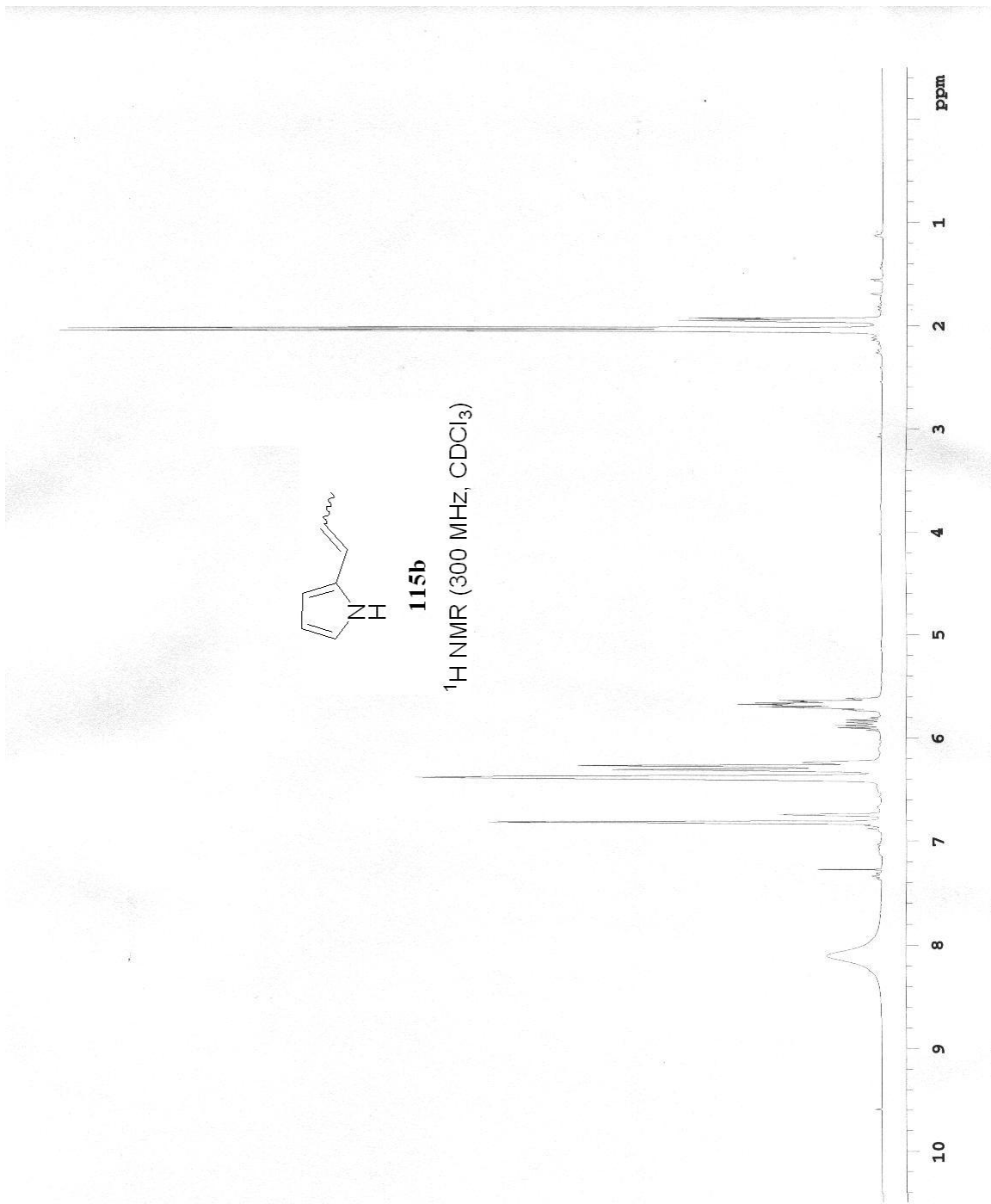




115a

^{13}C NMR (75 MHz, CDCl_3)

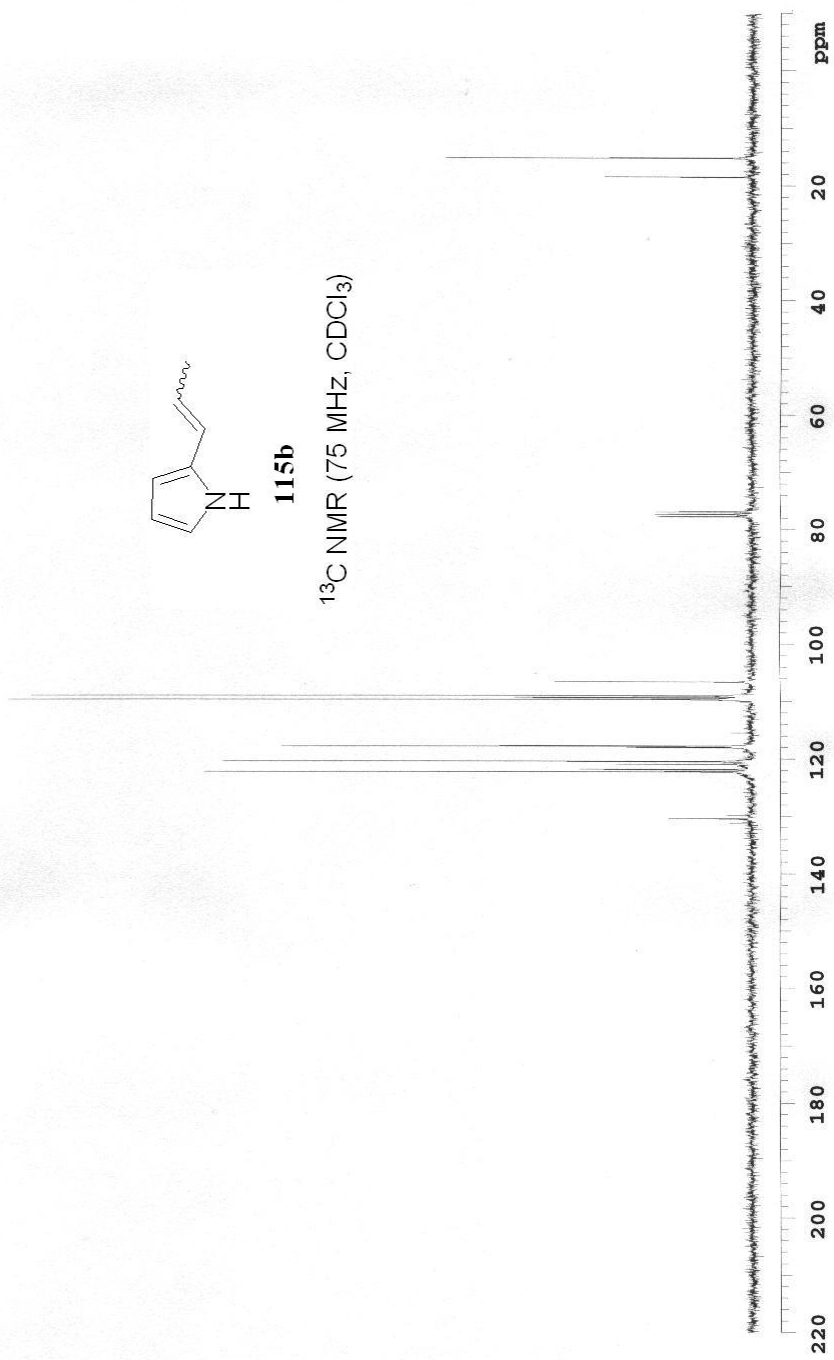


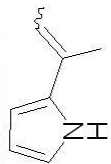




115b

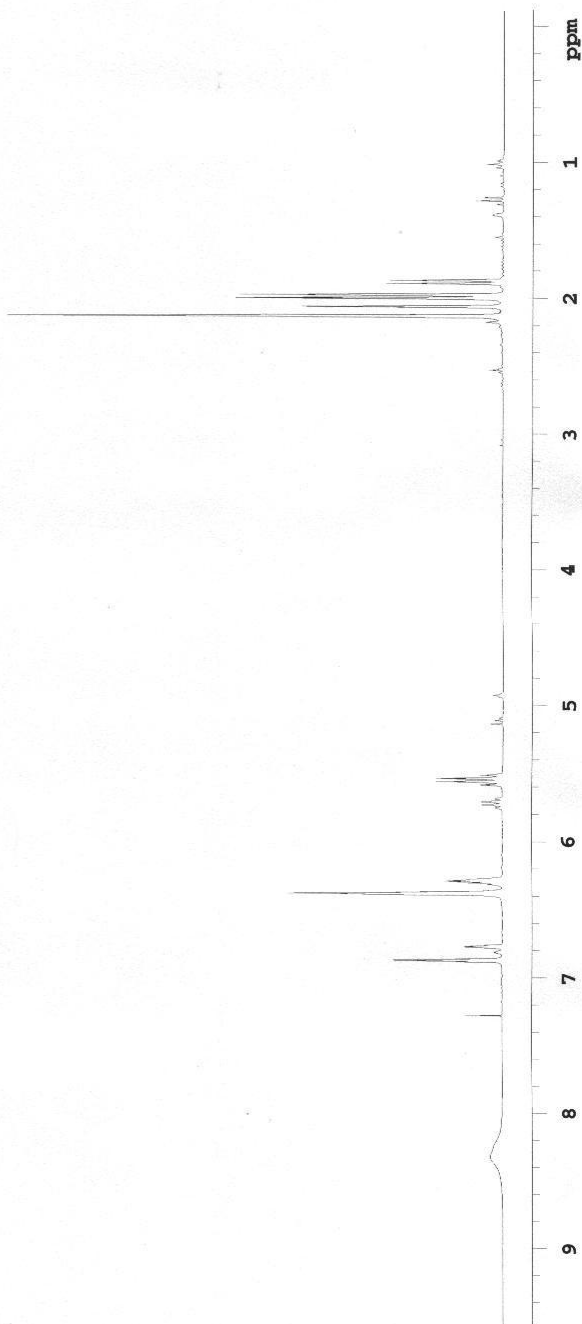
¹³C NMR (75 MHz, CDCl₃)

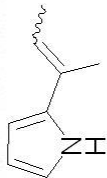




115c

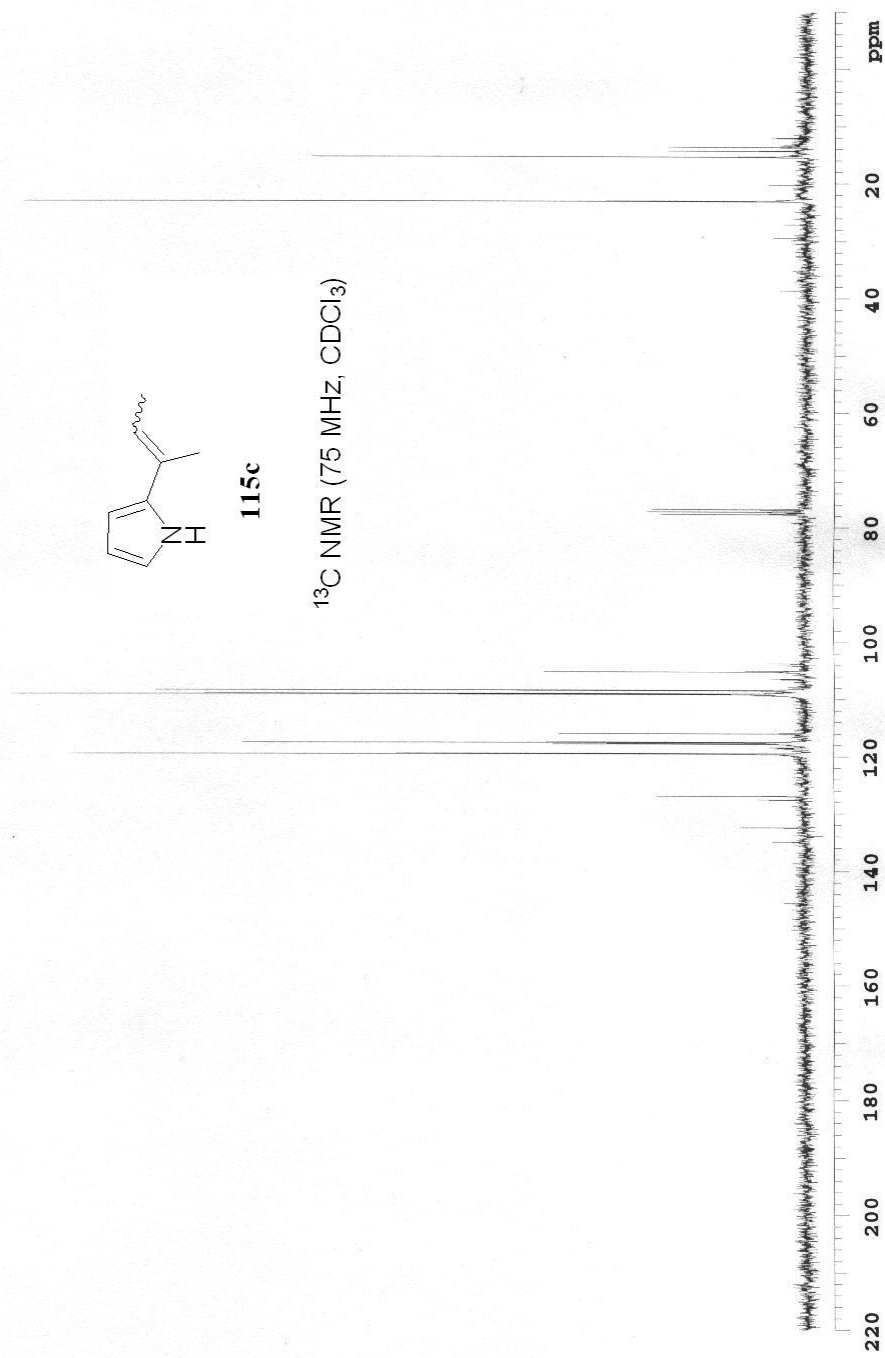
¹H NMR (300 MHz, CDCl₃)

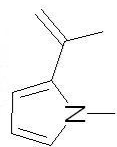




115c

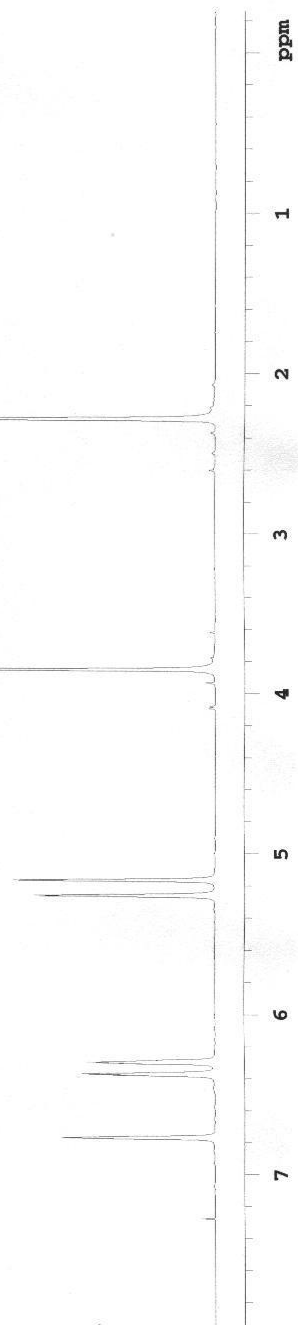
^{13}C NMR (75 MHz, CDCl_3)

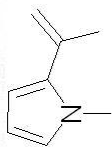




115e

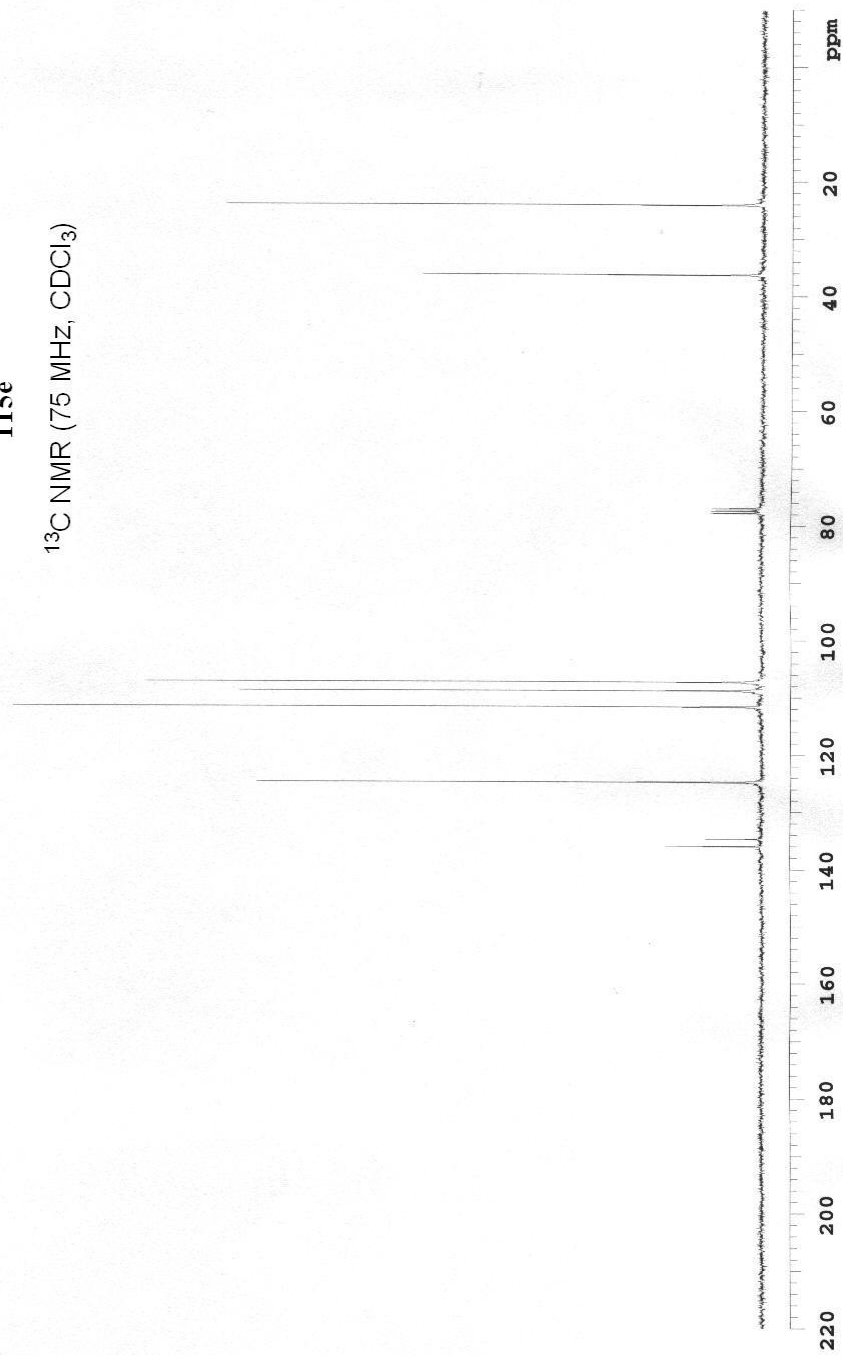
¹H NMR (300 MHz, CDCl₃)

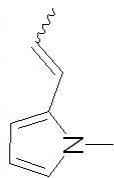




115e

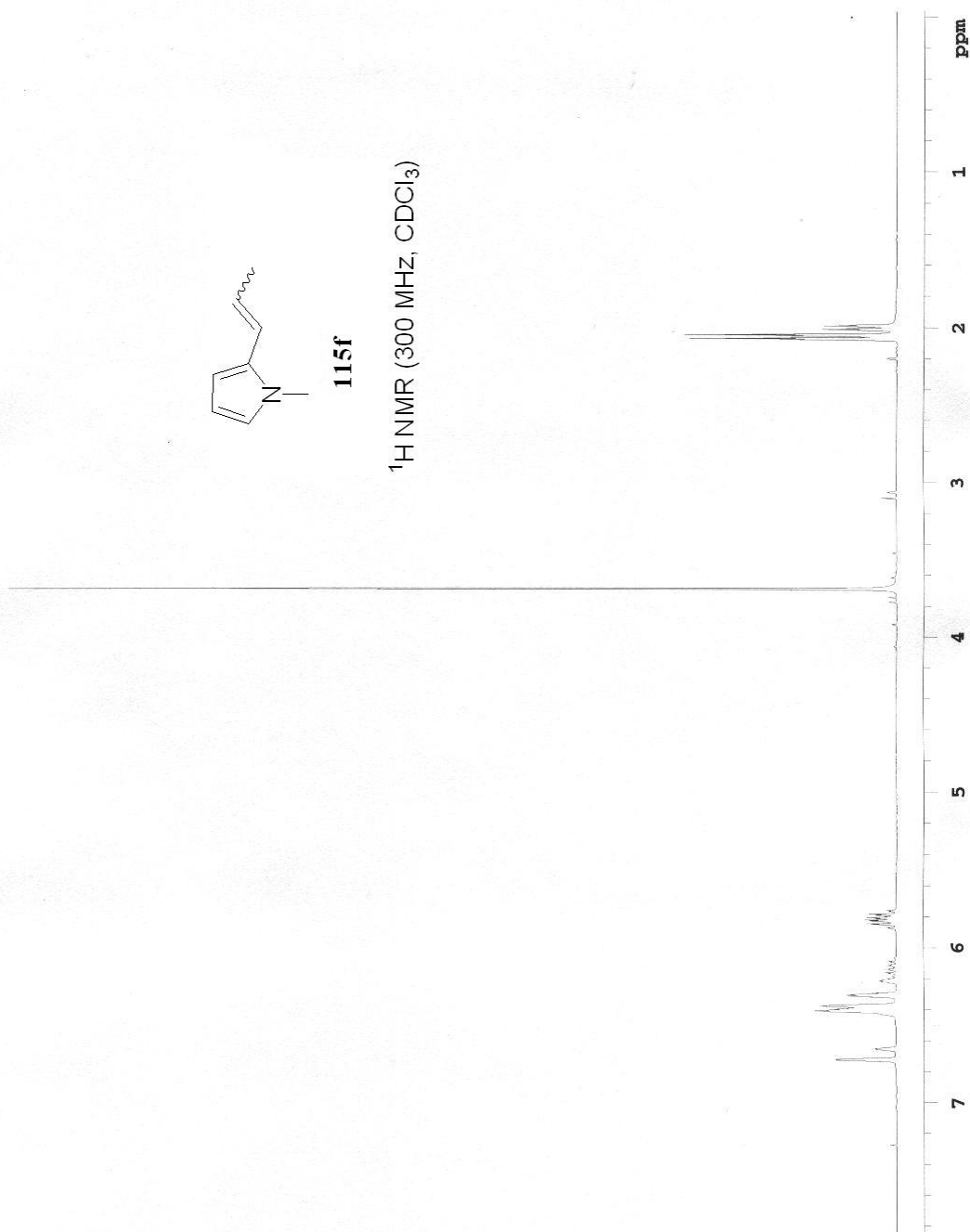
^{13}C NMR (75 MHz, CDCl_3)





115f

$^1\text{H NMR}$ (300 MHz, CDCl_3)

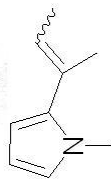




115f

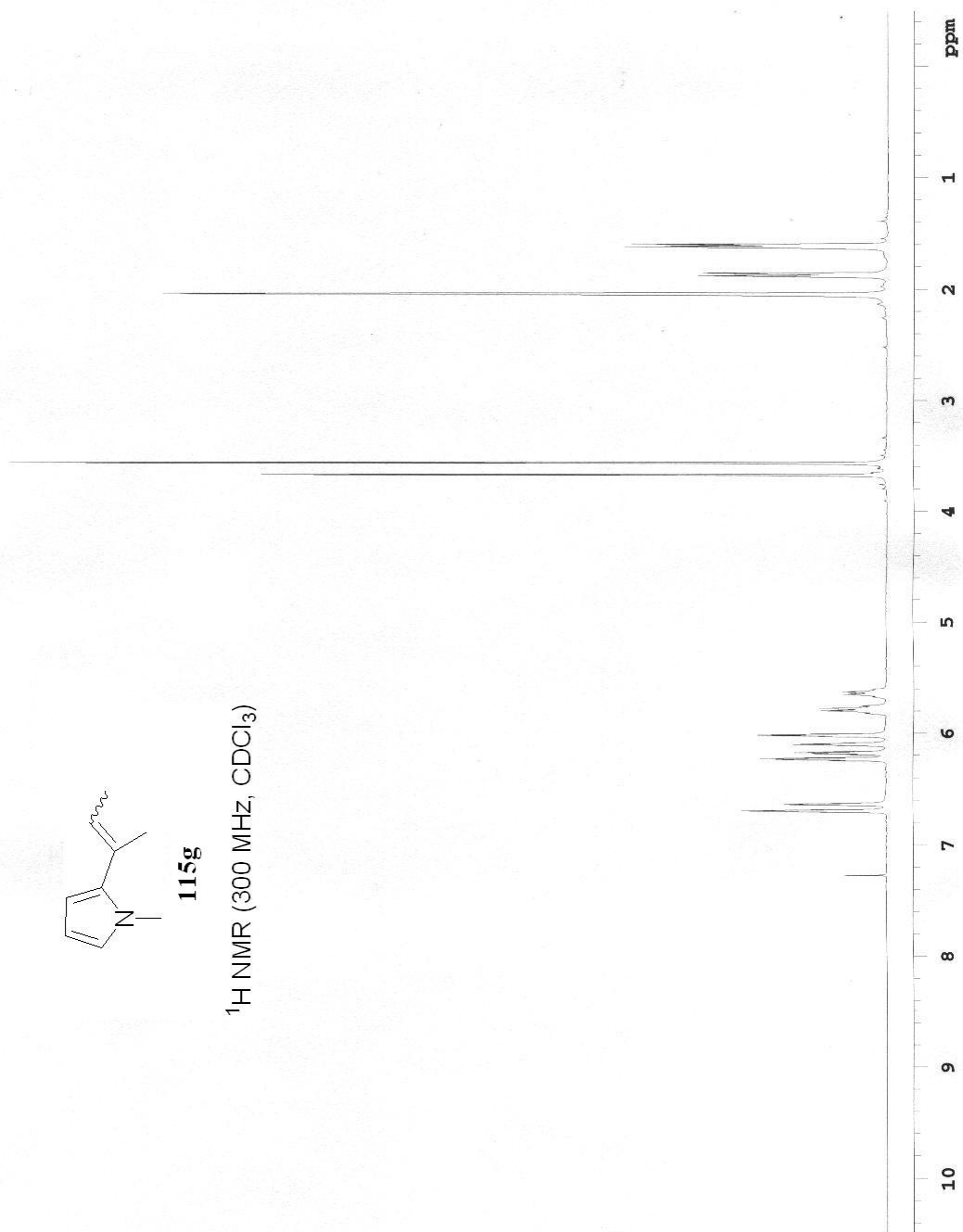
^{13}C NMR (75 MHz, CDCl_3)

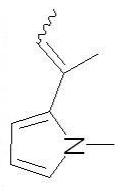




115g

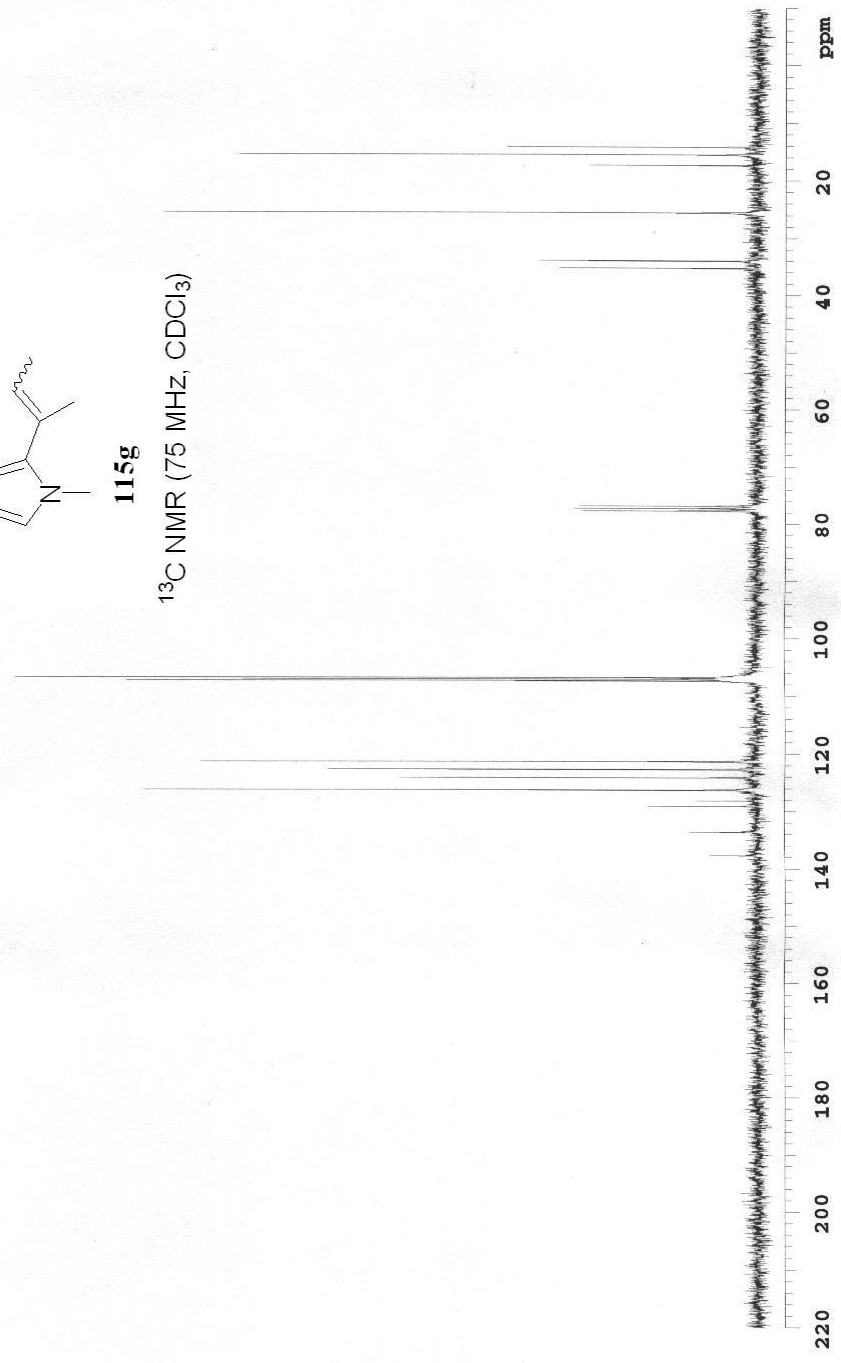
^1H NMR (300 MHz, CDCl_3)

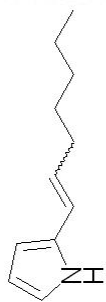




115g

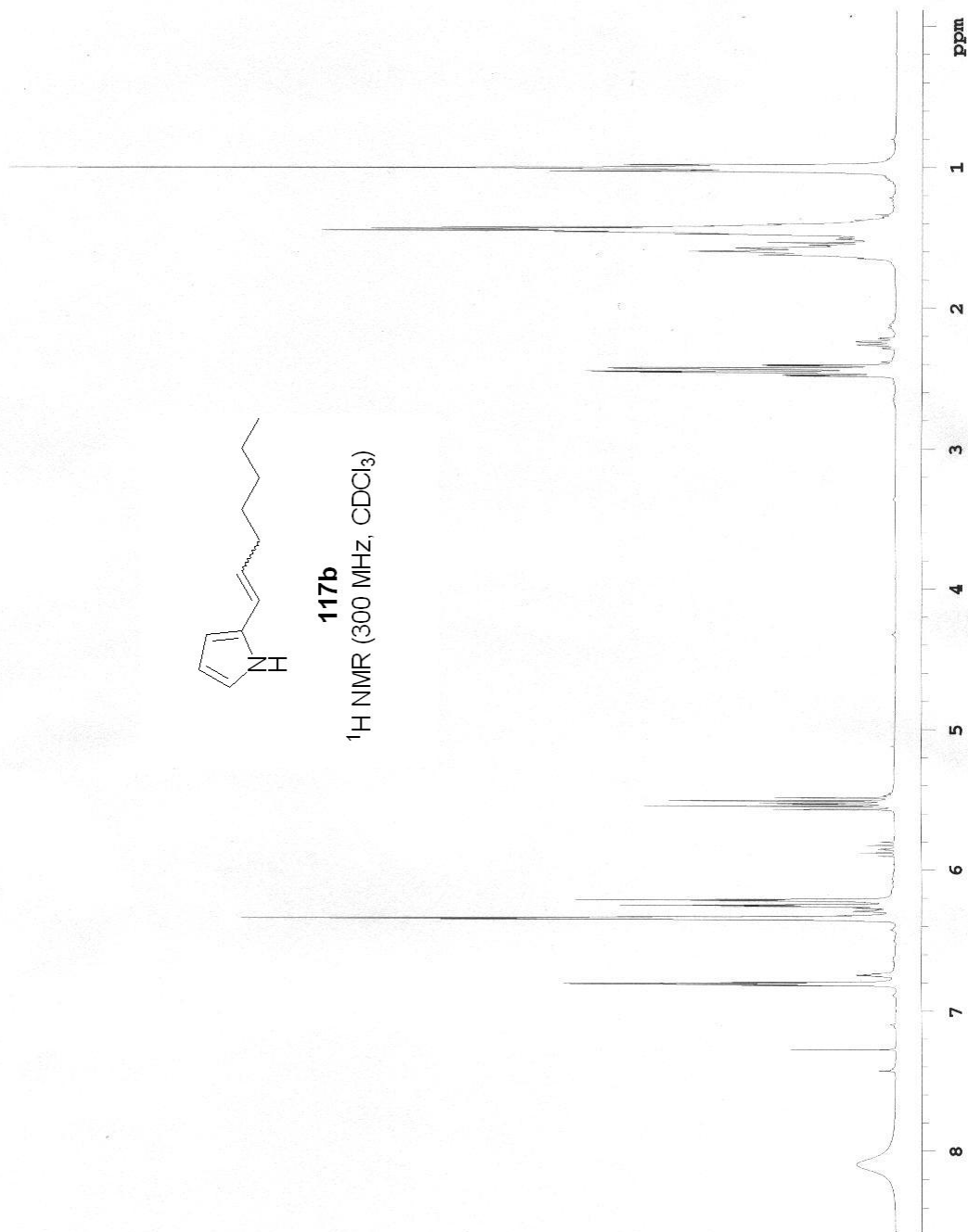
^{13}C NMR (75 MHz, CDCl_3)

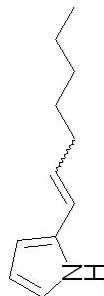




117b

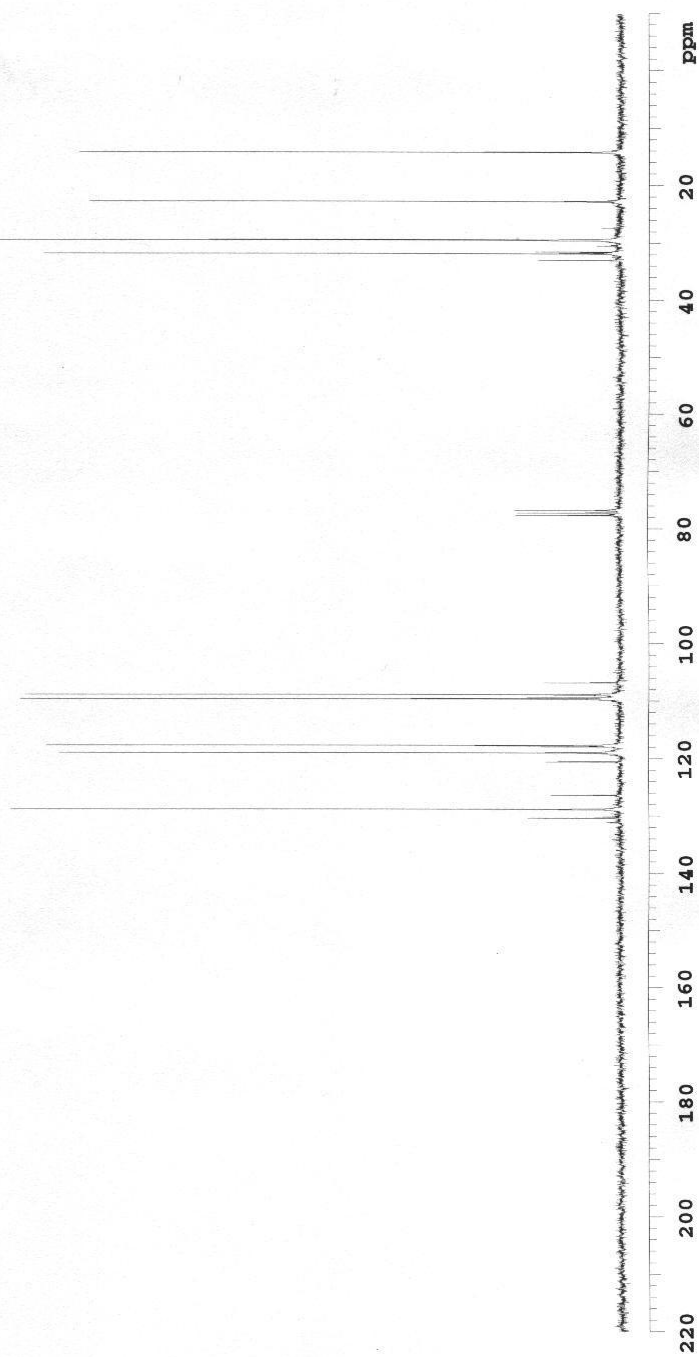
¹H NMR (300 MHz, CDCl₃)

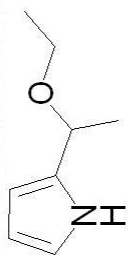




117b

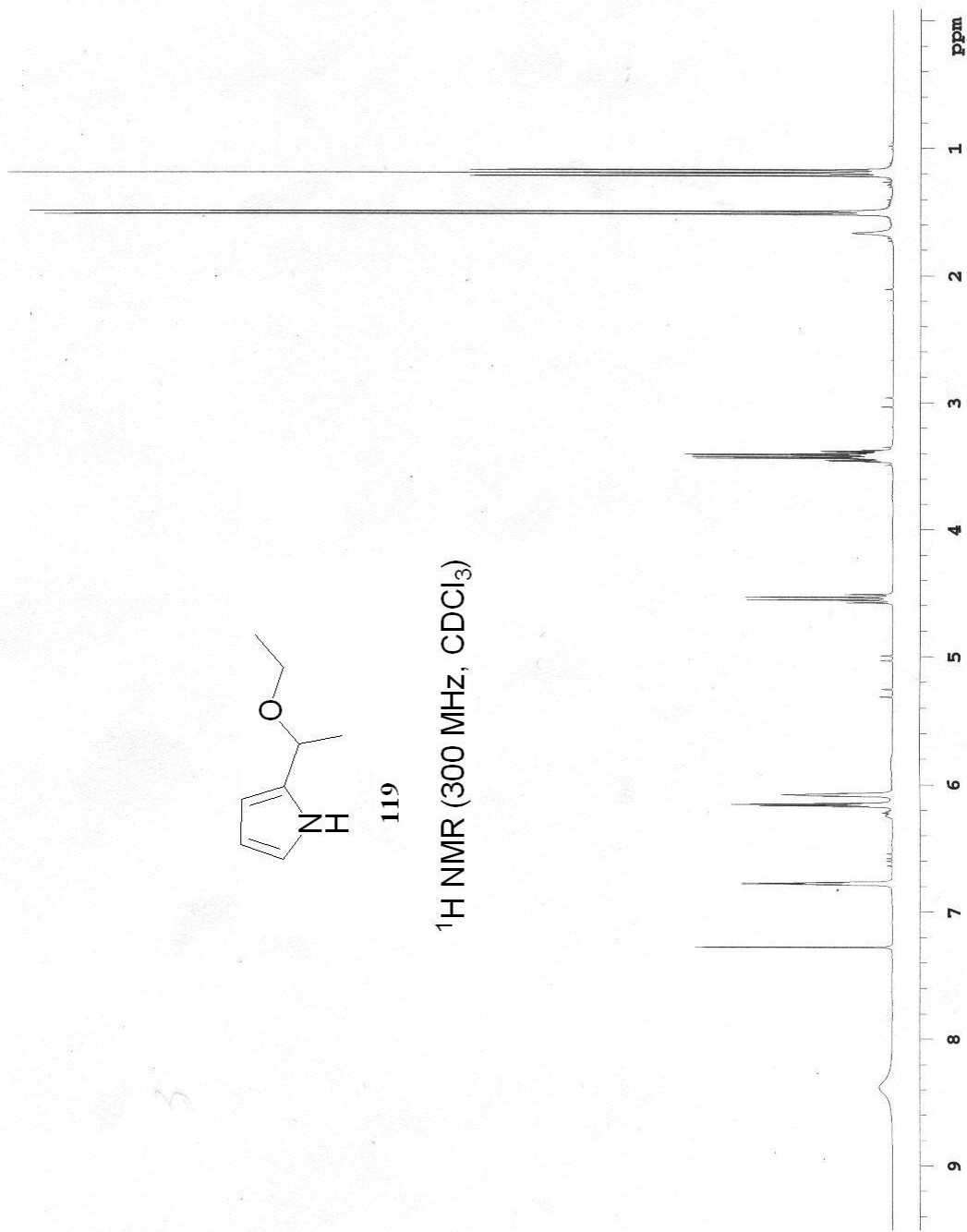
^{13}C NMR (75 MHz, CDCl_3)

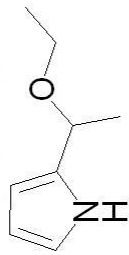




119

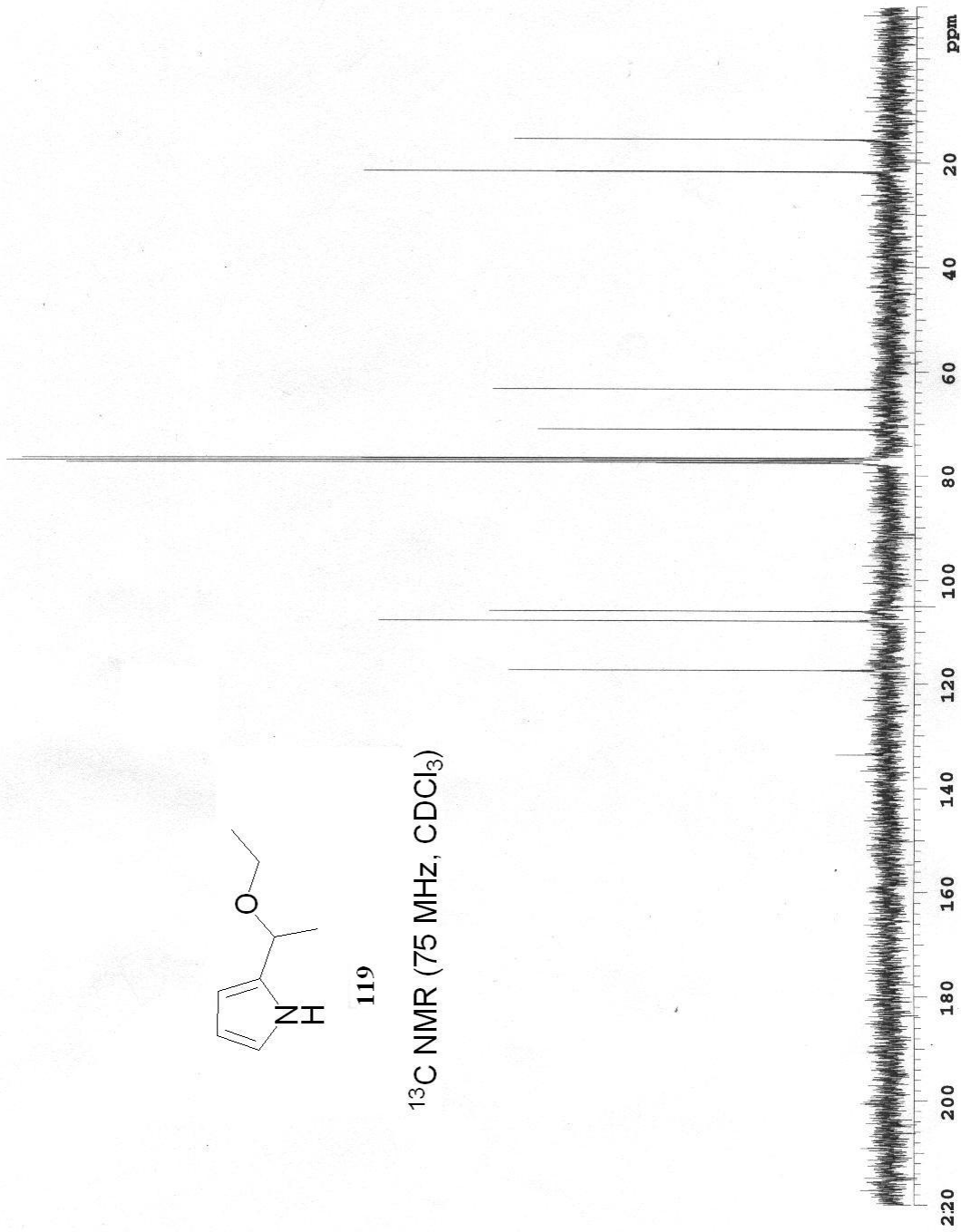
^1H NMR (300 MHz, CDCl_3)

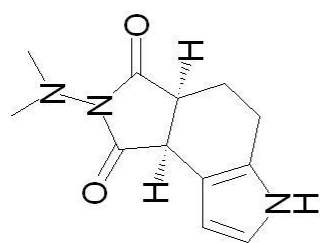




119

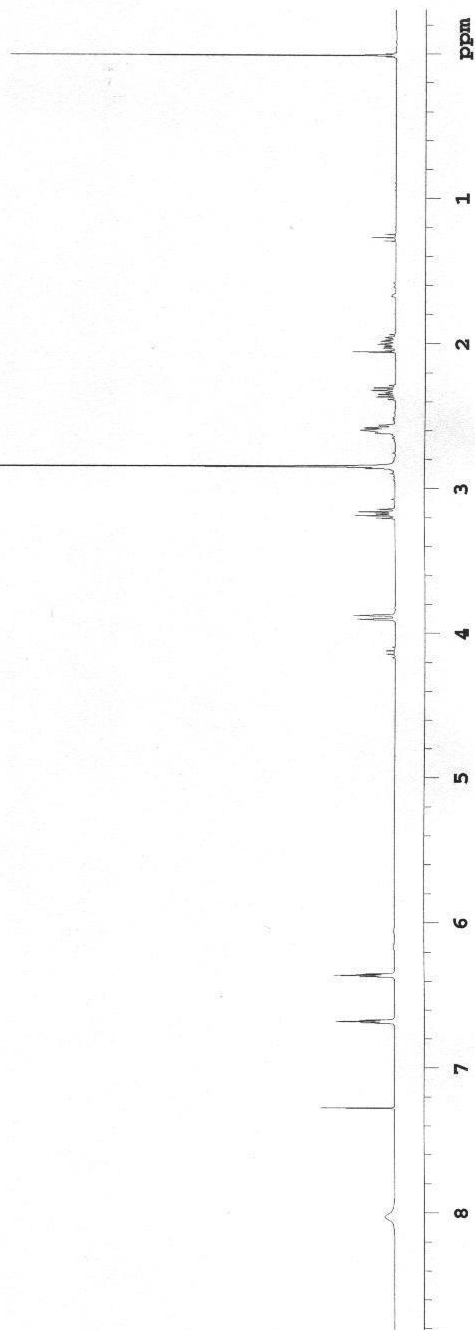
^{13}C NMR (75 MHz, CDCl_3)

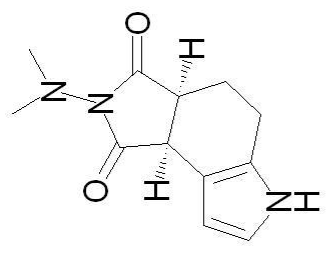




122

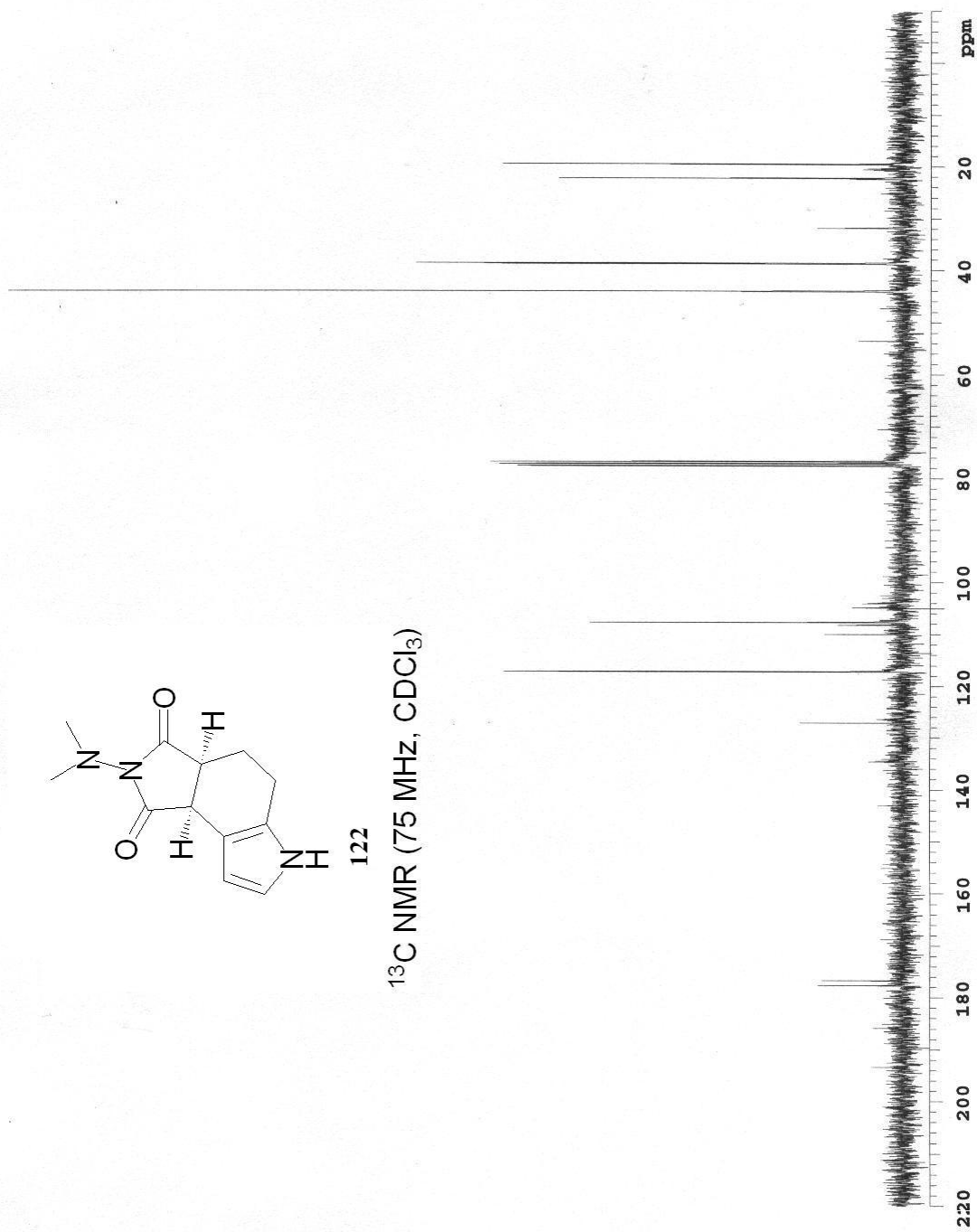
¹H NMR (300 MHz, CDCl₃)

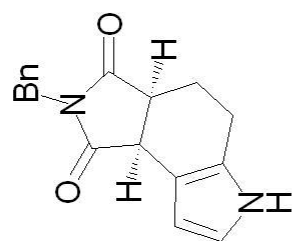




122

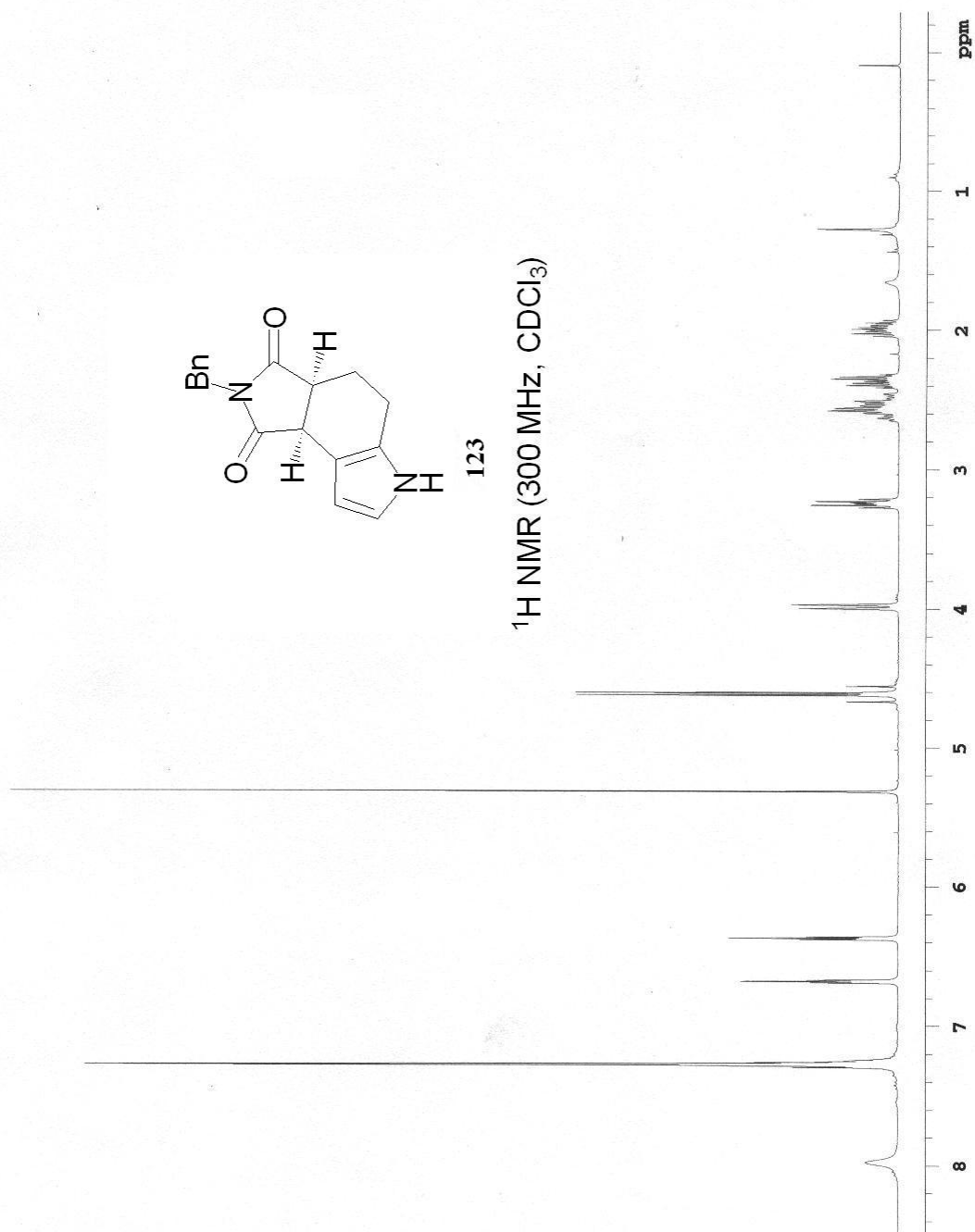
¹³C NMR (75 MHz, CDCl₃)

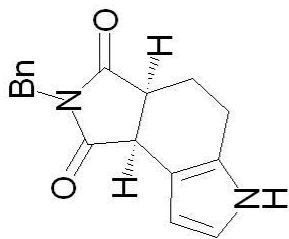




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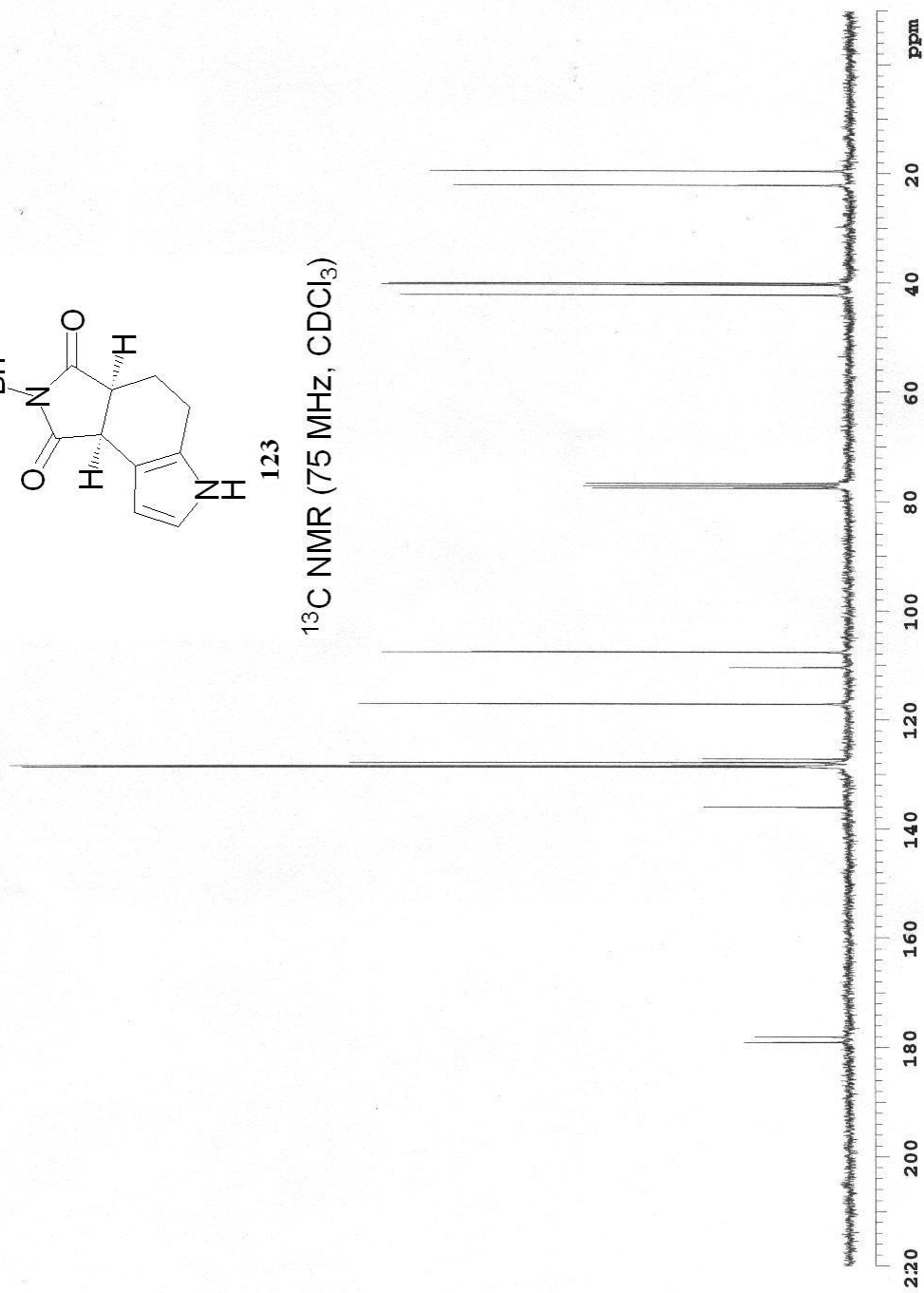
^1H NMR (300 MHz, CDCl_3)

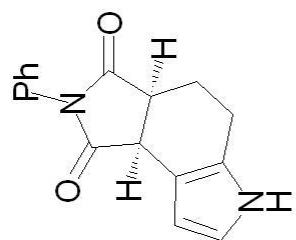




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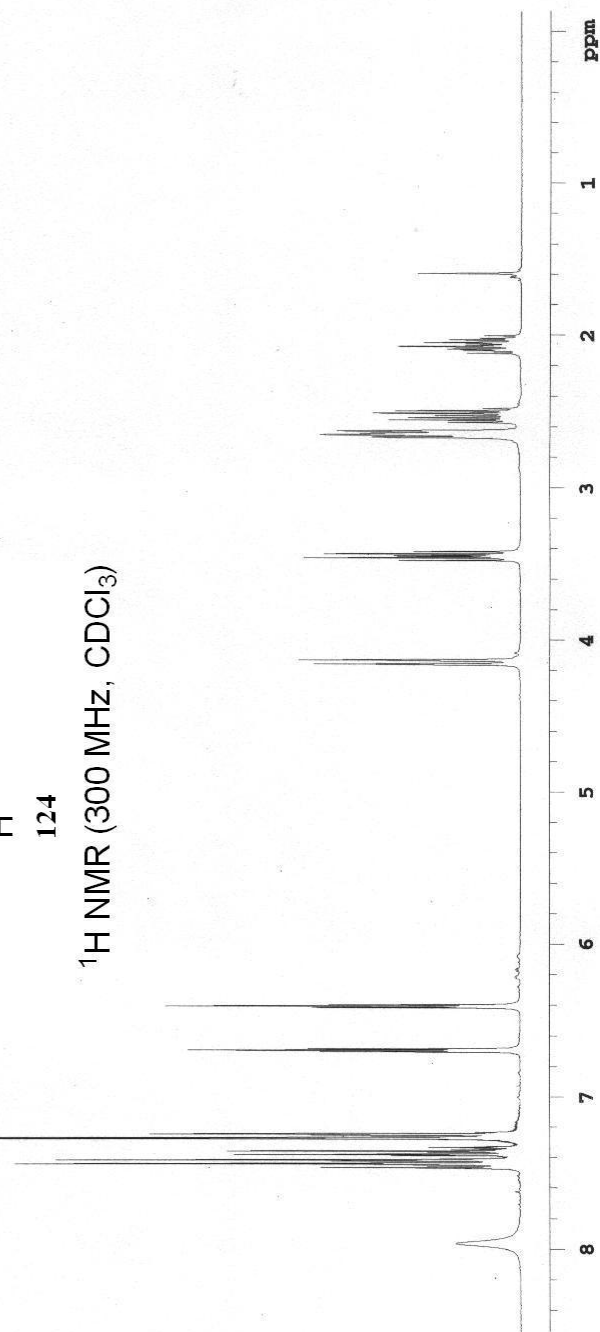
^{13}C NMR (75 MHz, CDCl_3)

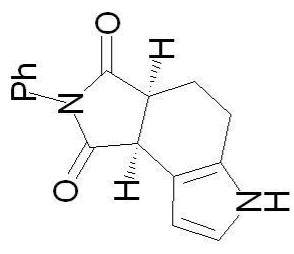




124

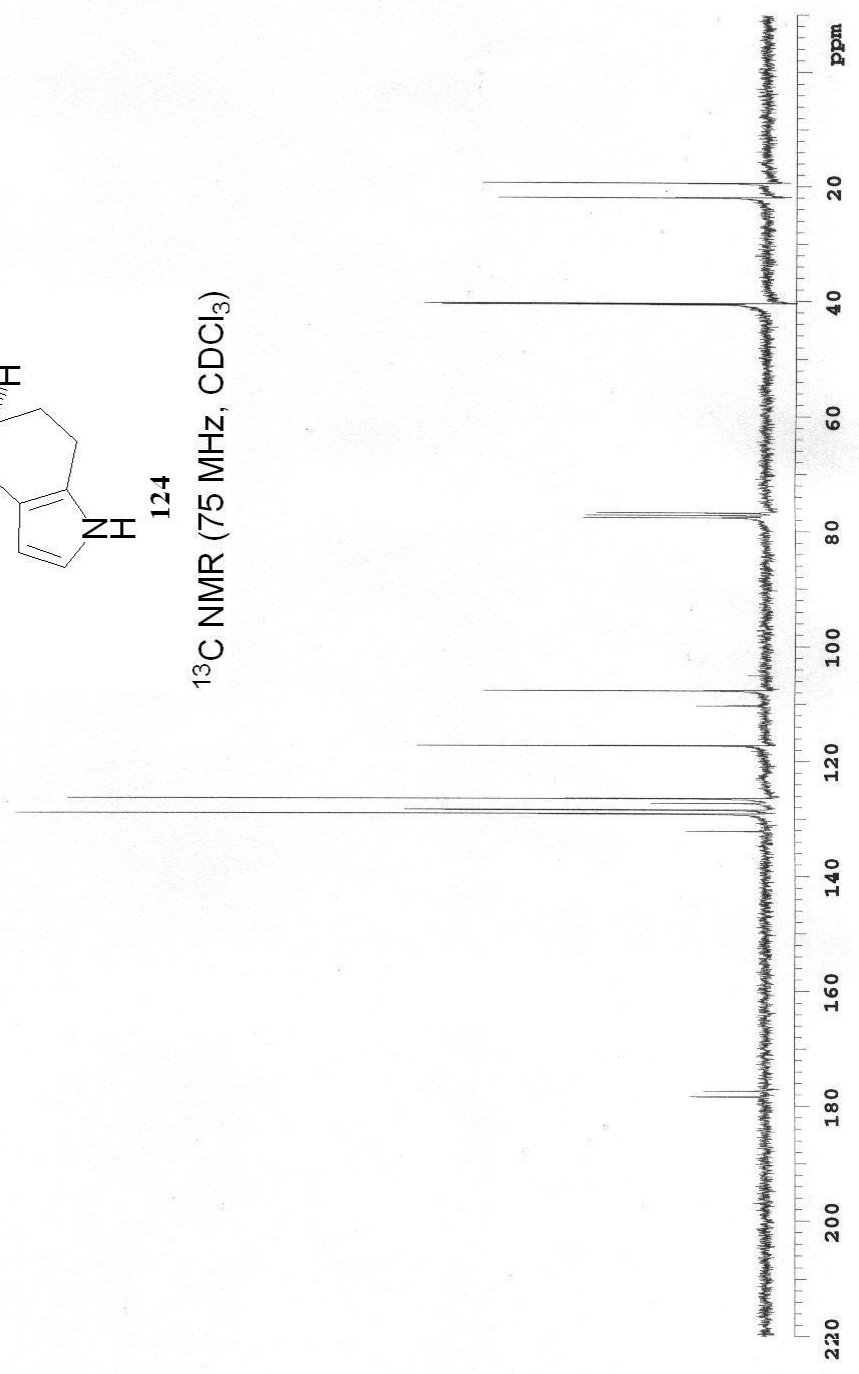
$^1\text{H NMR}$ (300 MHz, CDCl_3)

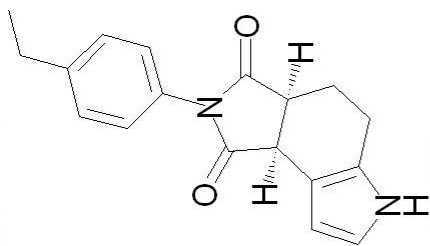




124

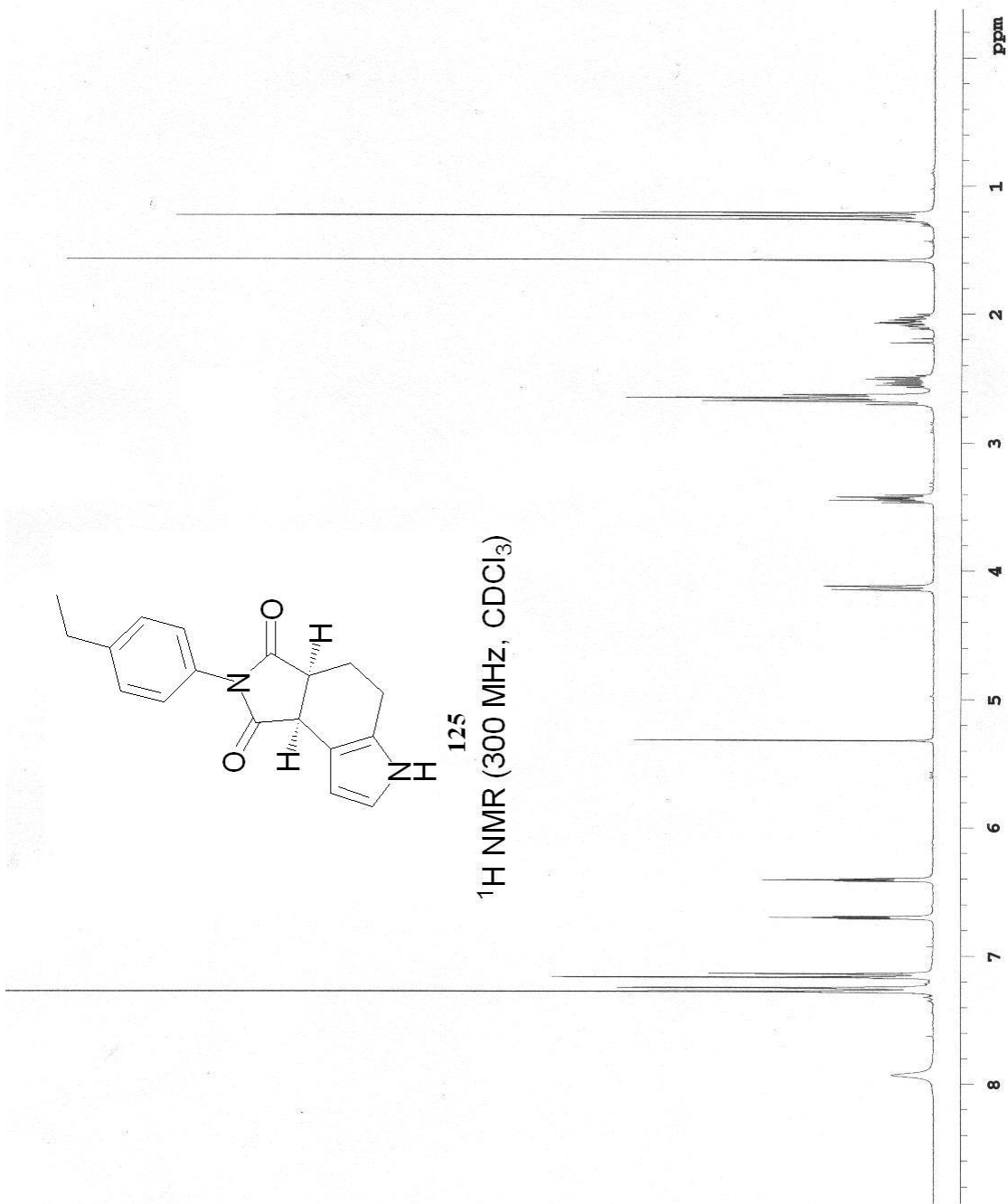
^{13}C NMR (75 MHz, CDCl_3)

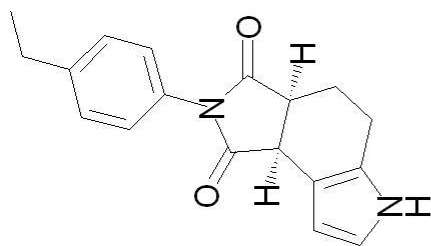




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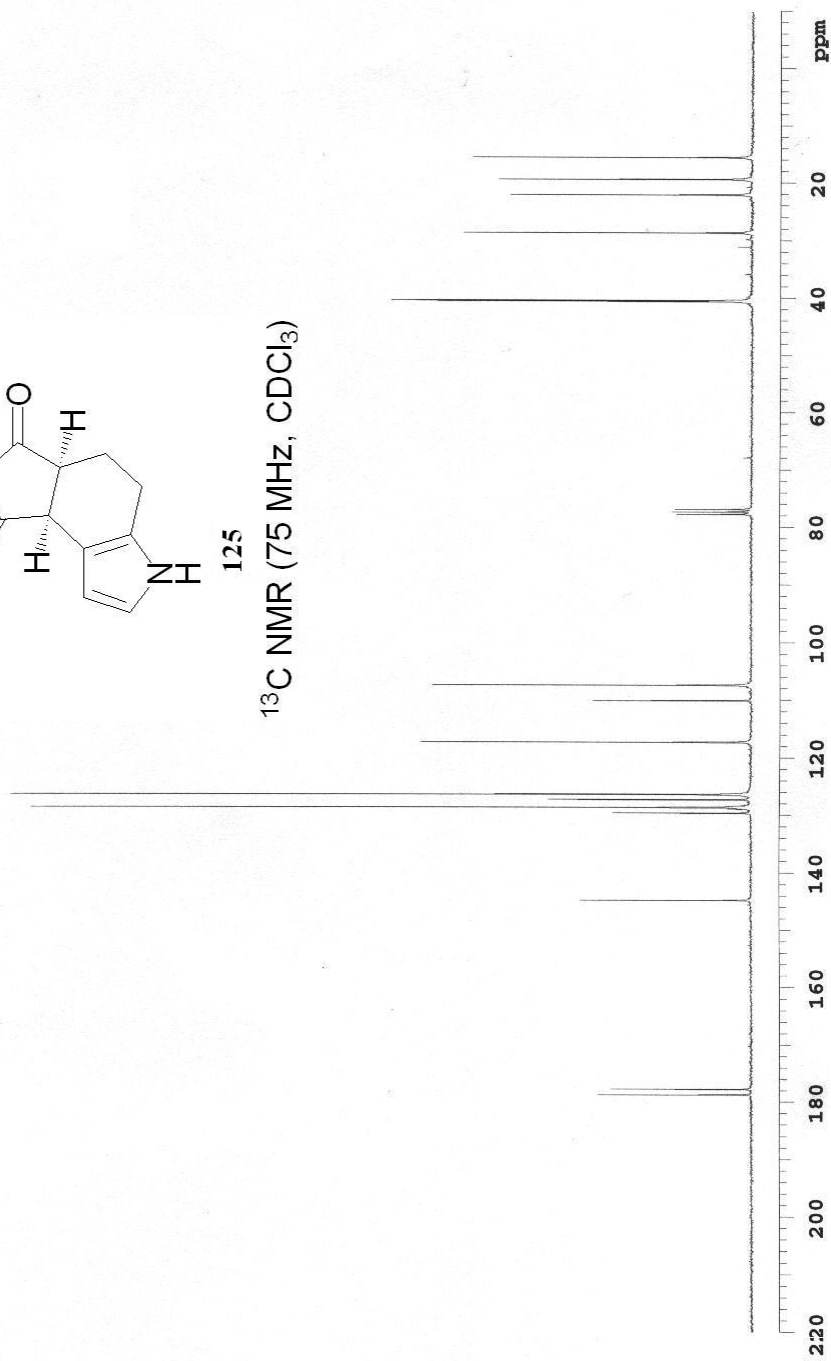
¹H NMR (300 MHz, CDCl₃)

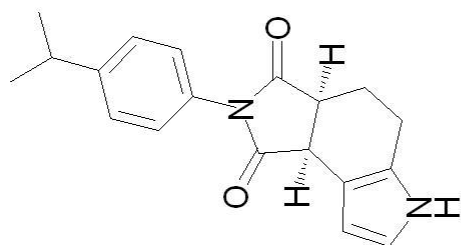




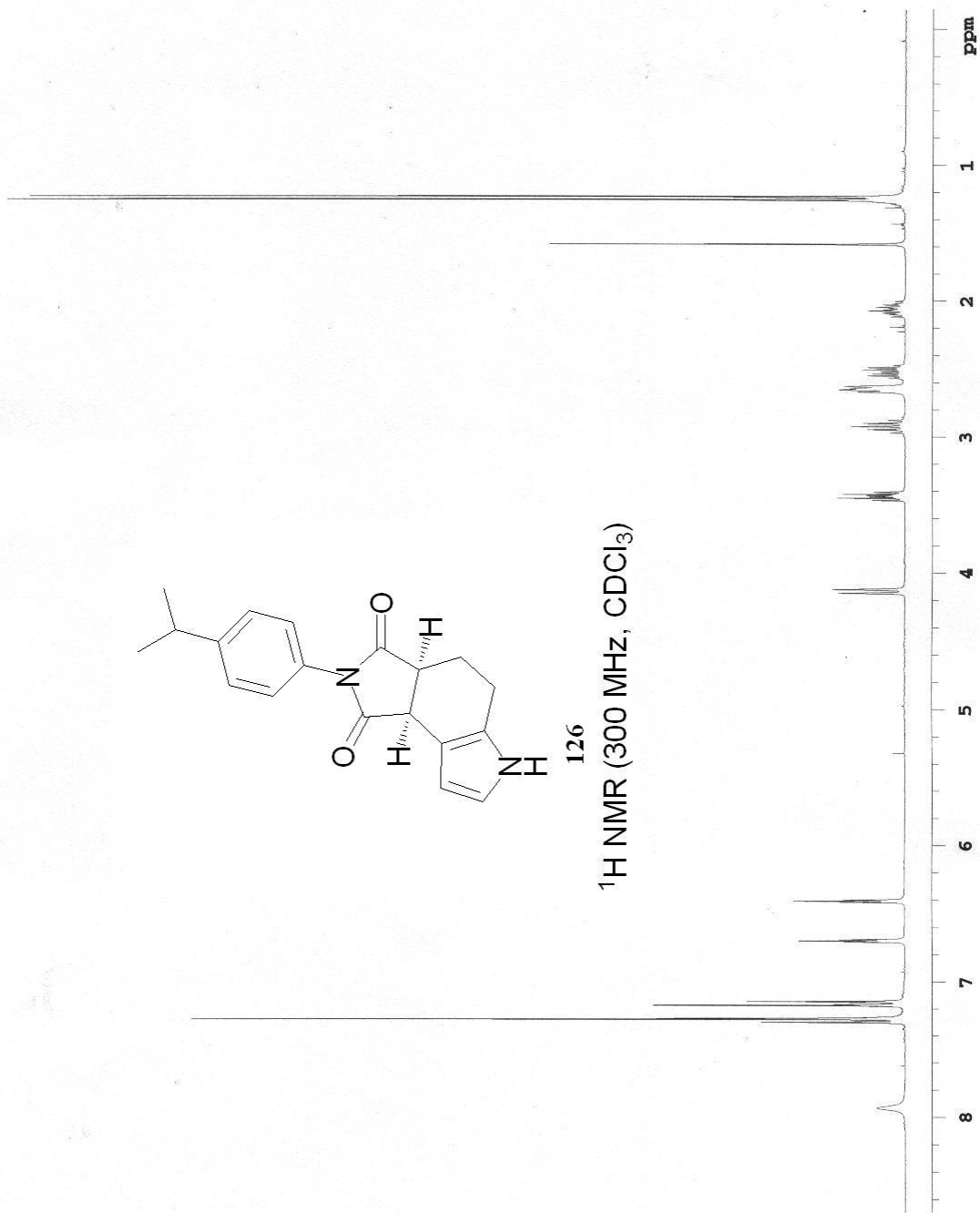
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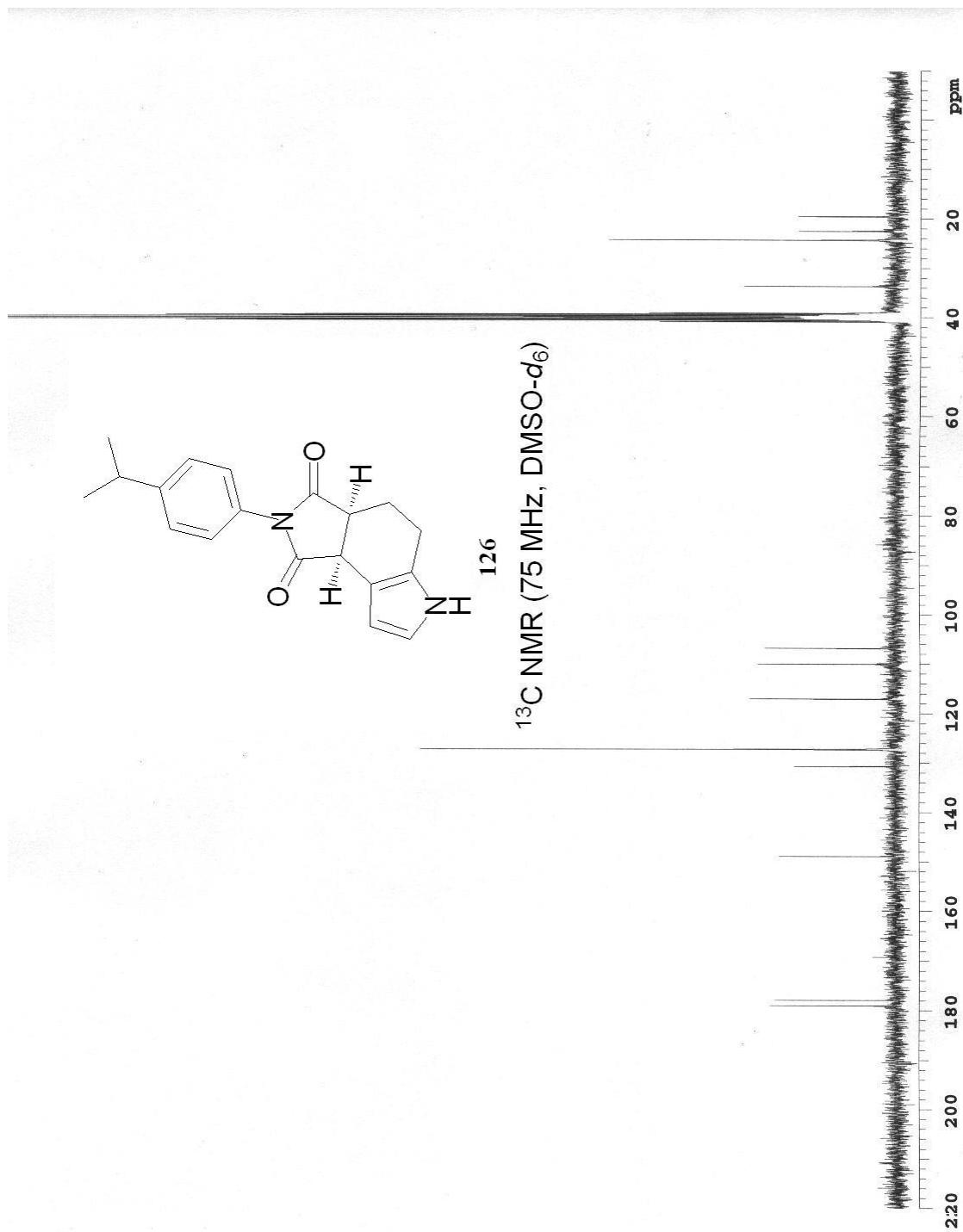
^{13}C NMR (75 MHz, CDCl_3)

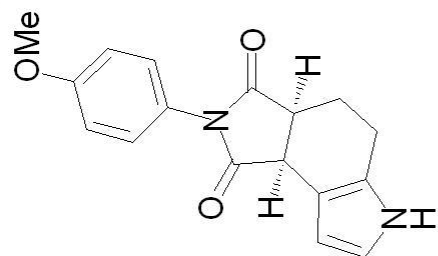




126
¹H NMR (300 MHz, CDCl₃)

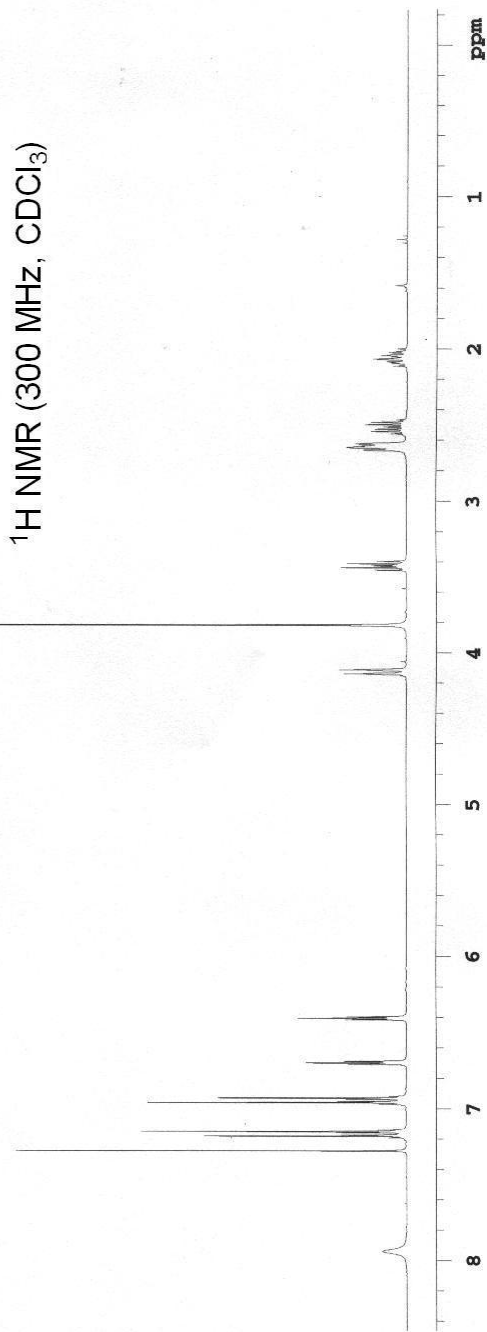


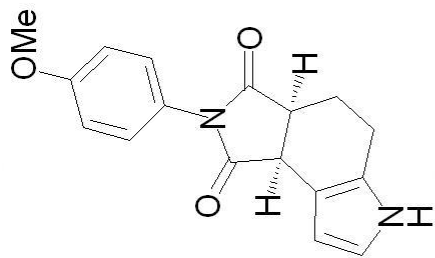




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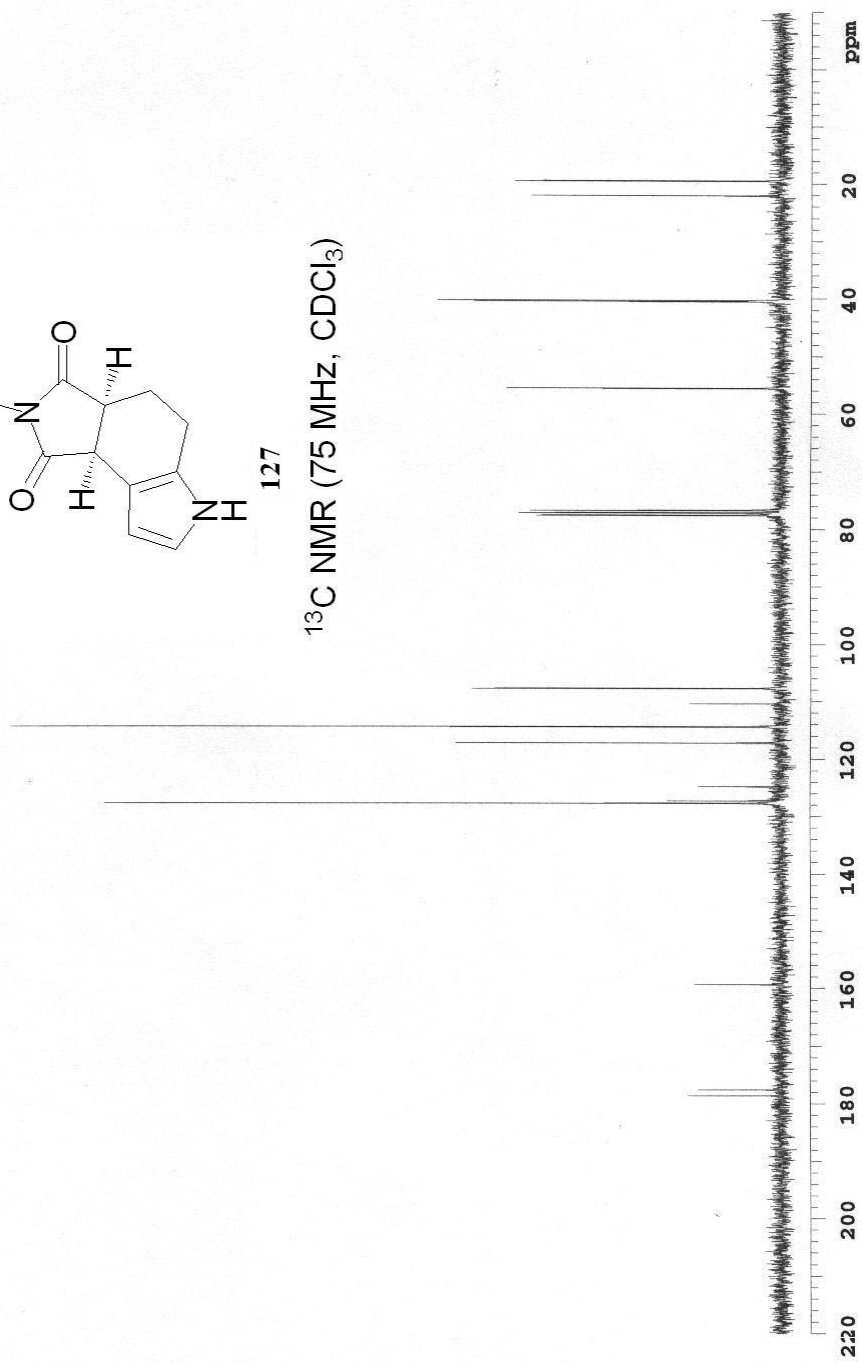
$^1\text{H NMR}$ (300 MHz, CDCl_3)

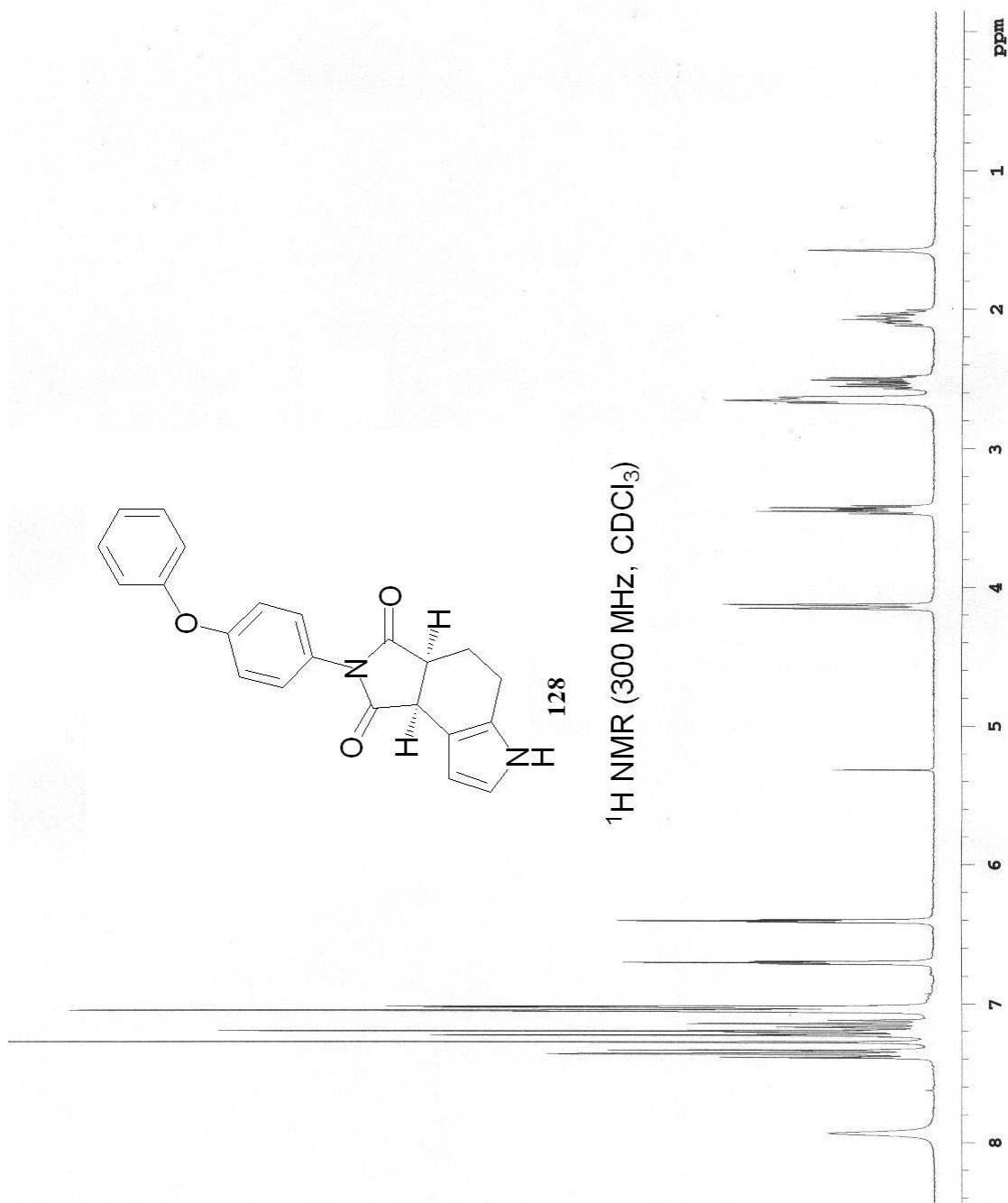


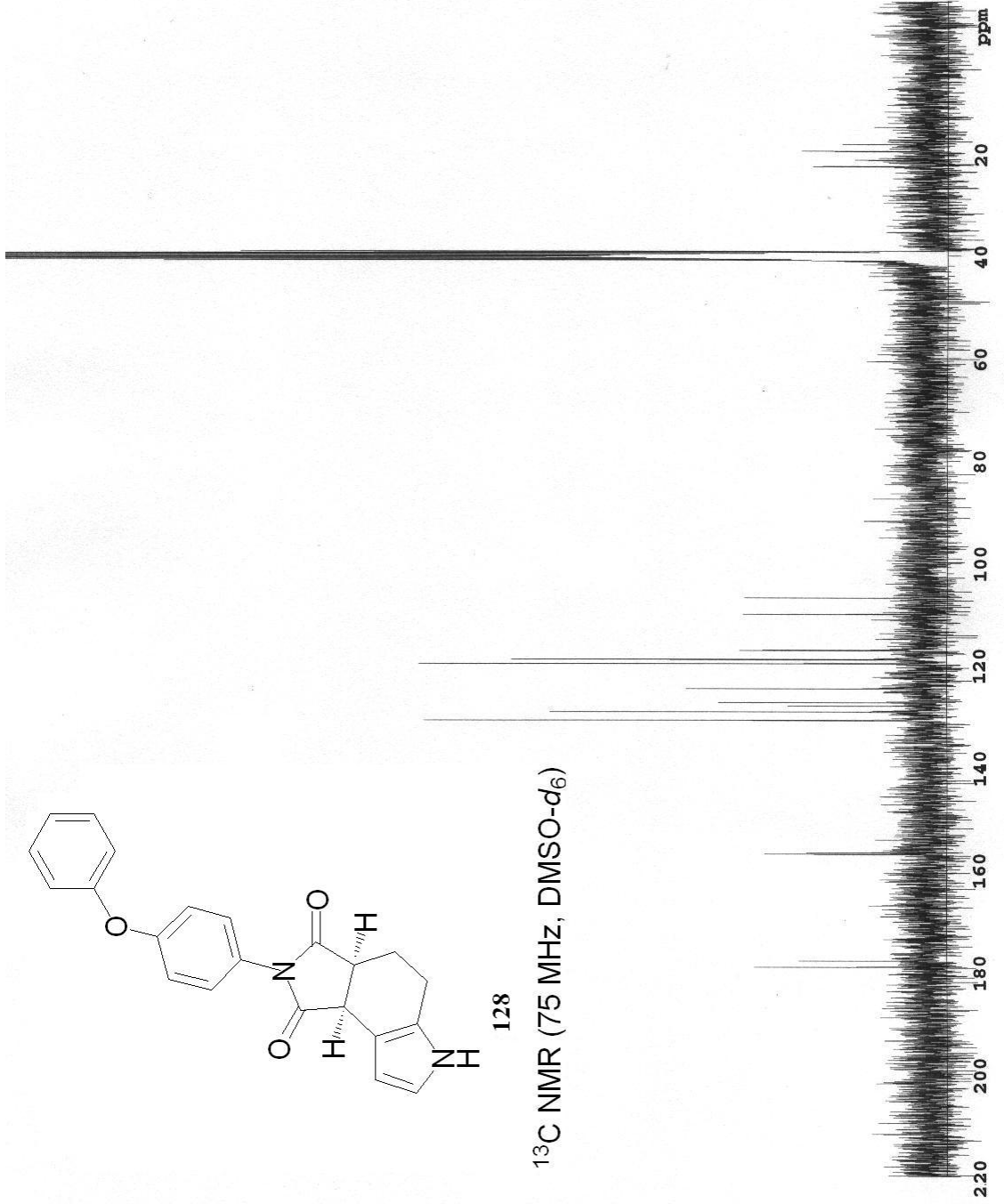


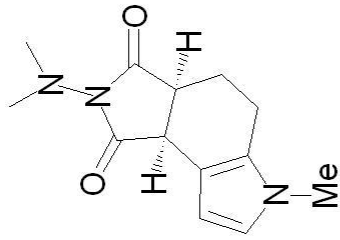
127

^{13}C NMR (75 MHz, CDCl_3)



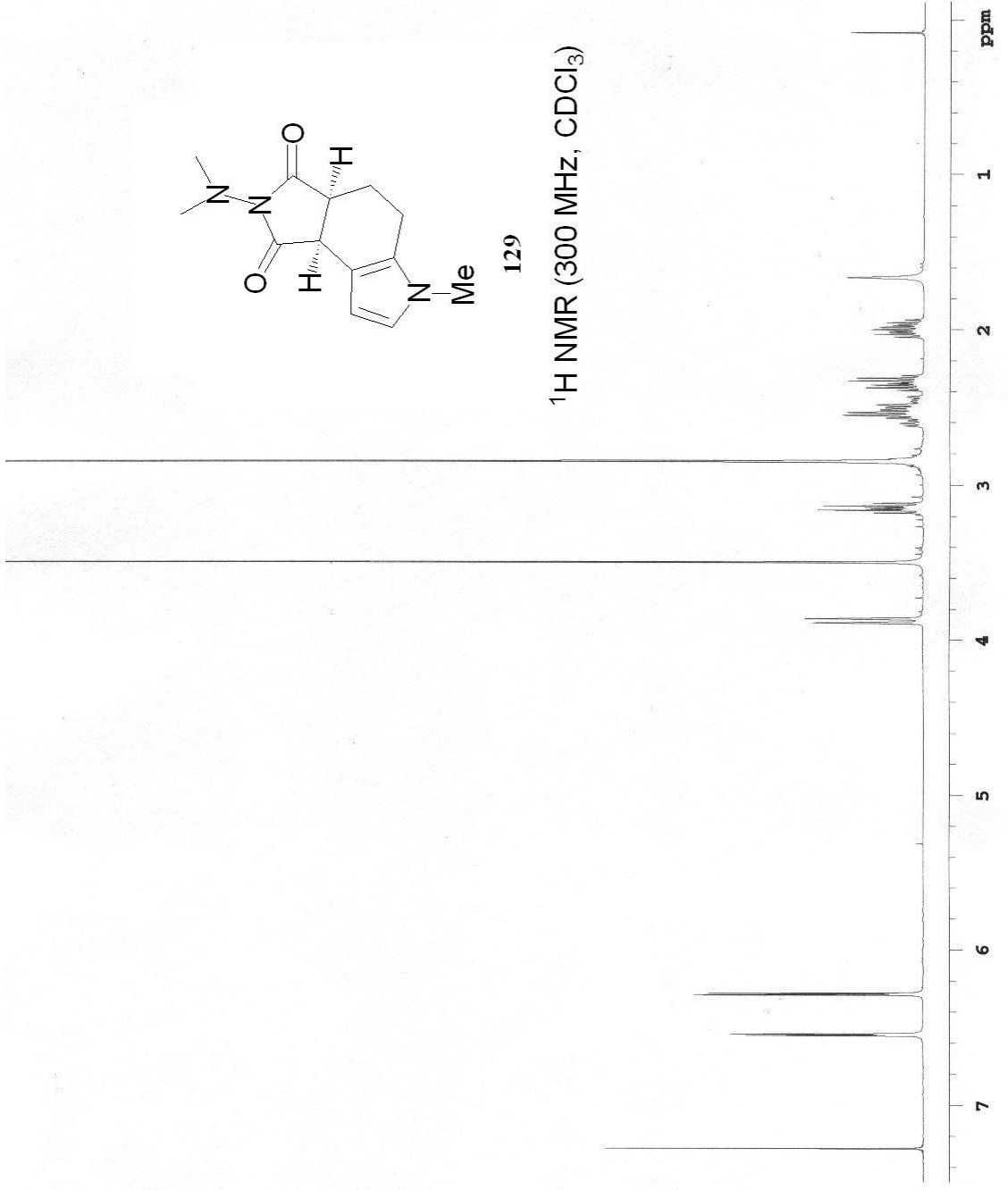


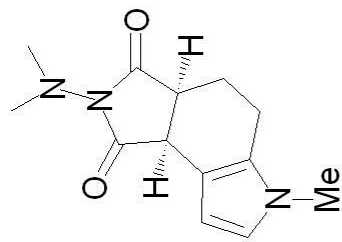




129

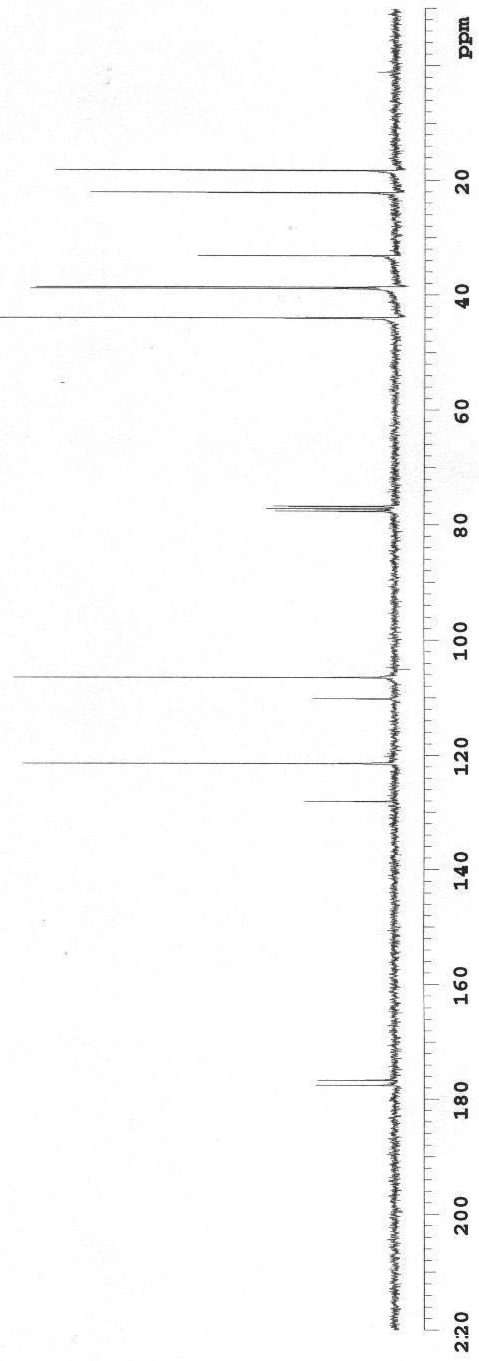
¹H NMR (300 MHz, CDCl₃)

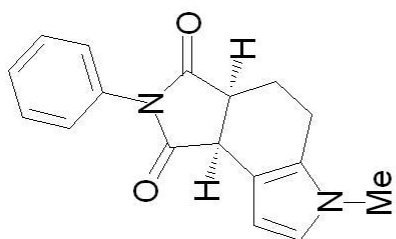




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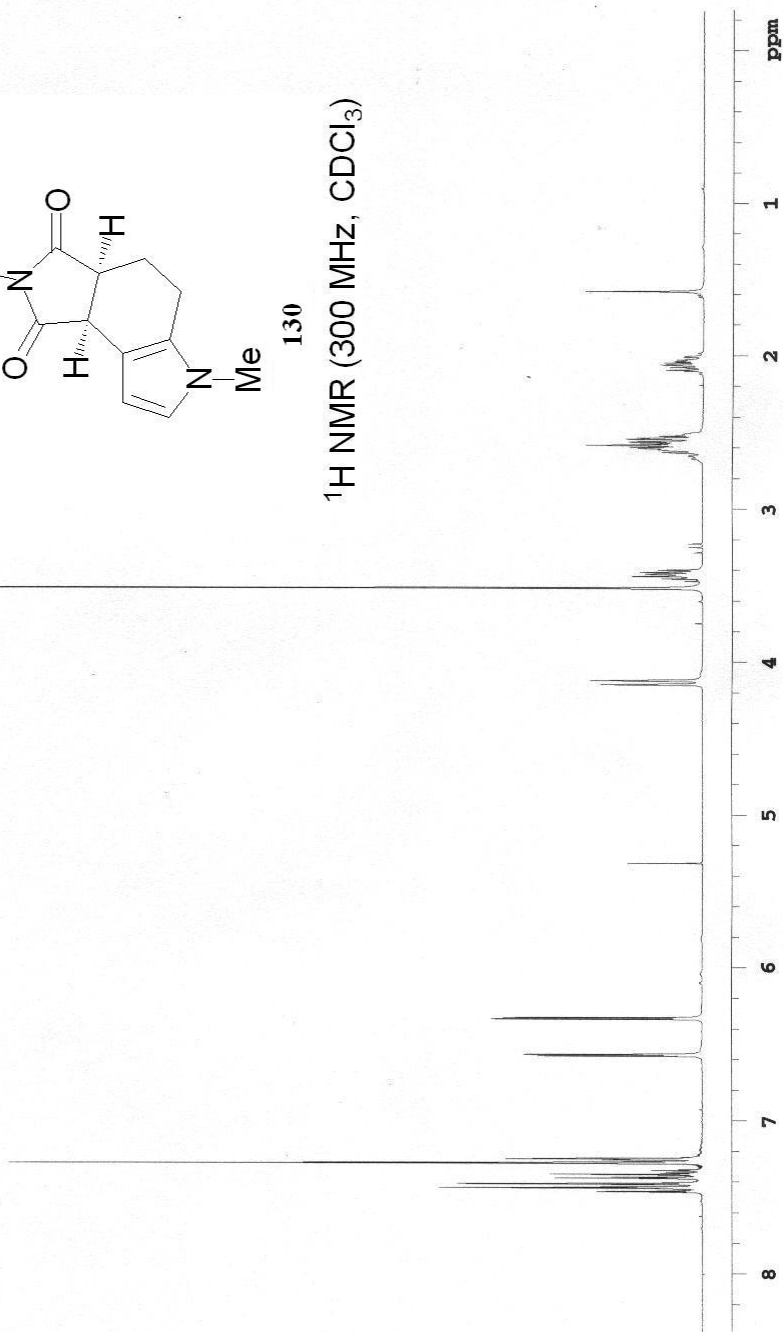
^{13}C NMR (75 MHz, CDCl_3)

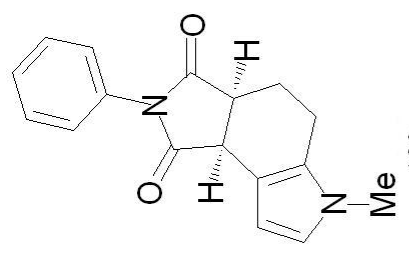




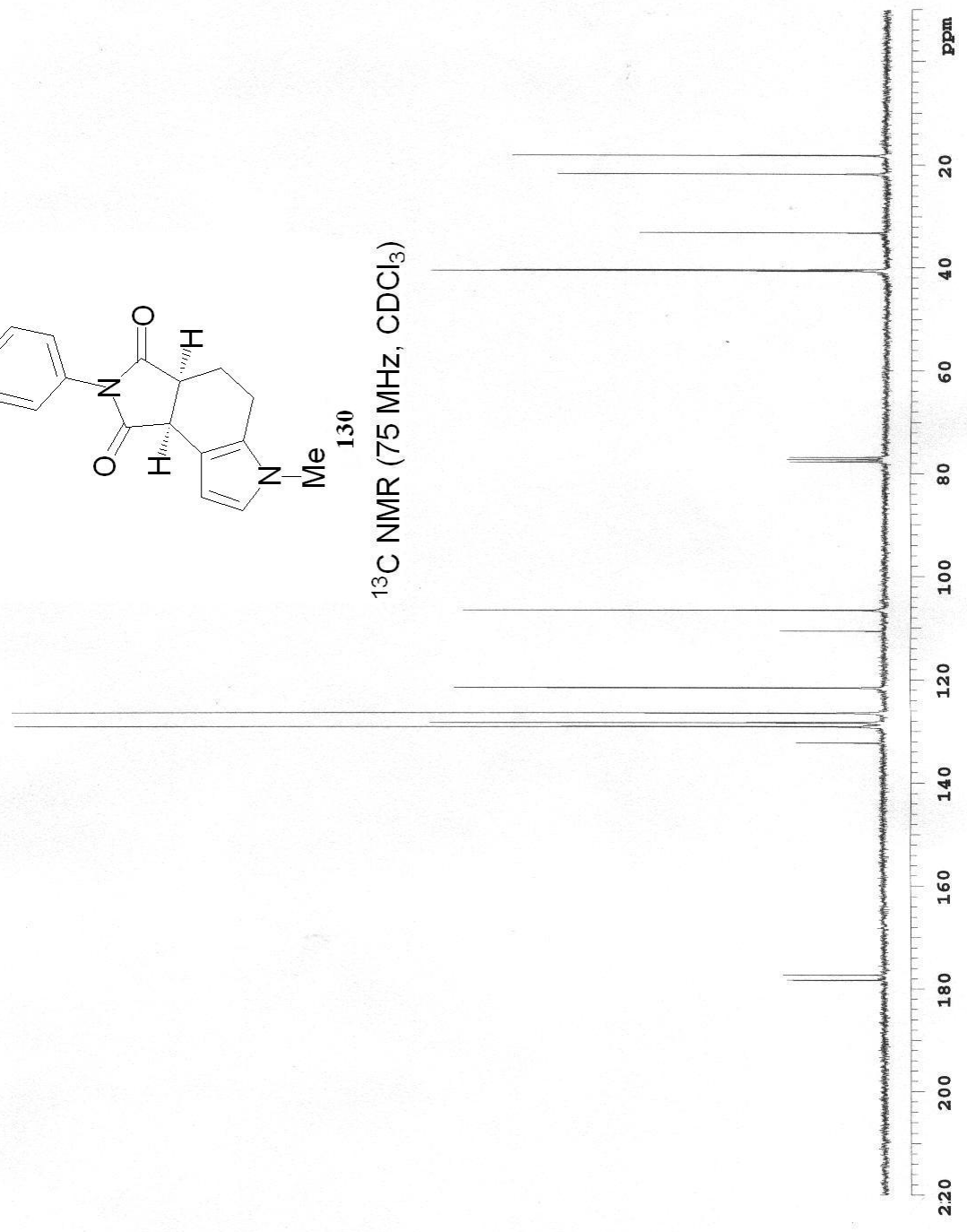
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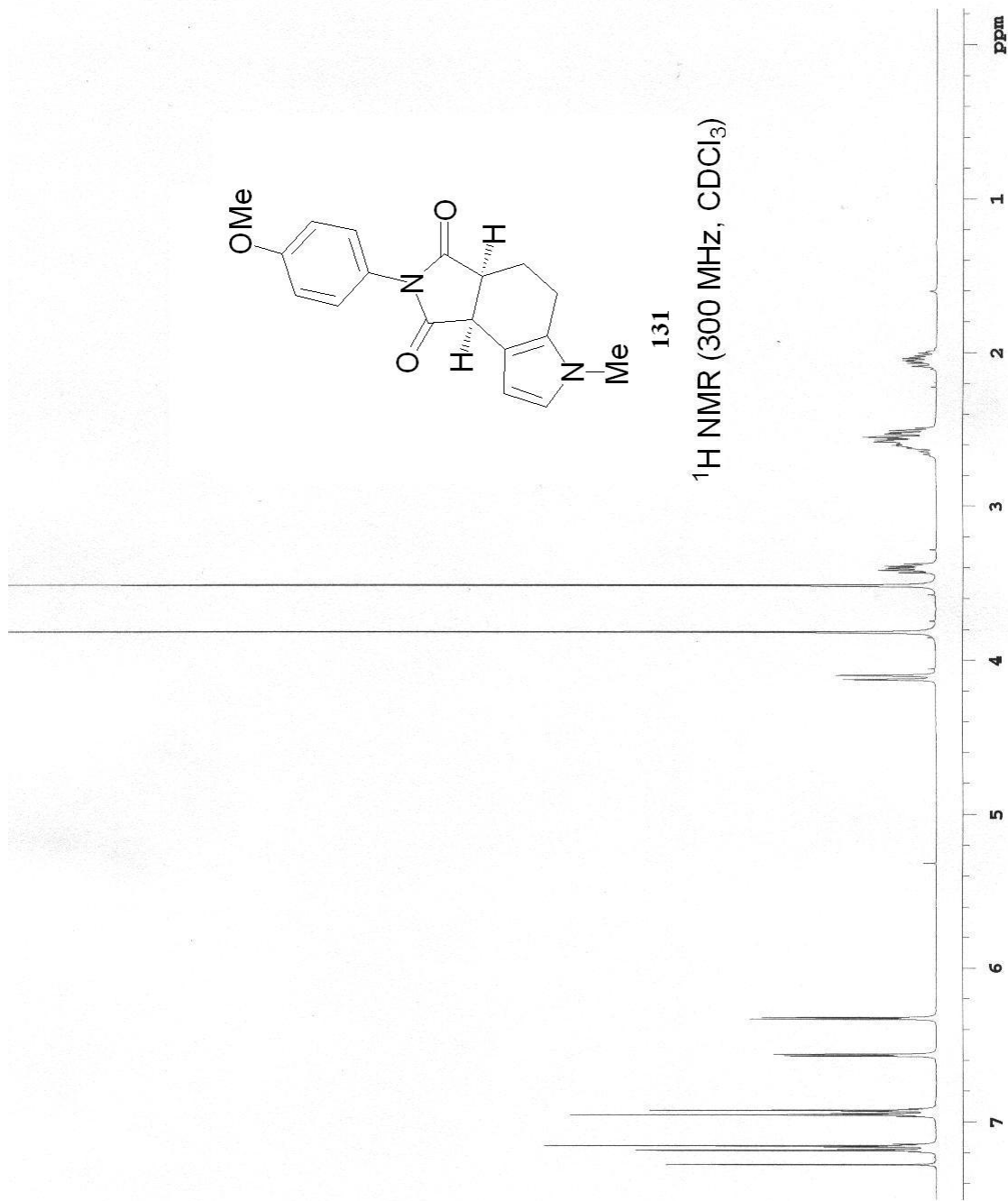
^1H NMR (300 MHz, CDCl_3)

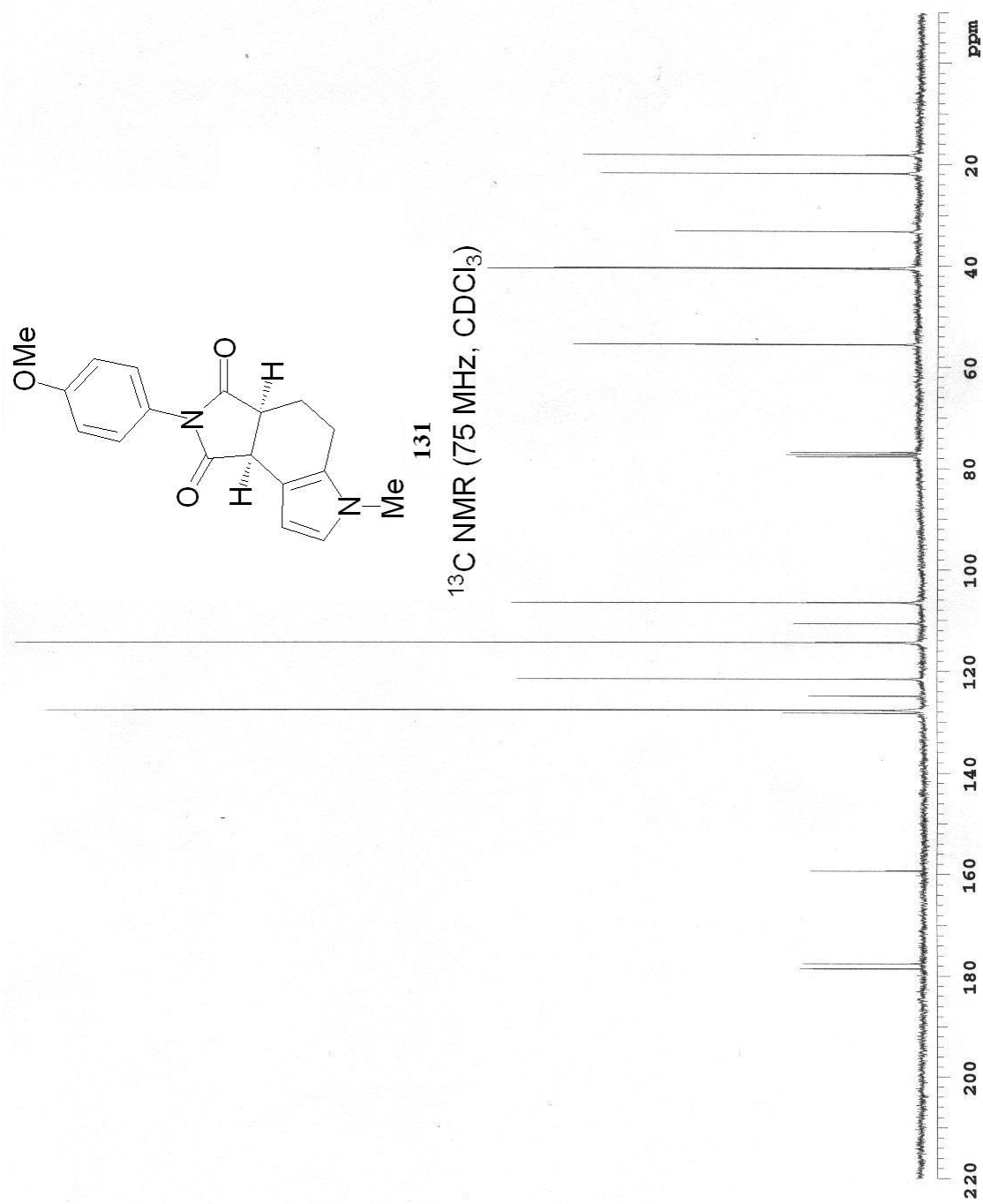


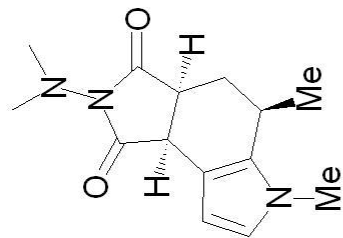


¹³C NMR (75 MHz, CDCl₃)





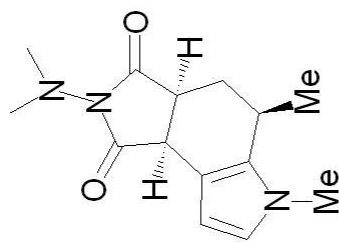




132

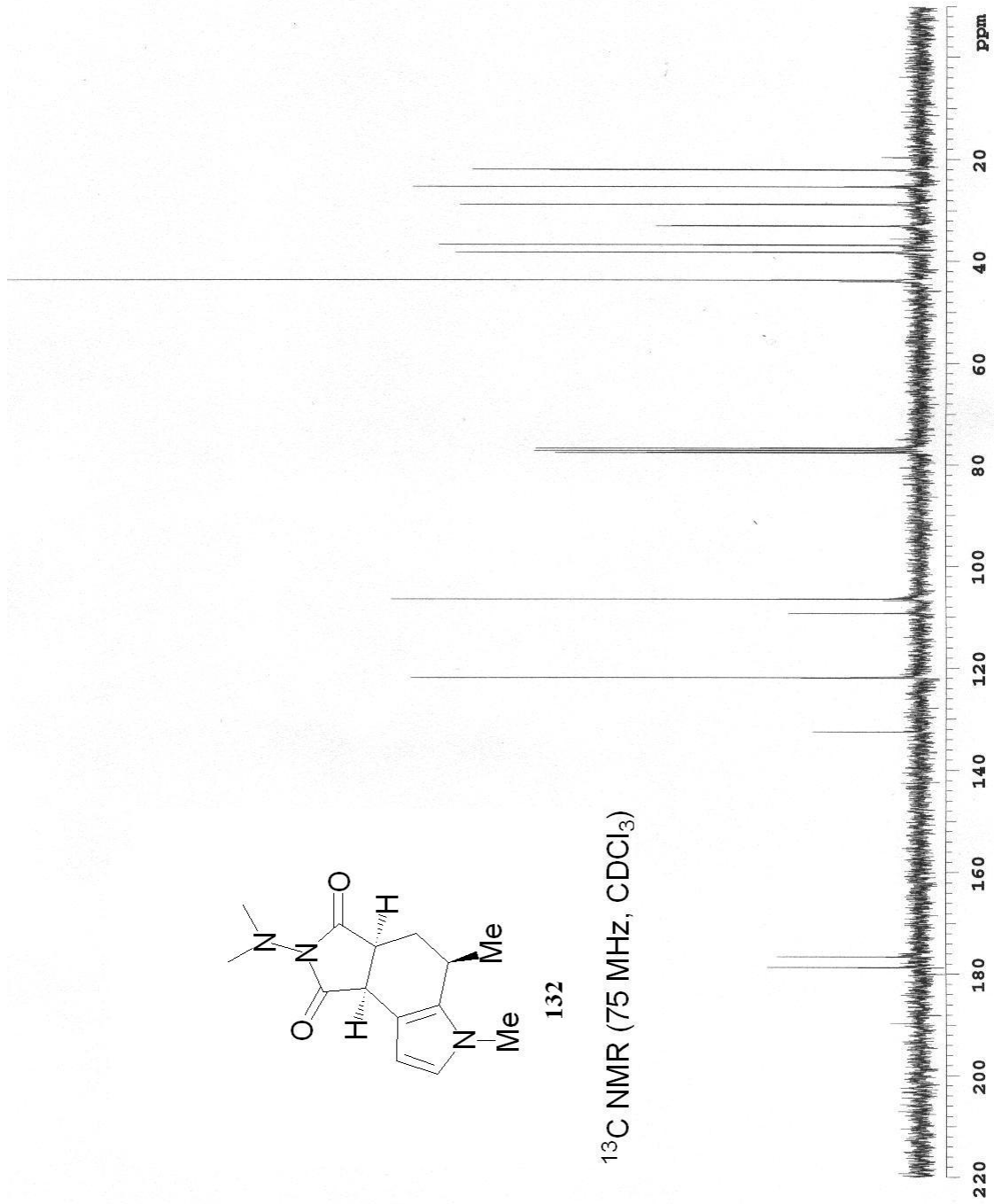
¹H NMR (300 MHz, CDCl₃)

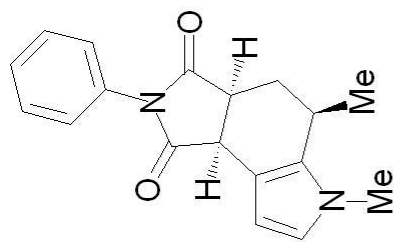




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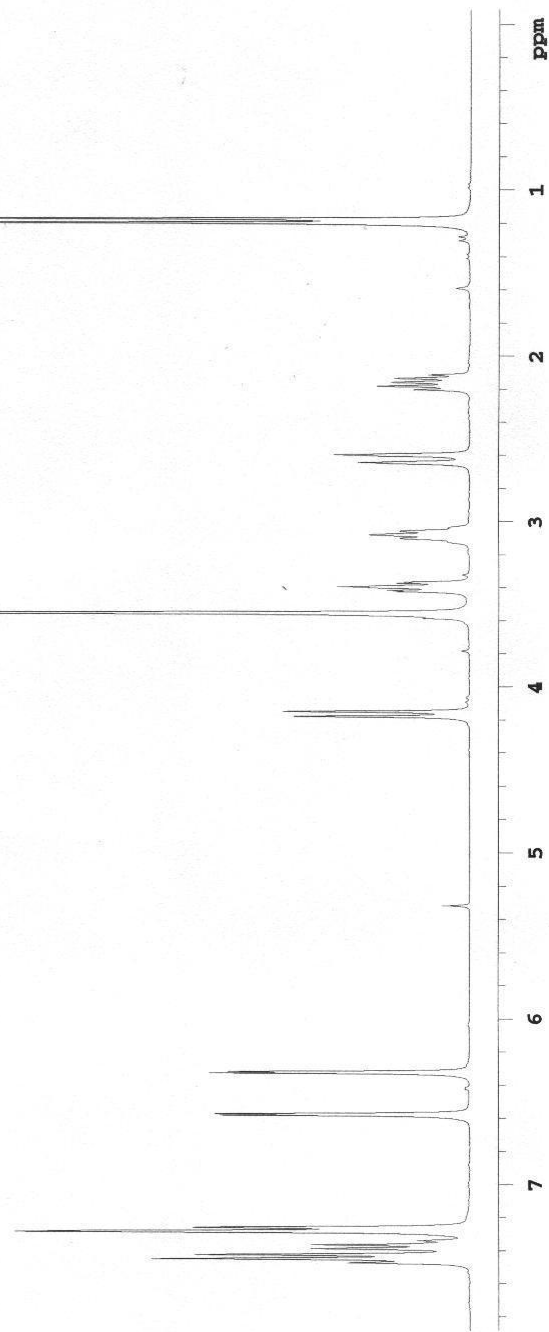
¹³C NMR (75 MHz, CDCl₃)

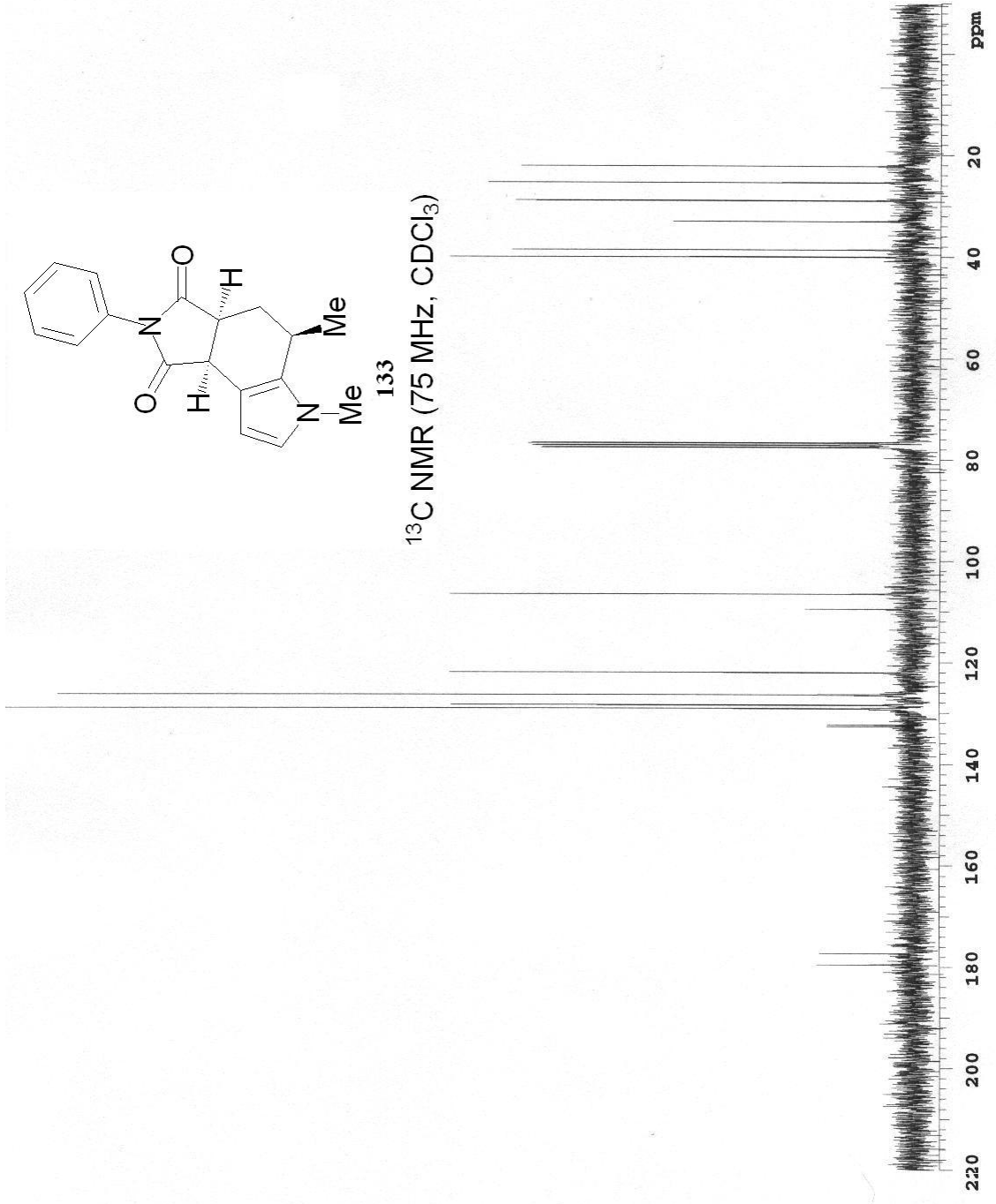


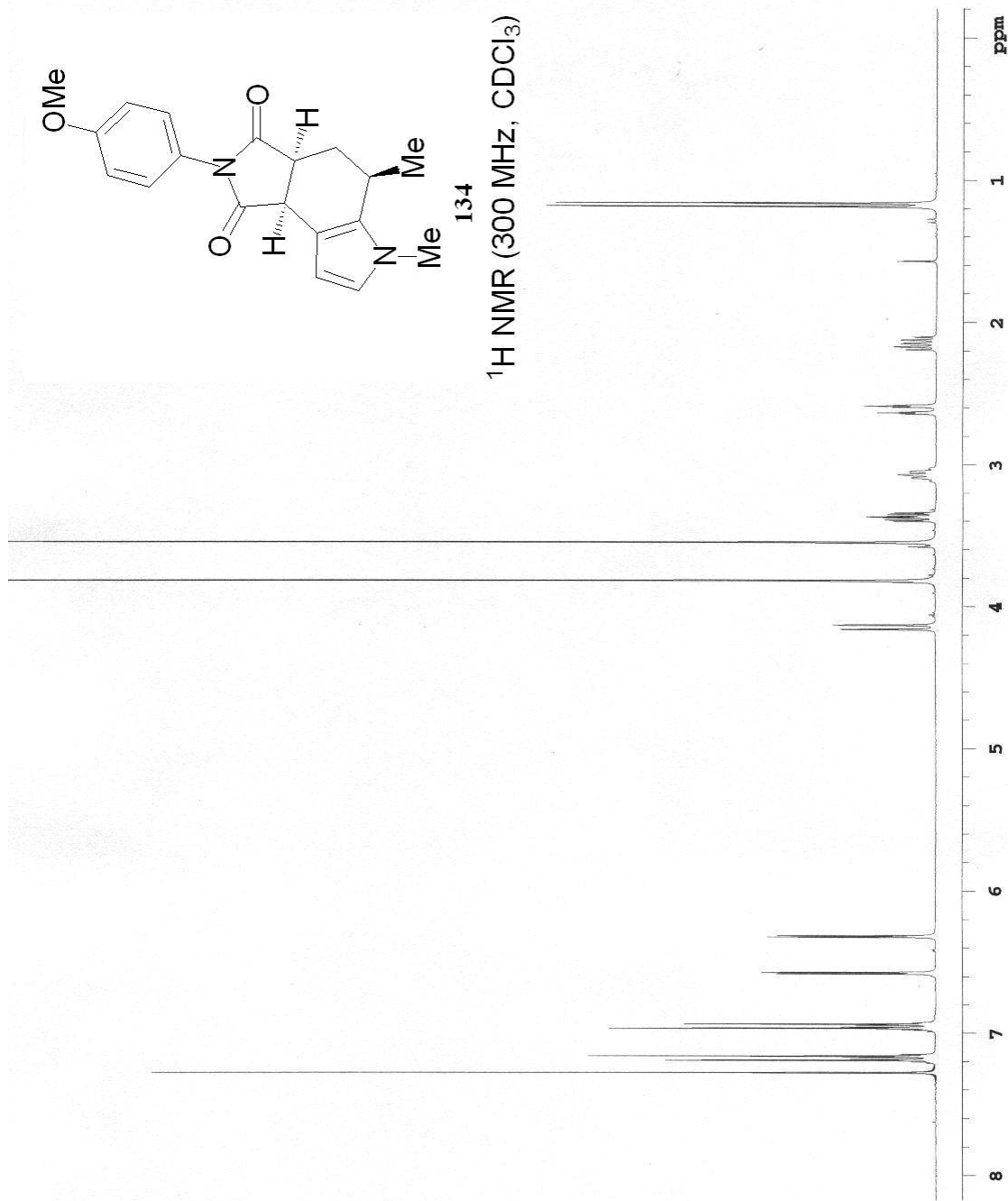


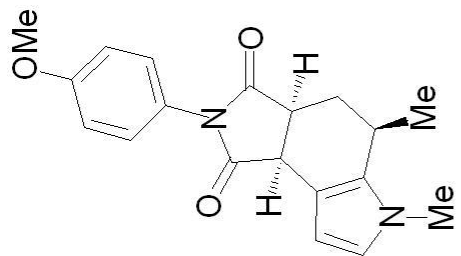
133

$^1\text{H NMR}$ (300 MHz, CDCl_3)



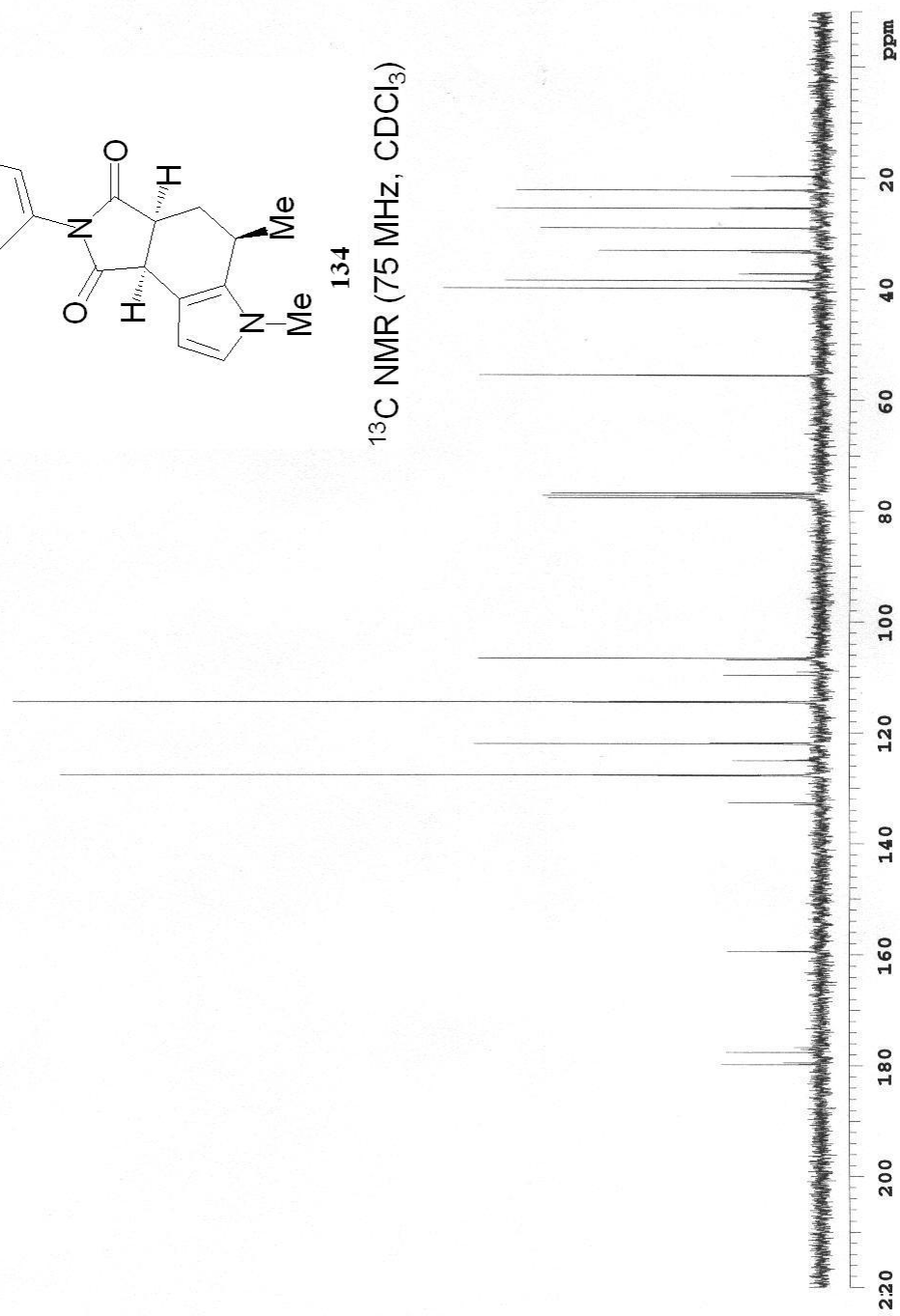


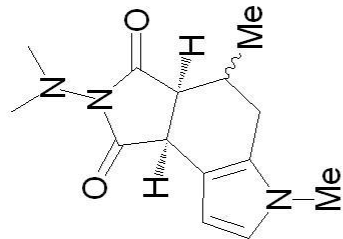




134

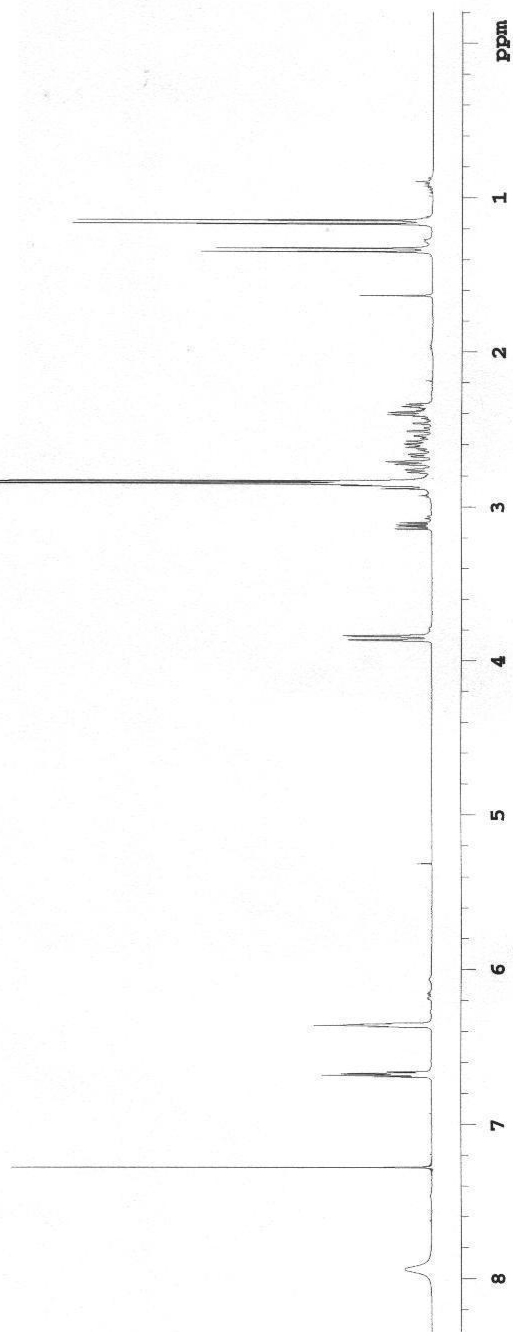
^{13}C NMR (75 MHz, CDCl_3)

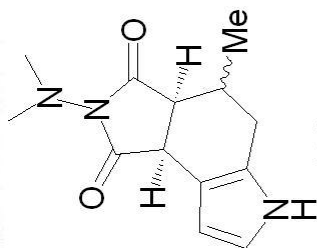




135

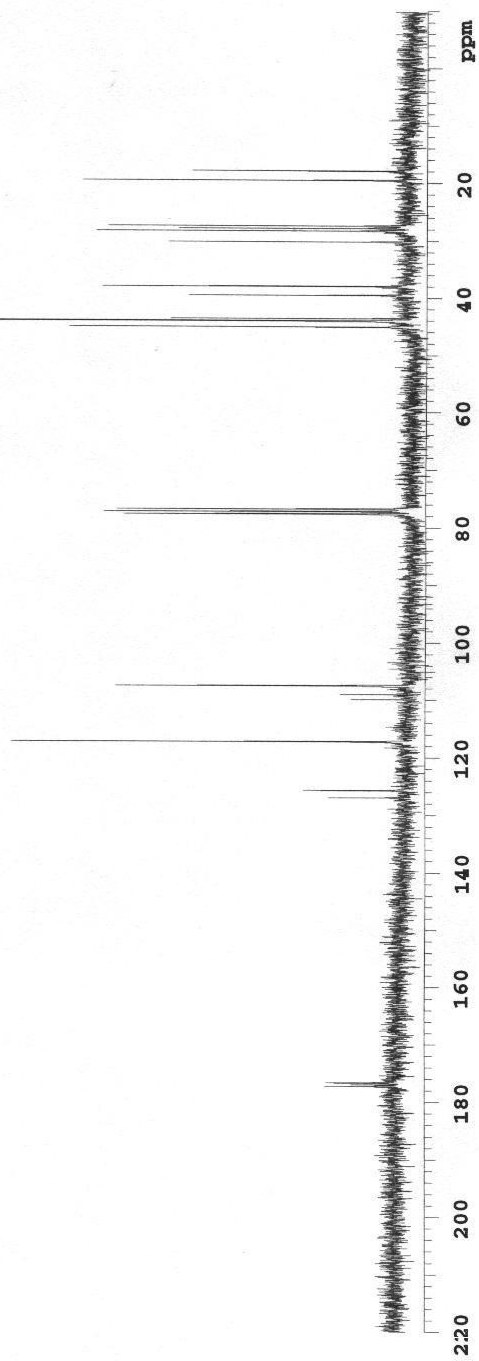
^1H NMR (300 MHz, CDCl_3)

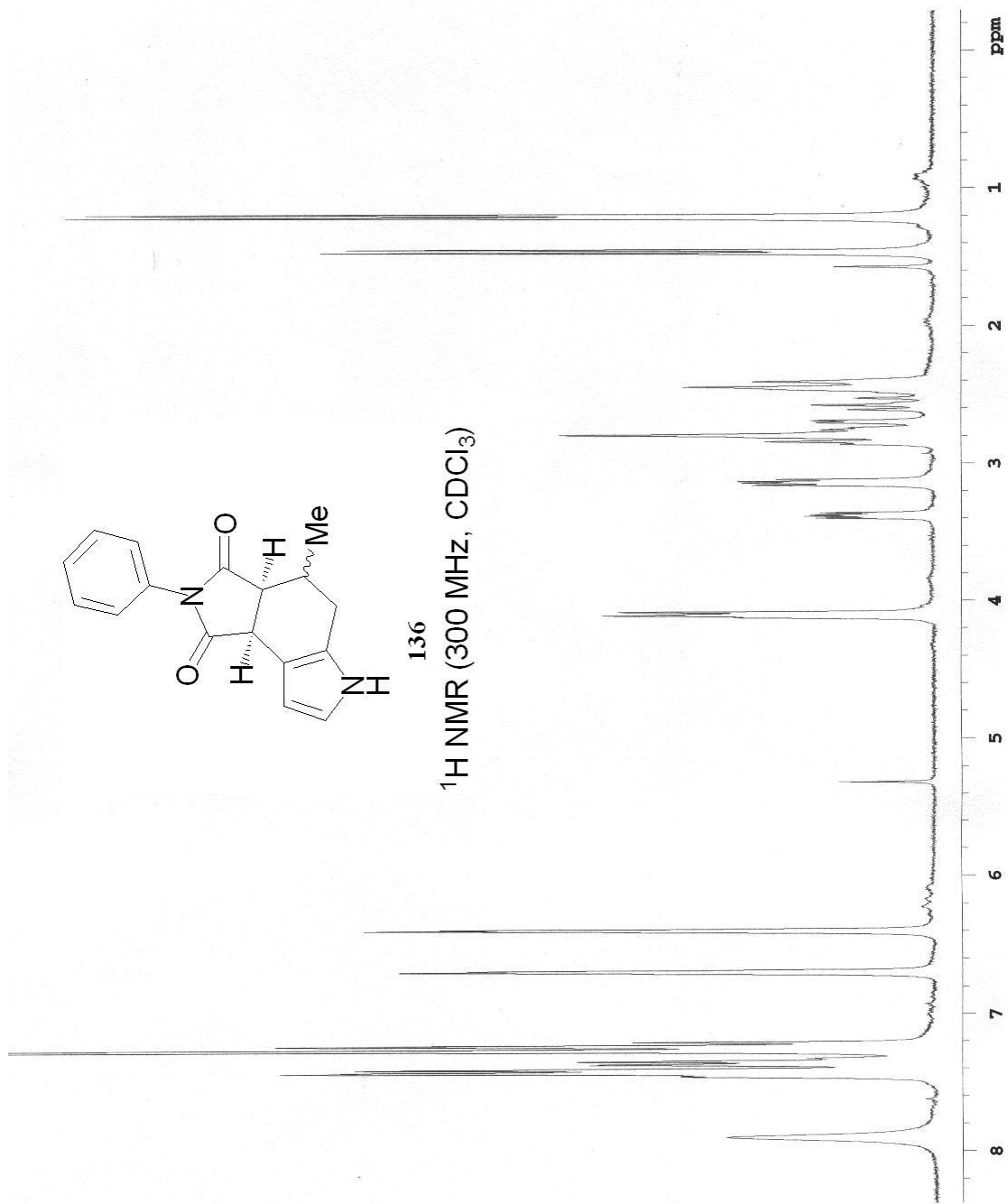


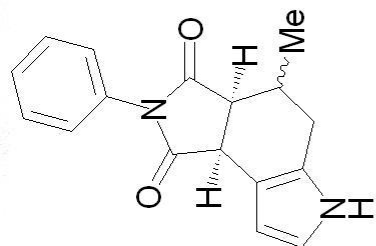


135

¹³C NMR (75 MHz, CDCl₃)

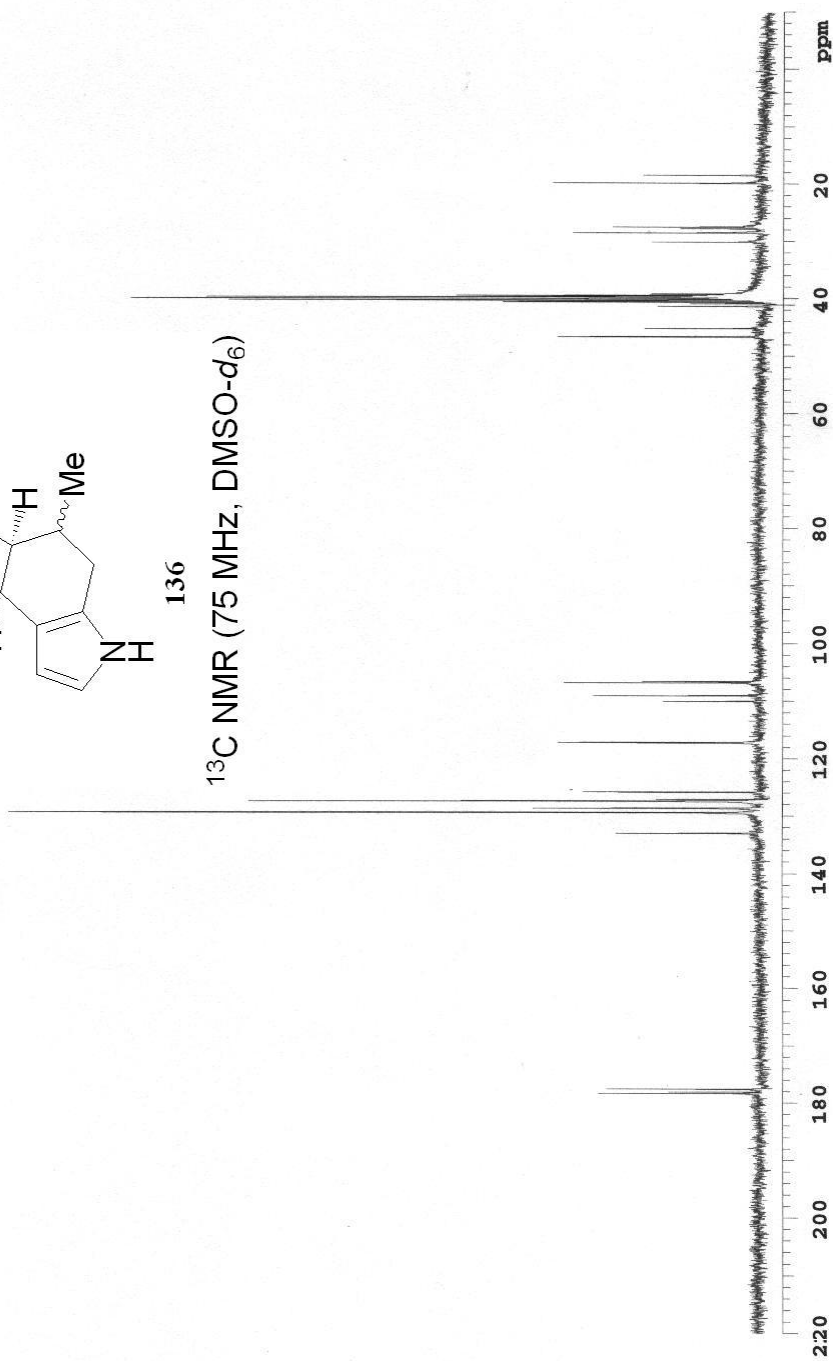


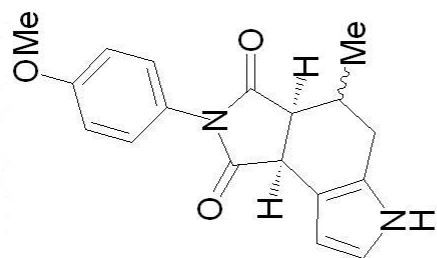




136

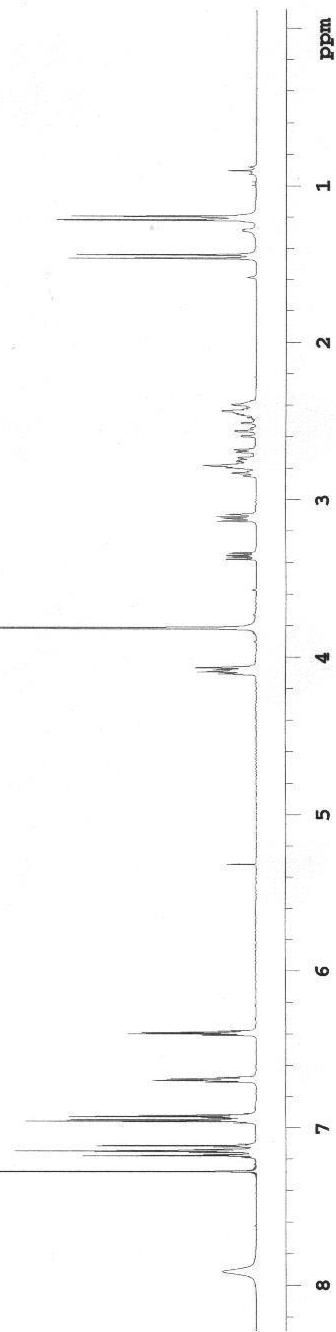
¹³C NMR (75 MHz, DMSO-d₆)

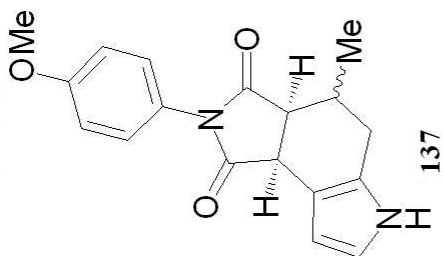




137

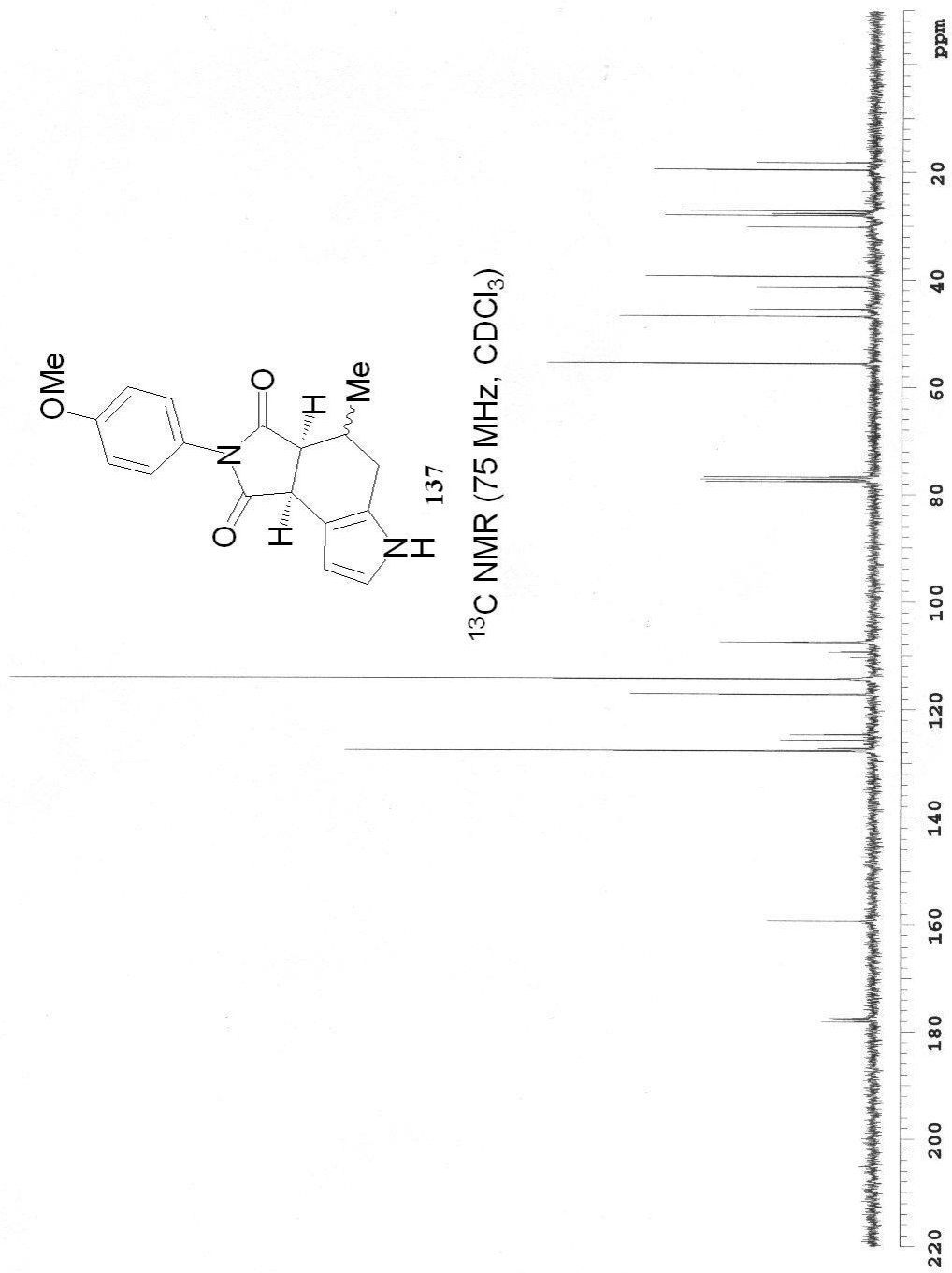
^1H NMR (300 MHz, CDCl_3)

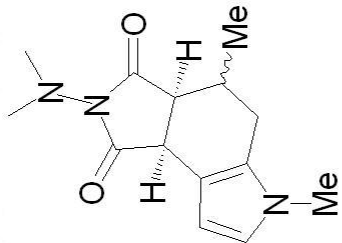




^{13}C NMR (75 MHz, CDCl_3)

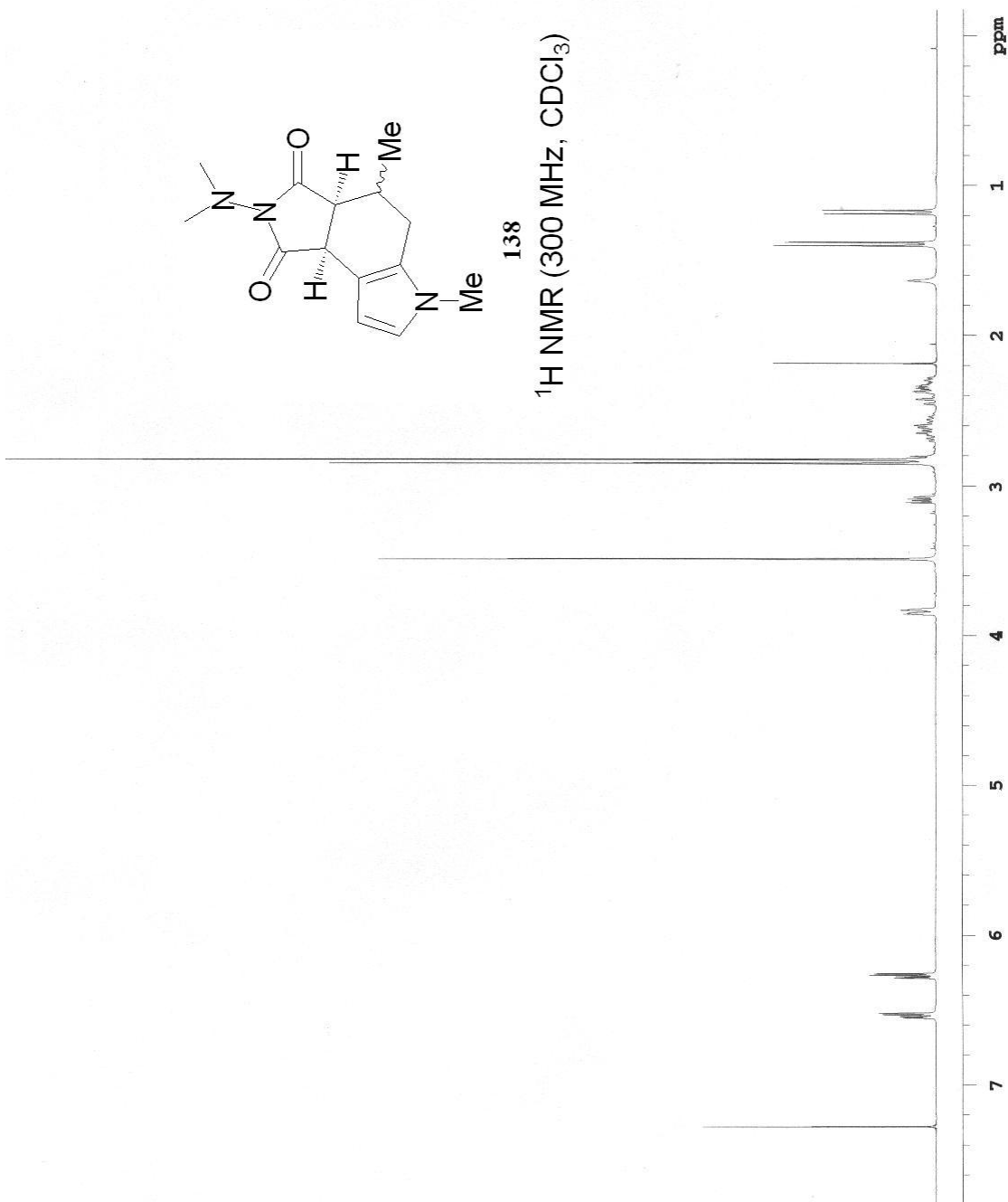
137

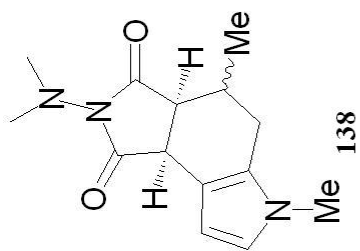




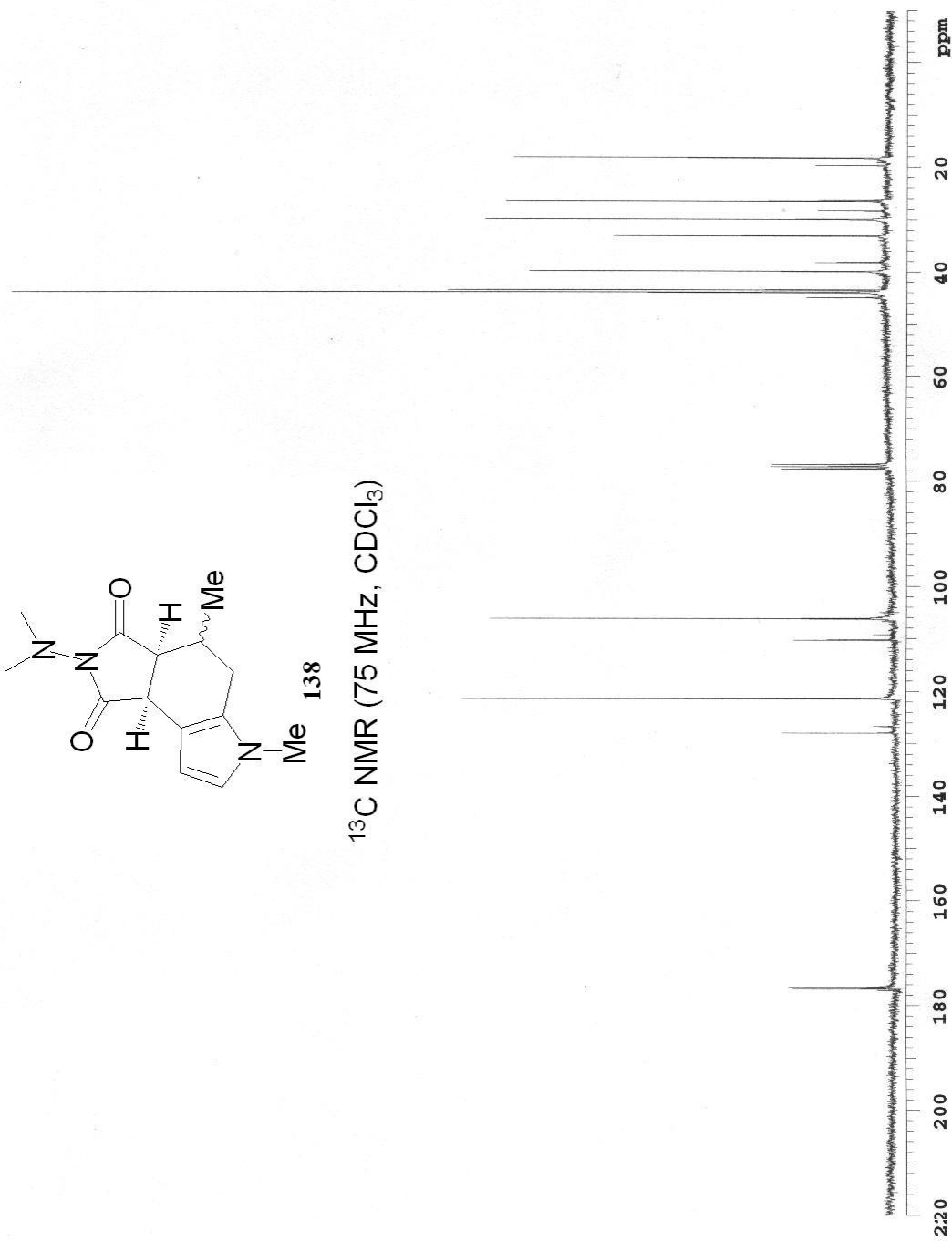
138

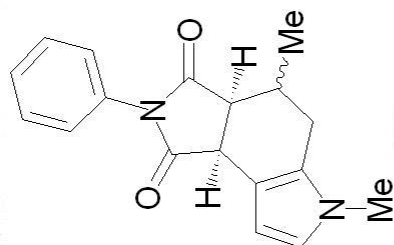
^1H NMR (300 MHz, CDCl_3)



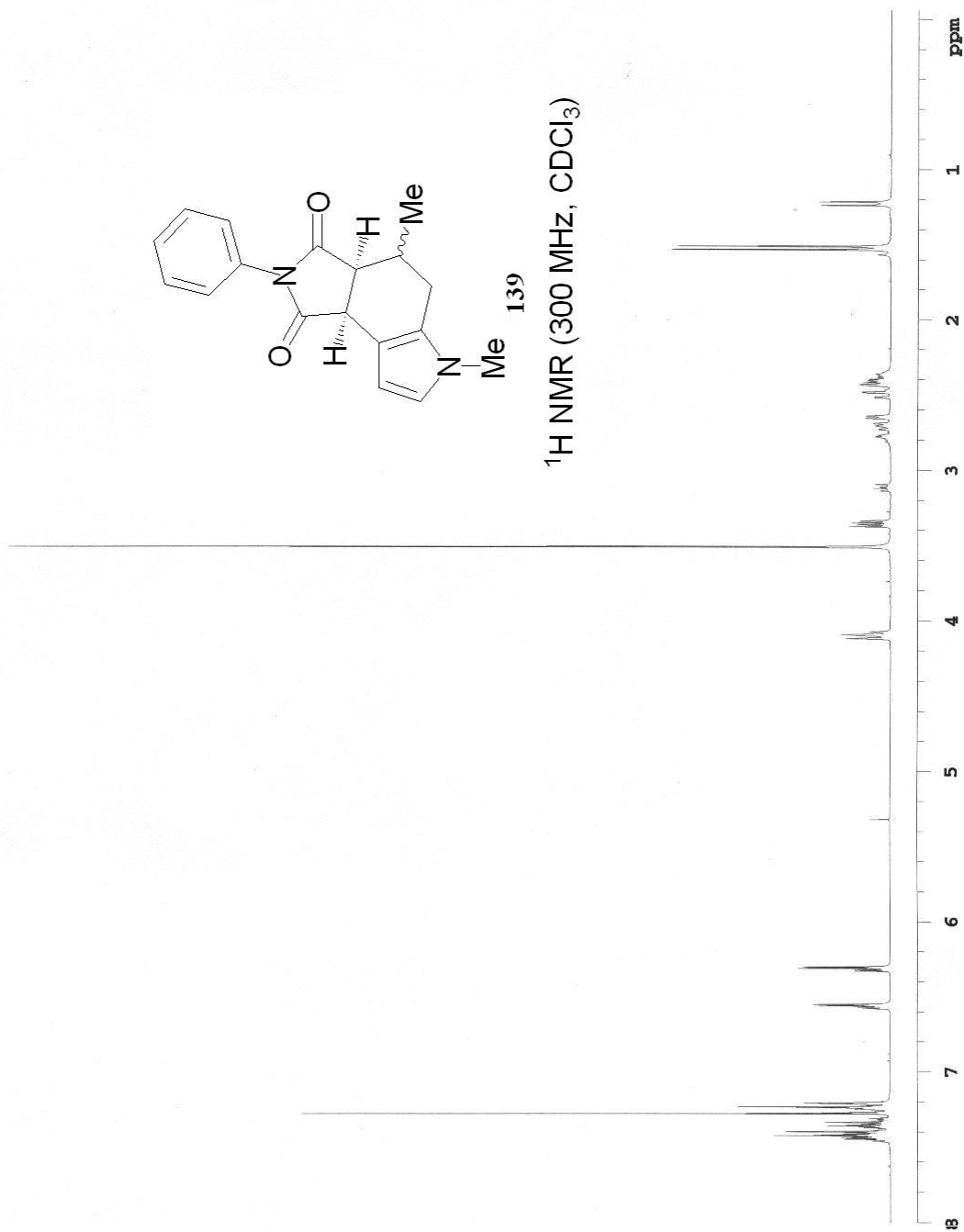


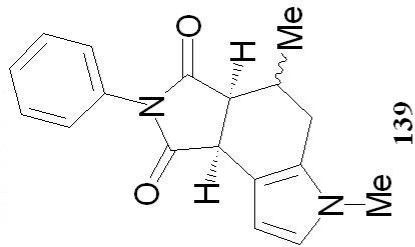
¹³C NMR (75 MHz, CDCl₃)





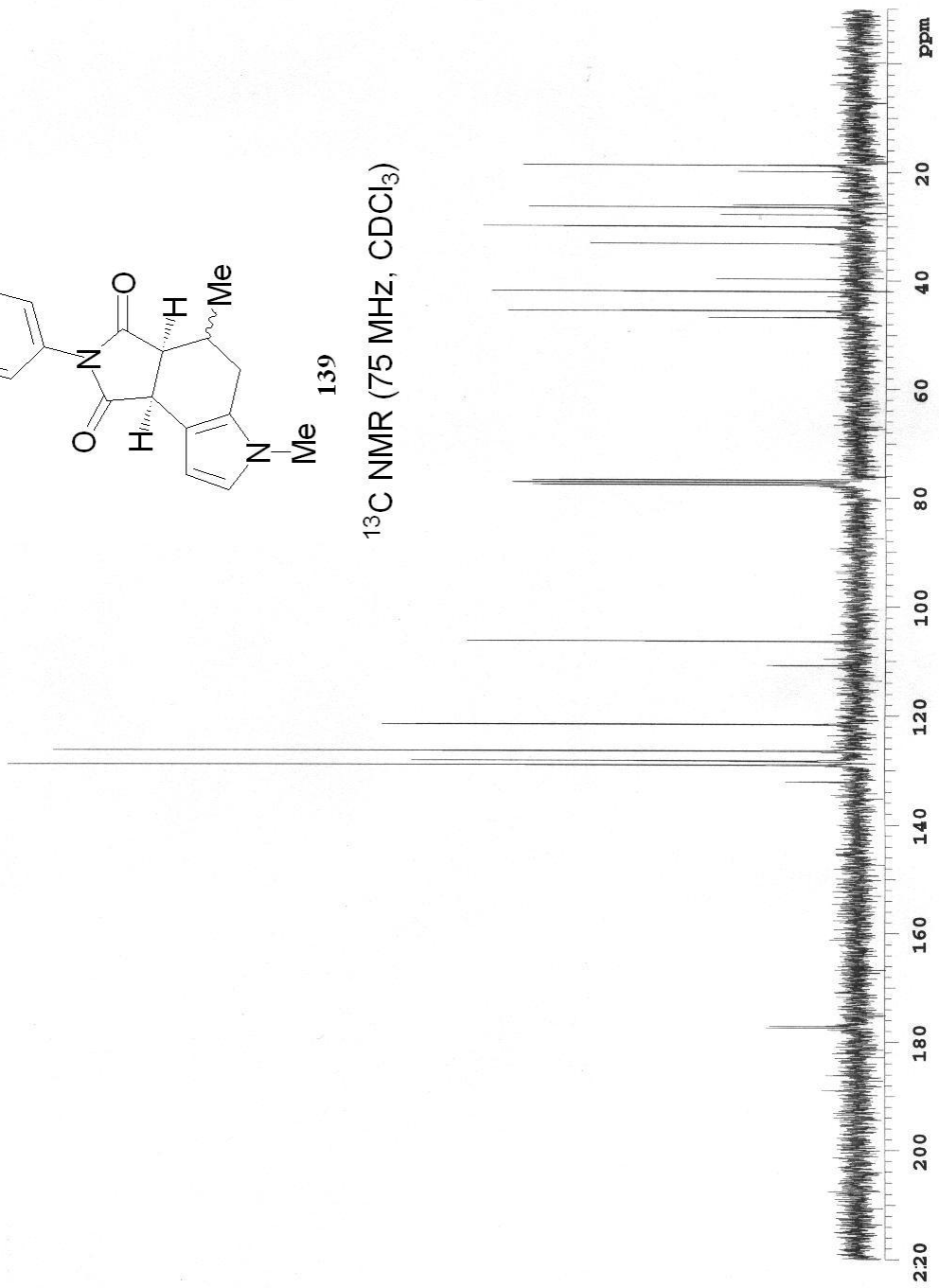
¹H NMR (300 MHz, CDCl₃)

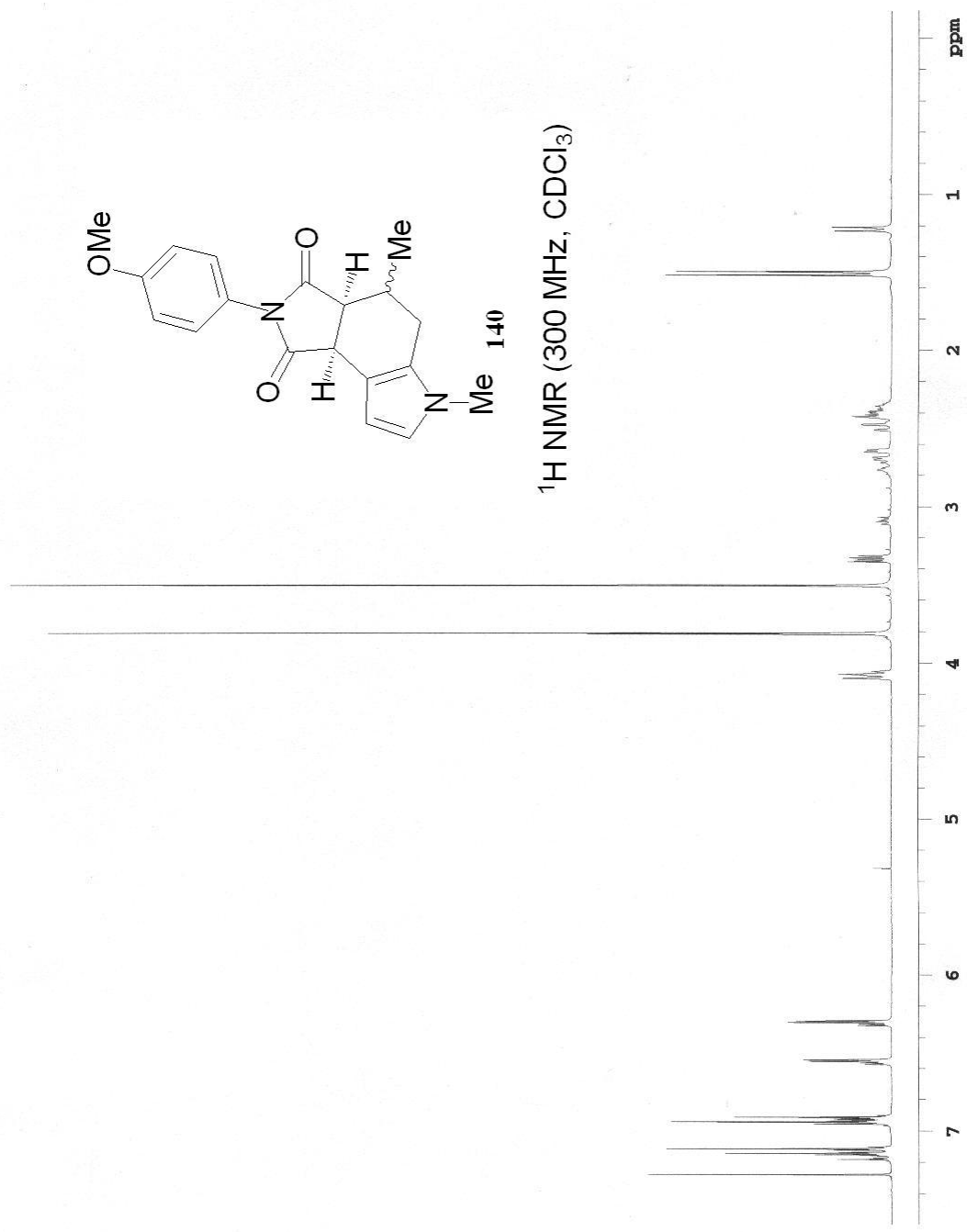


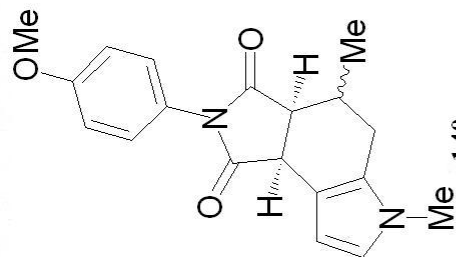


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¹³C NMR (75 MHz, CDCl₃)

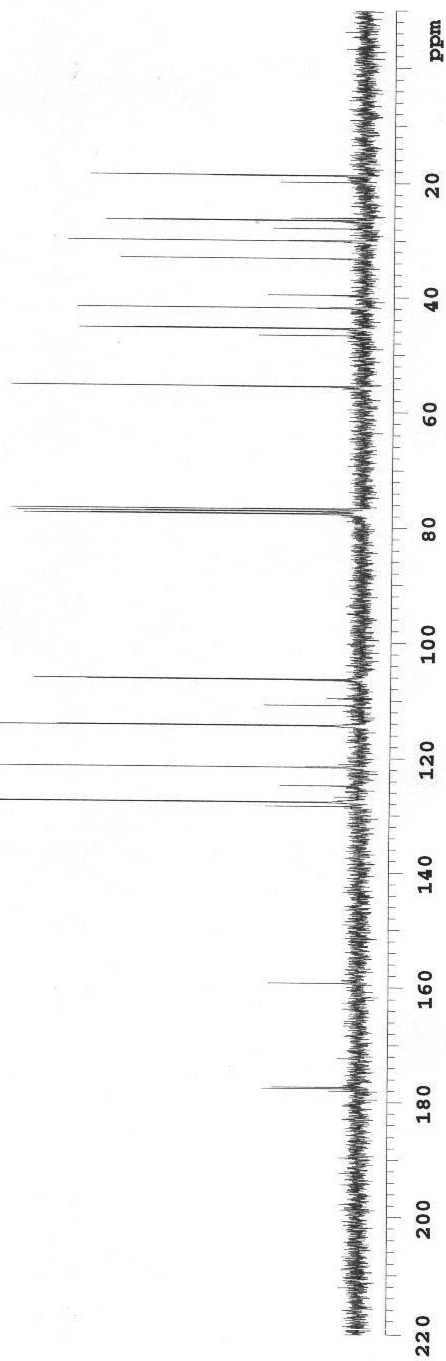


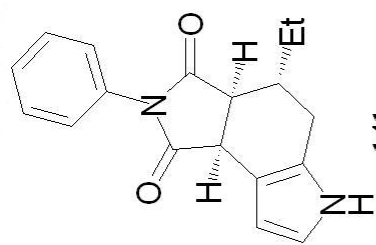




¹³C NMR (75 MHz, CDCl₃)

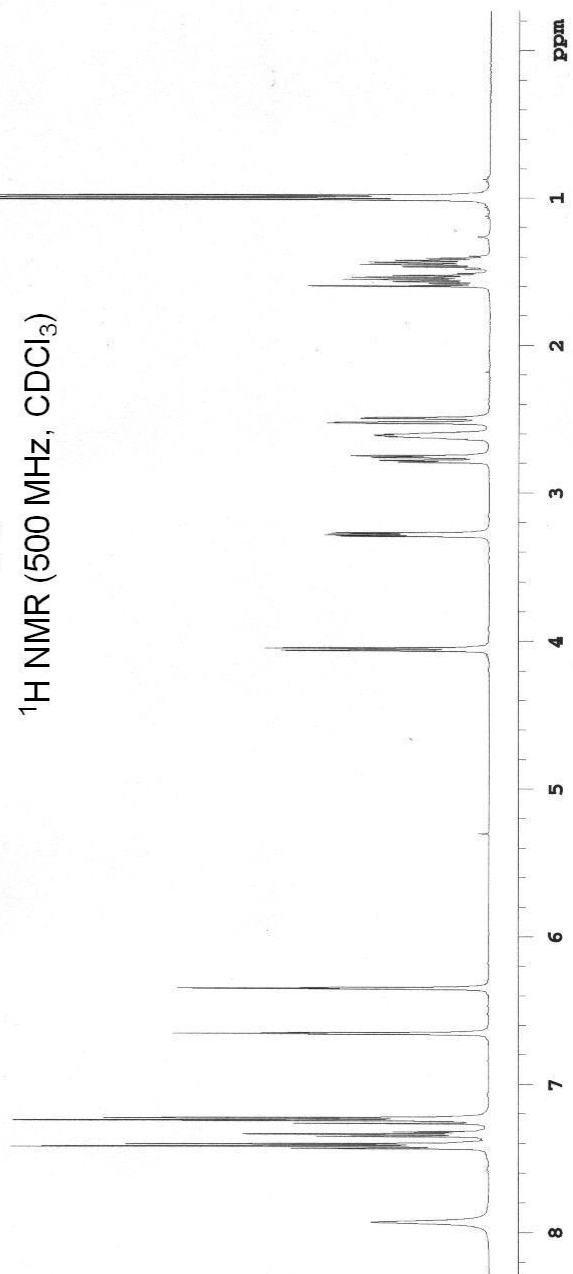
140

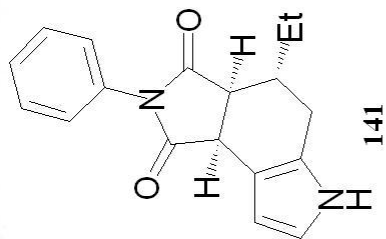




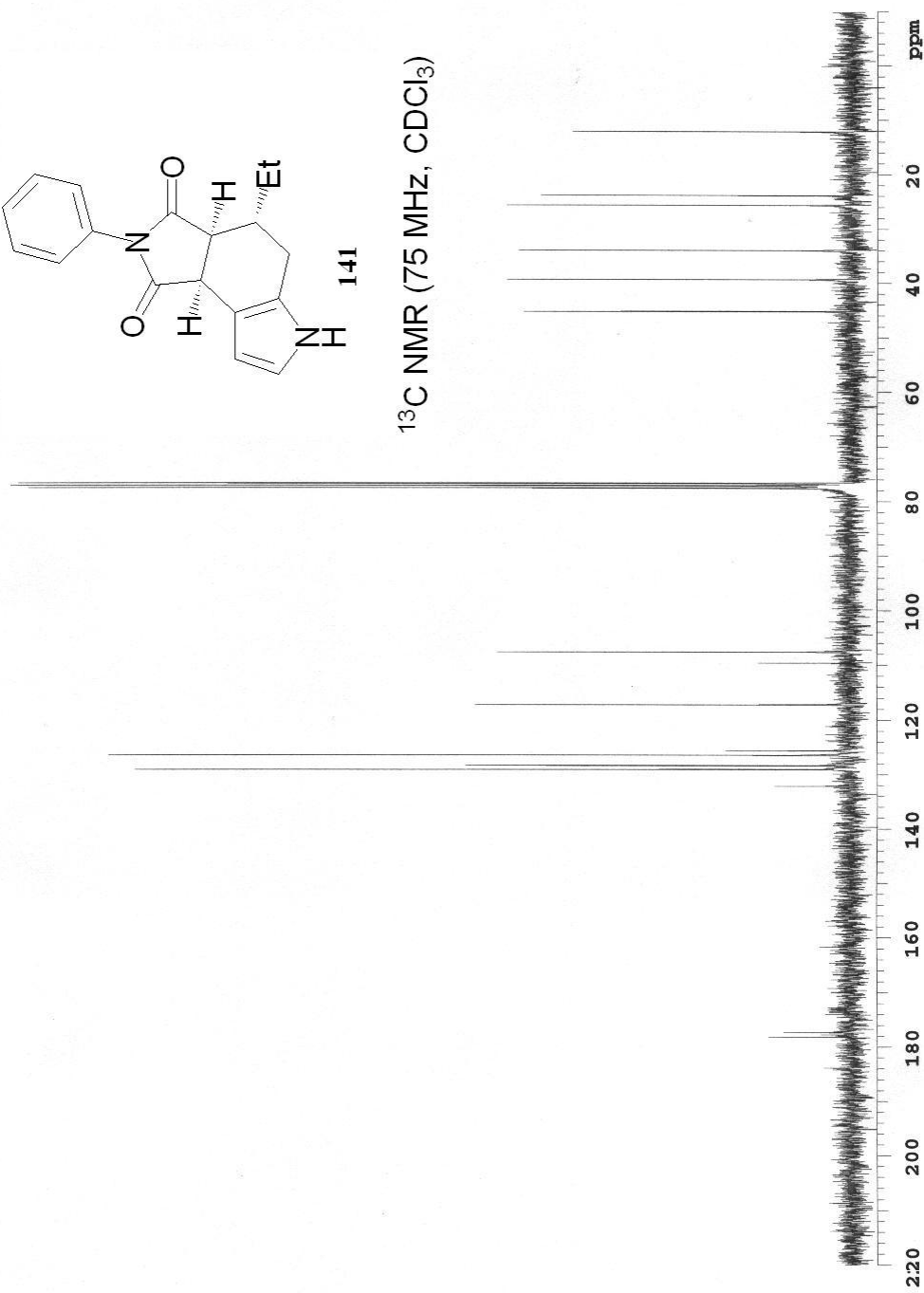
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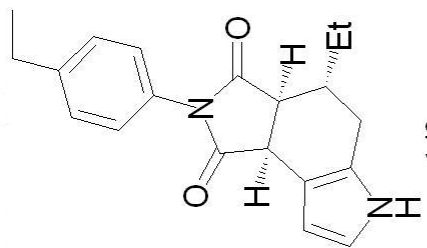
^1H NMR (500 MHz, CDCl_3)





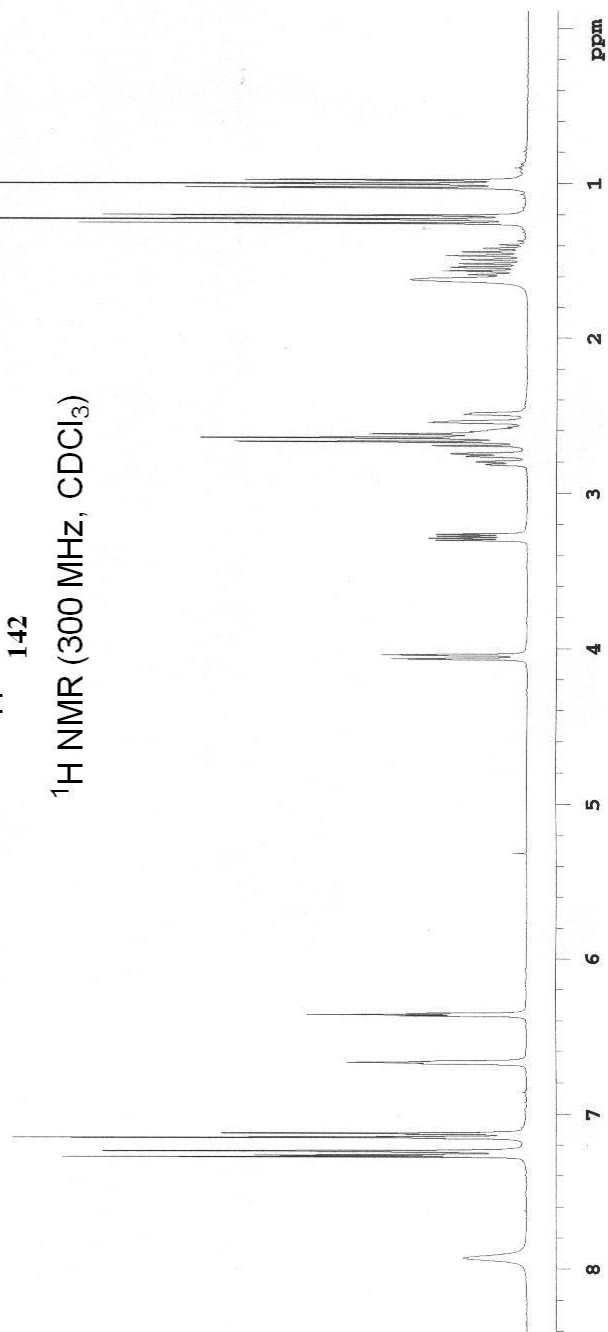
^{13}C NMR (75 MHz, CDCl_3)

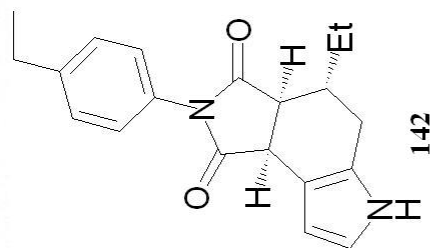




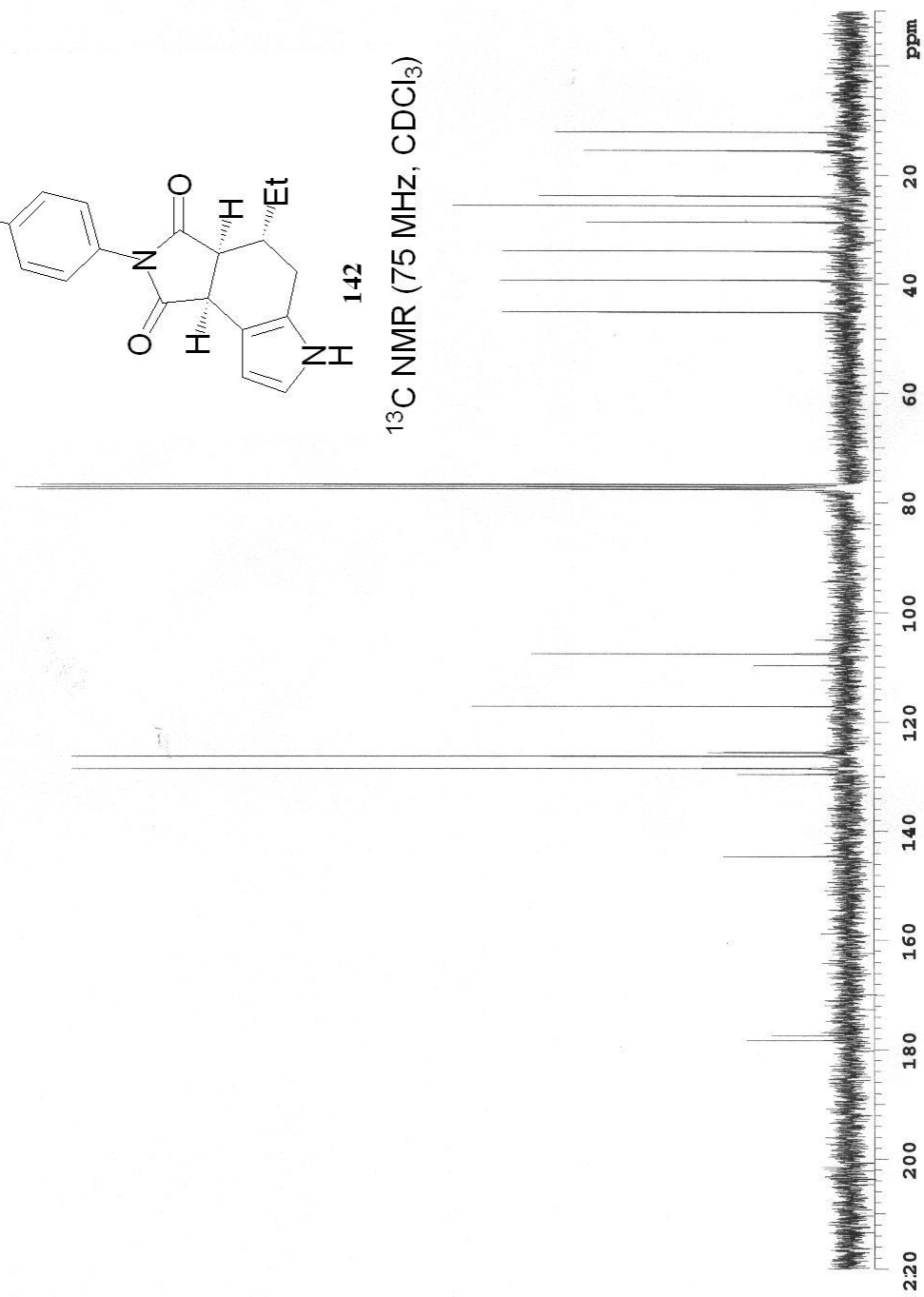
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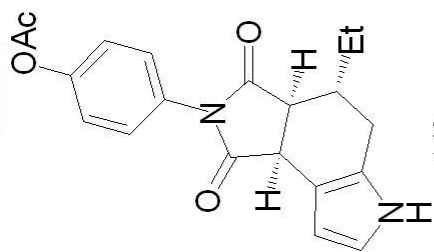
^1H NMR (300 MHz, CDCl_3)





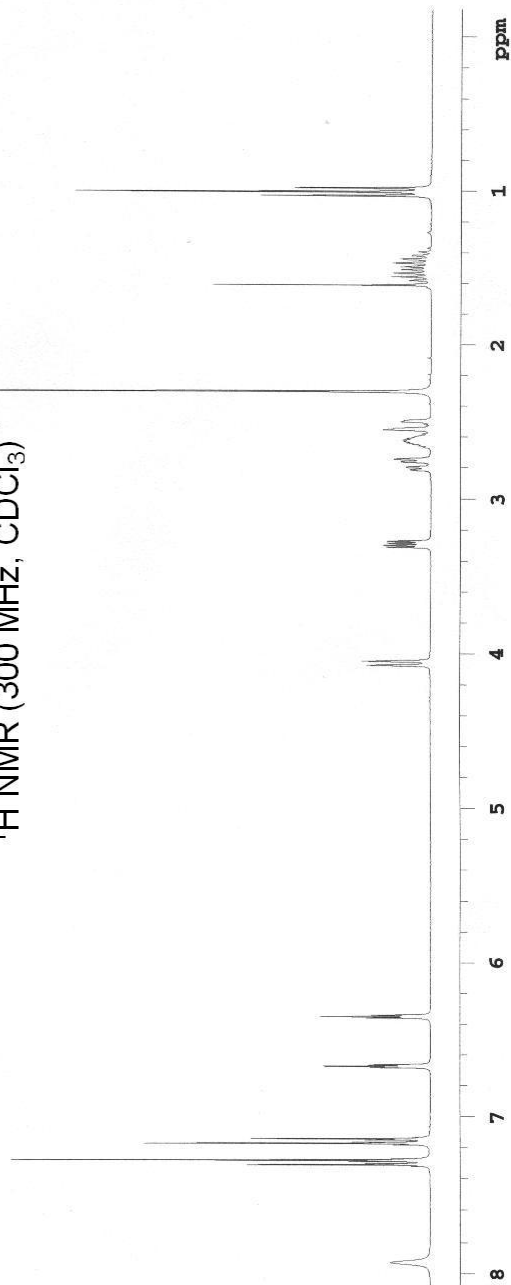
^{13}C NMR (75 MHz, CDCl_3)

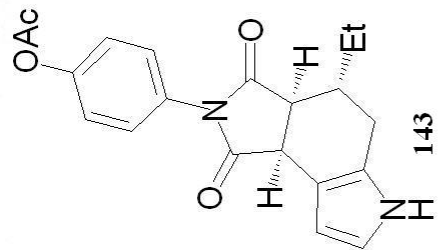




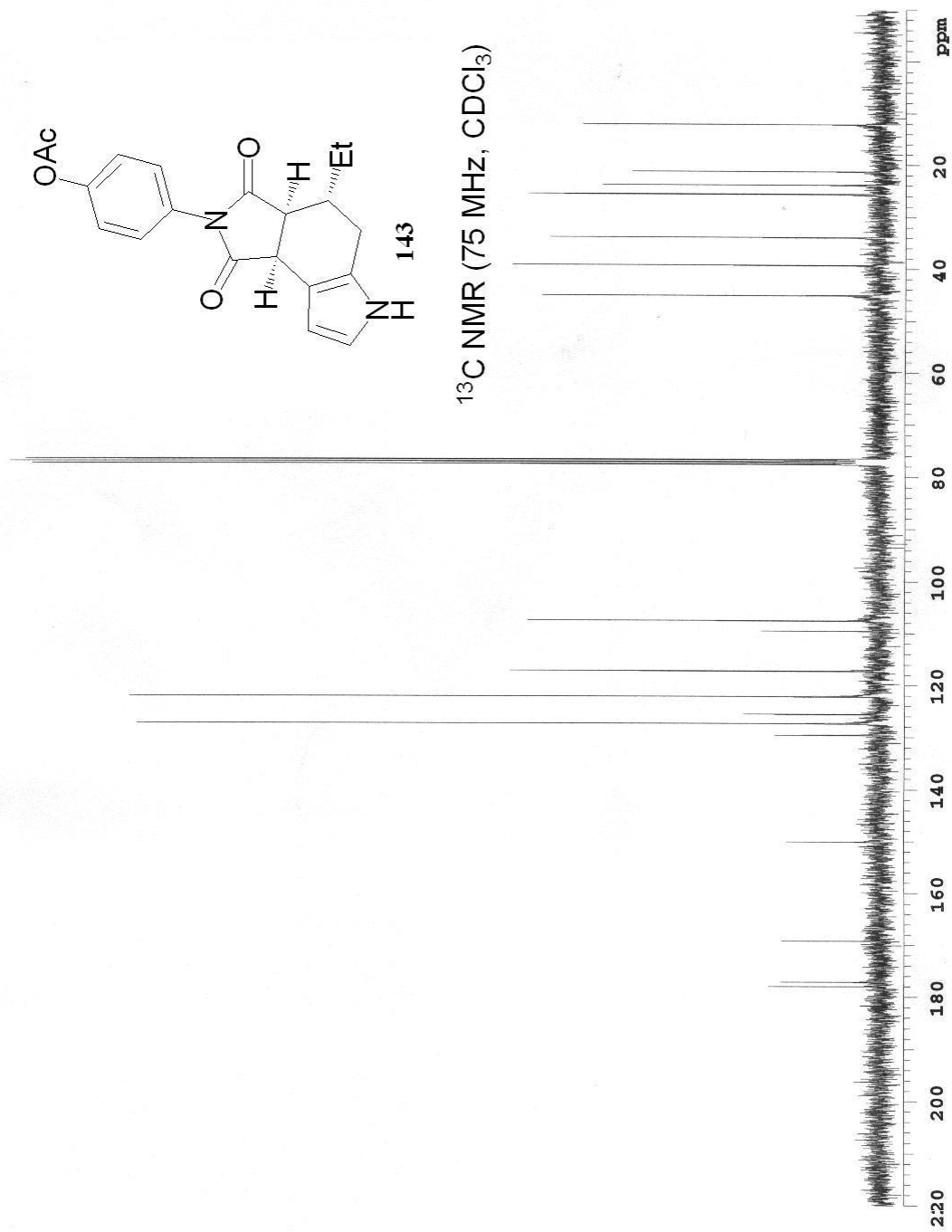
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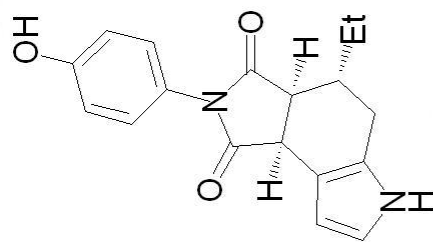
^1H NMR (300 MHz, CDCl_3)





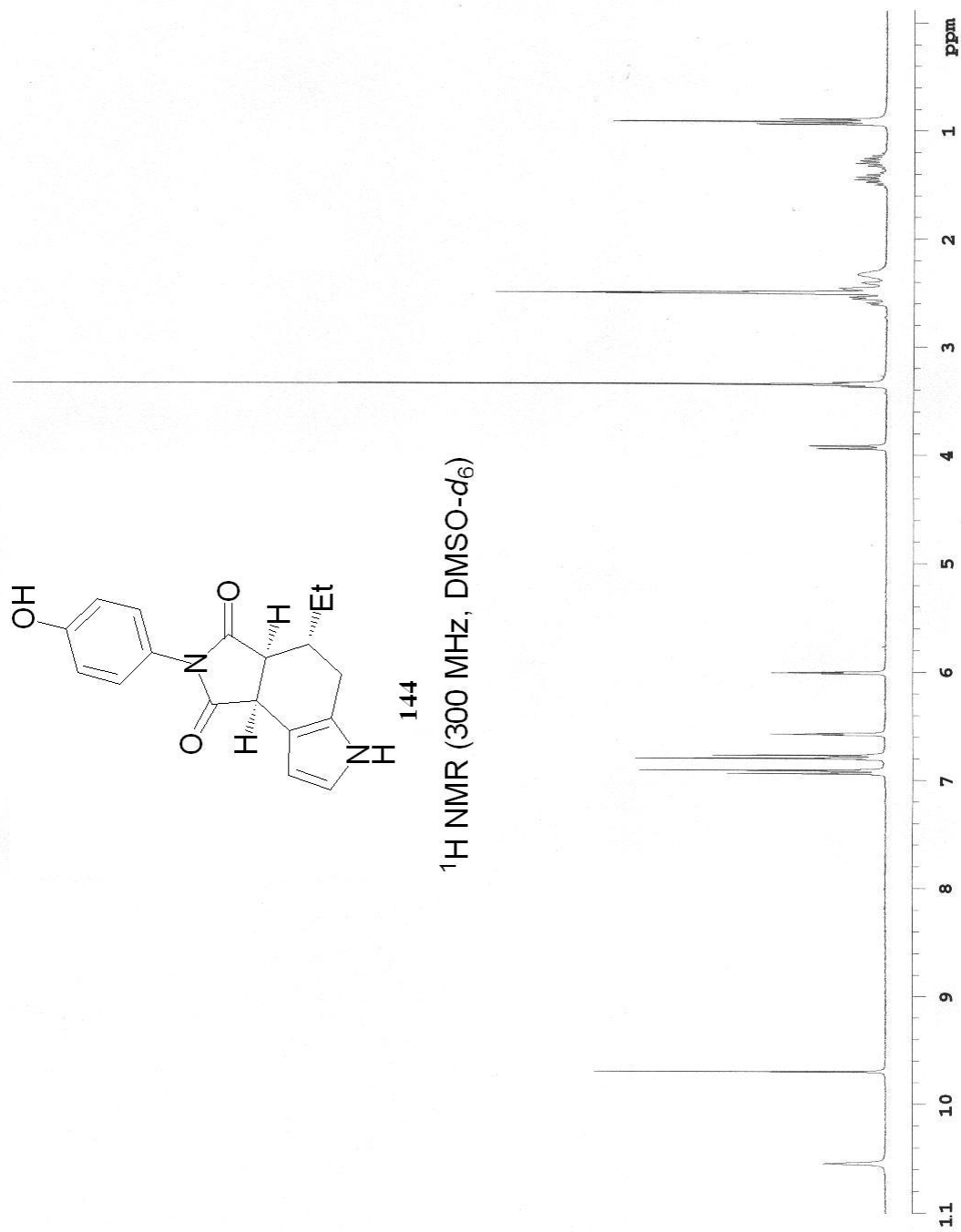
^{13}C NMR (75 MHz, CDCl_3)

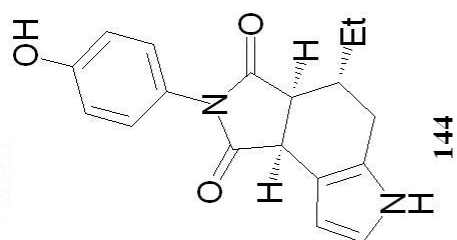




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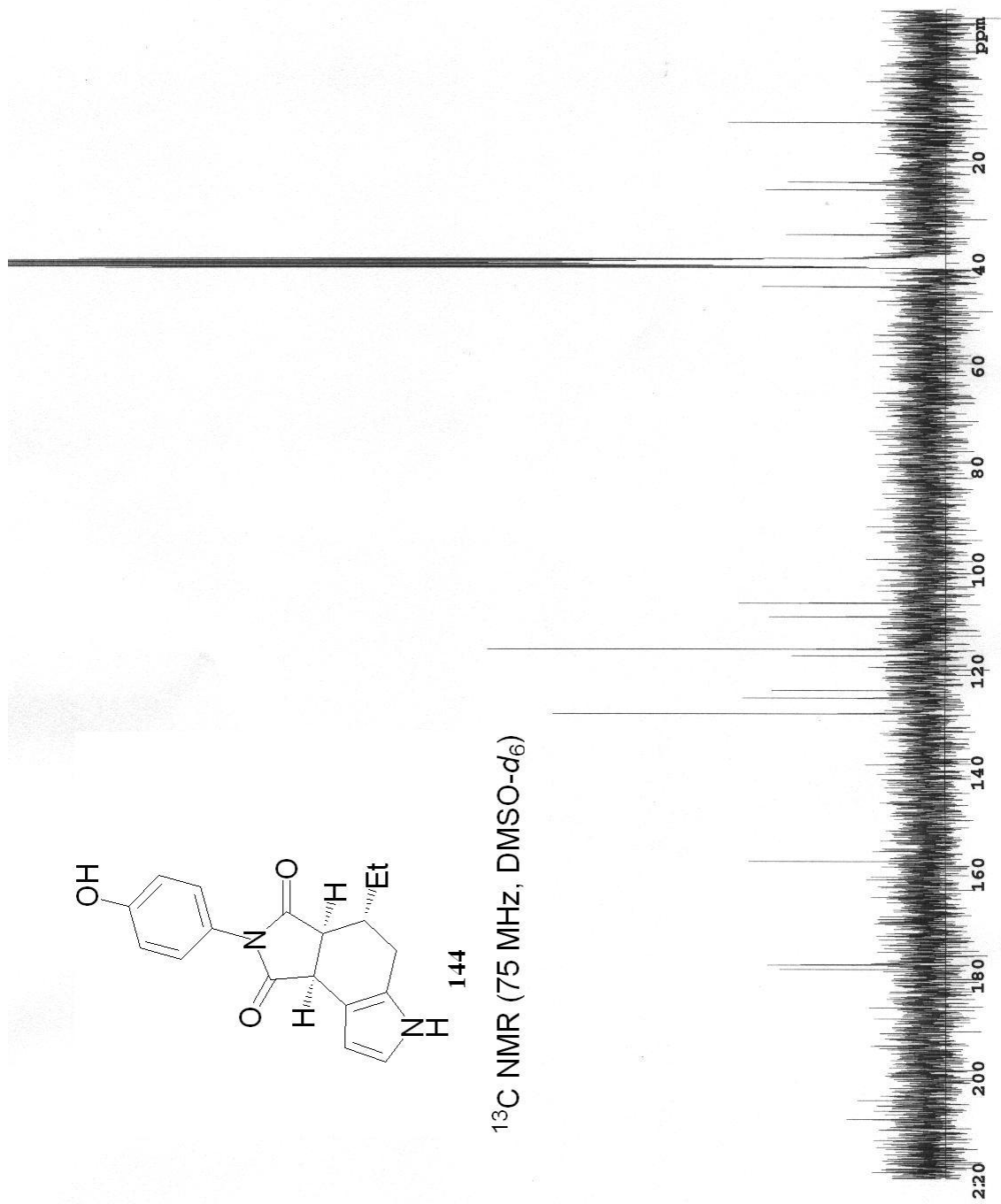
^1H NMR (300 MHz, DMSO- d_6)

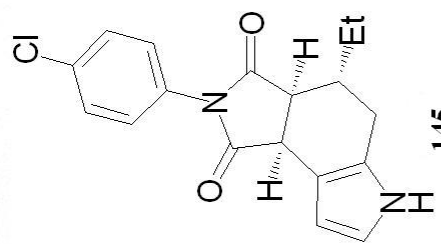




^{13}C NMR (75 MHz, $\text{DMSO}-d_6$)

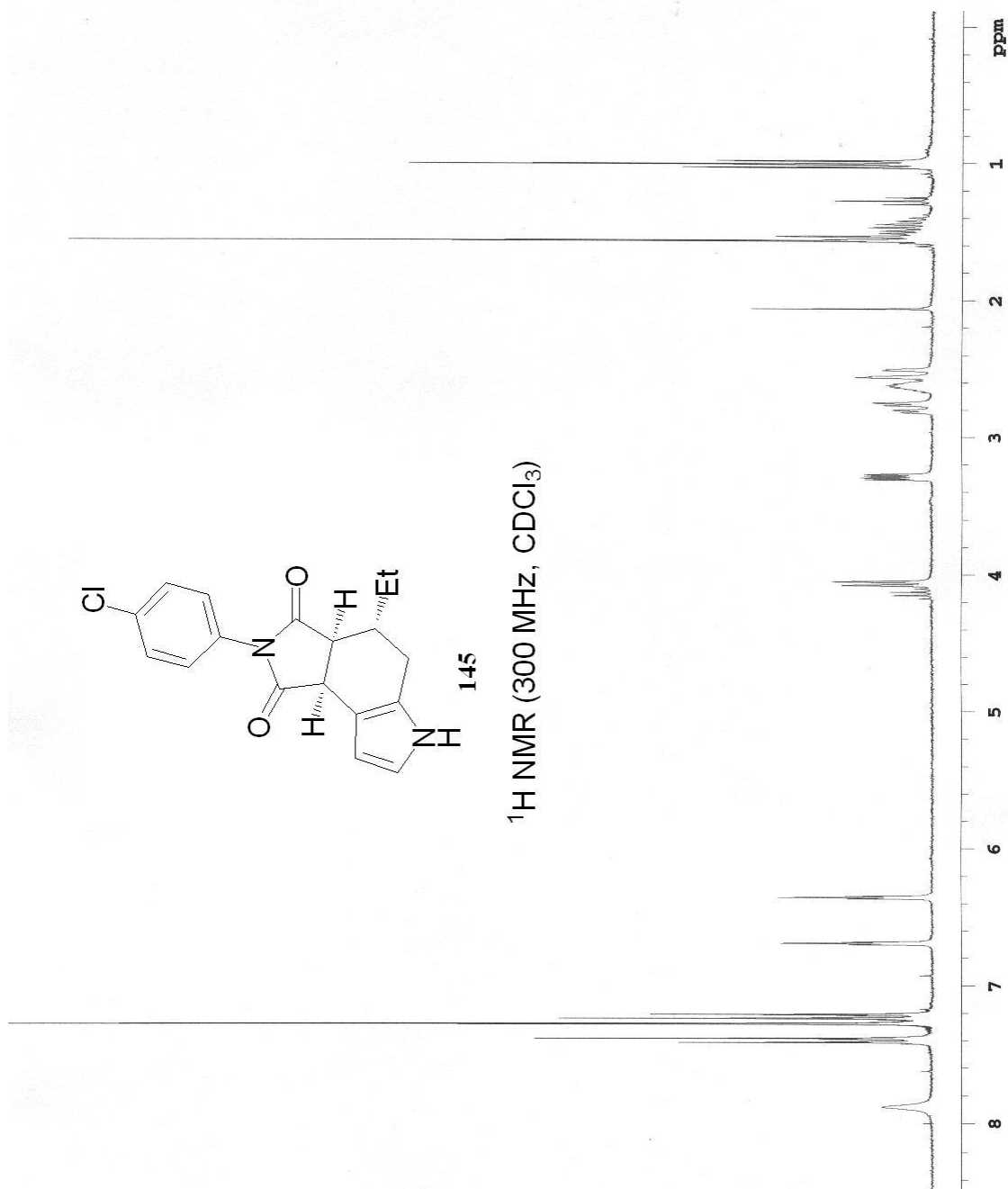
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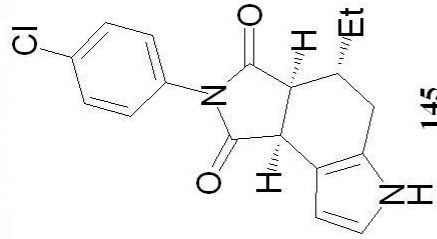




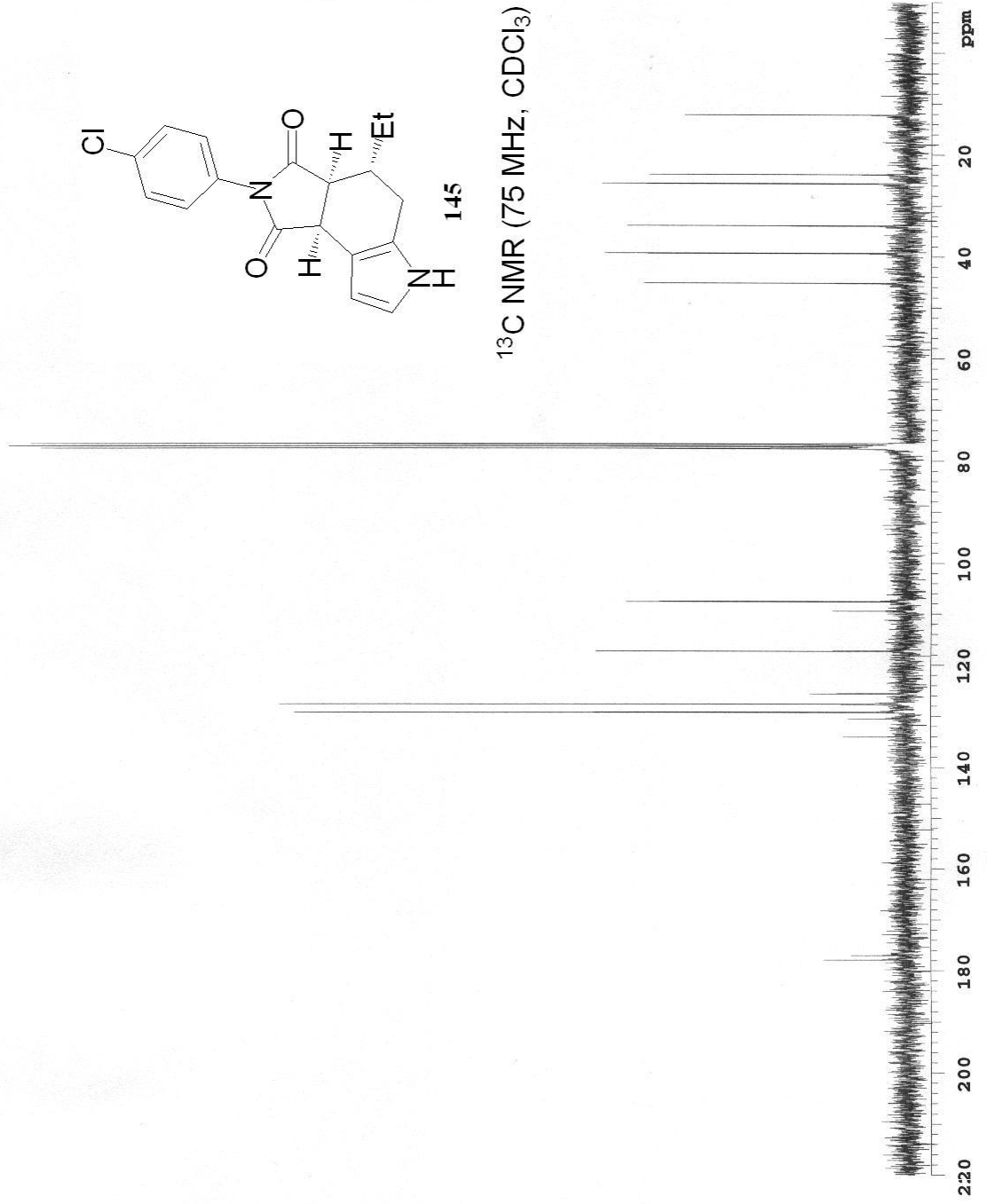
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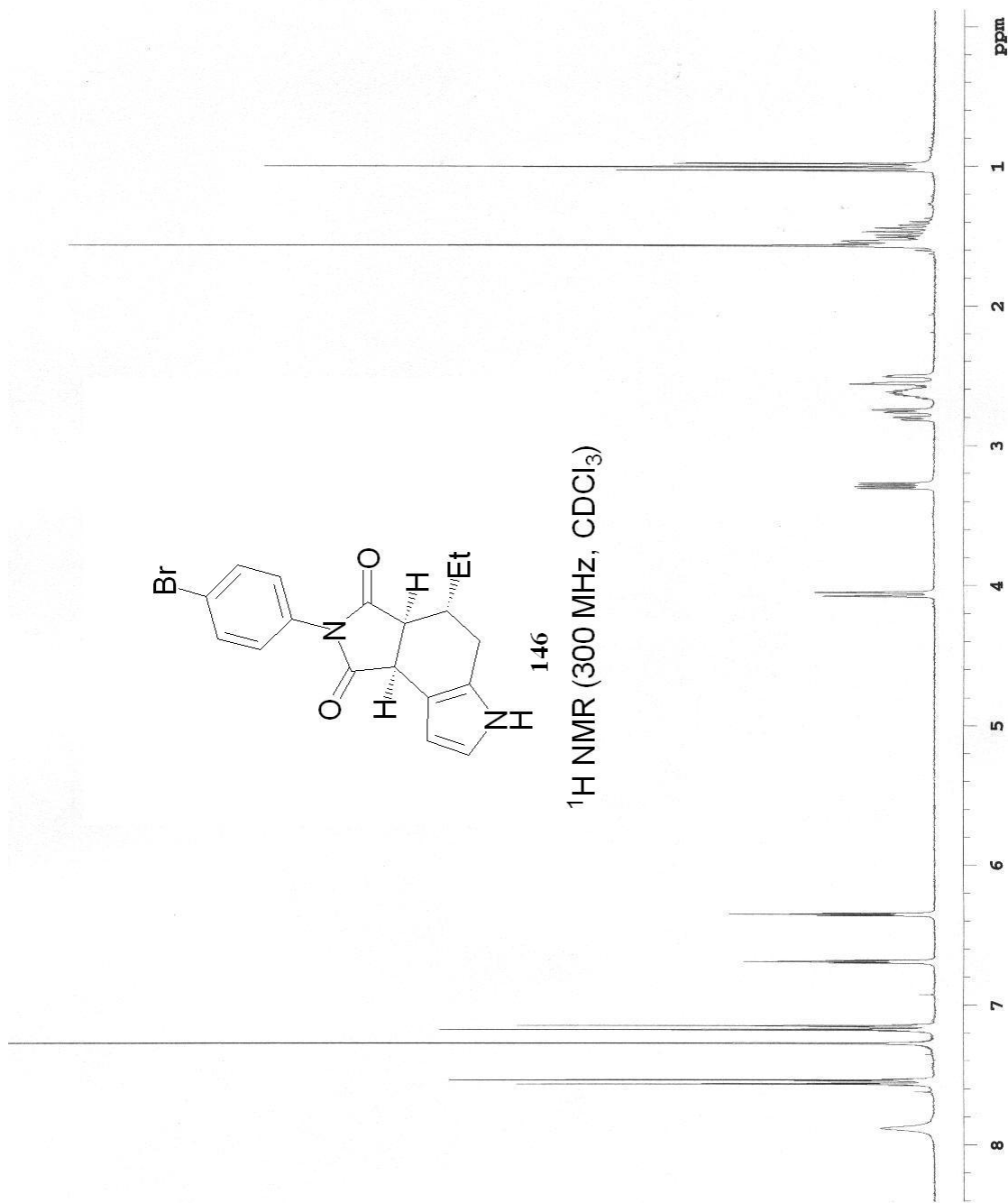
$^1\text{H NMR}$ (300 MHz, CDCl_3)

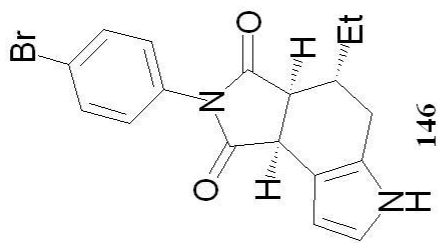




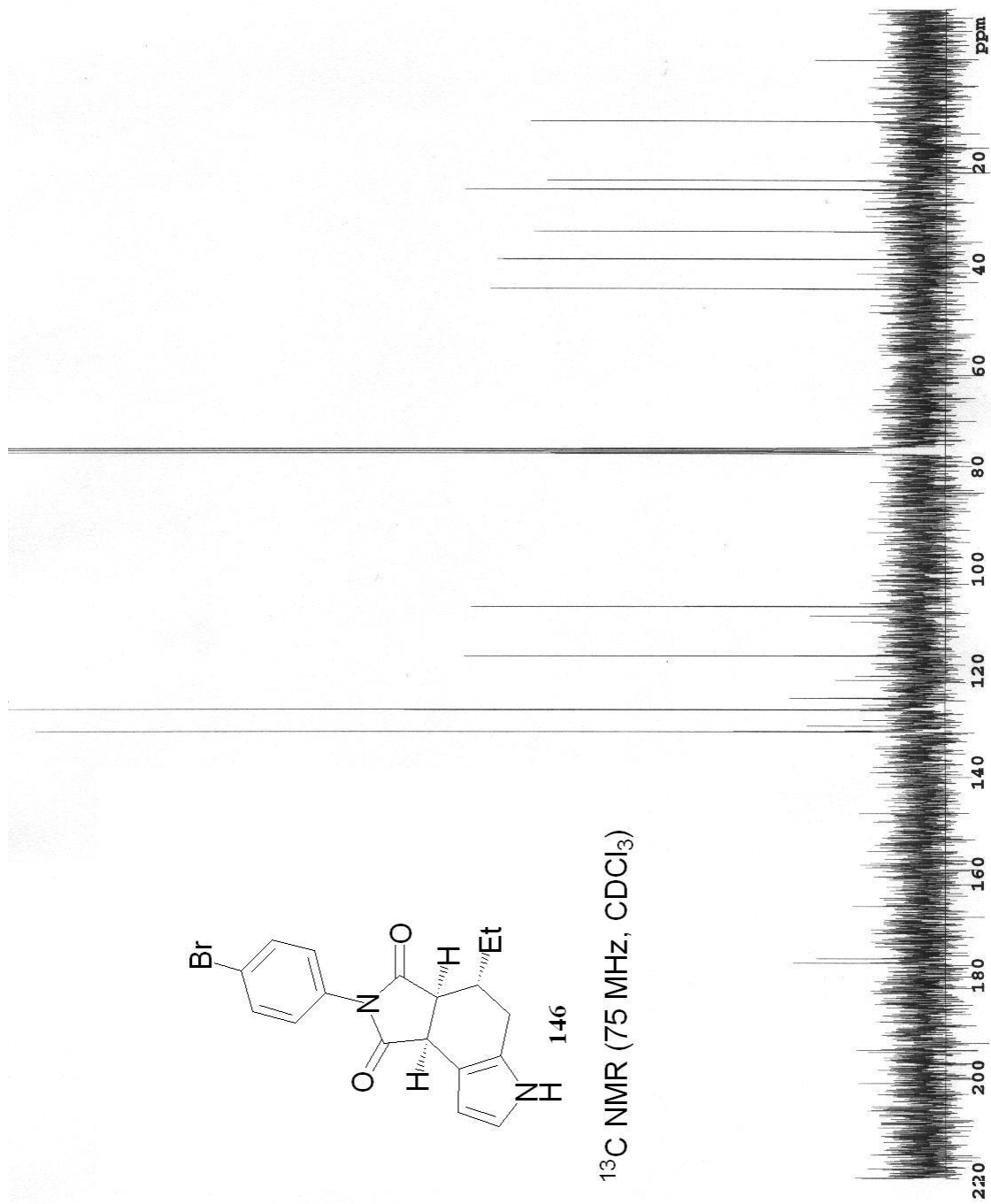
^{13}C NMR (75 MHz, CDCl_3)

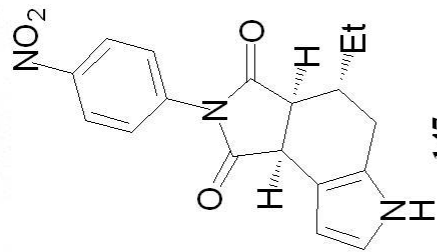






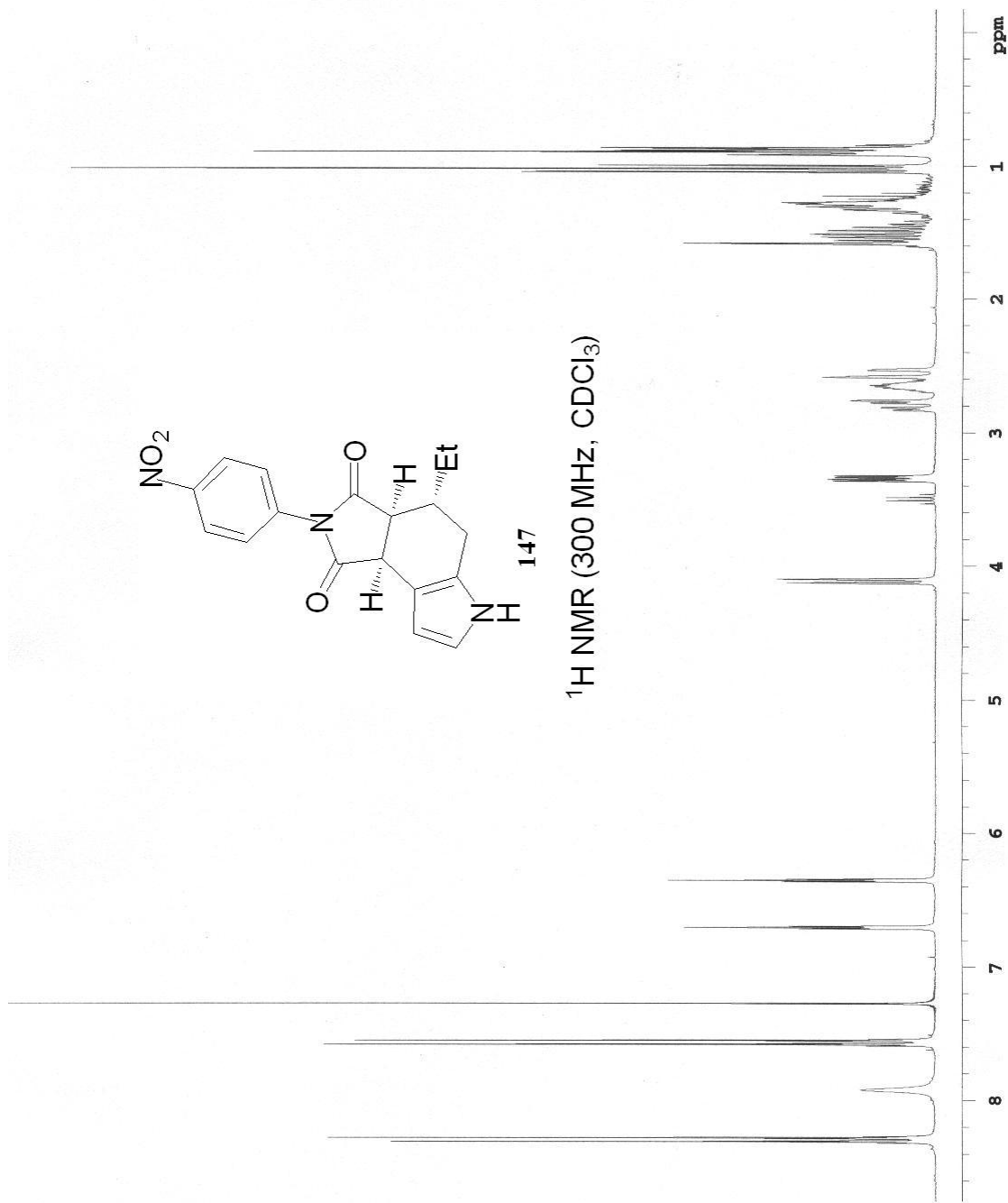
^{13}C NMR (75 MHz, CDCl_3)

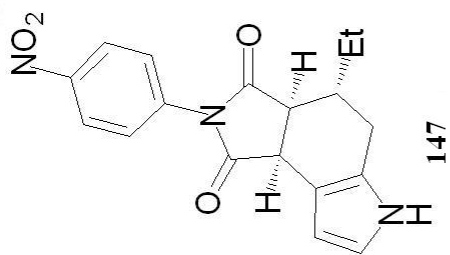




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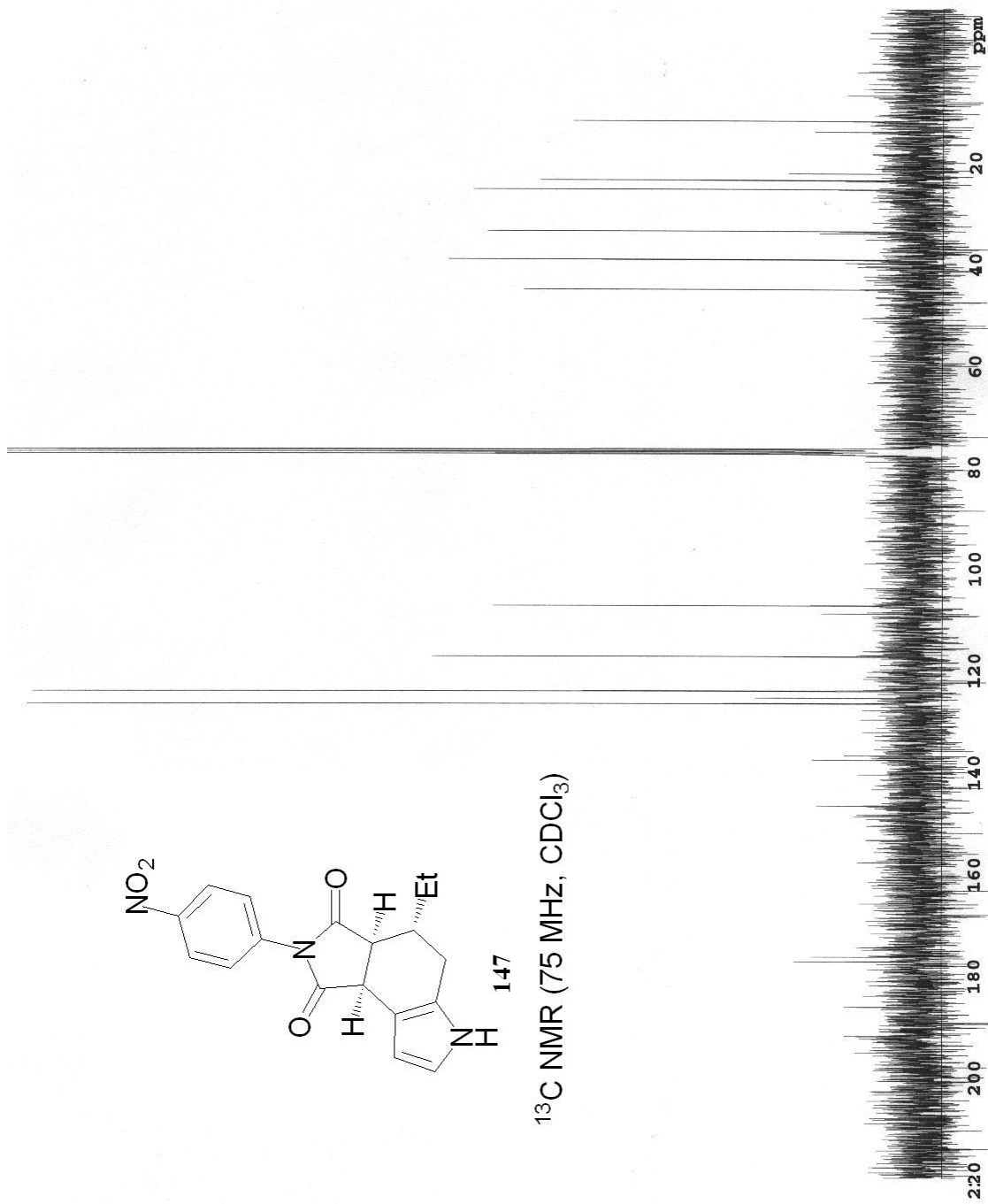
^1H NMR (300 MHz, CDCl_3)

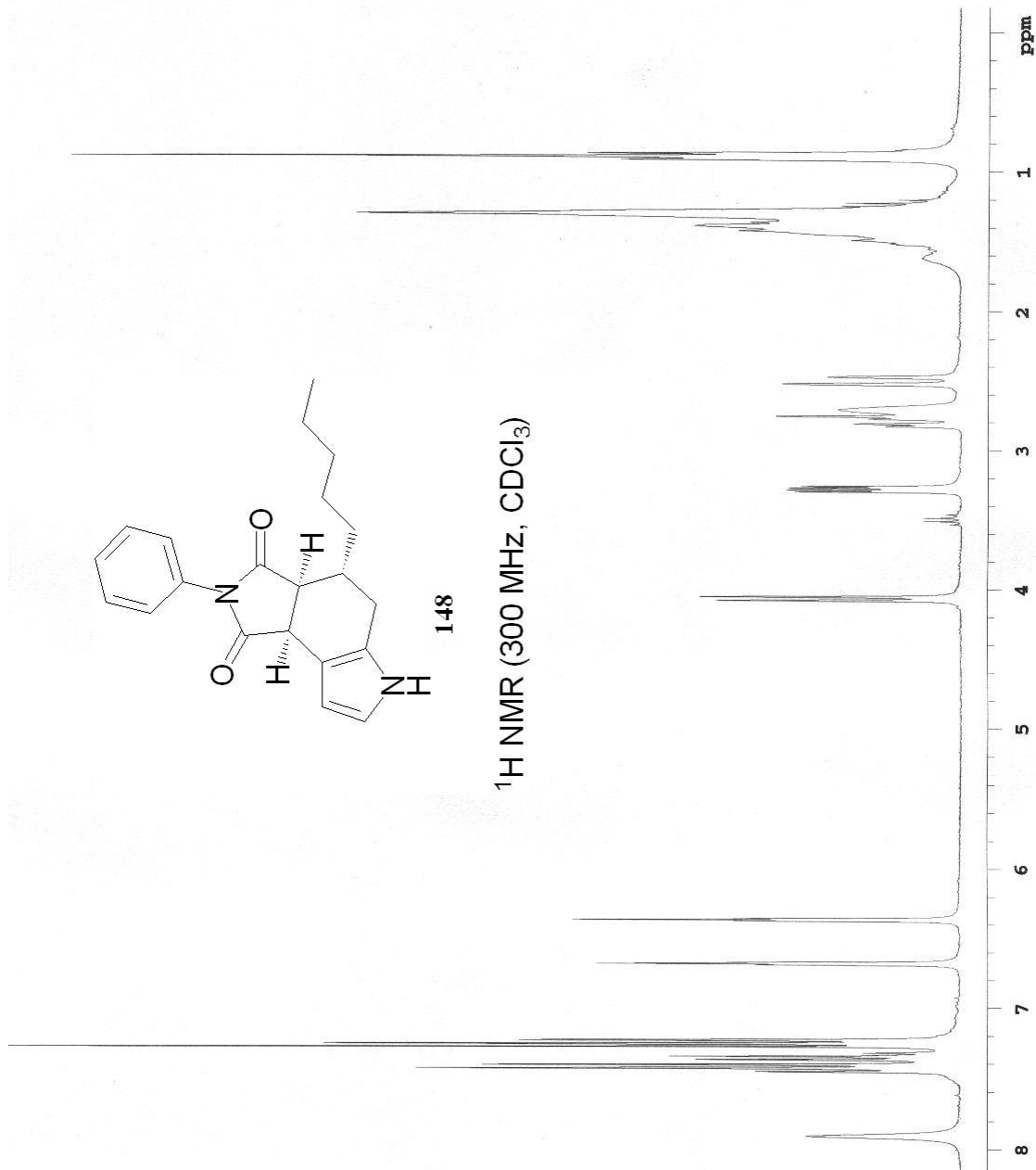


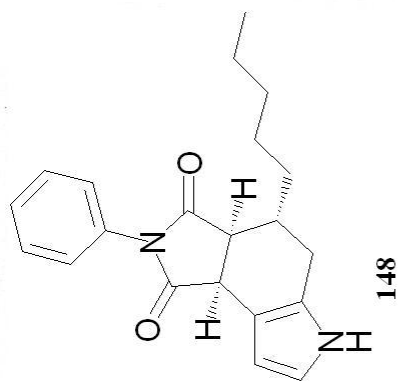


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^{13}C NMR (75 MHz, CDCl_3)

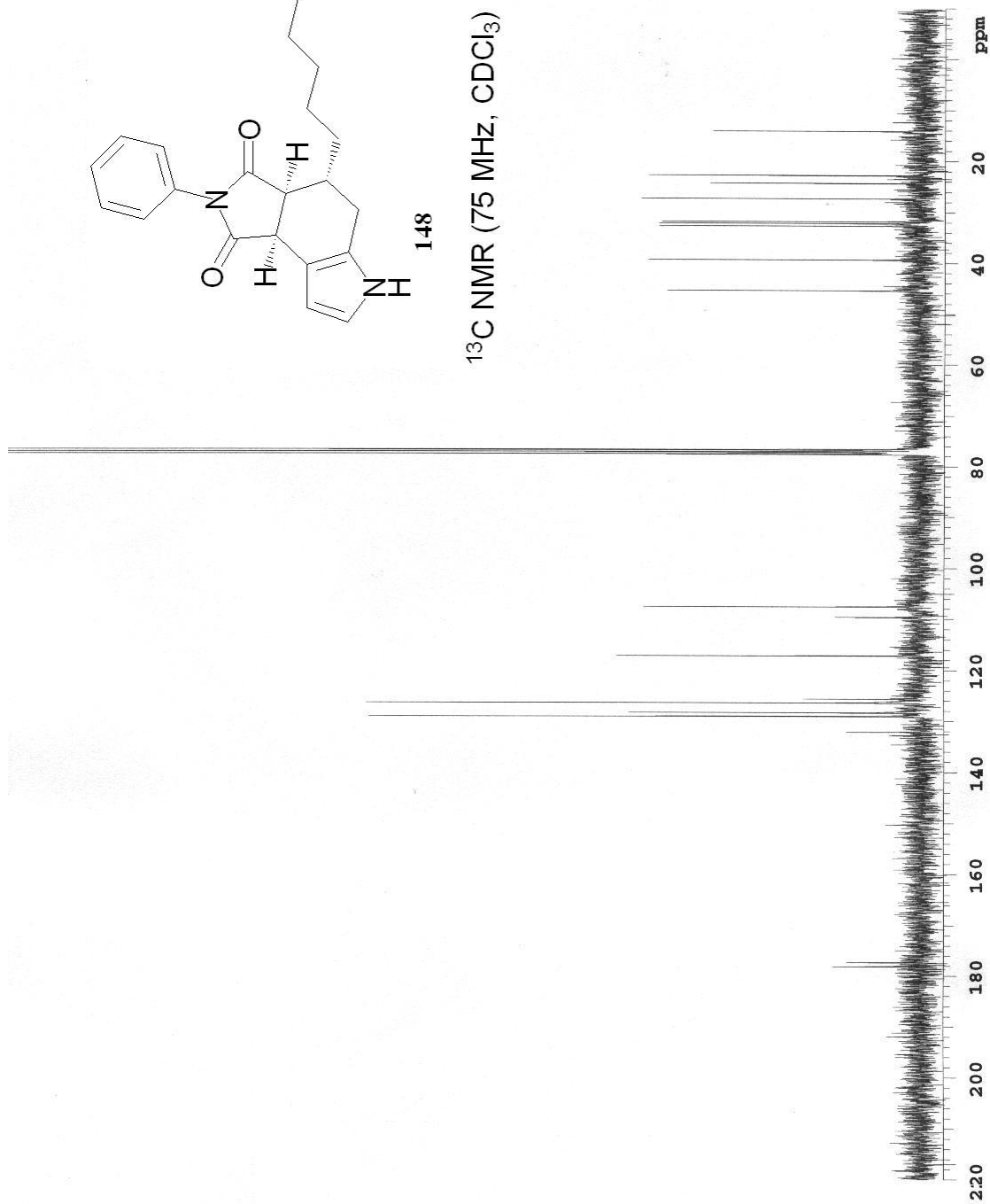


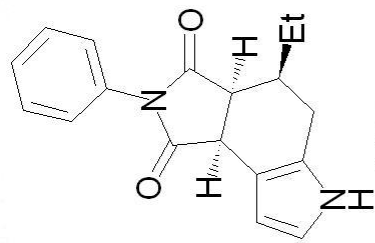




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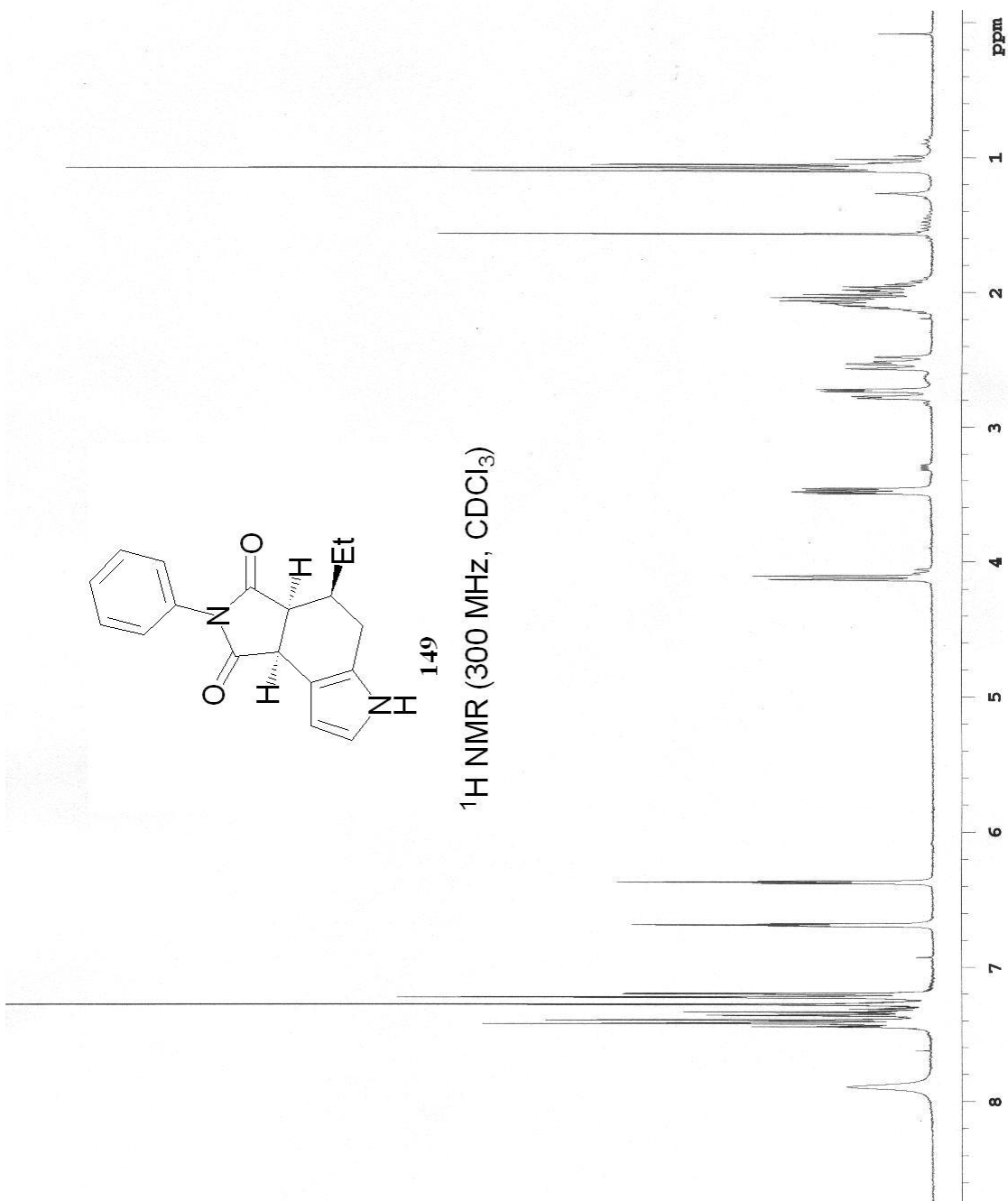
^{13}C NMR (75 MHz, CDCl_3)

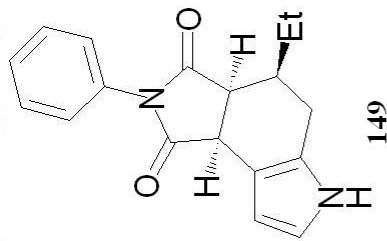




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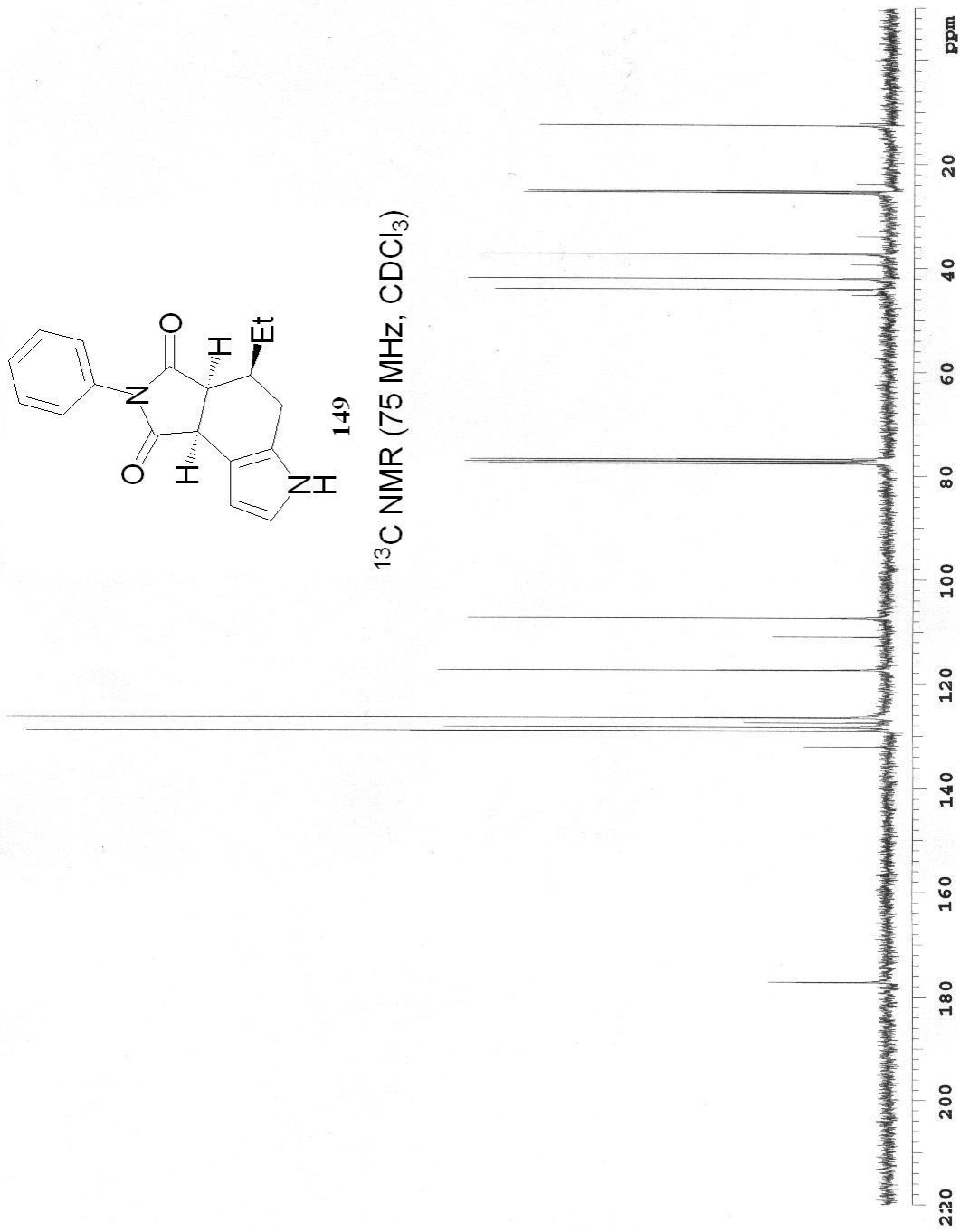
$^1\text{H NMR}$ (300 MHz, CDCl_3)

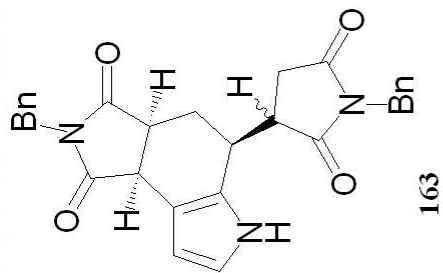




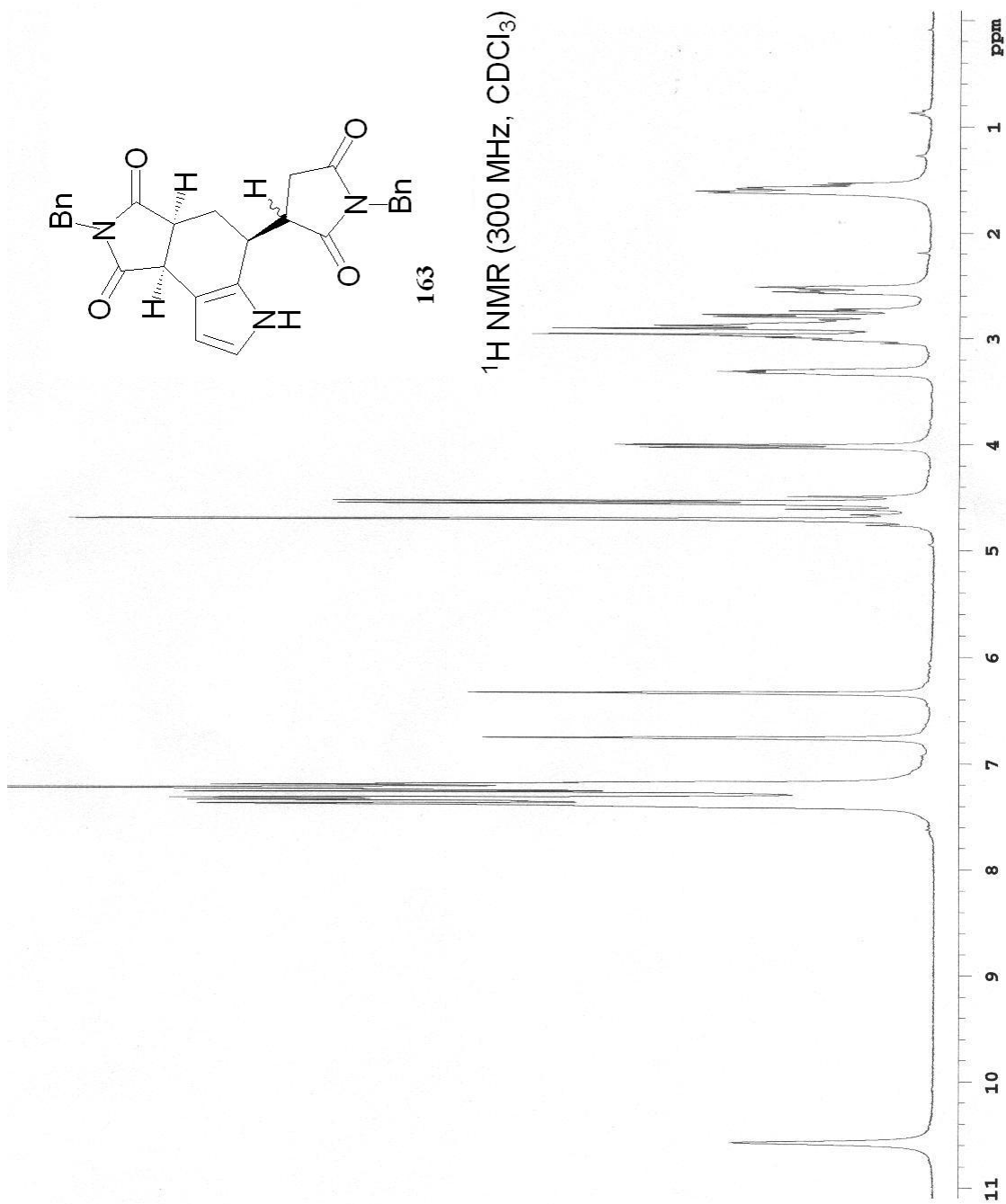
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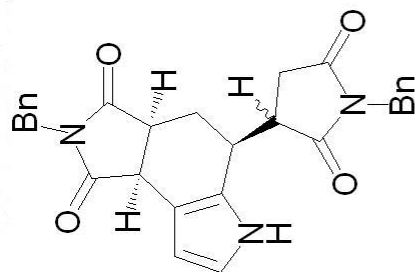
^{13}C NMR (75 MHz, CDCl_3)





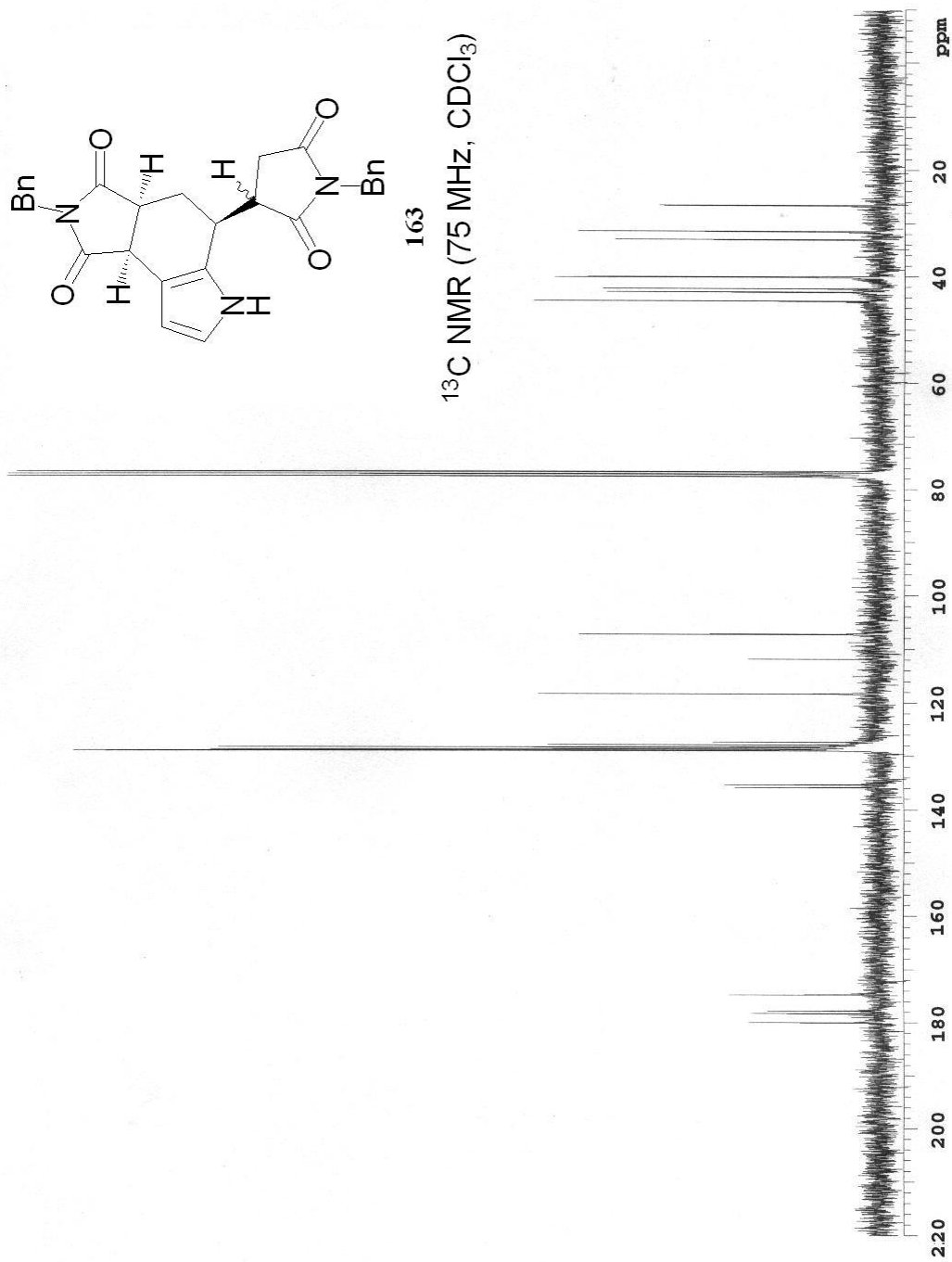
^1H NMR (300 MHz, CDCl_3)

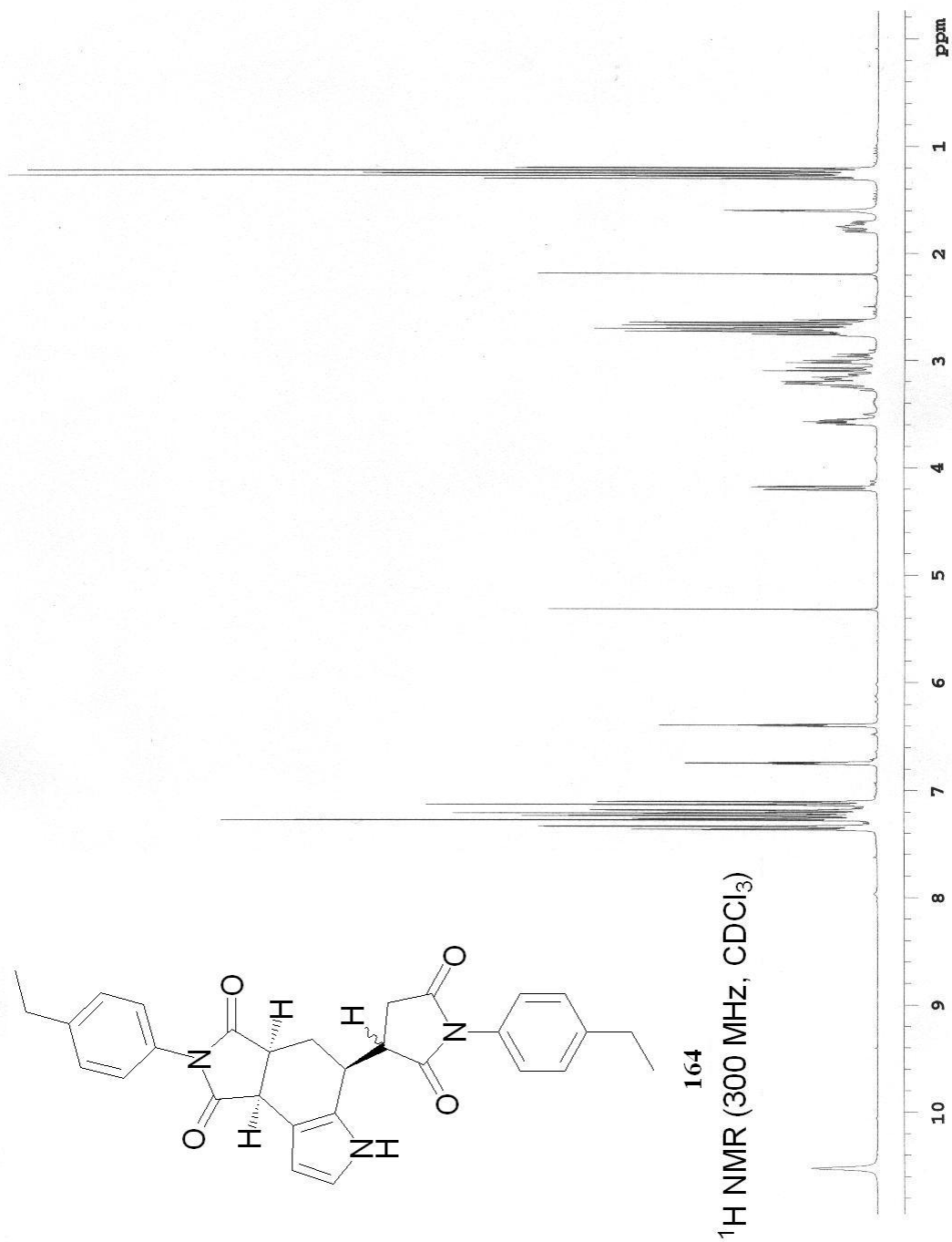




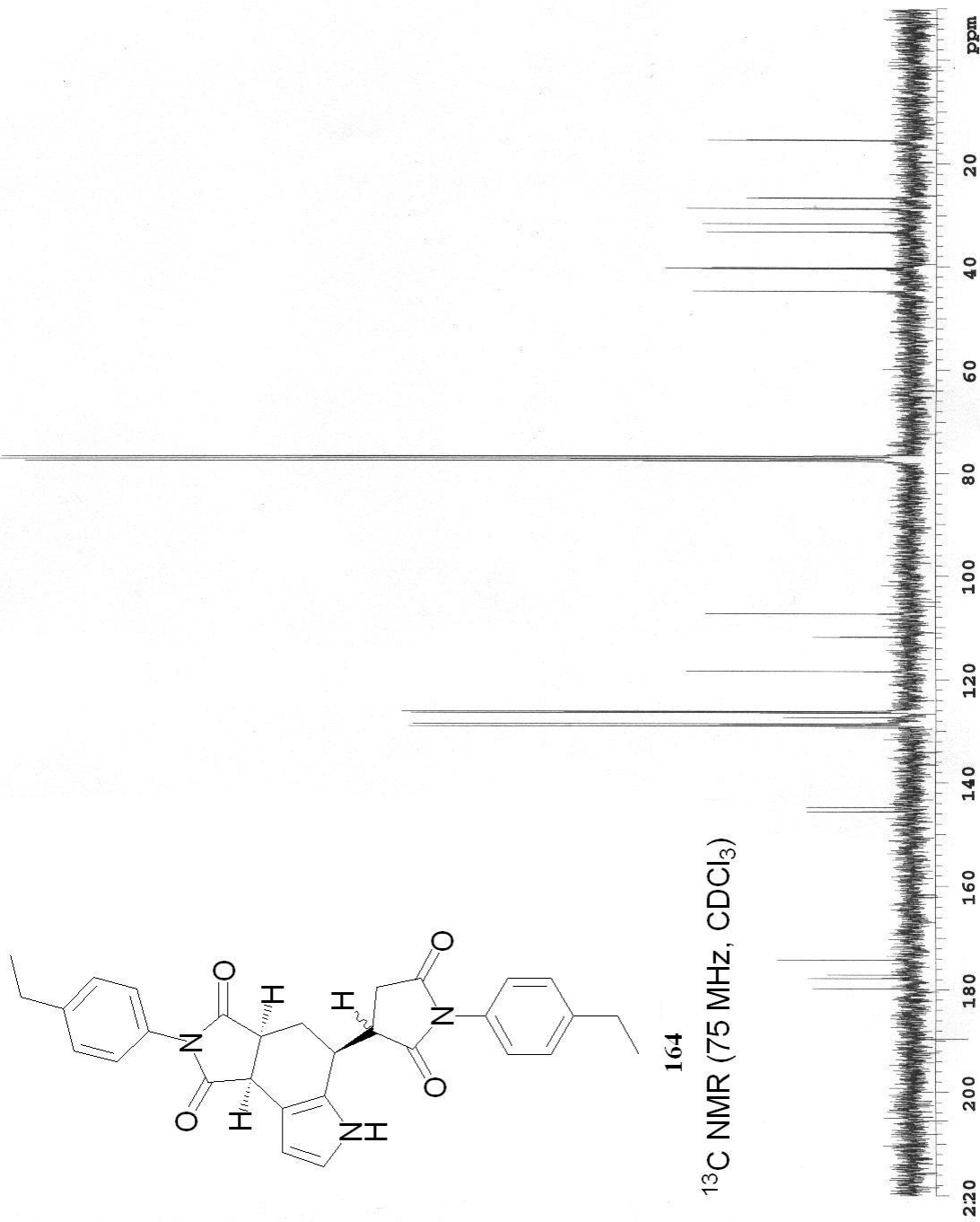
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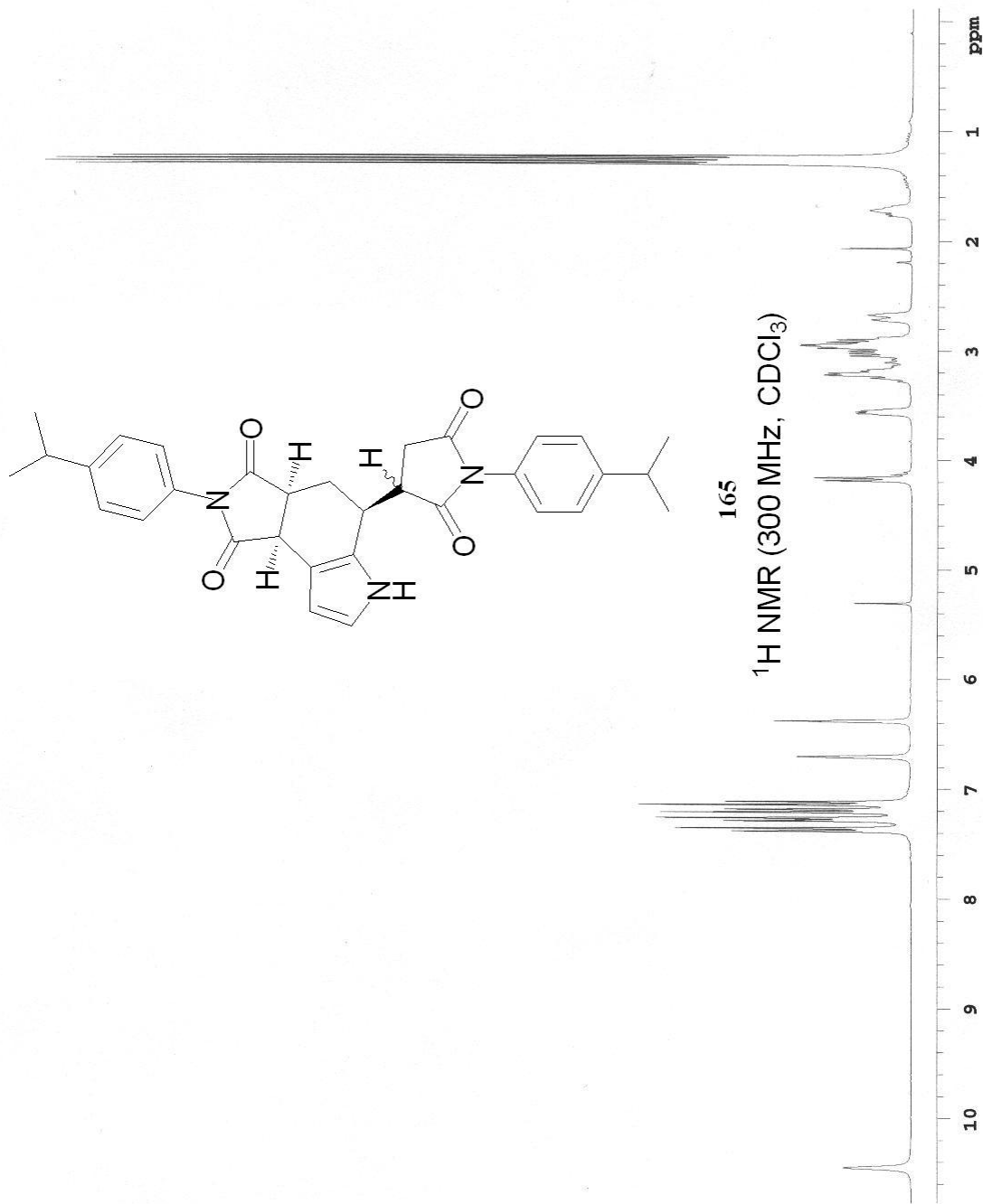
^{13}C NMR (75 MHz, CDCl_3)

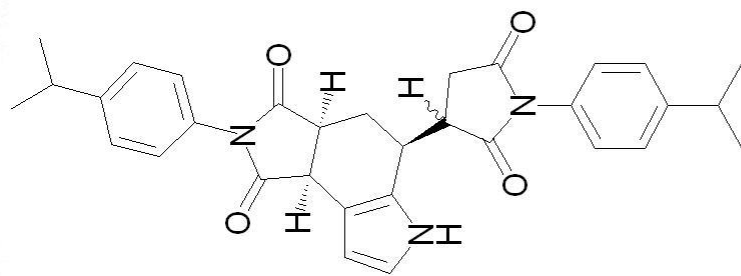




164
¹H NMR (300 MHz, CDCl₃)

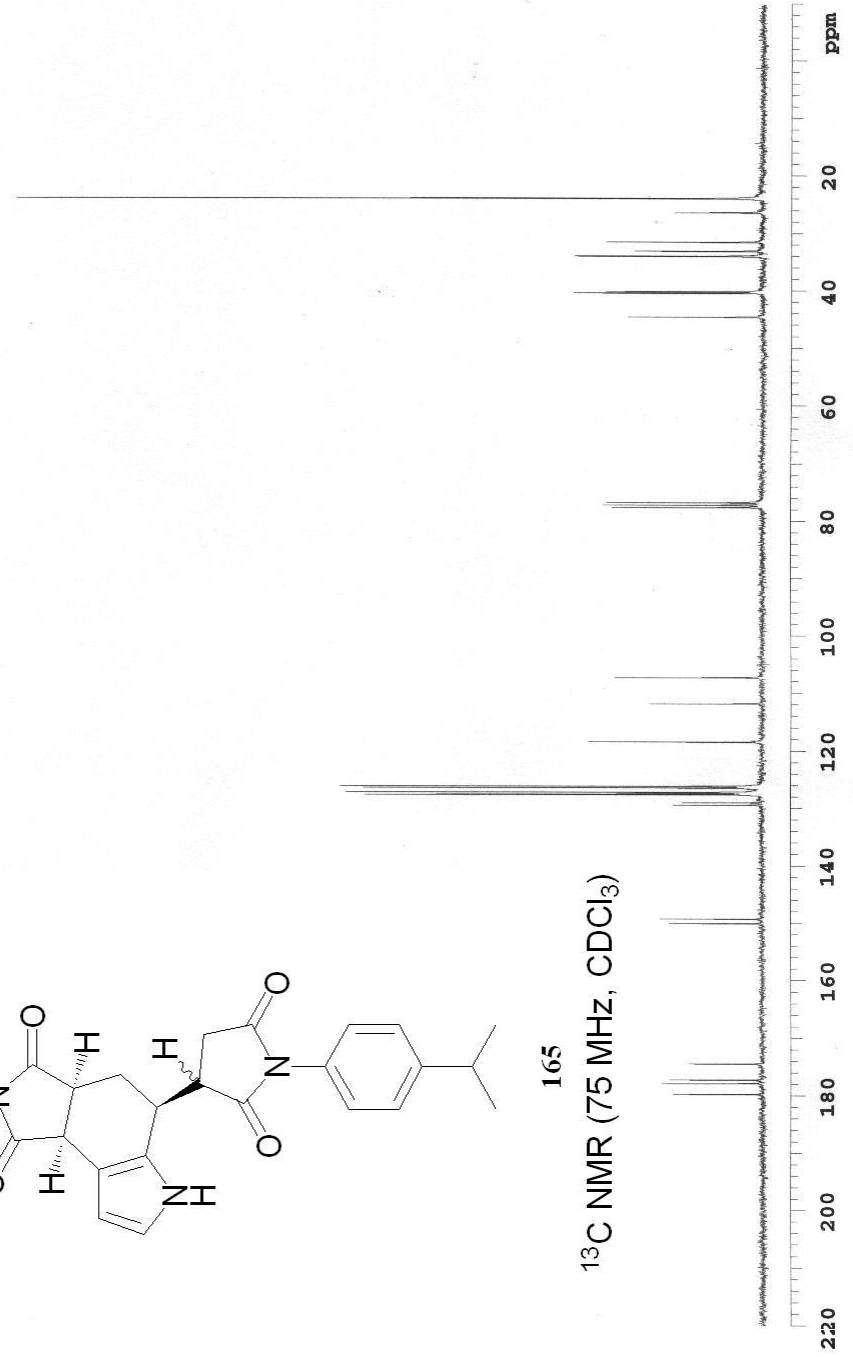


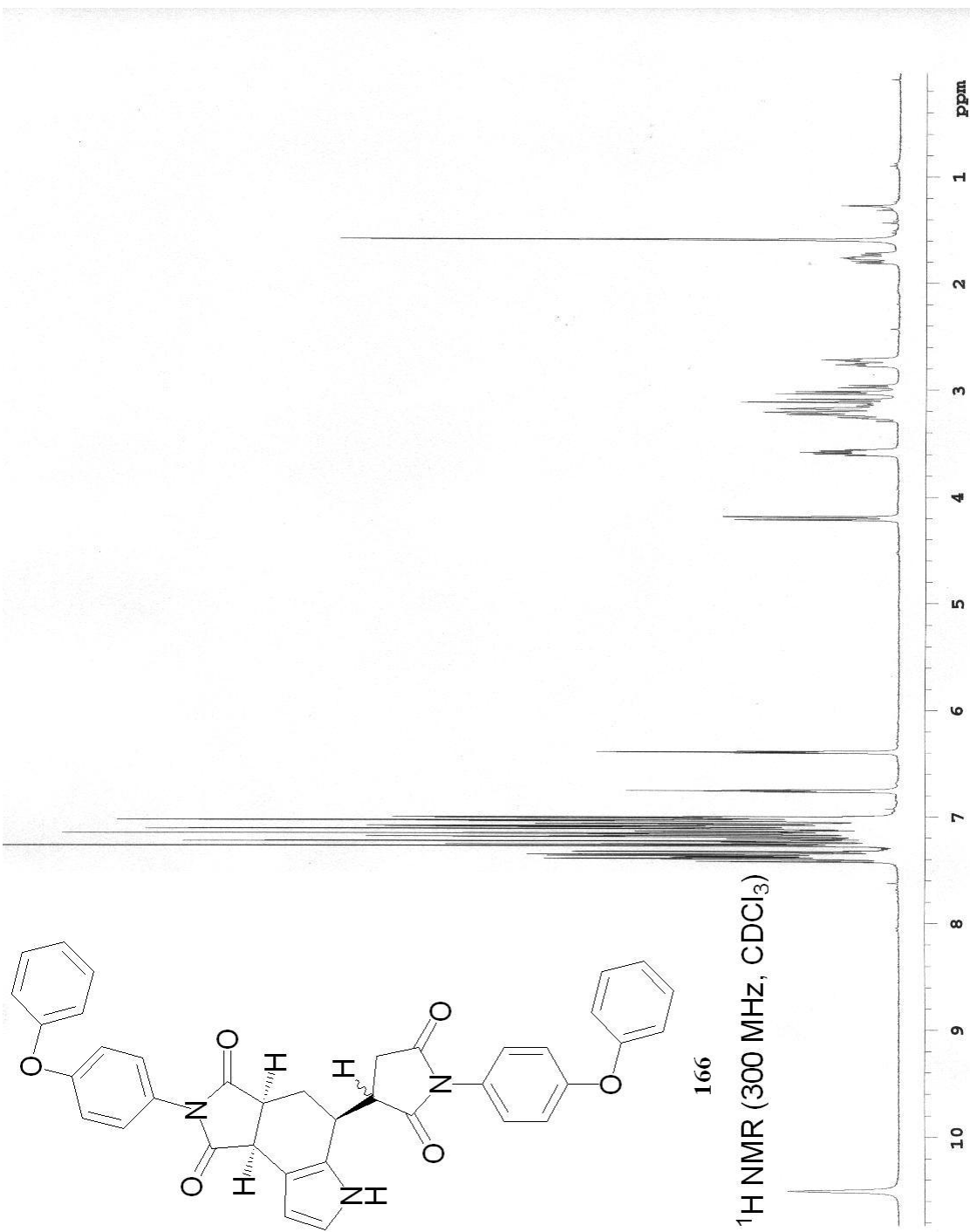


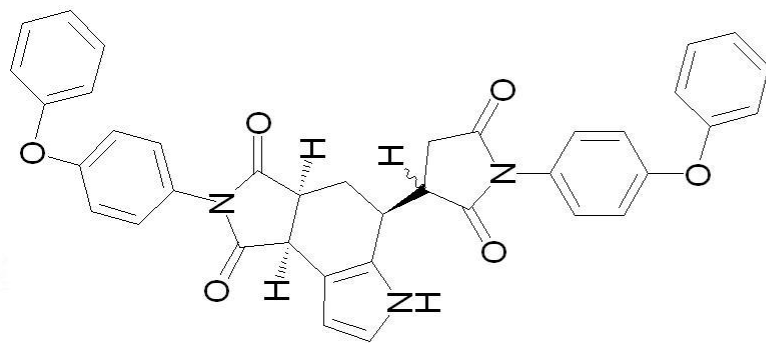


165

^{13}C NMR (75 MHz, CDCl_3)

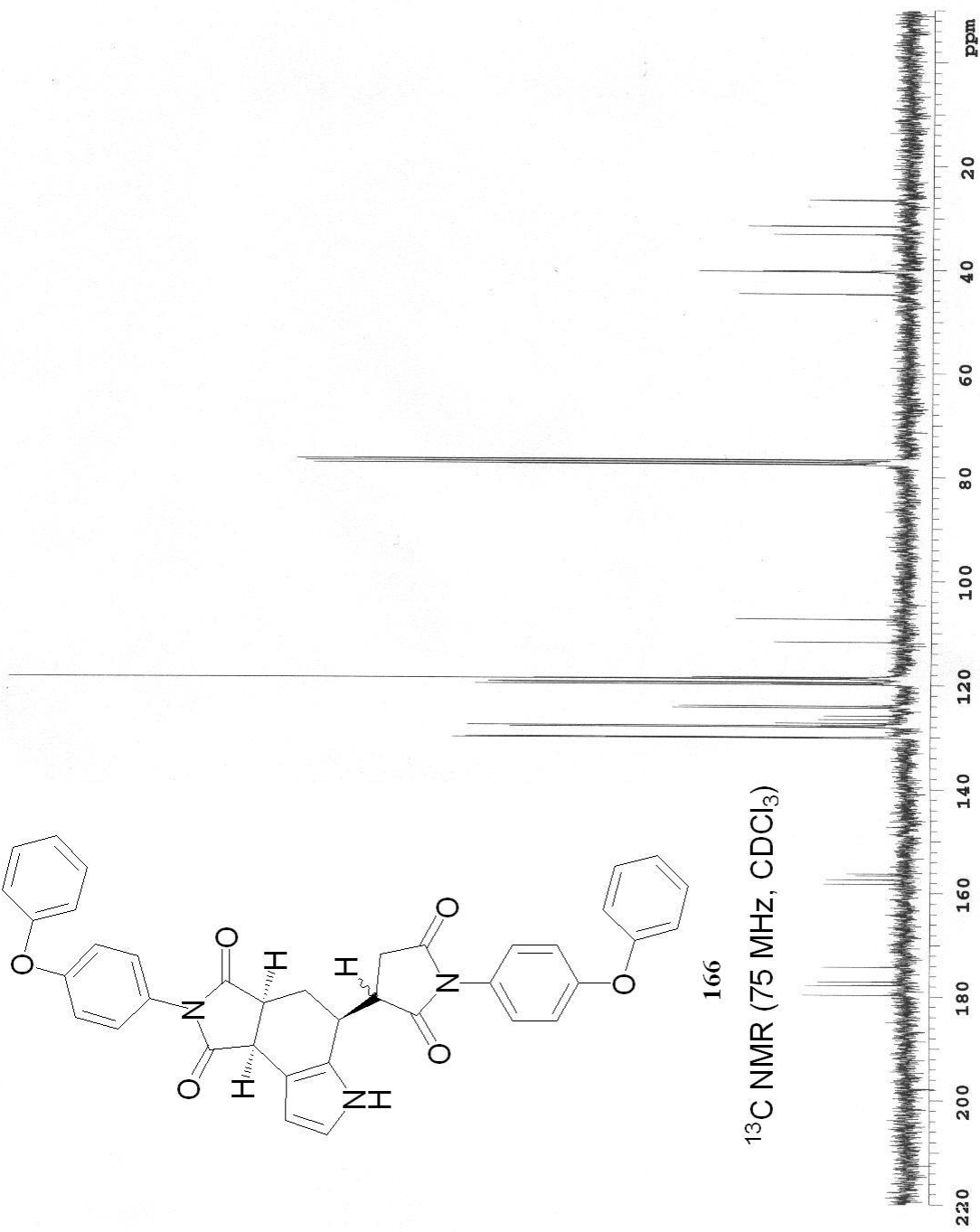


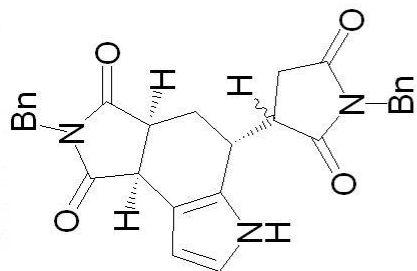




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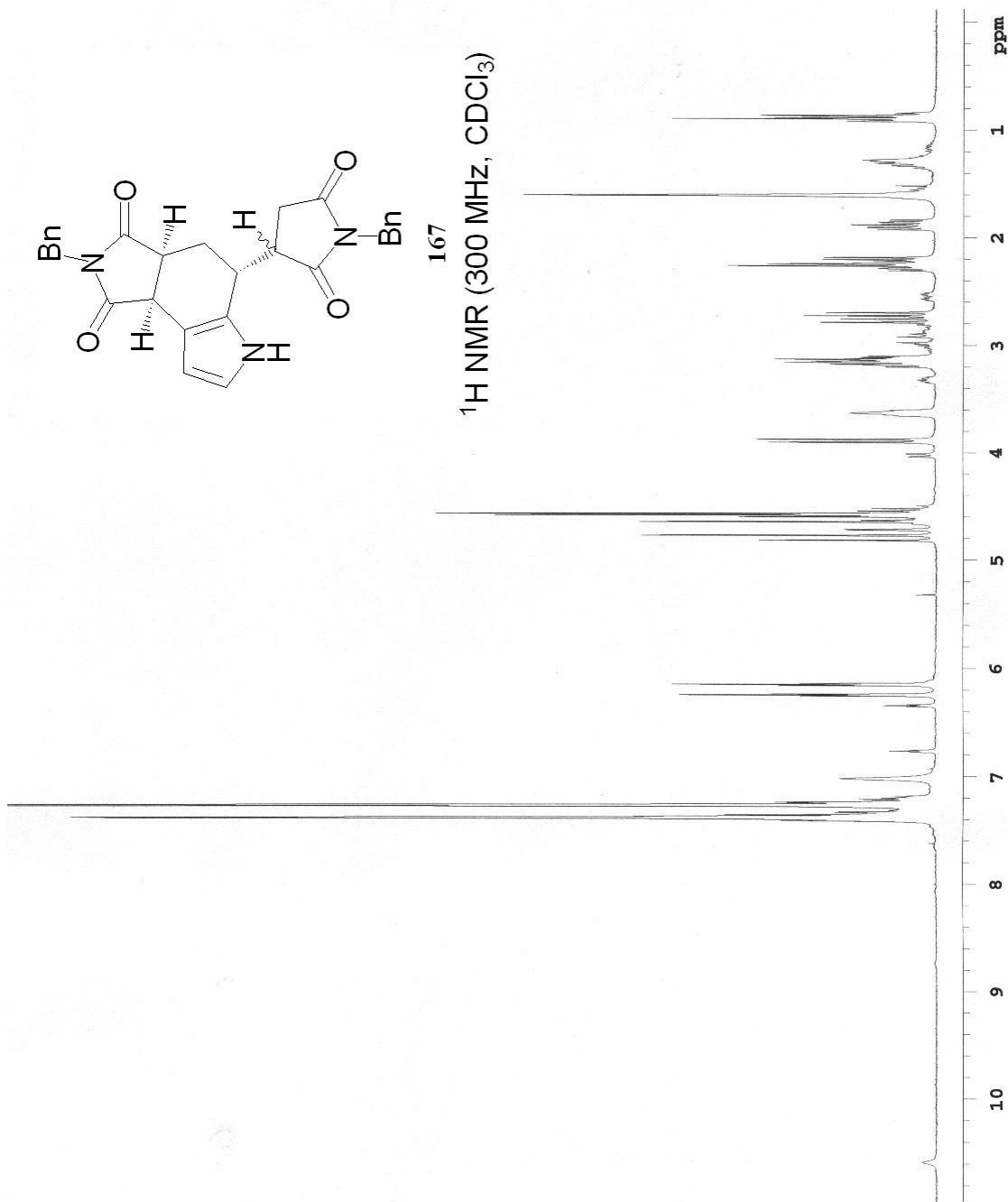
^{13}C NMR (75 MHz, CDCl_3)

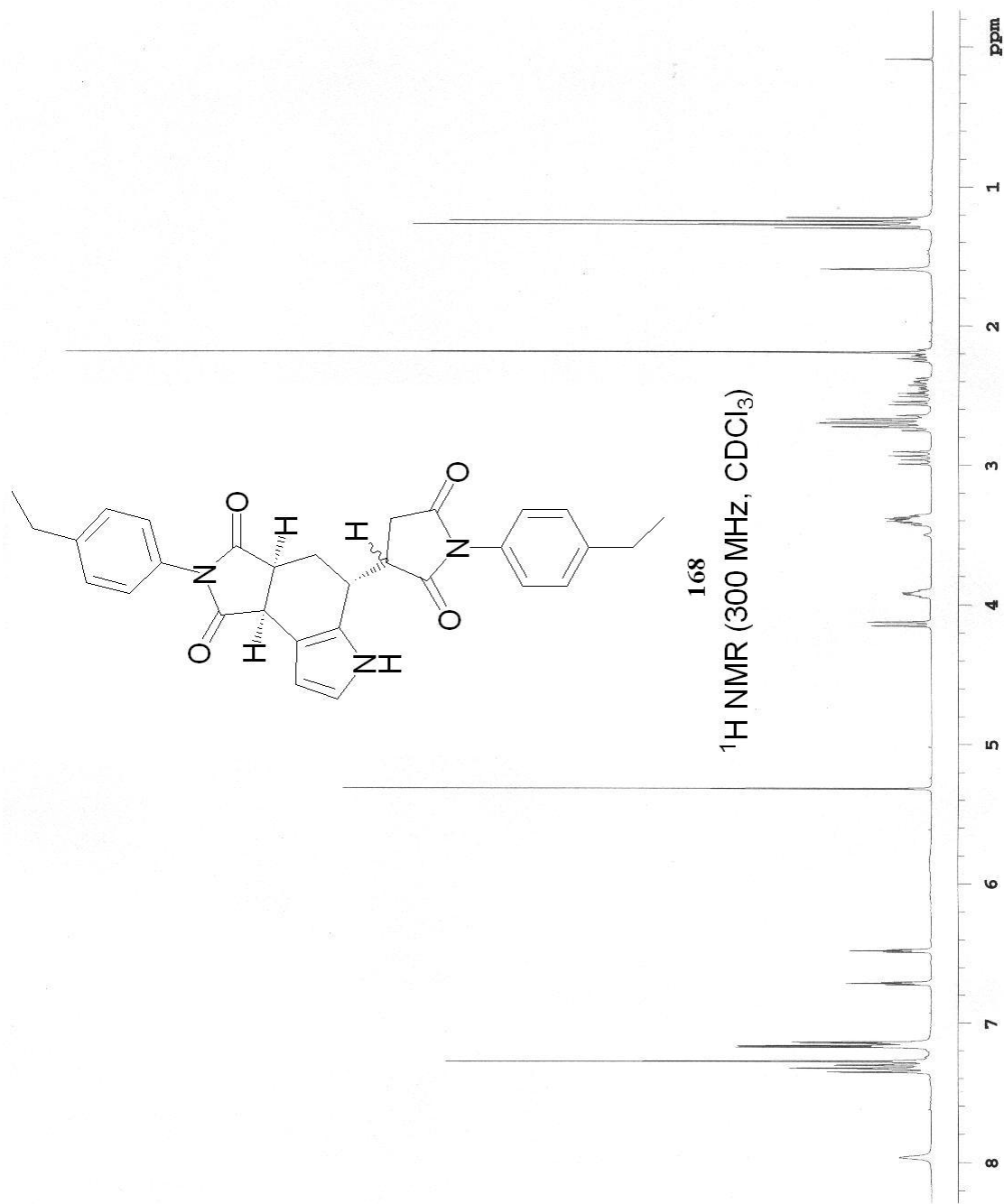


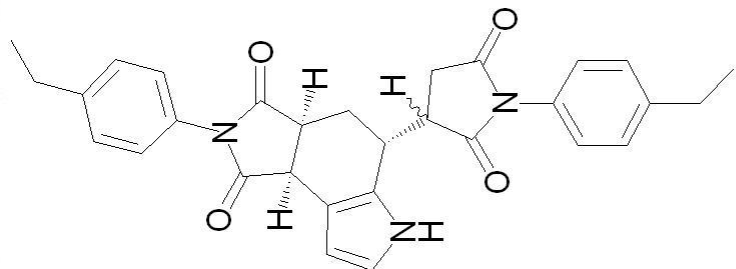


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^1H NMR (300 MHz, CDCl_3)

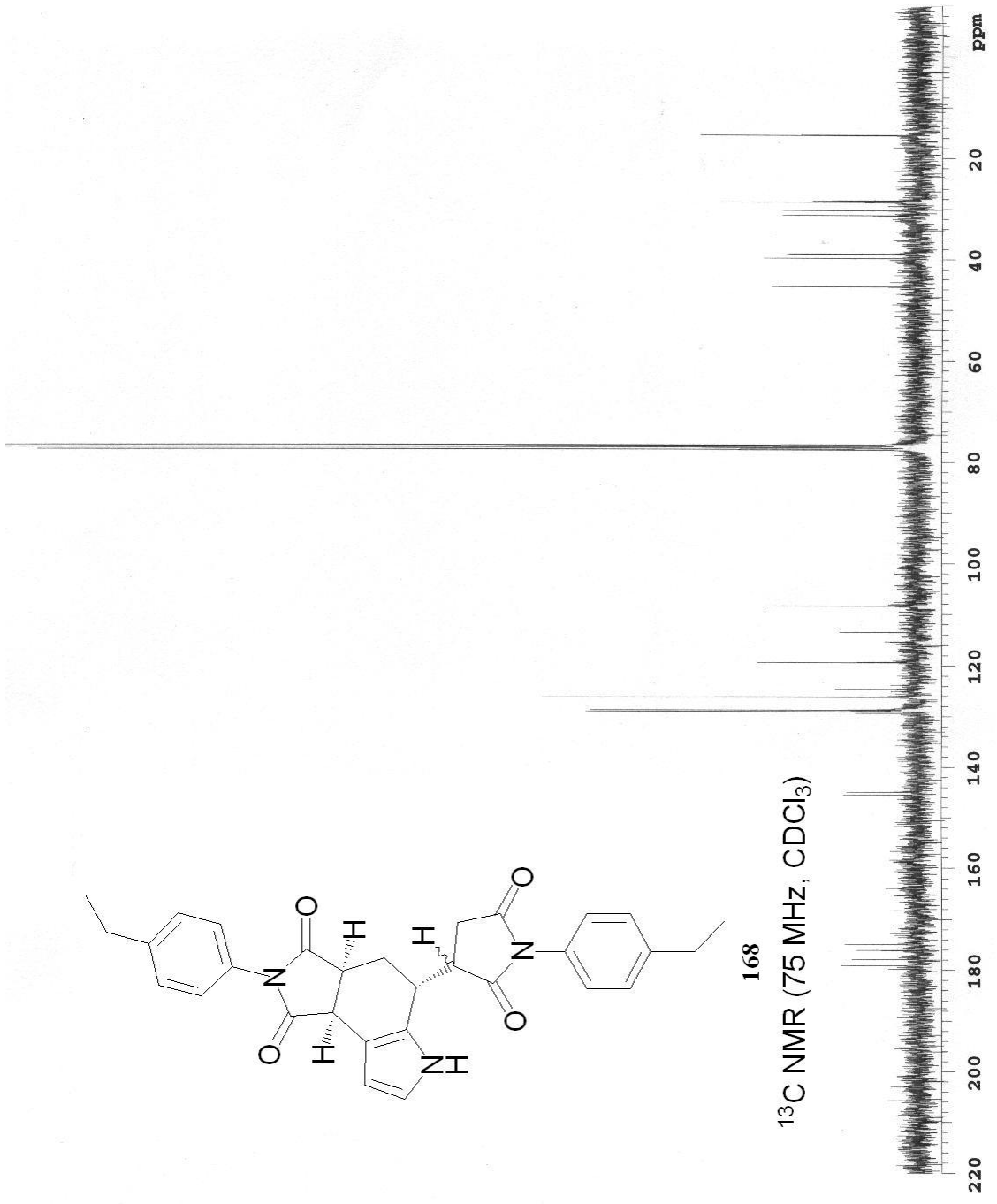


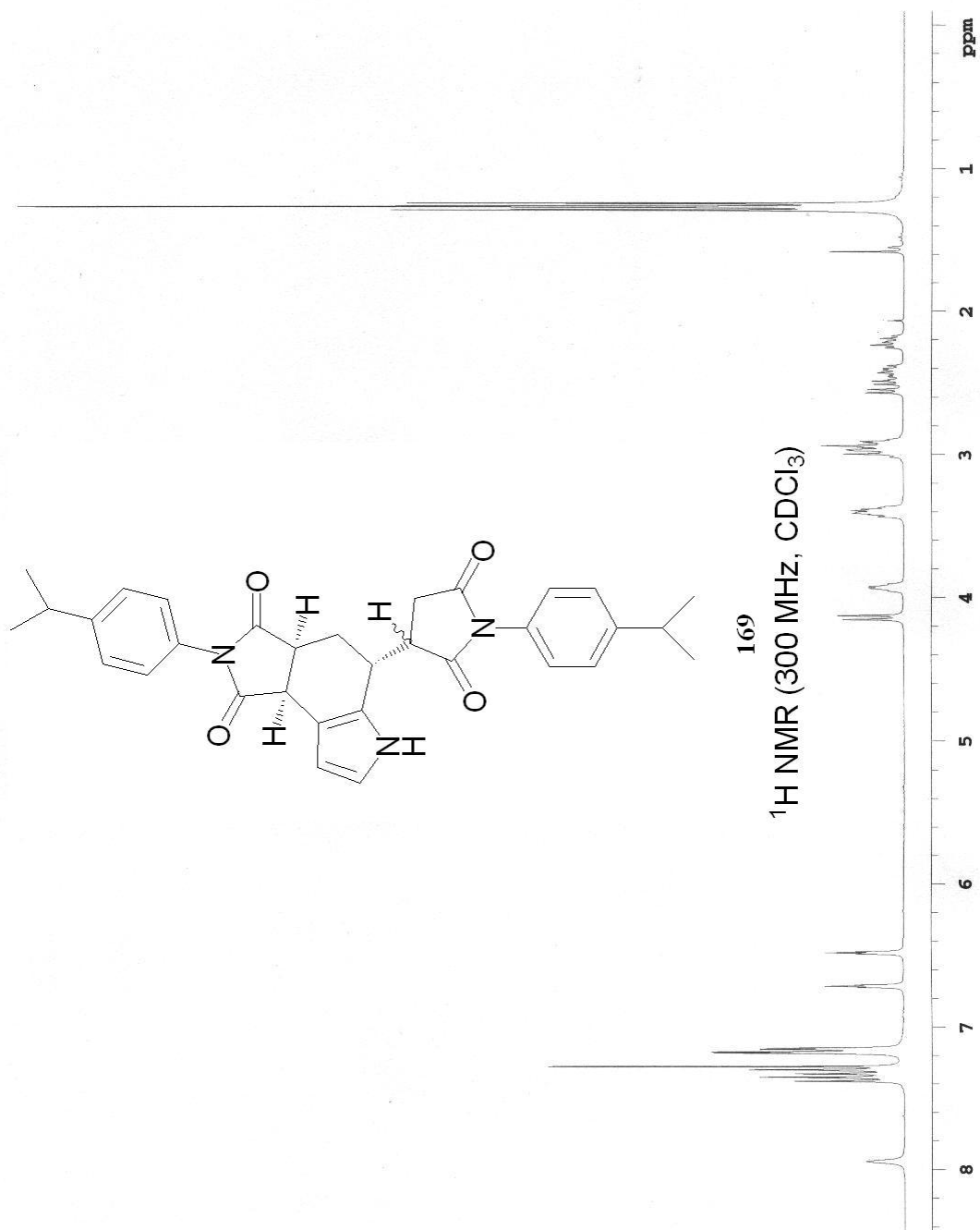


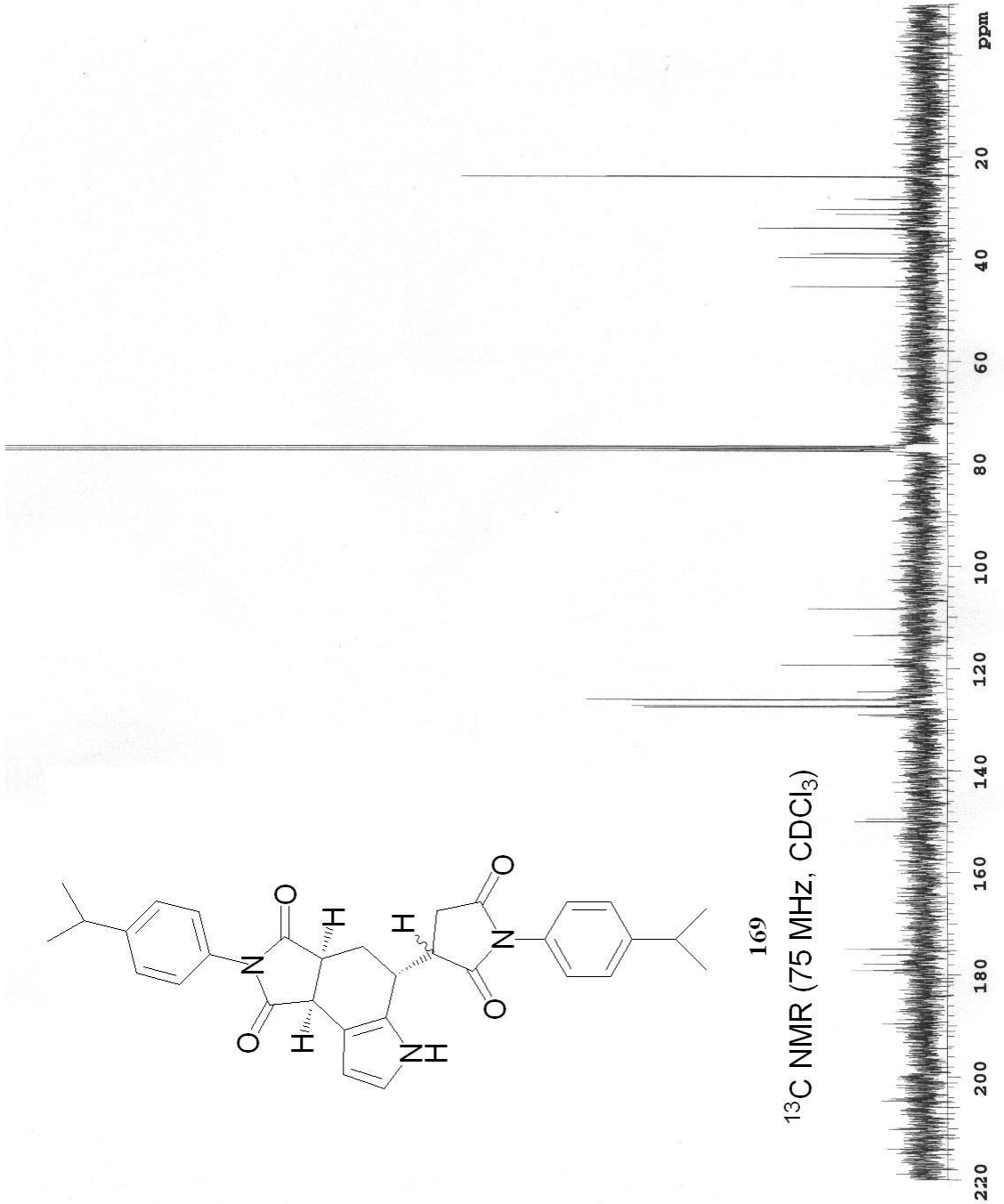


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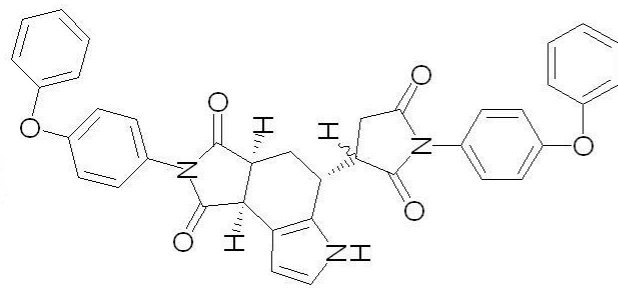
^{13}C NMR (75 MHz, CDCl_3)





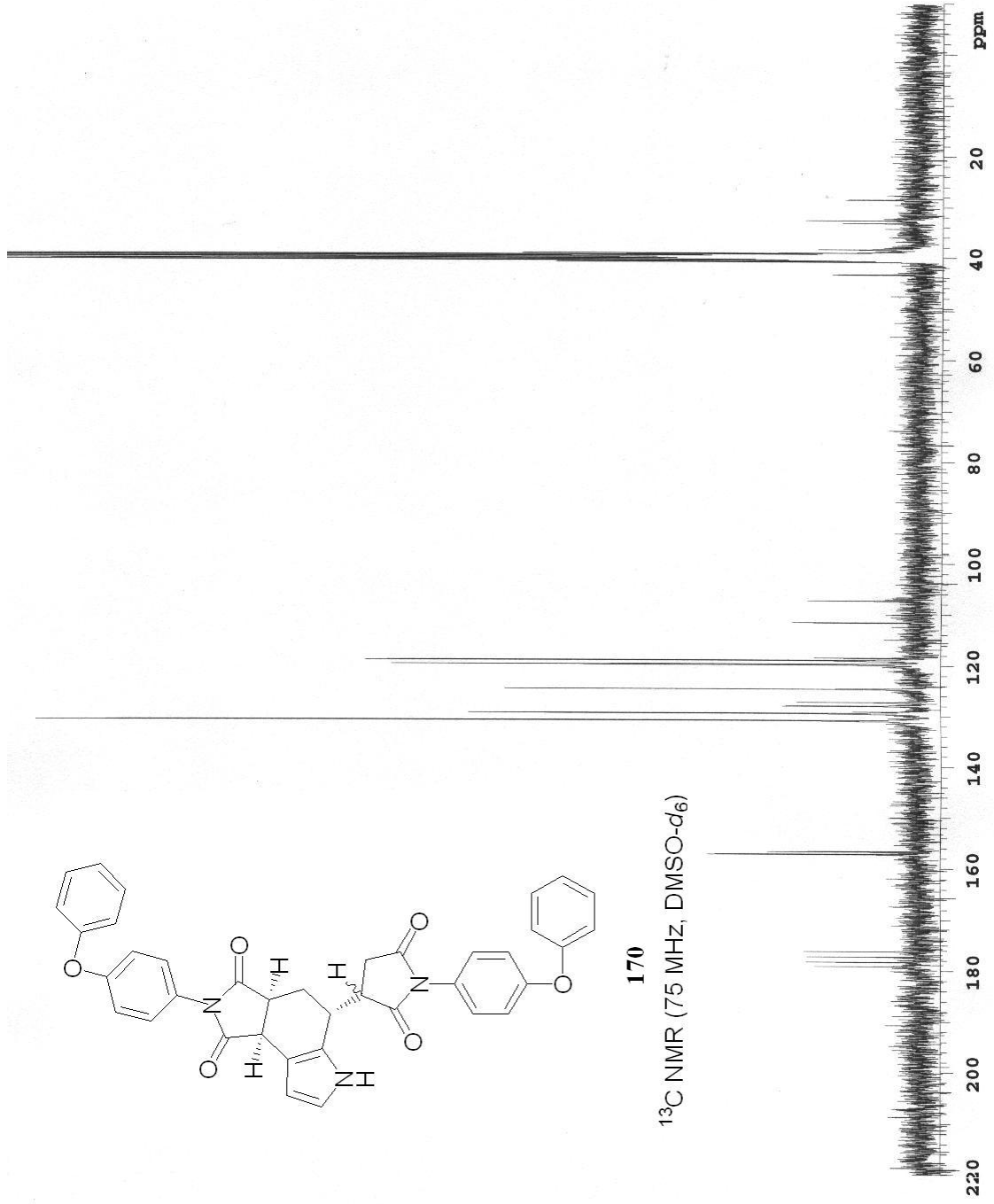


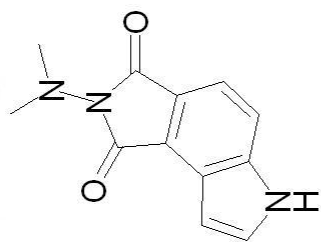




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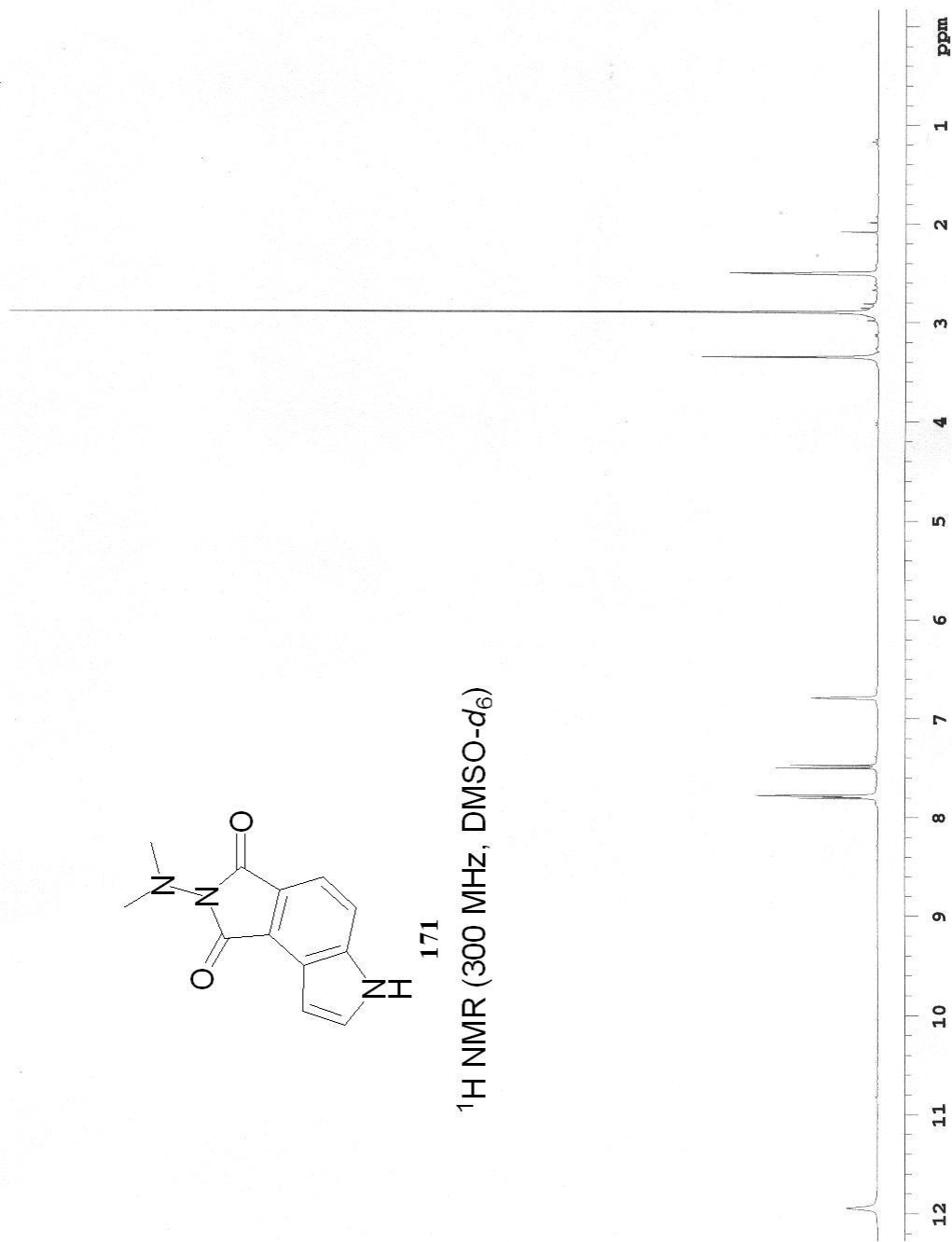
¹³C NMR (75 MHz, DMSO-d₆)

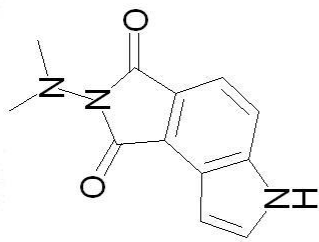




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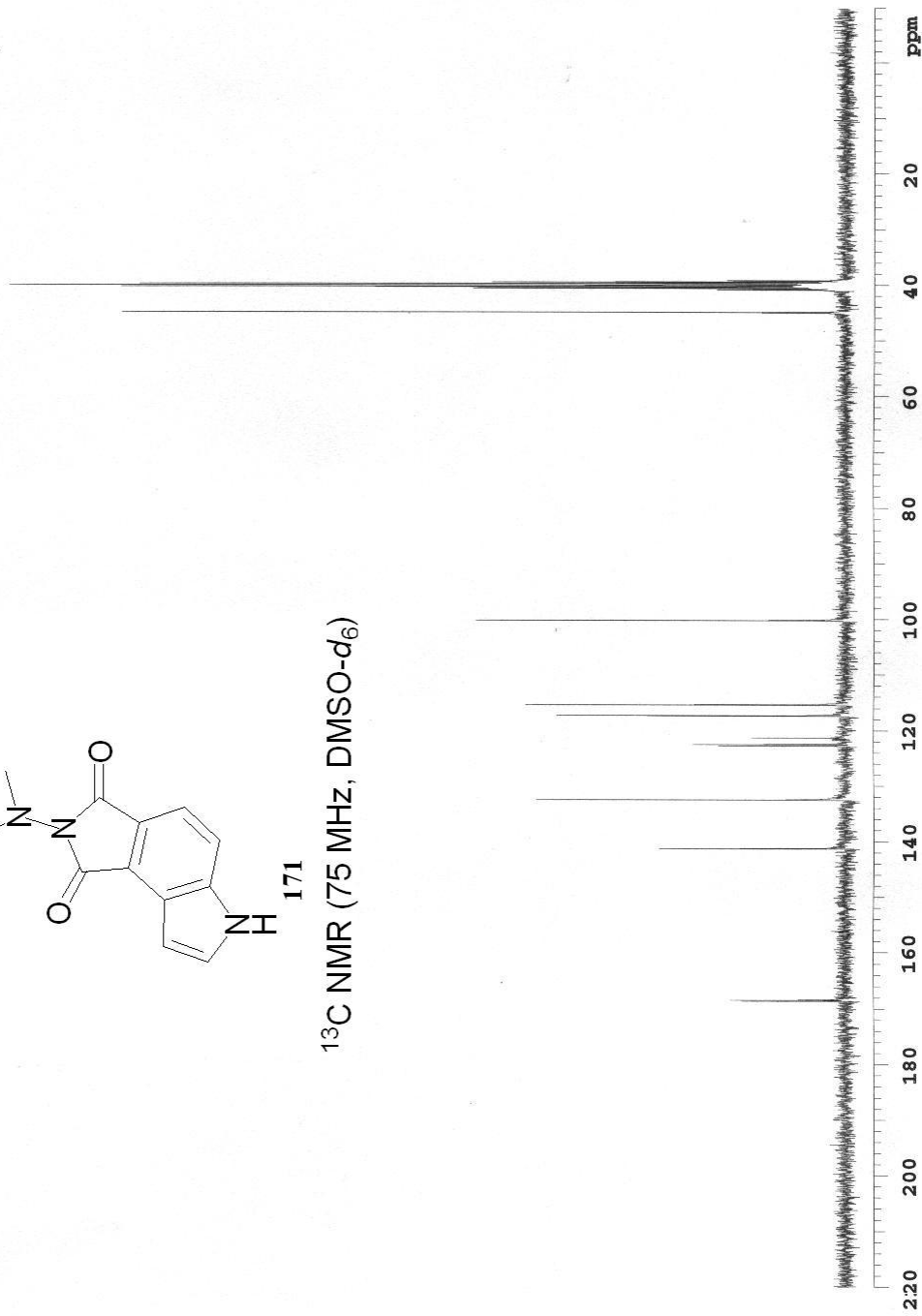
^1H NMR (300 MHz, $\text{DMSO-}d_6$)

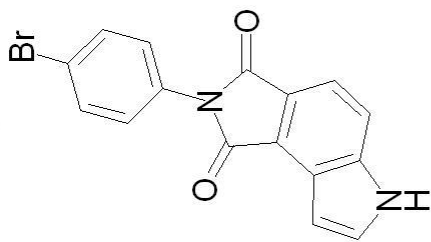




171

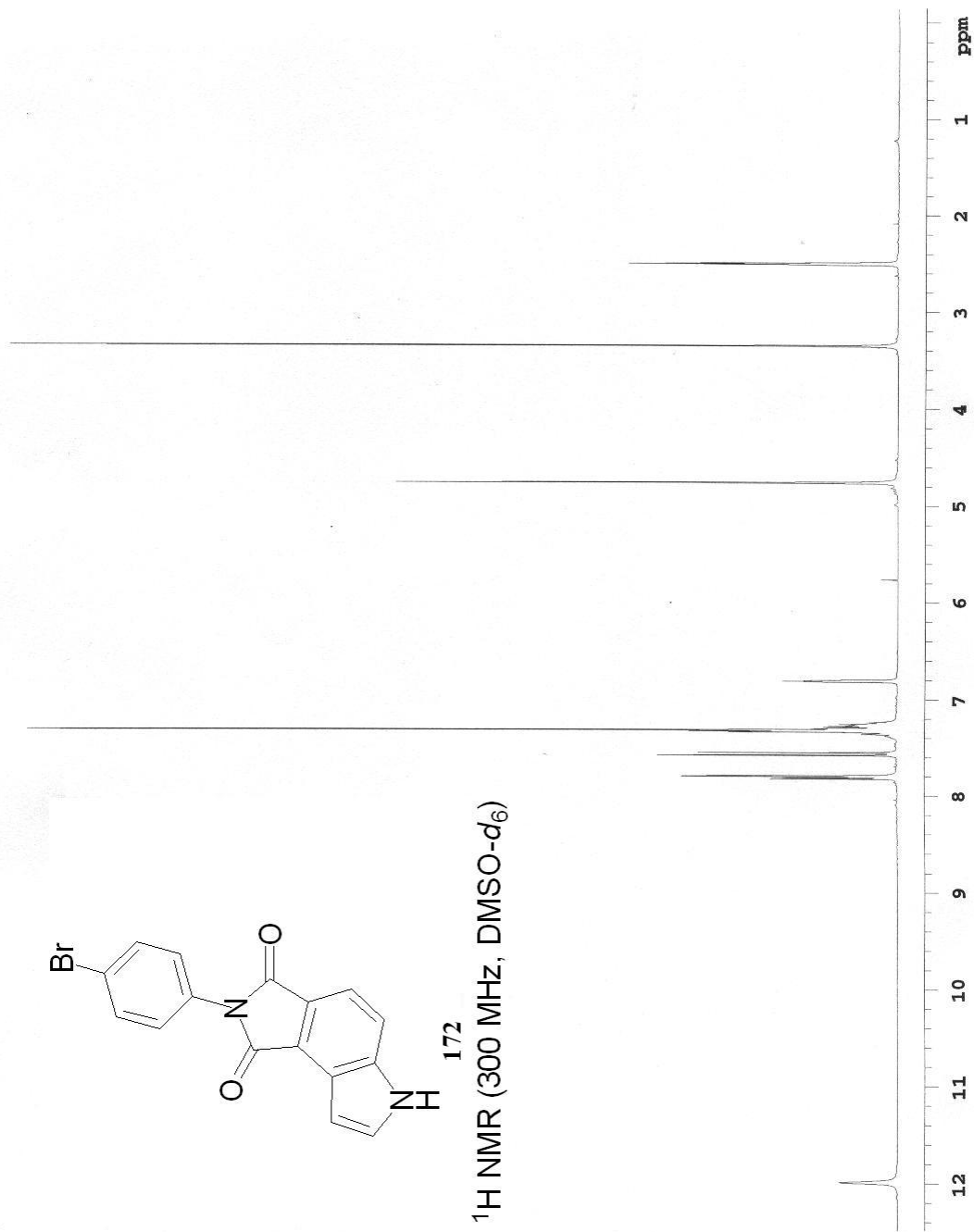
¹³C NMR (75 MHz, DMSO-d₆)

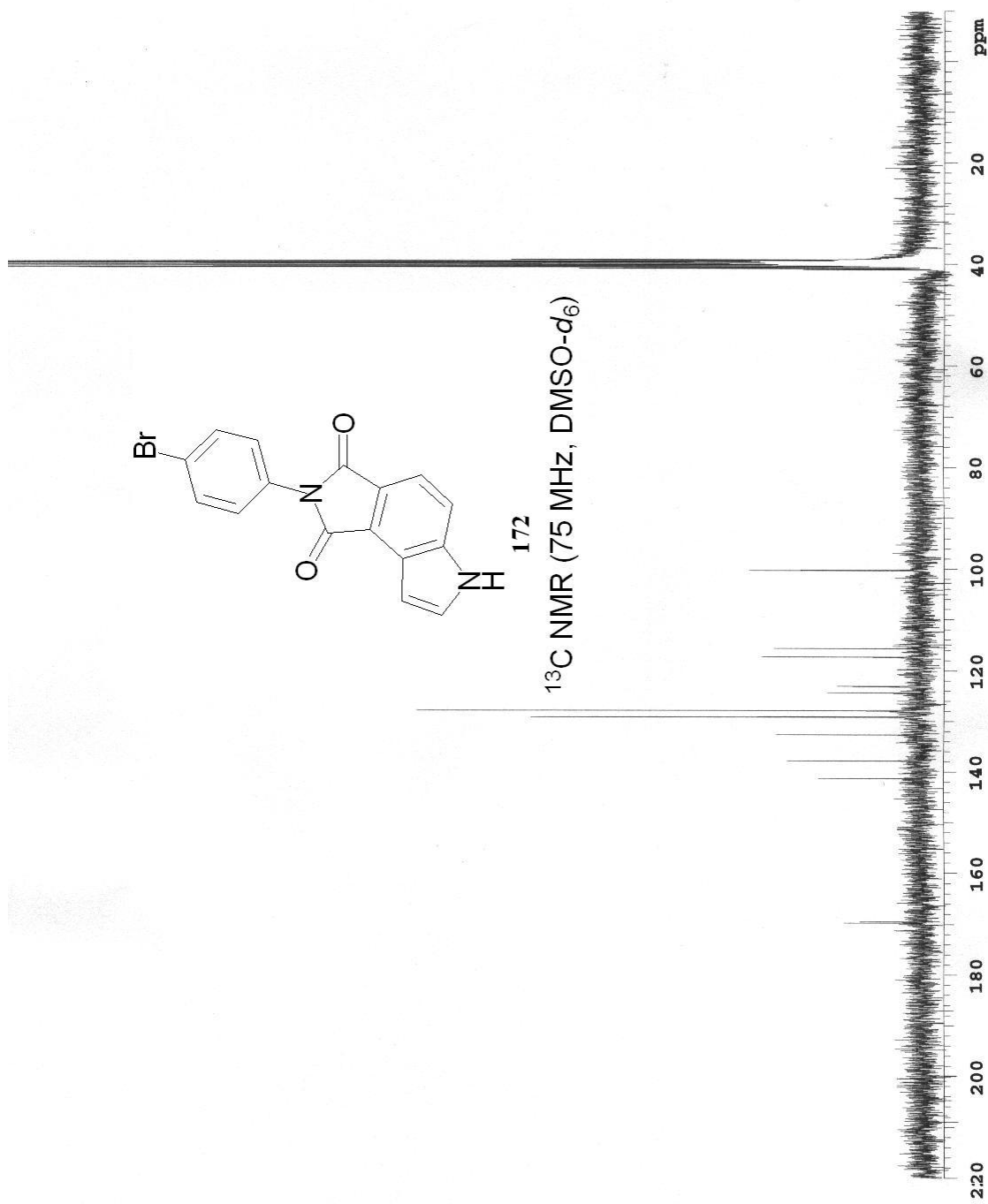


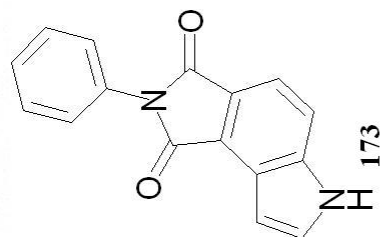


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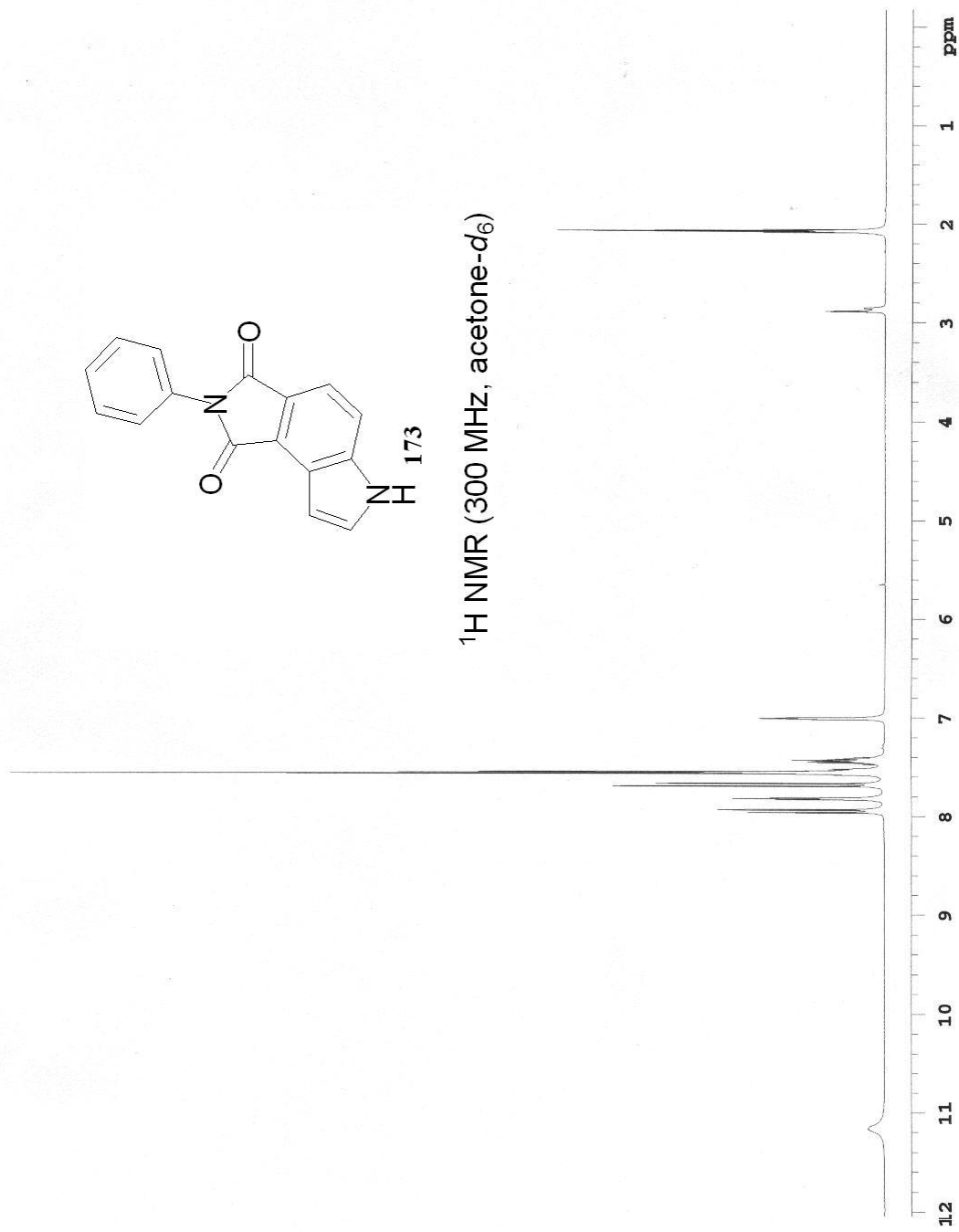
¹H NMR (300 MHz, DMSO-d₆)

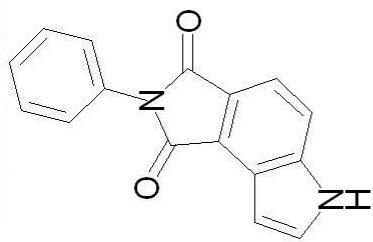






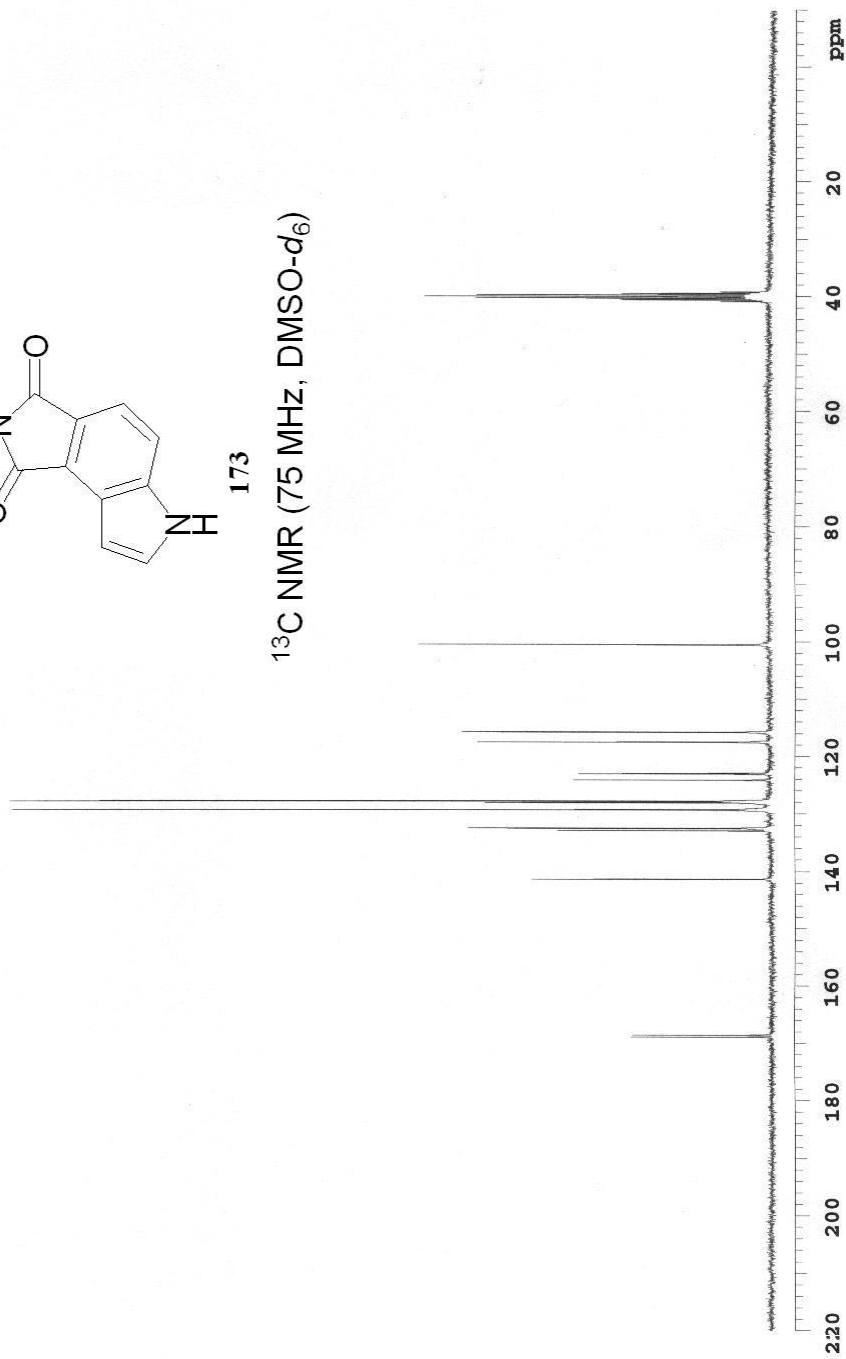
^1H NMR (300 MHz, acetone- d_6)

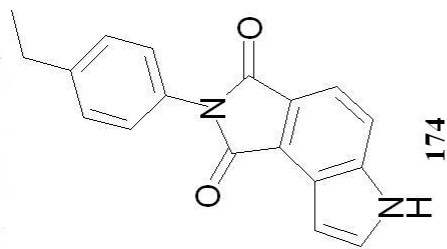




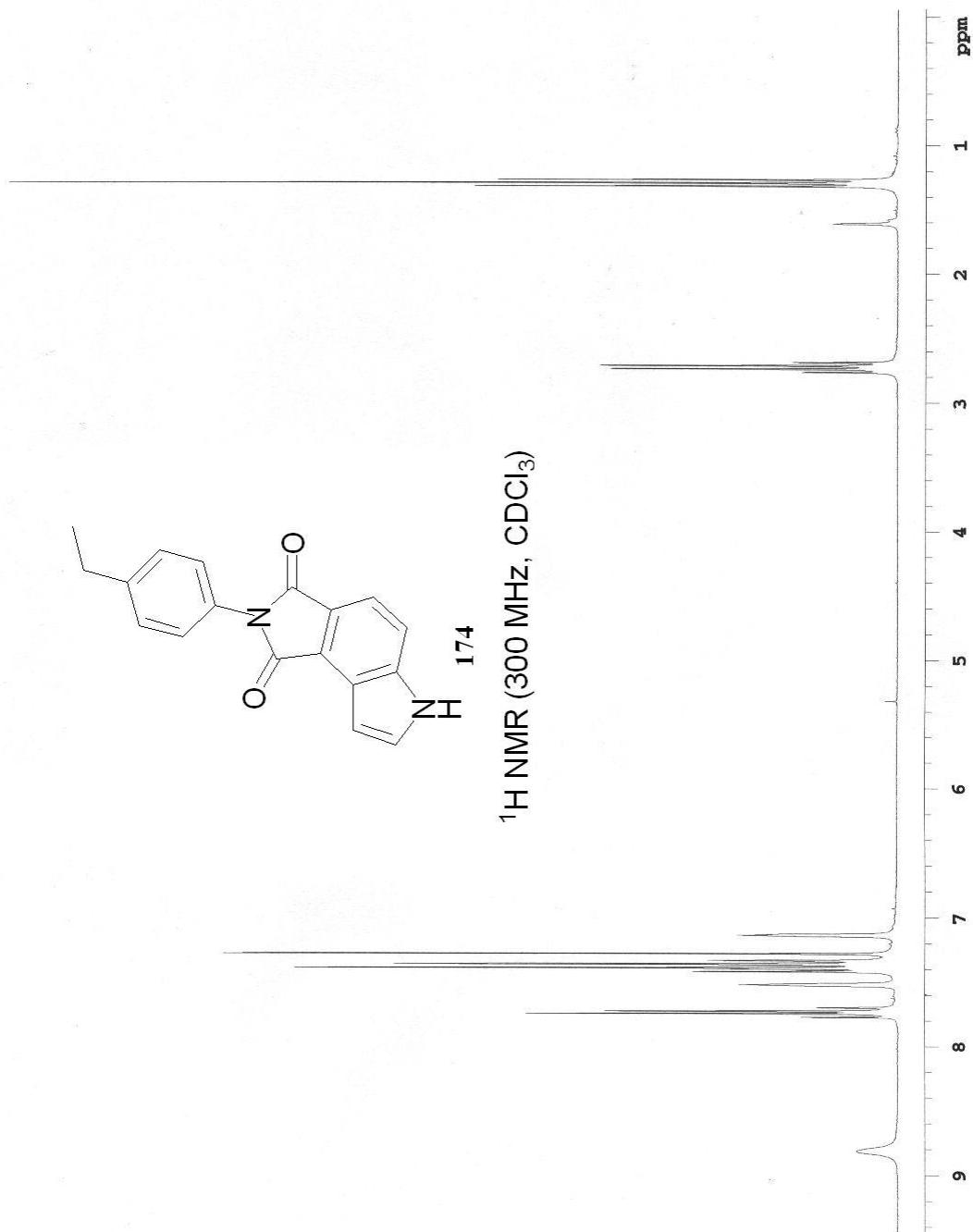
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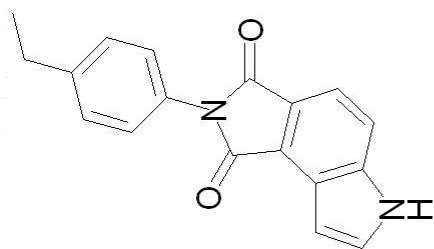
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)





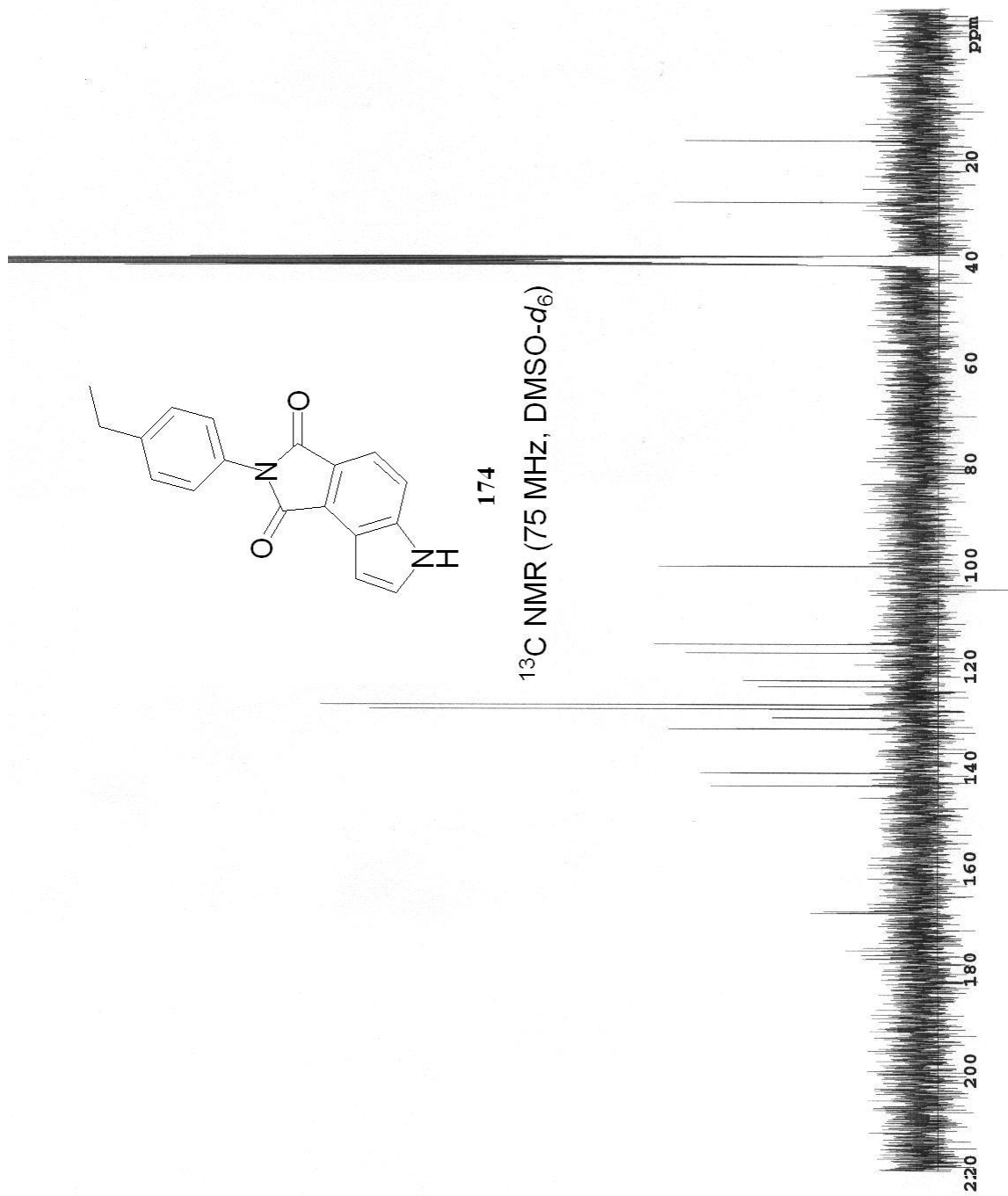
^1H NMR (300 MHz, CDCl_3)

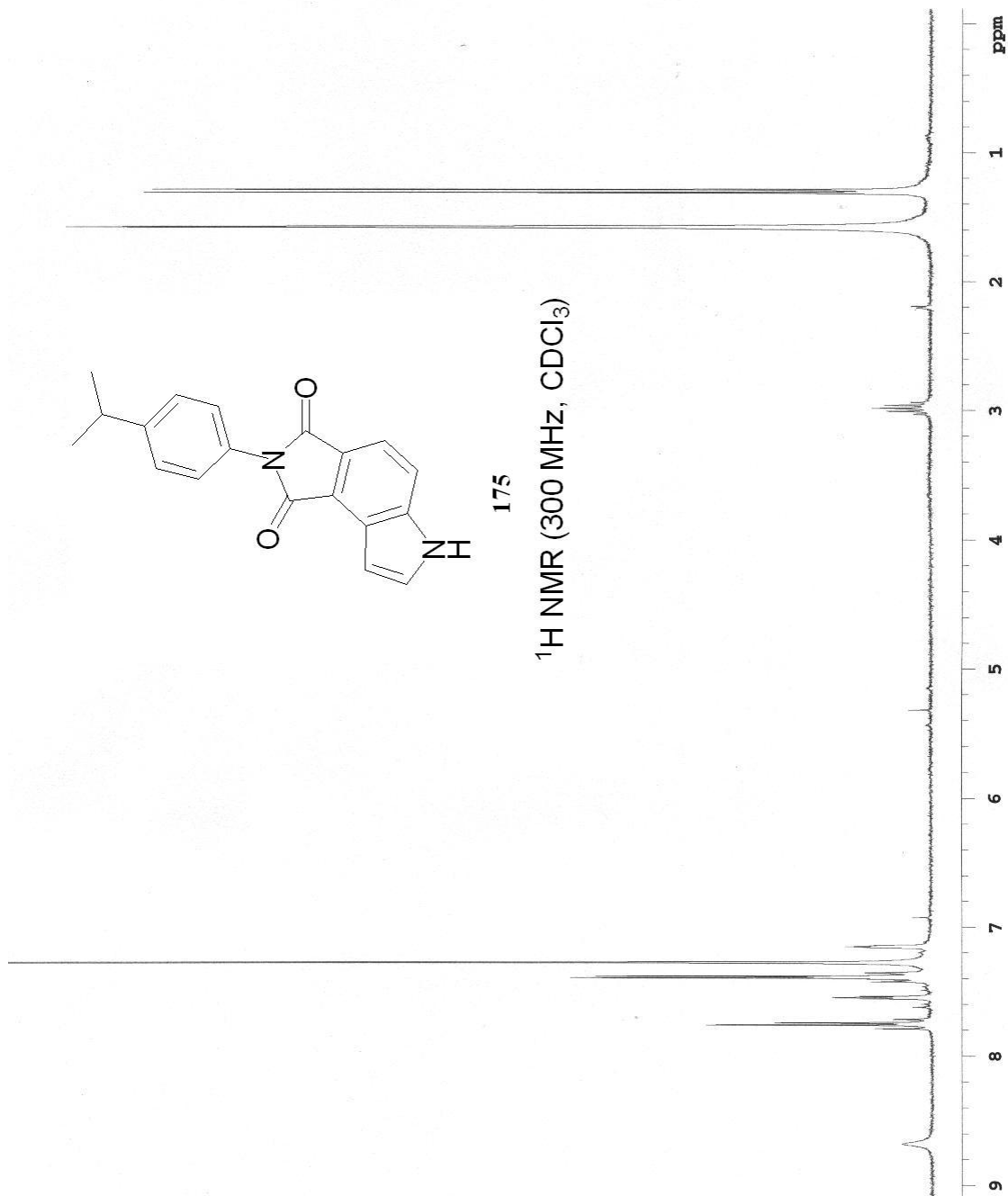


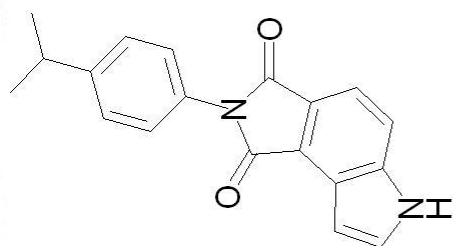


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^{13}C NMR (75 MHz, DMSO- d_6)

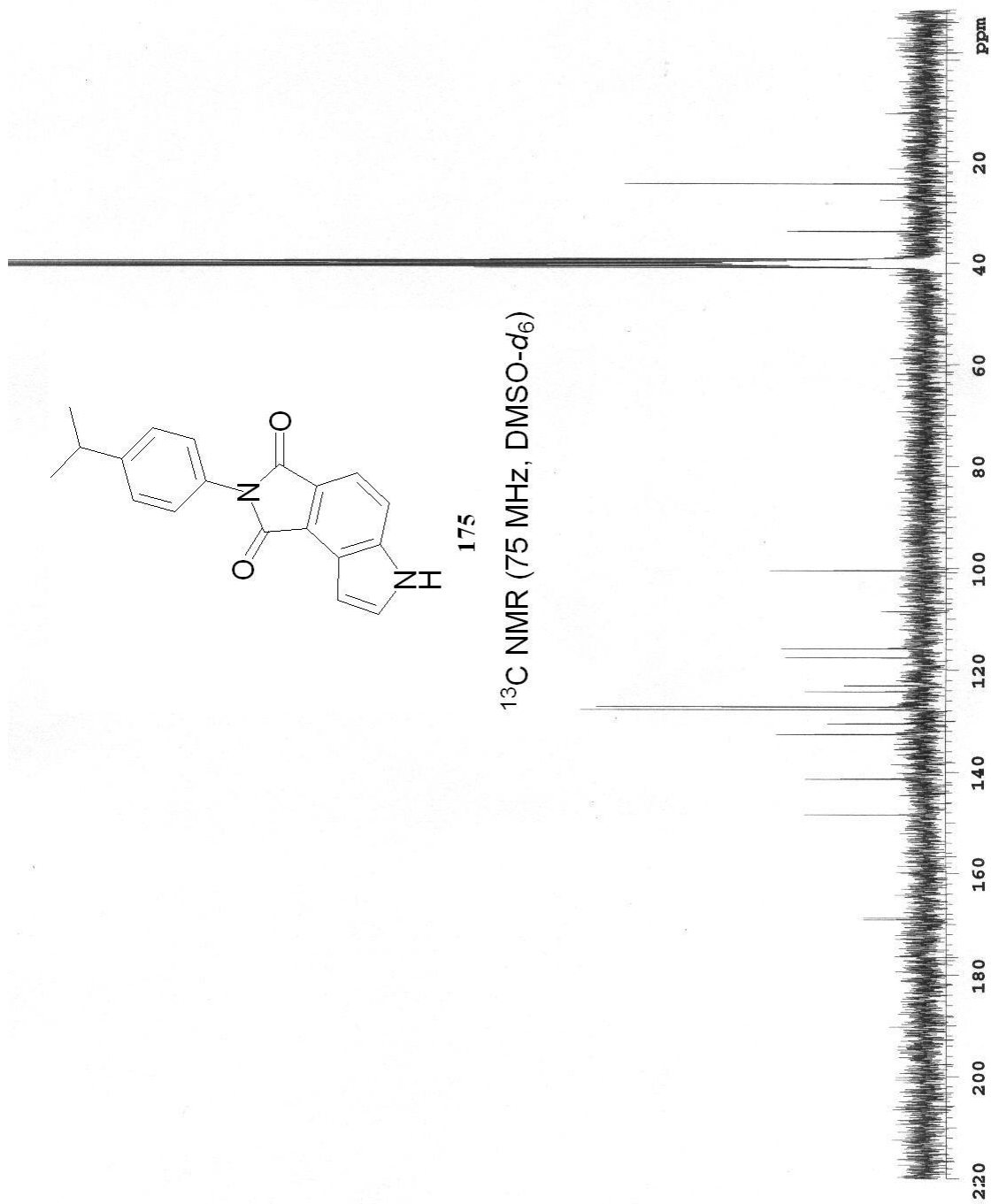


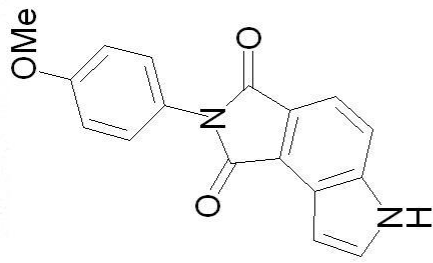




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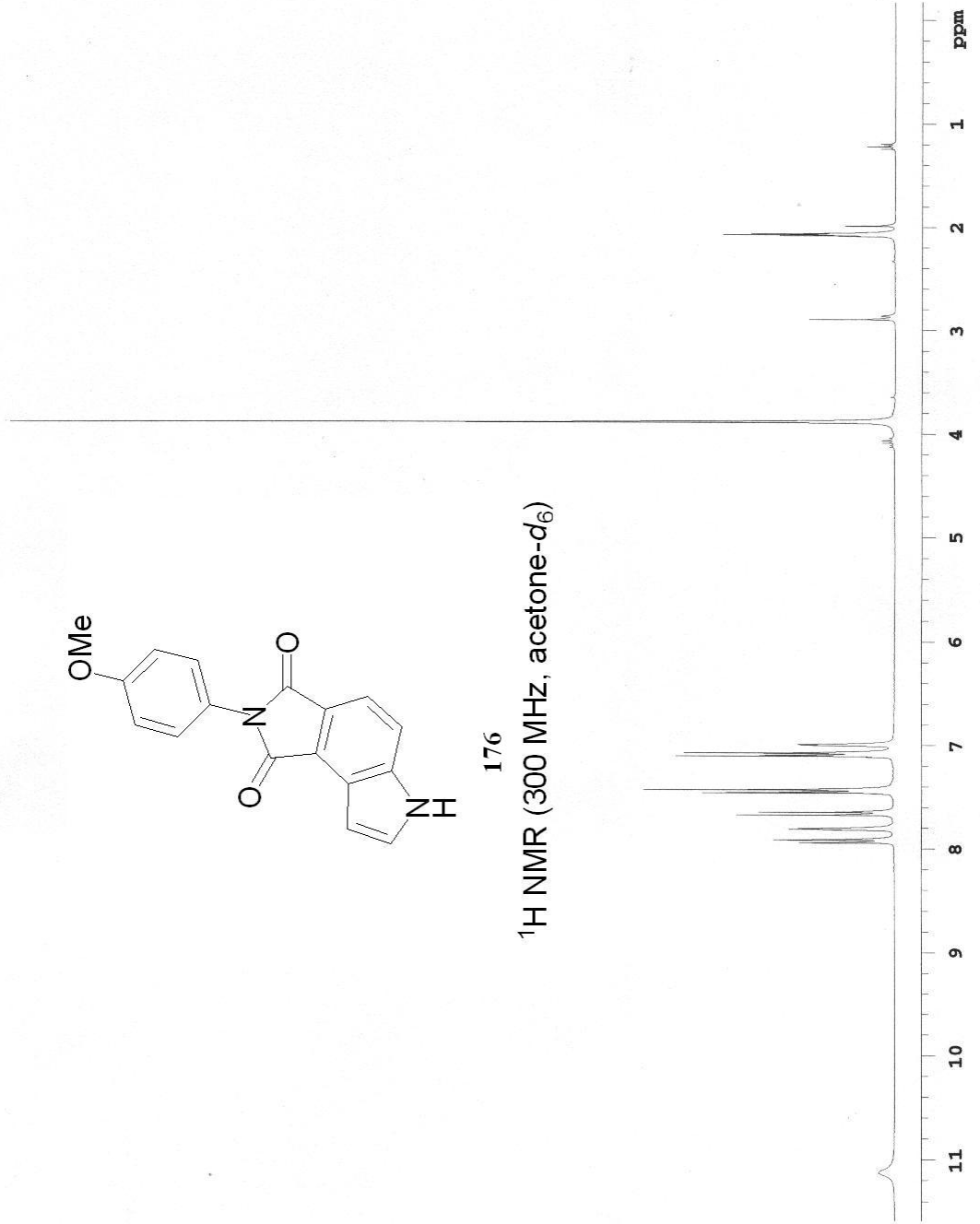
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)

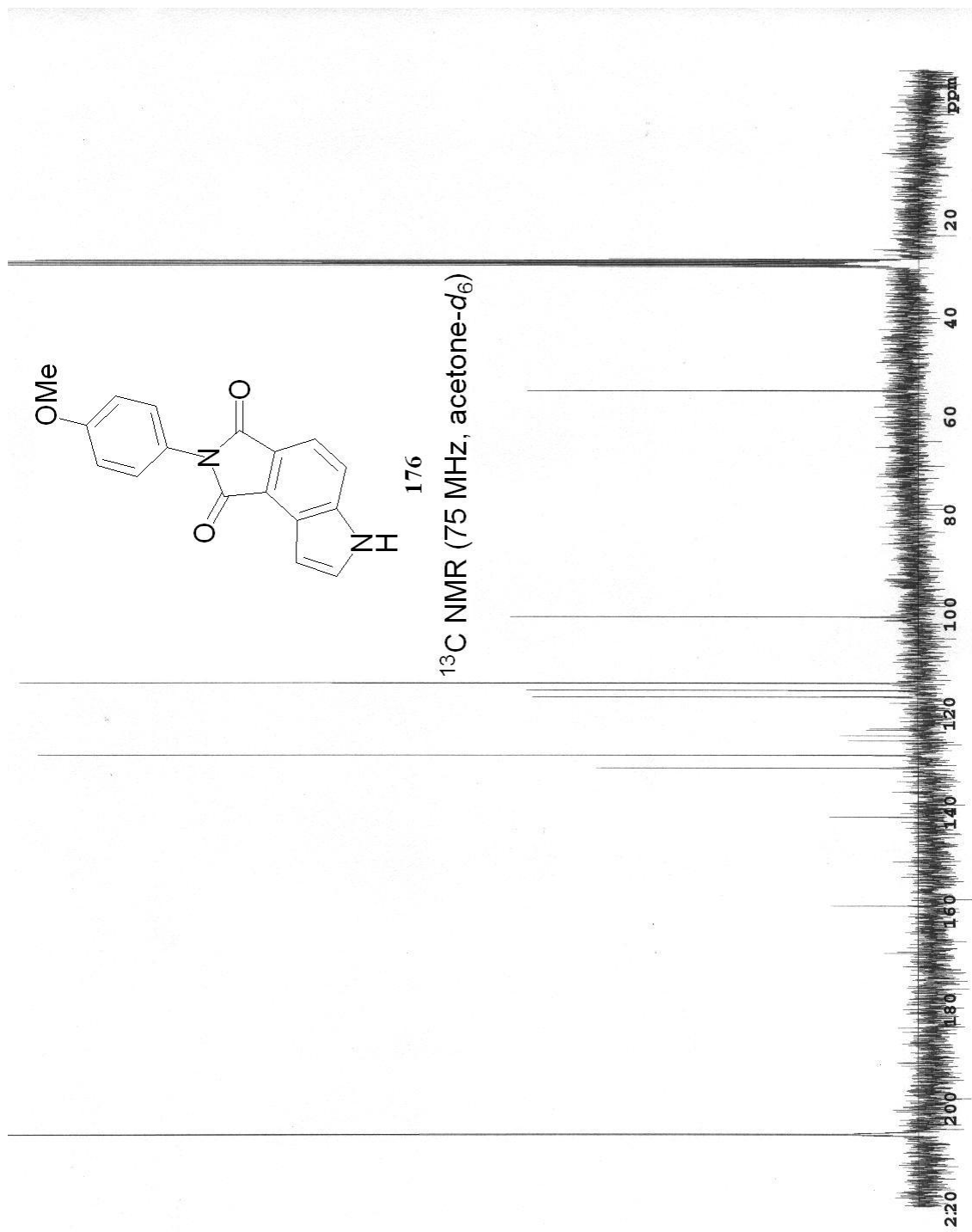


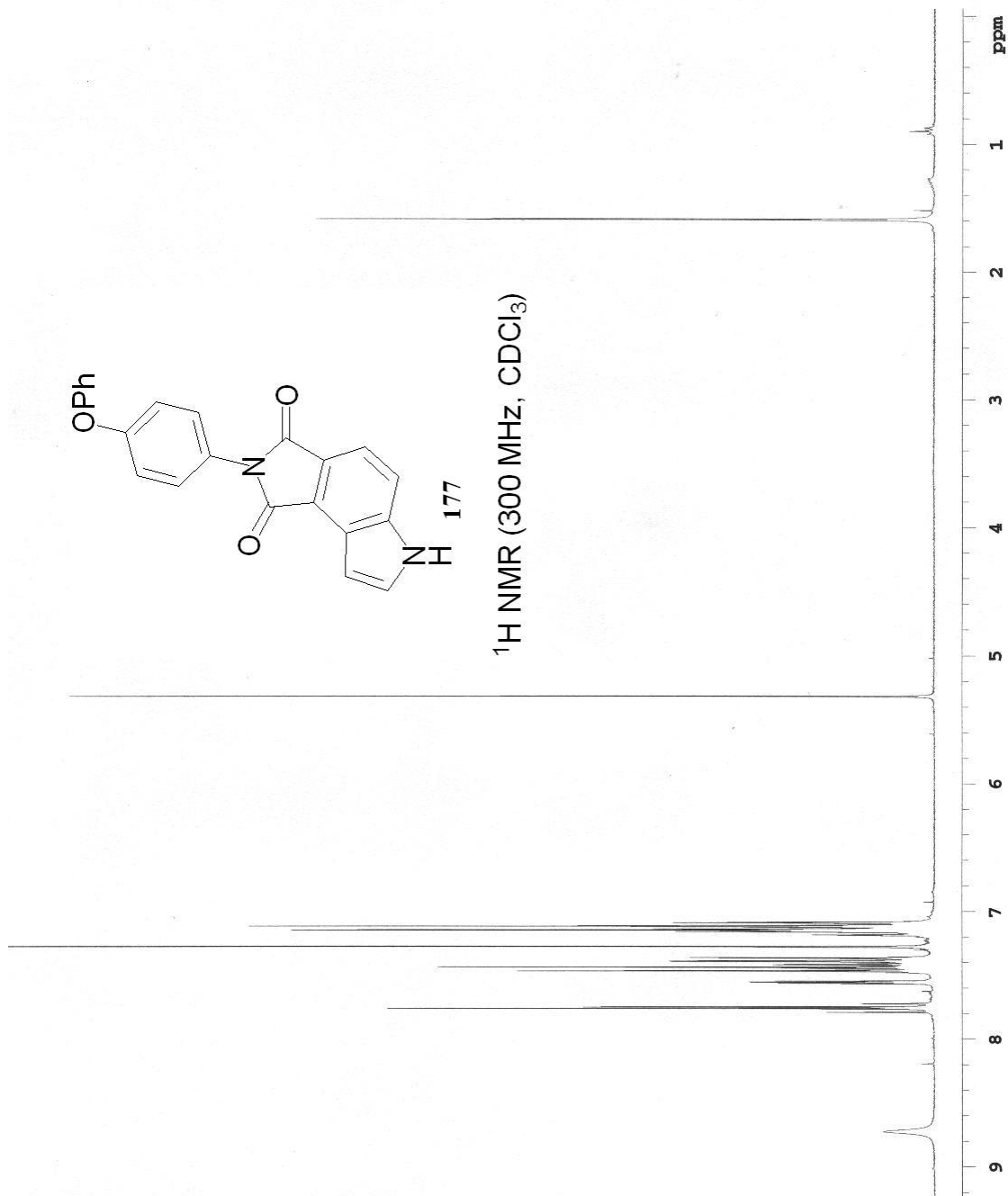


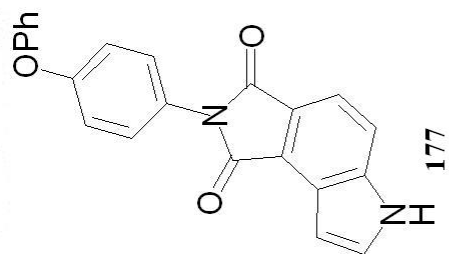
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¹H NMR (300 MHz, acetone-d₆)

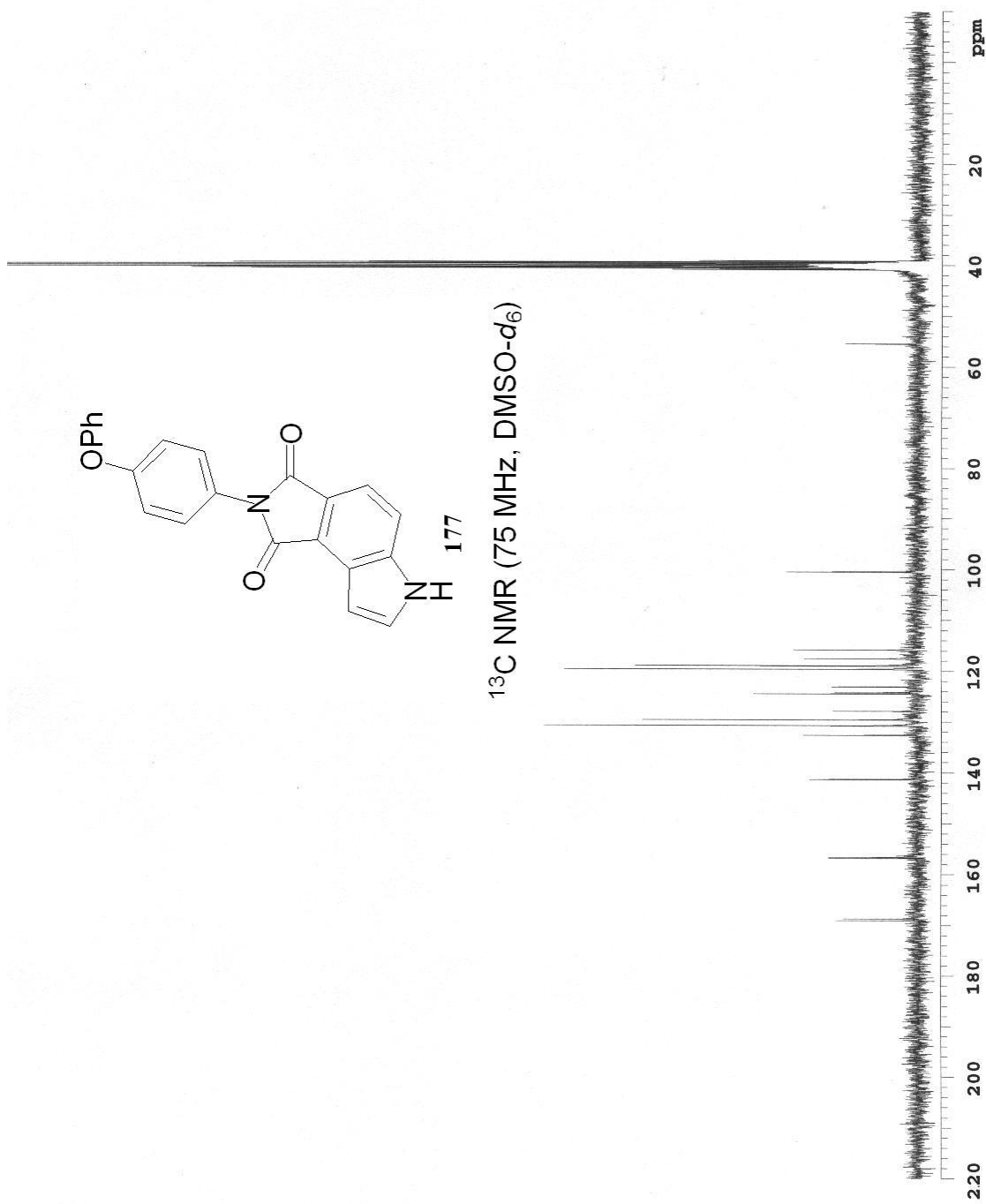


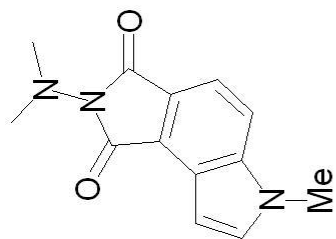






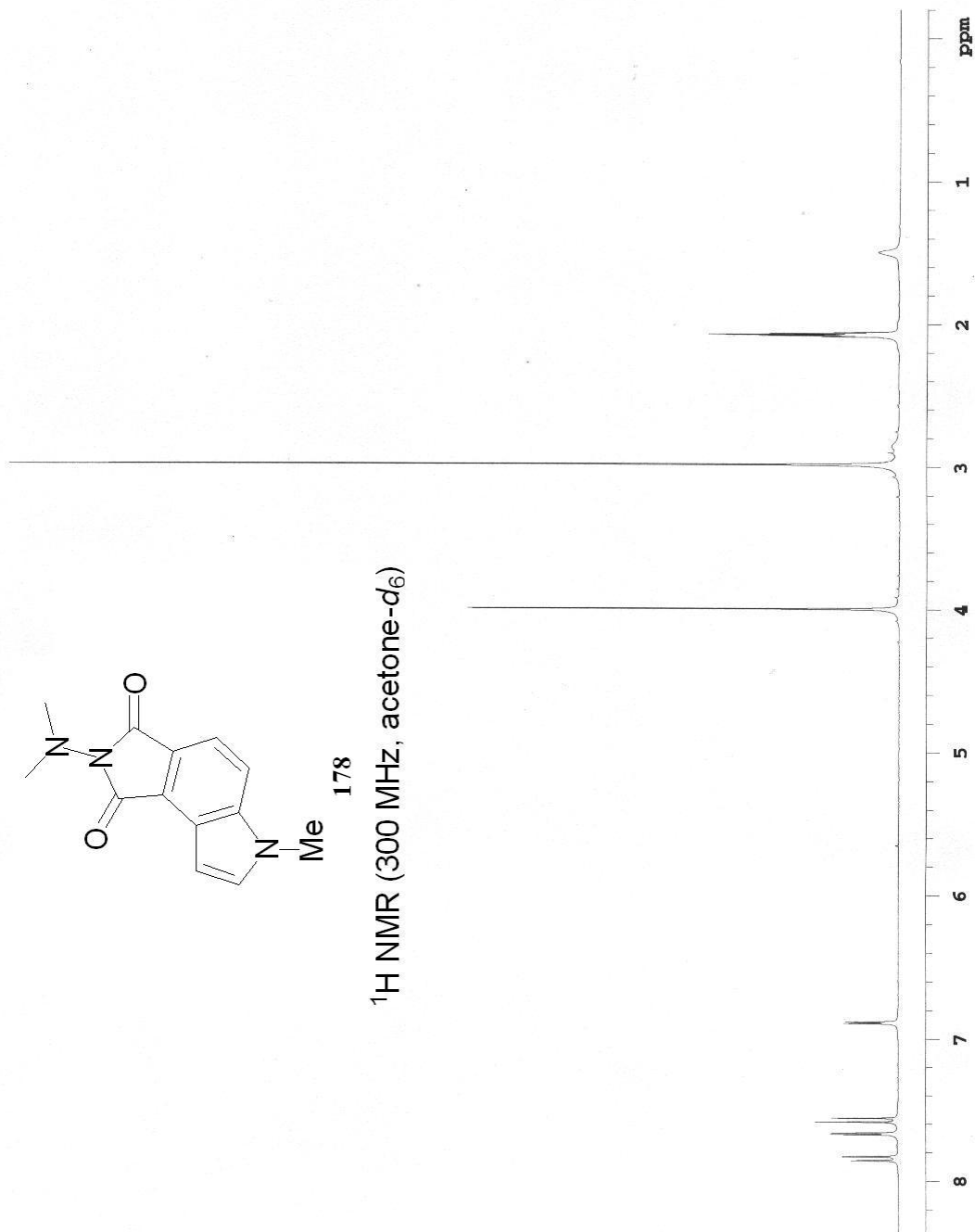
^{13}C NMR (75 MHz, DMSO- d_6)

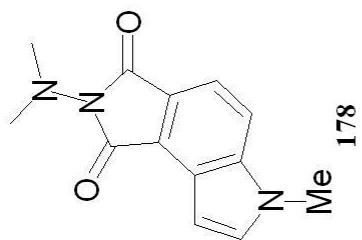




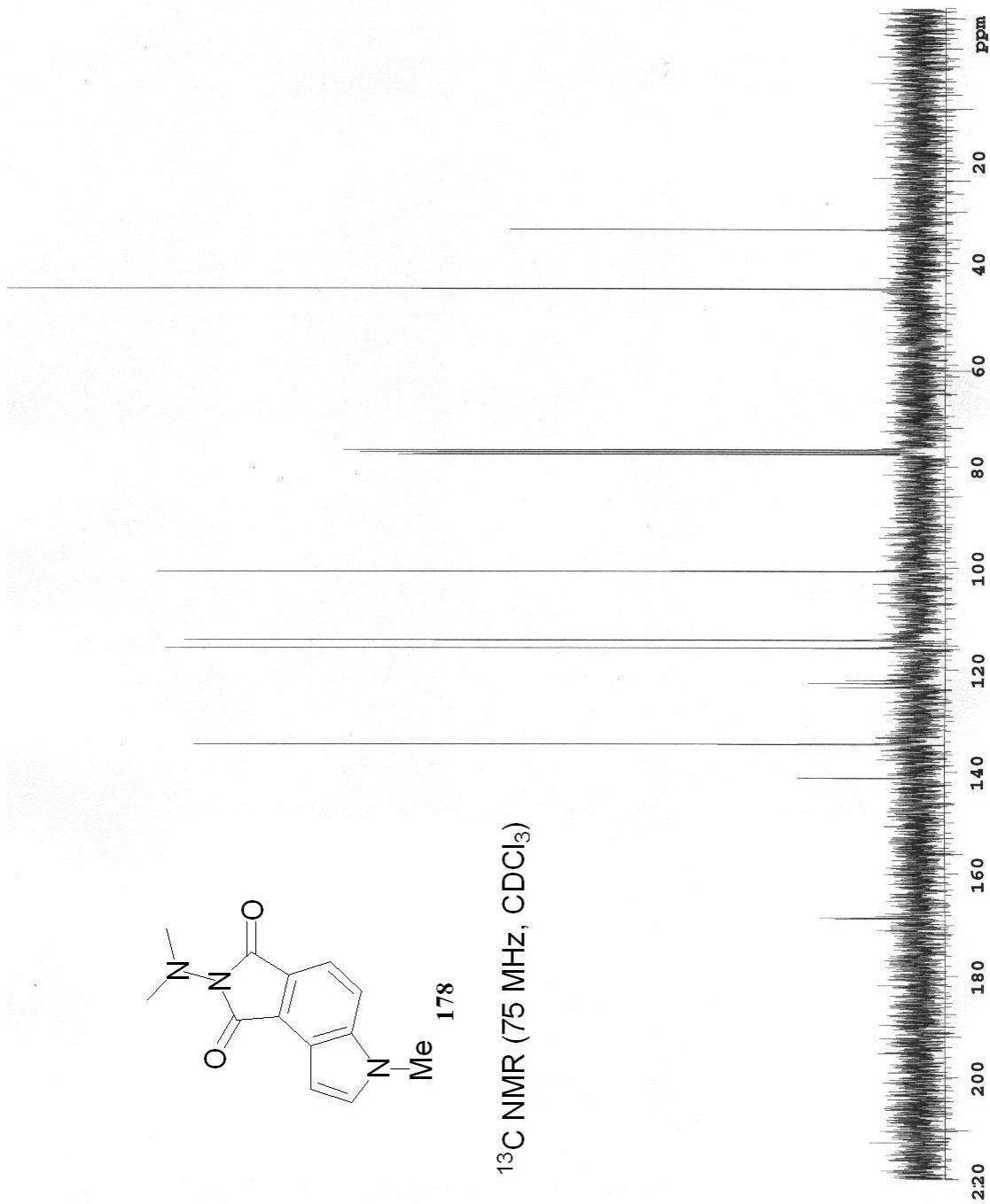
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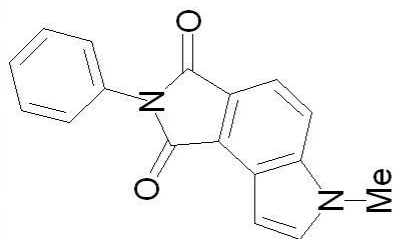
¹H NMR (300 MHz, acetone-d₆)





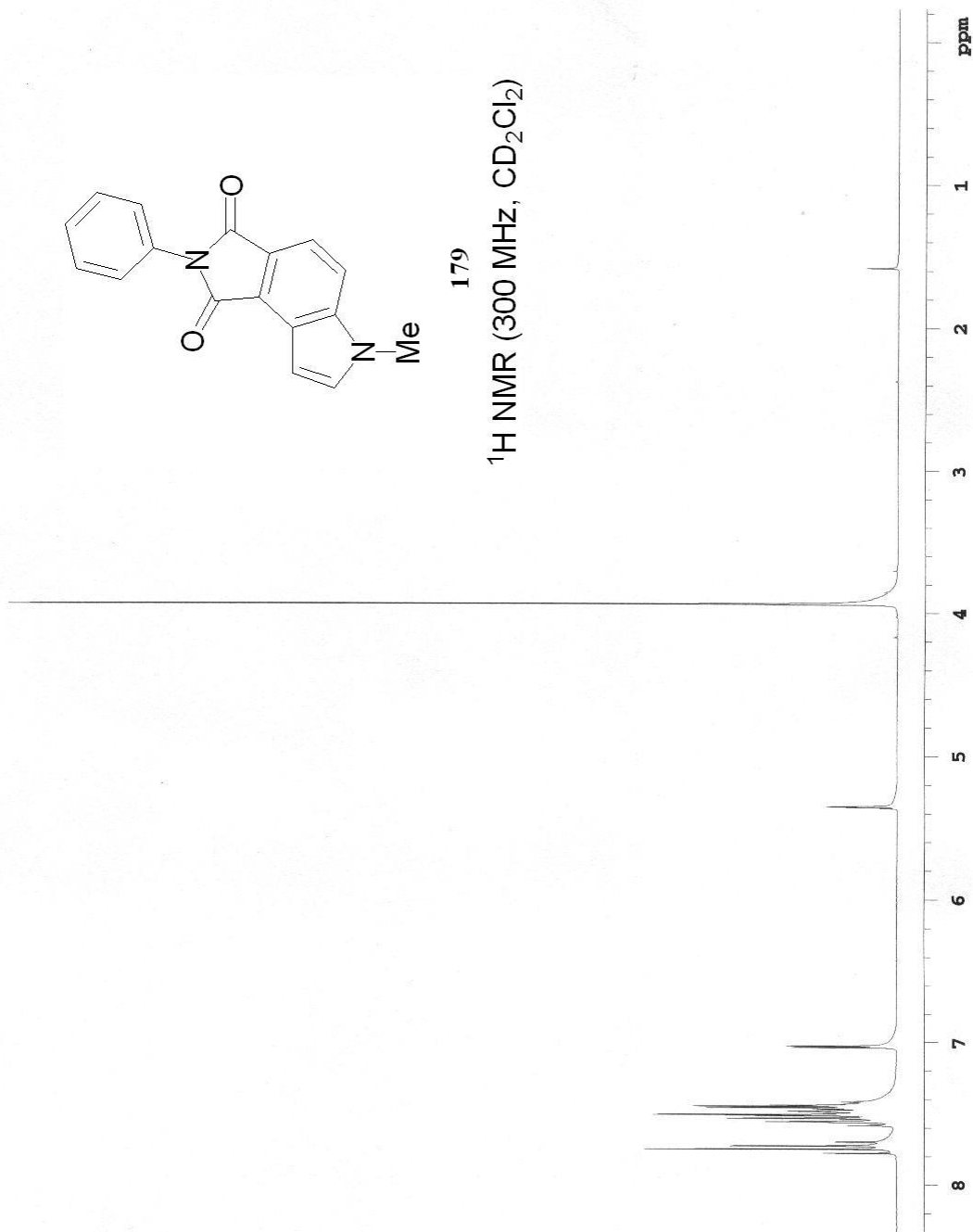
^{13}C NMR (75 MHz, CDCl_3)

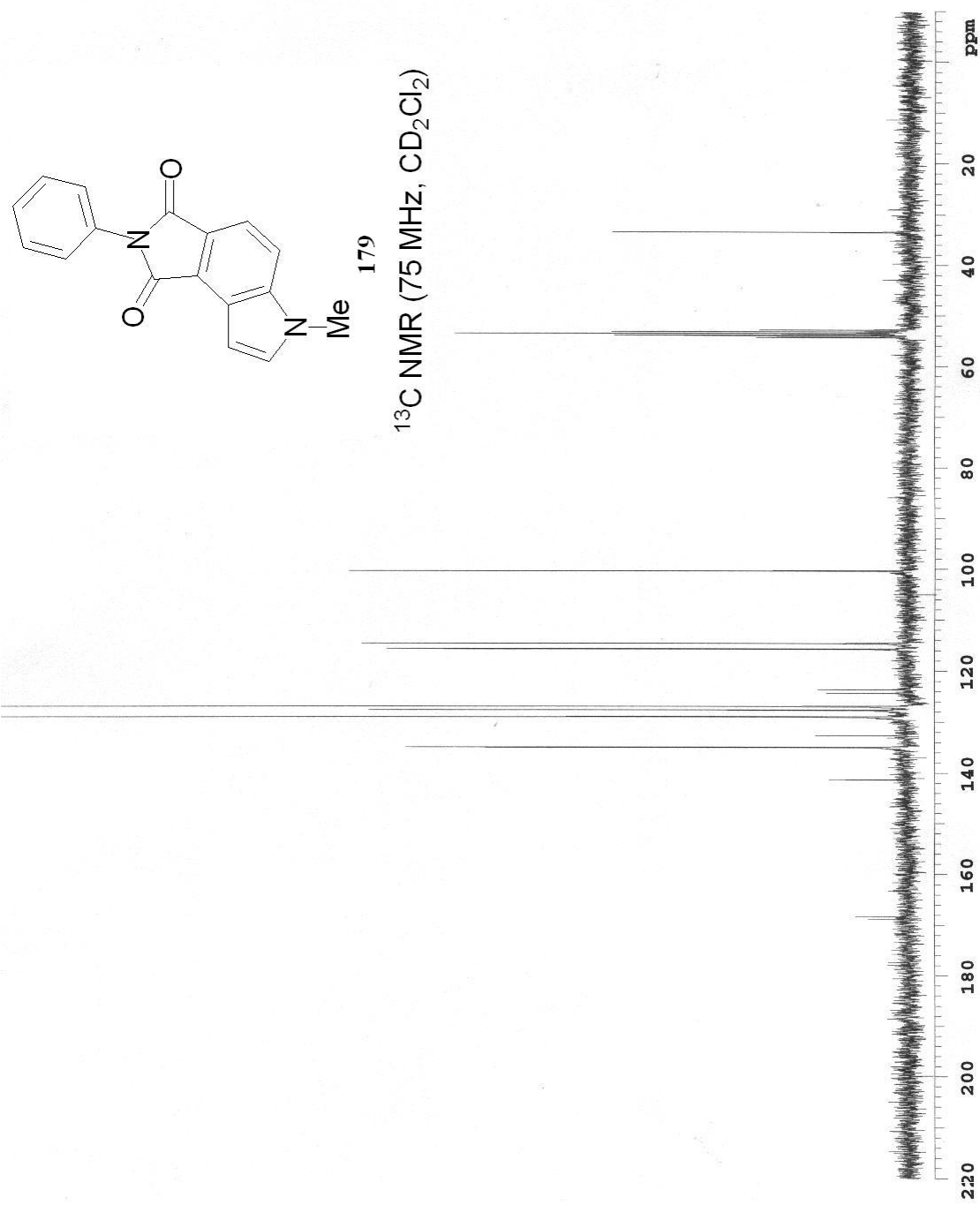


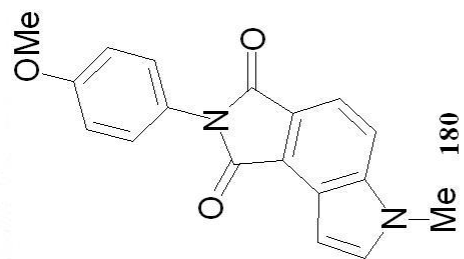


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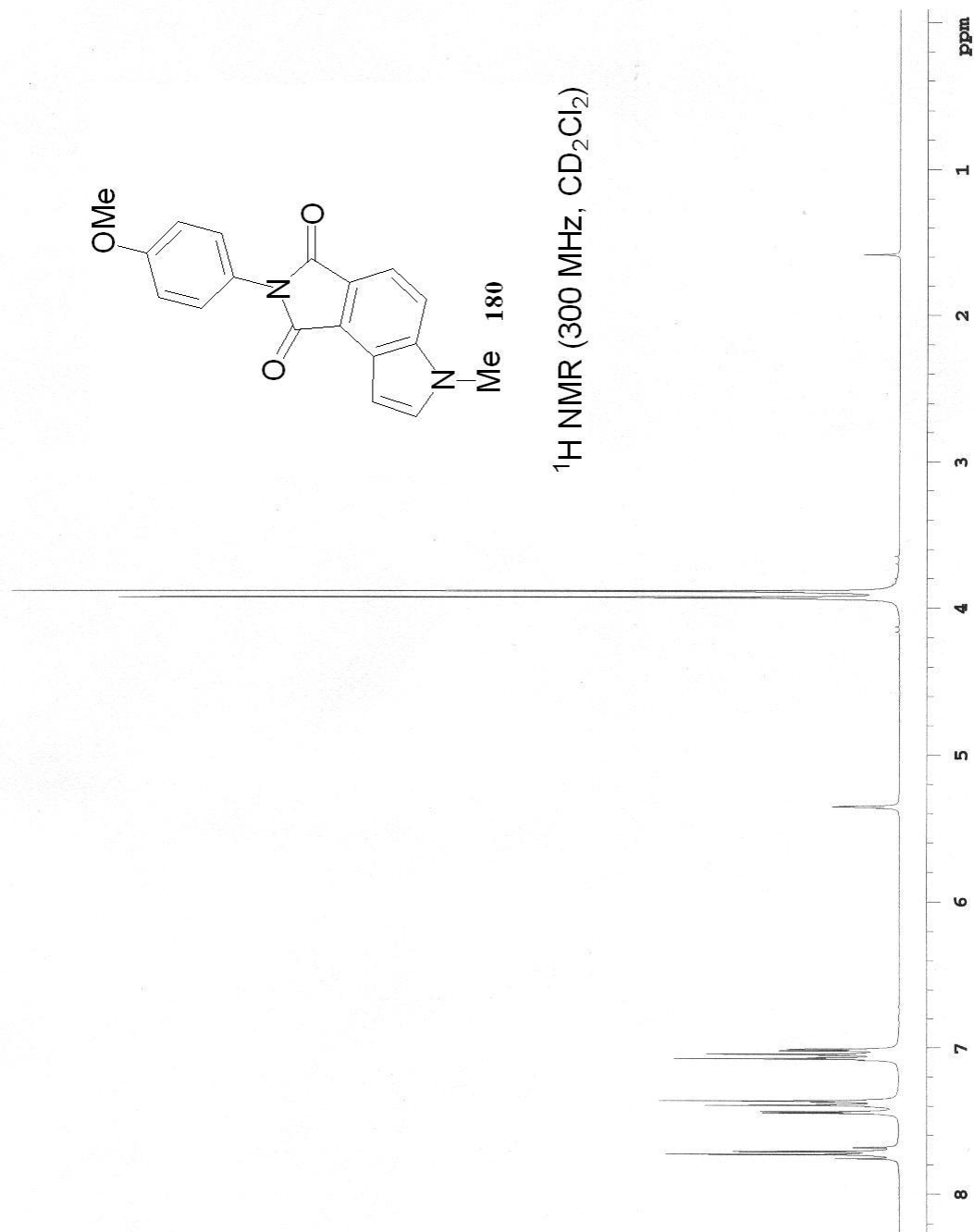
^1H NMR (300 MHz, CD_2Cl_2)

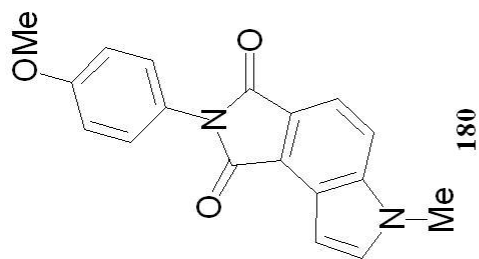




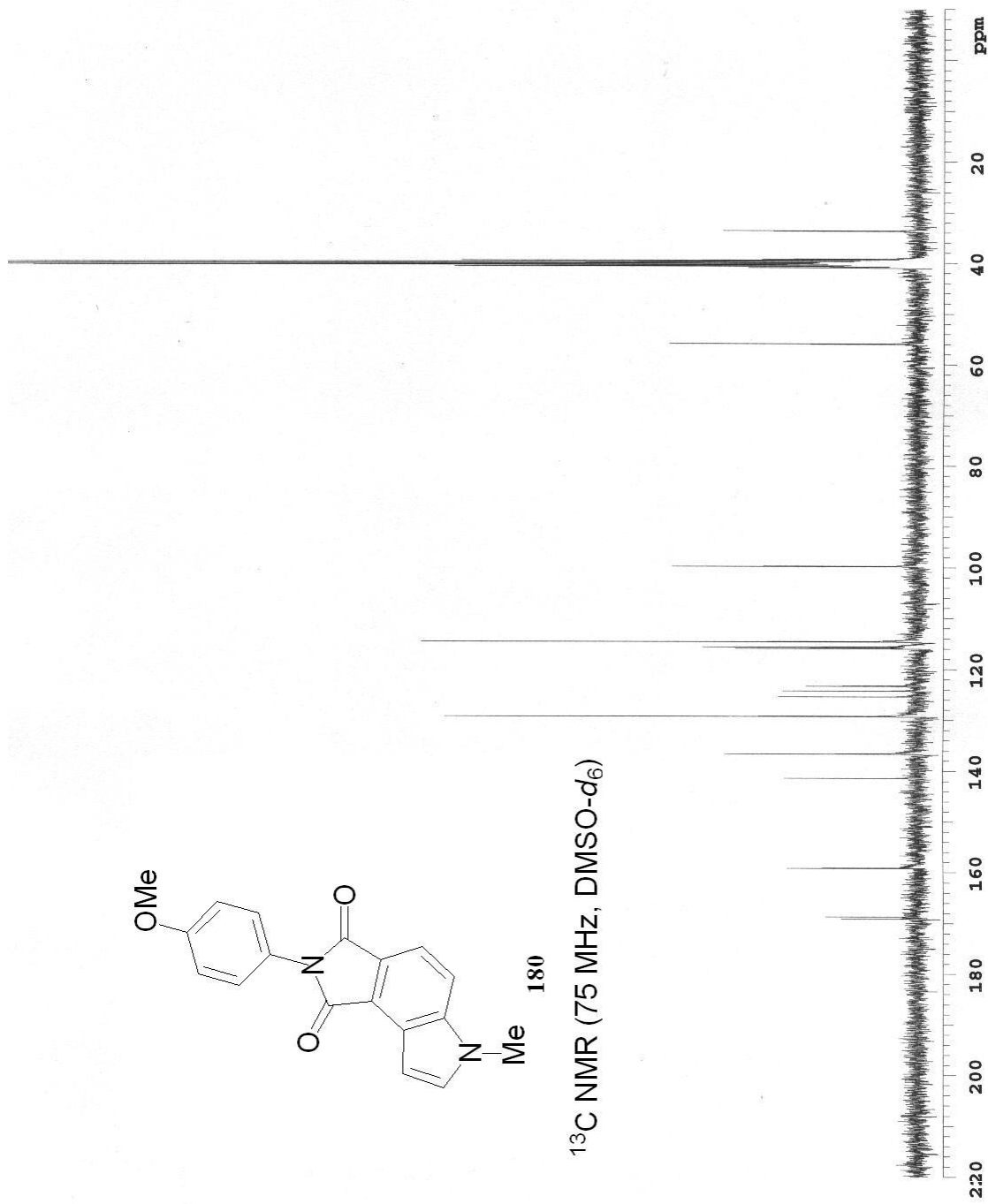


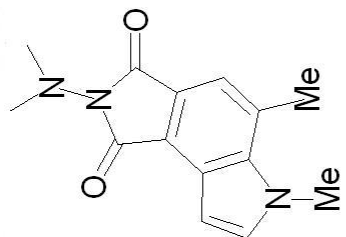
^1H NMR (300 MHz, CD_2Cl_2)



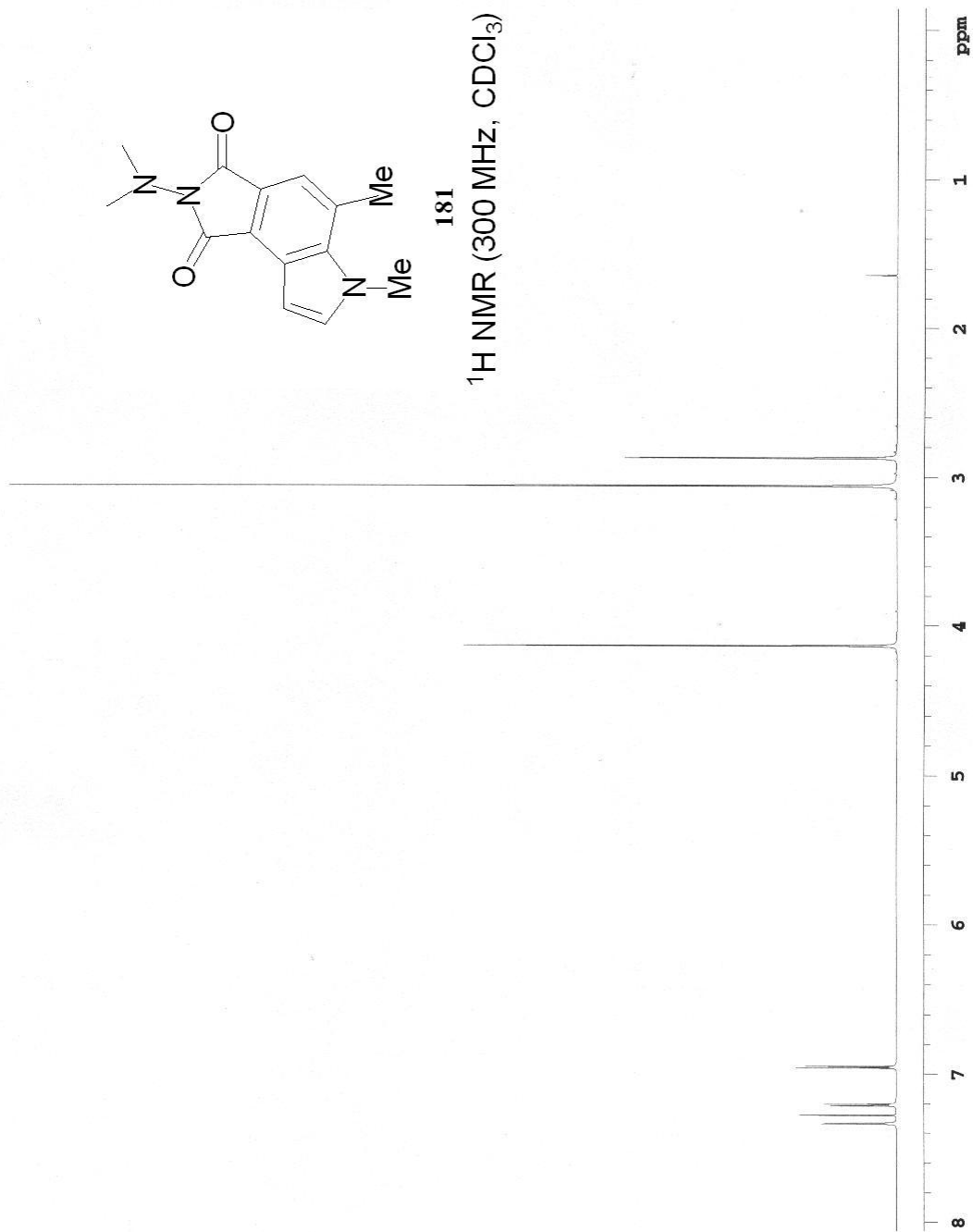


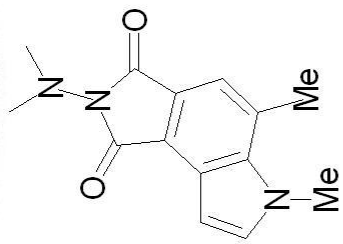
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)





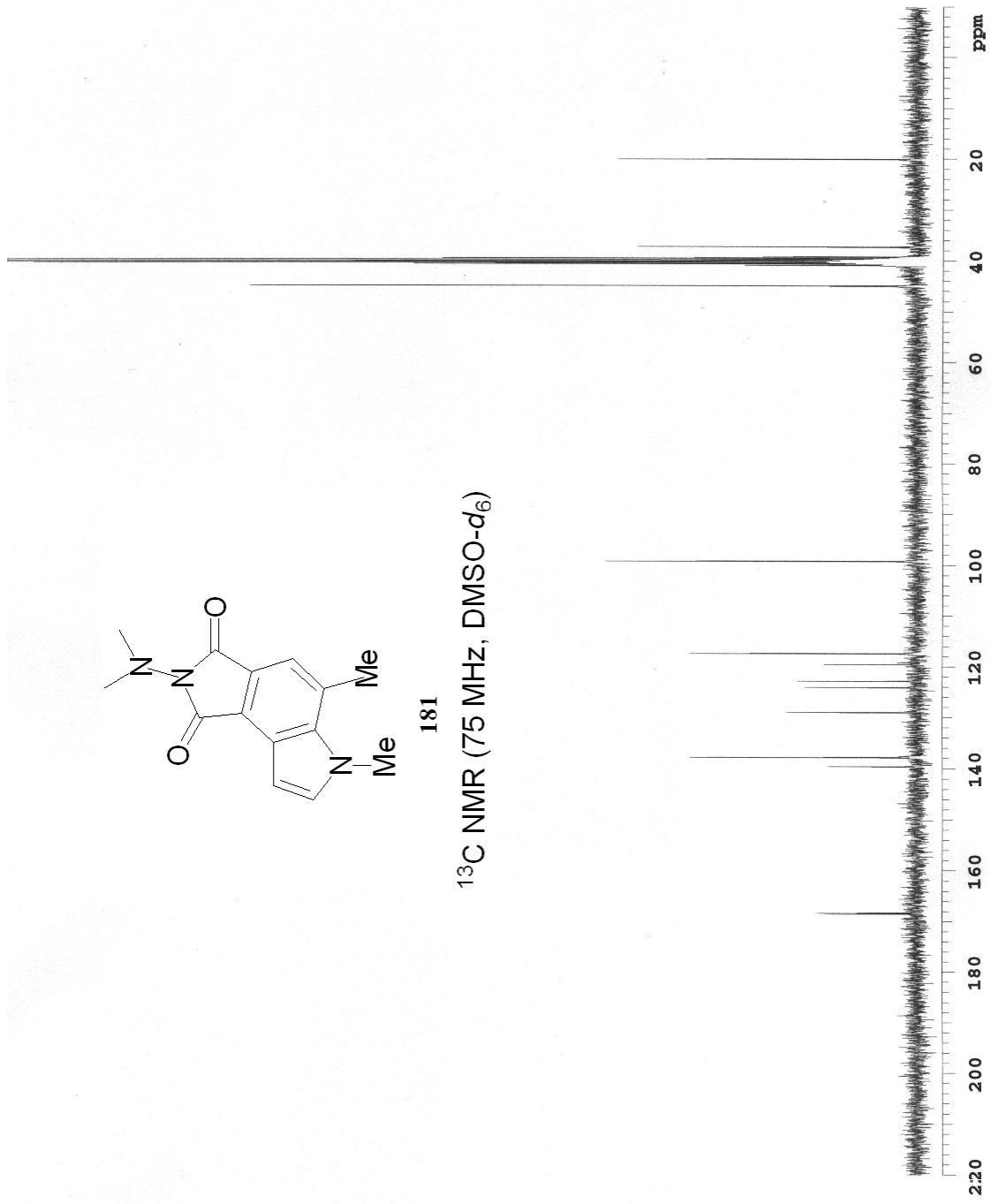
181
¹H NMR (300 MHz, CDCl₃)

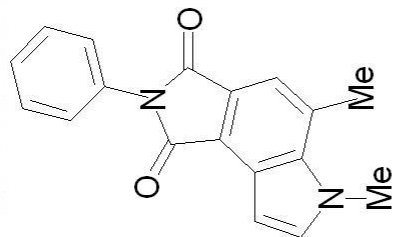




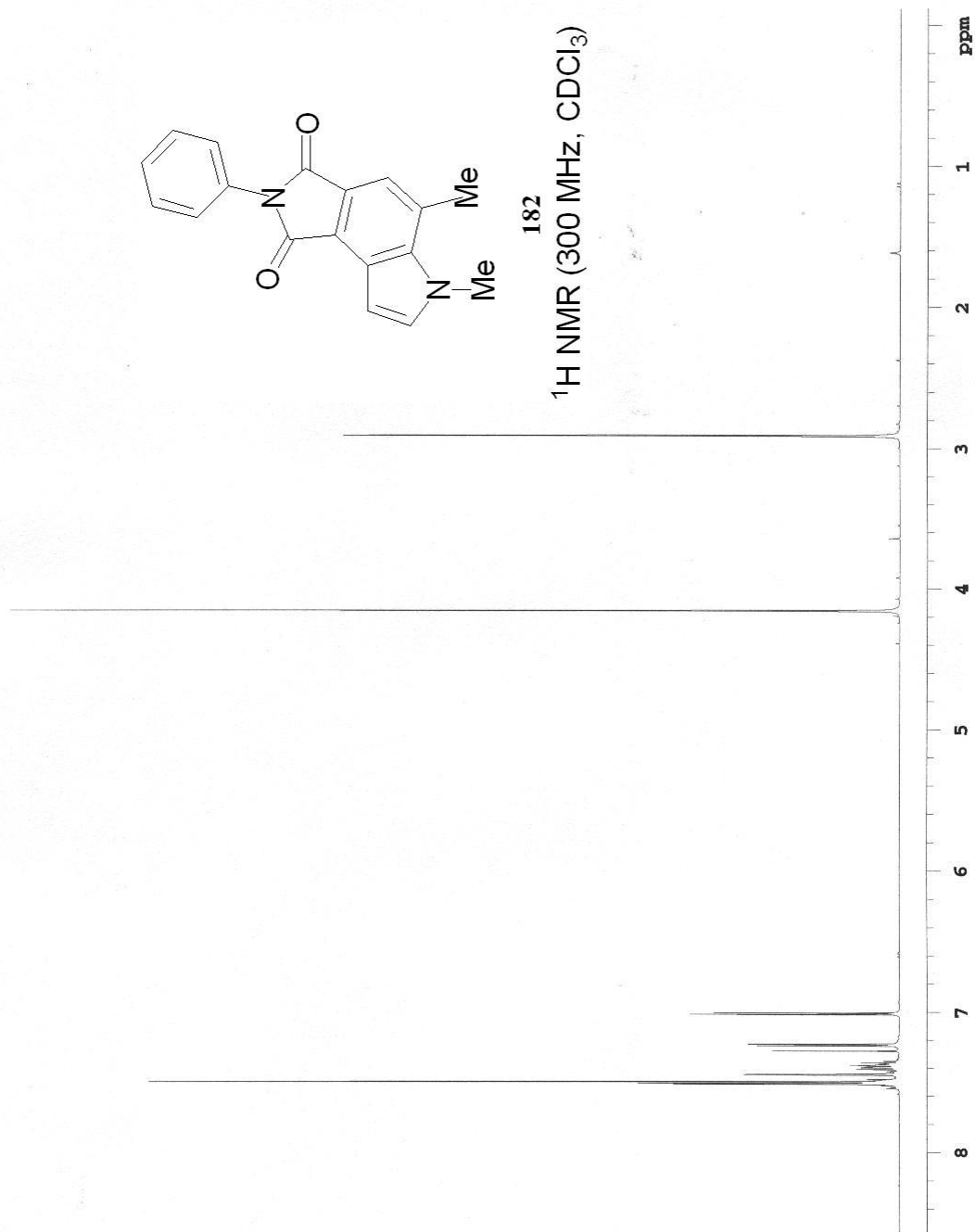
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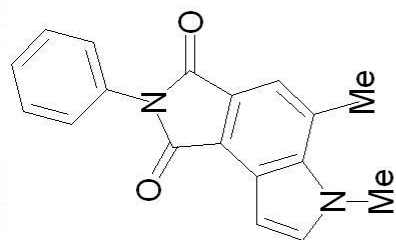
¹³C NMR (75 MHz, DMSO-d₆)





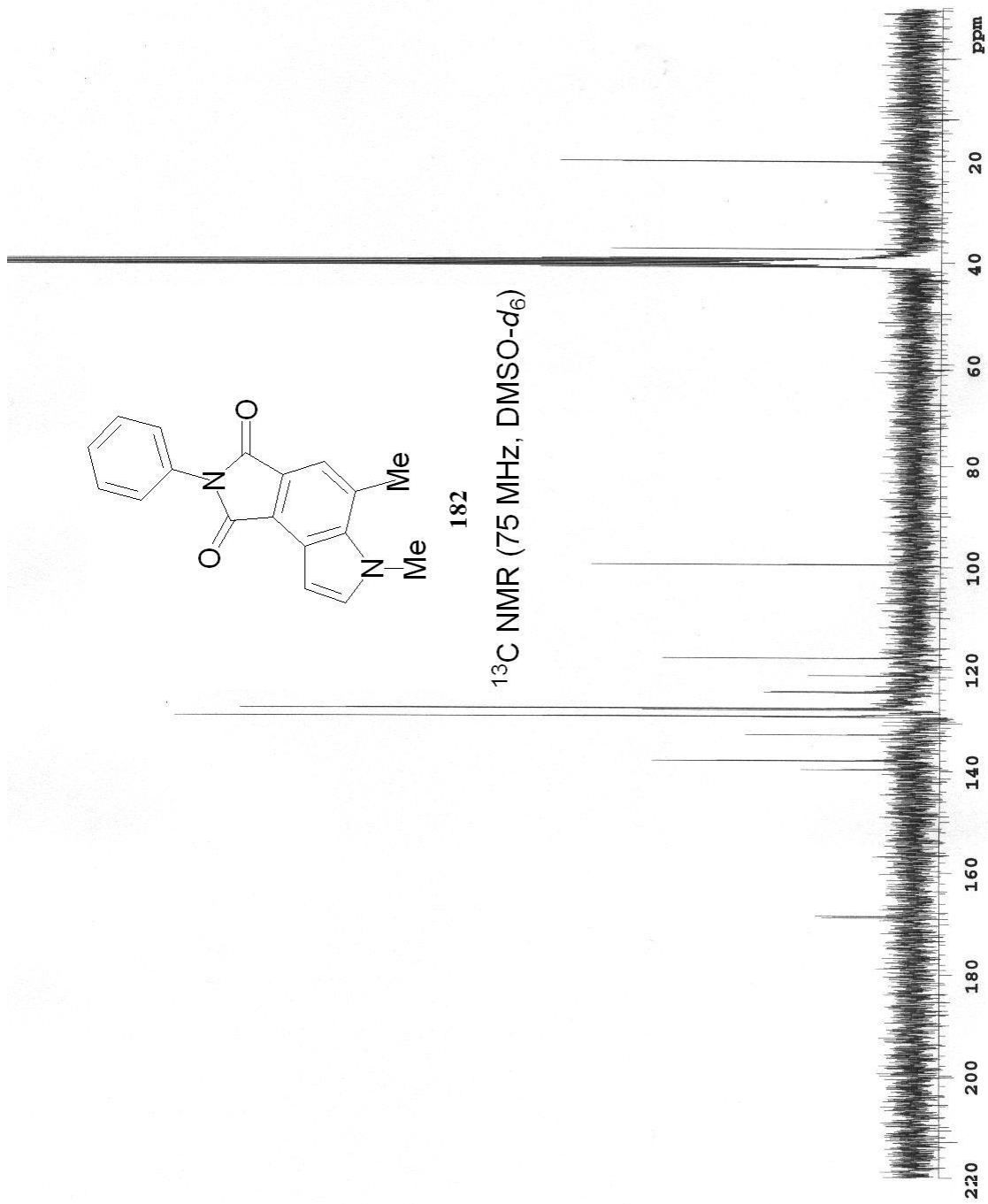
182
 $^1\text{H NMR}$ (300 MHz, CDCl_3)

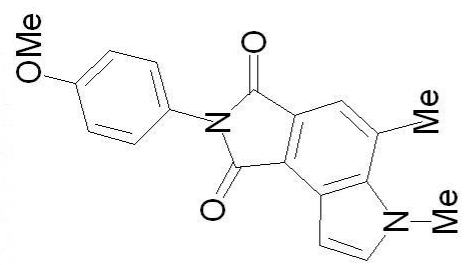




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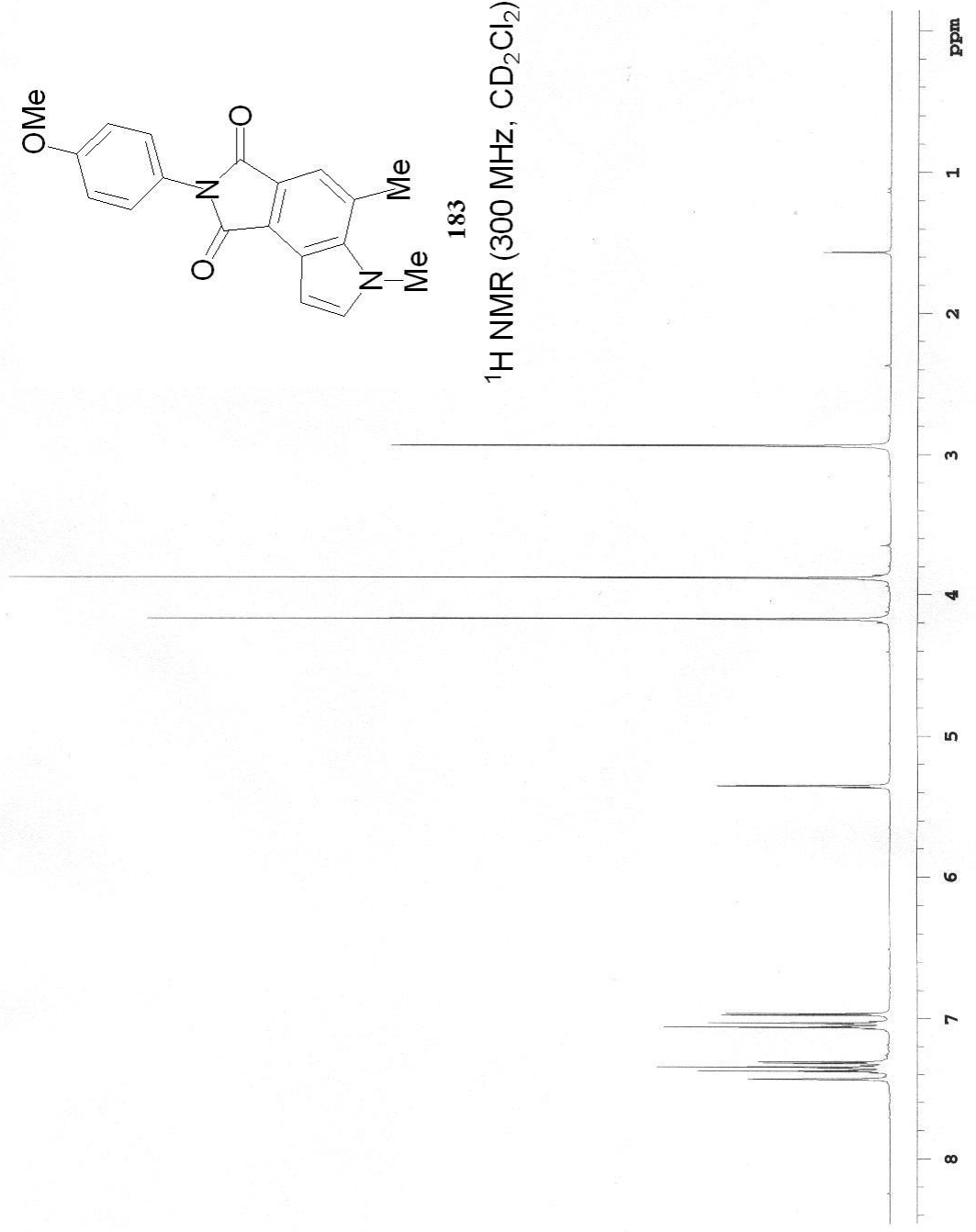
^{13}C NMR (75 MHz, DMSO- d_6)

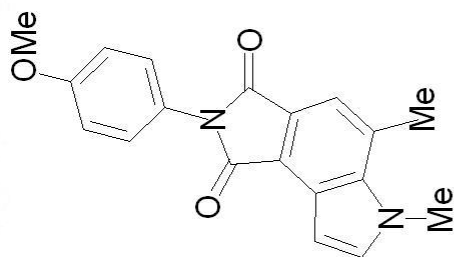




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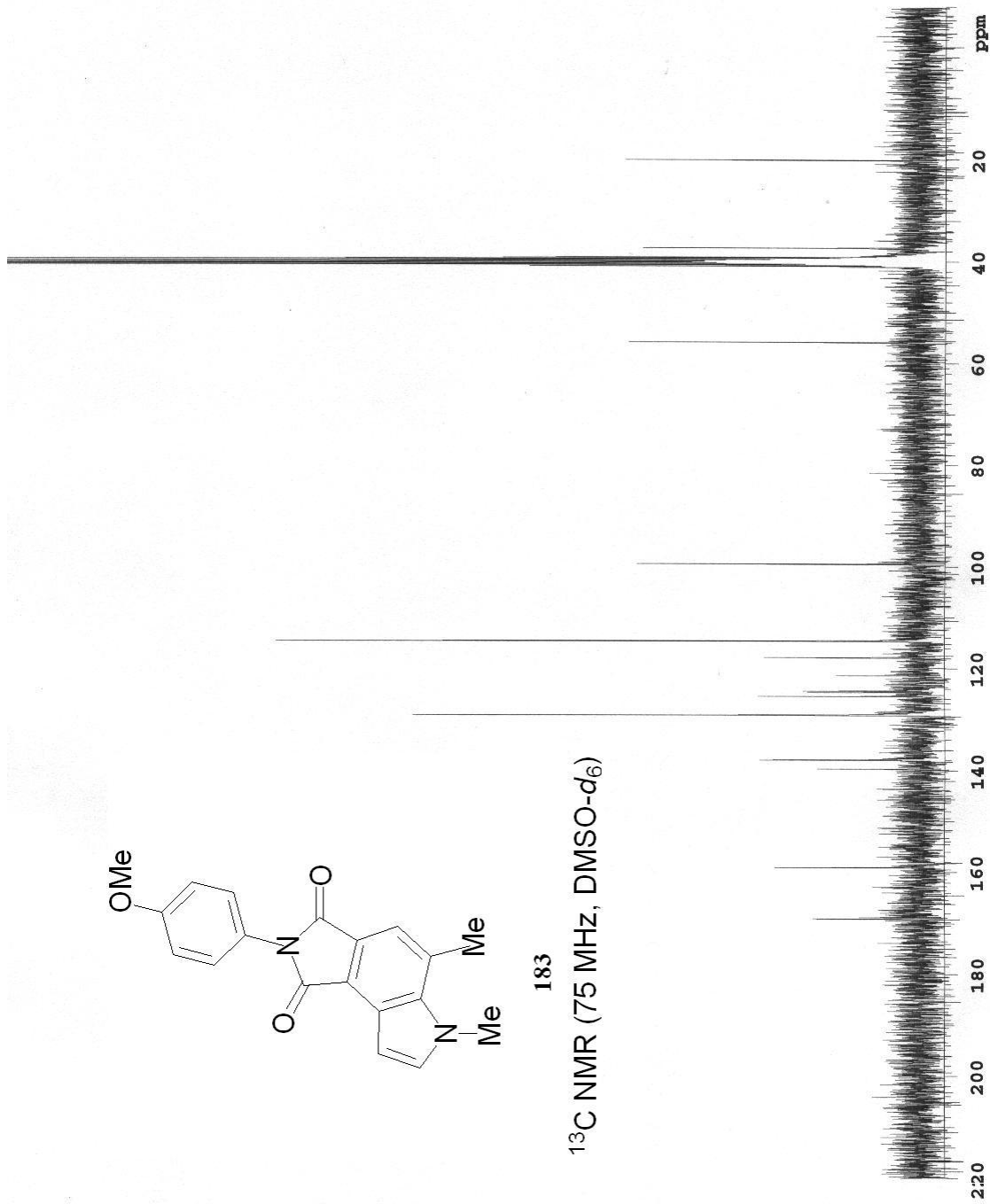
$^1\text{H NMR}$ (300 MHz, CD_2Cl_2)

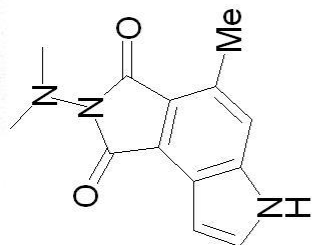




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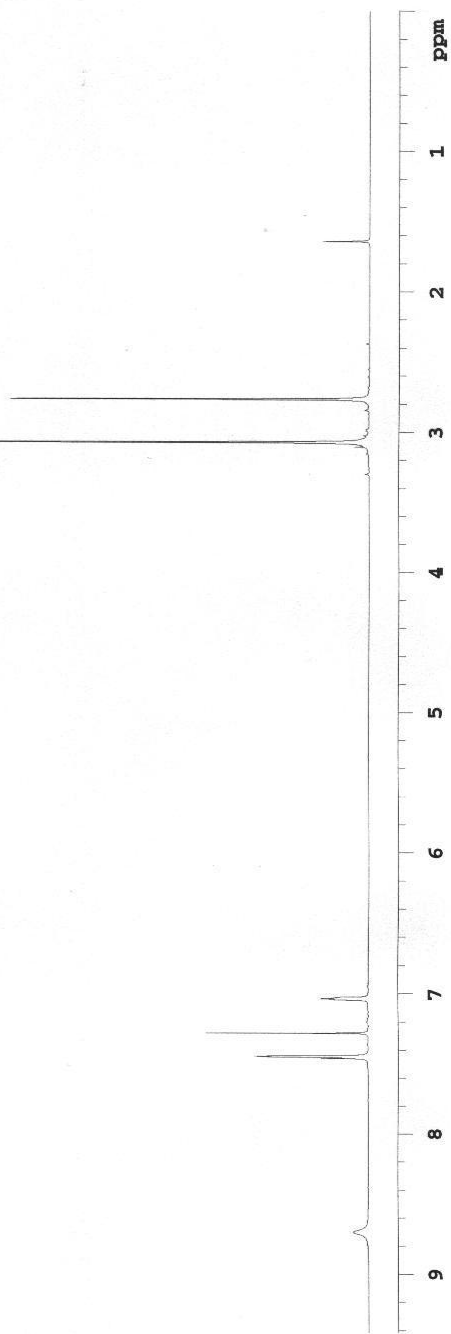
¹³C NMR (75 MHz, DMSO-d₆)

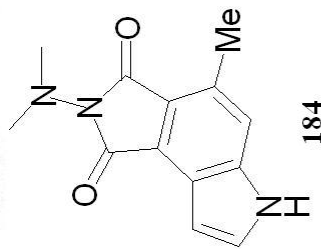




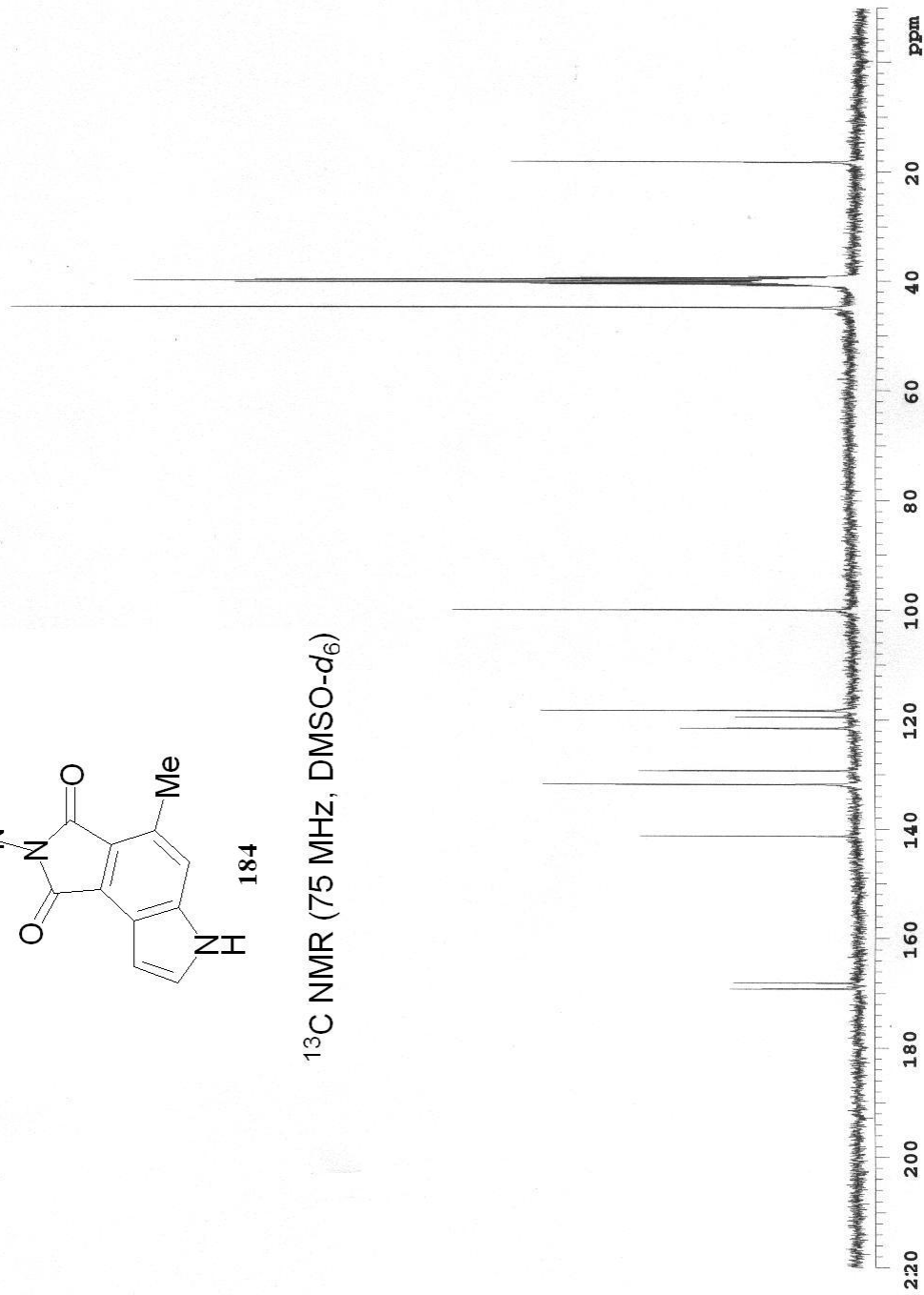
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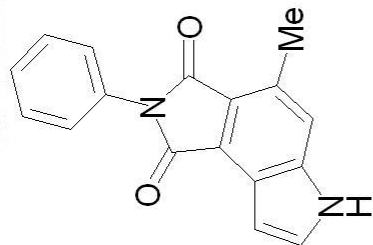
$^1\text{H NMR}$ (300 MHz, CDCl_3)





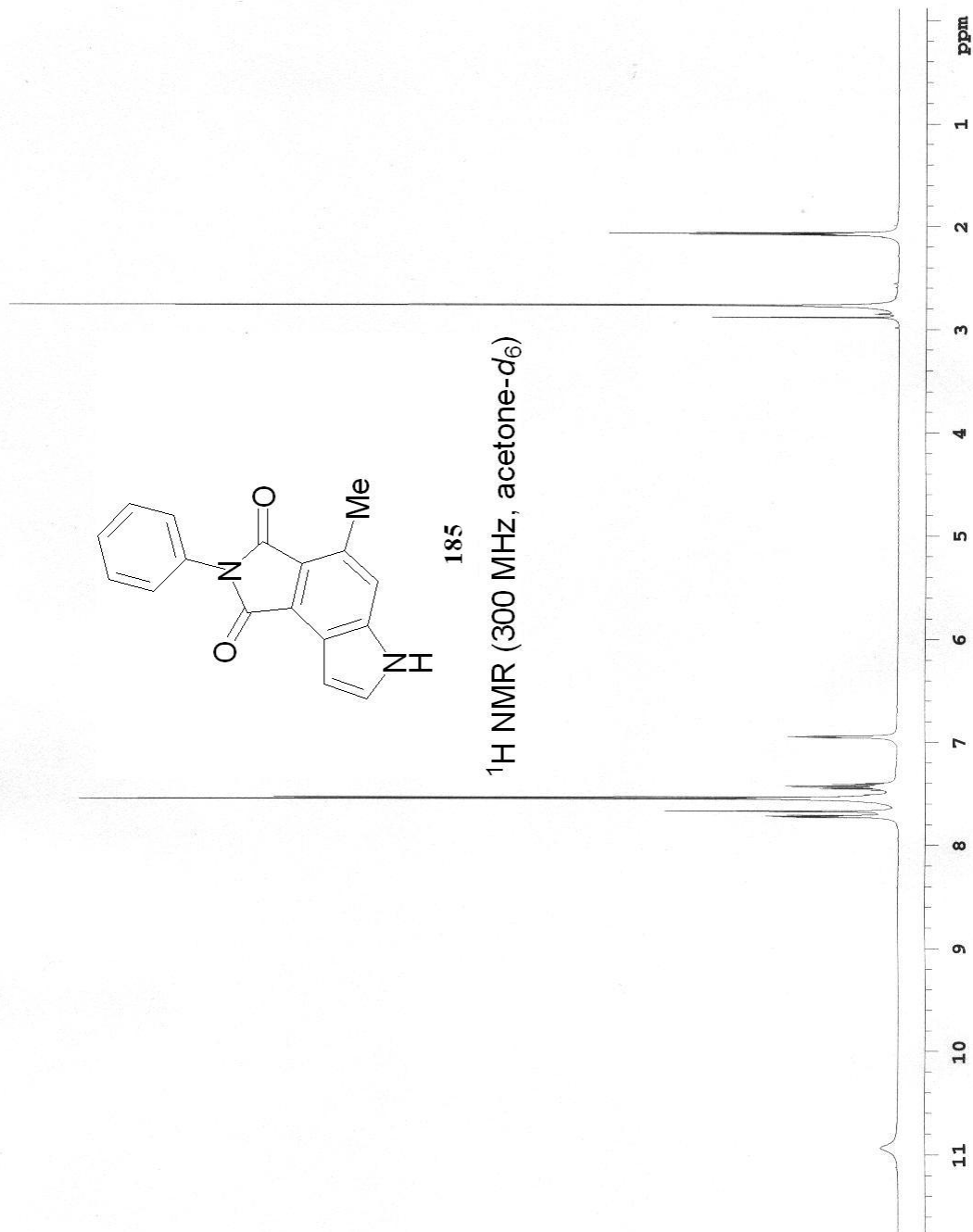
^{13}C NMR (75 MHz, DMSO- d_6)

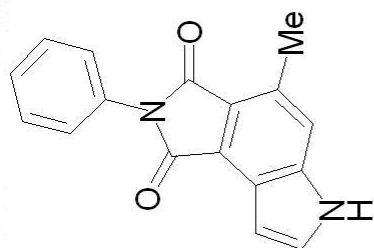




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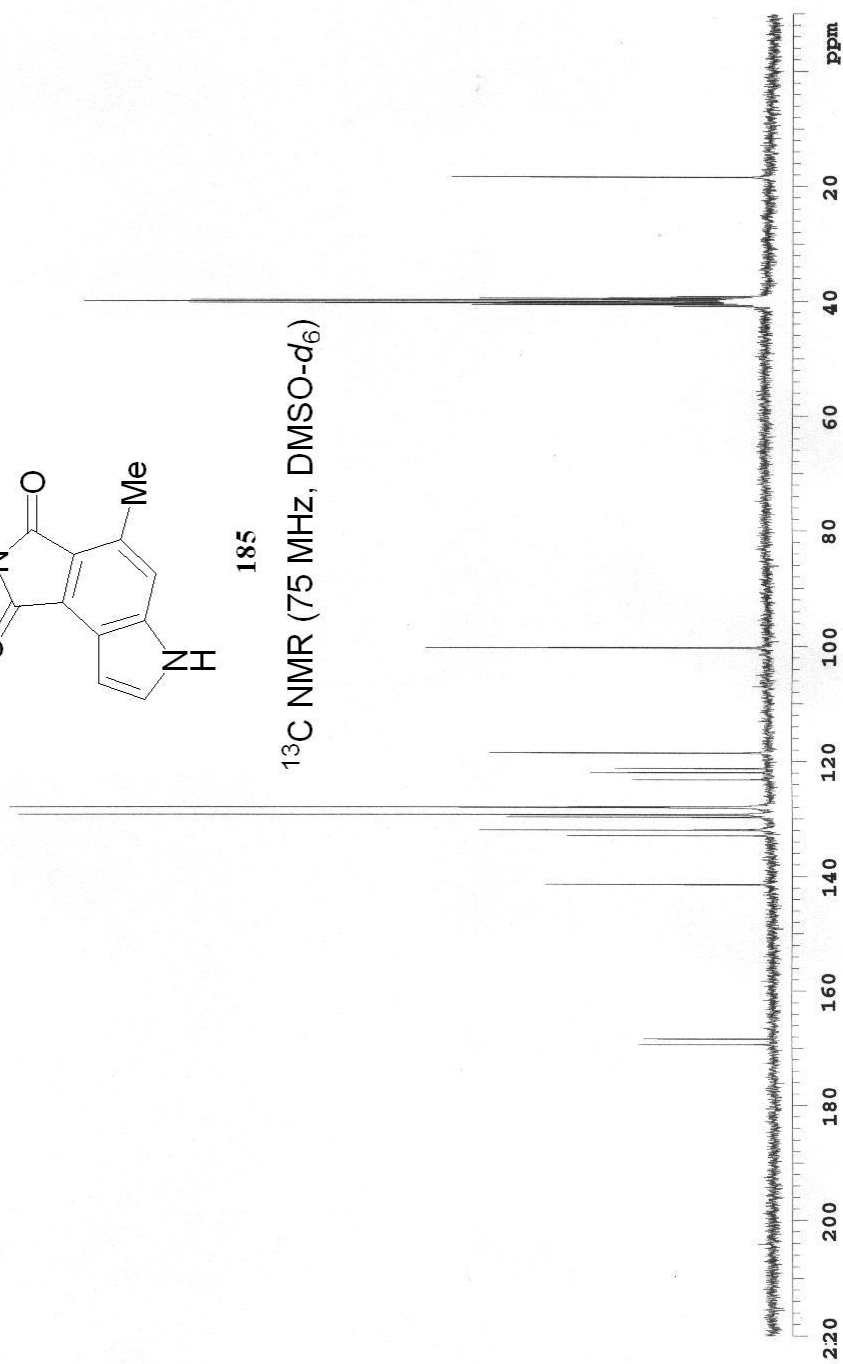
^1H NMR (300 MHz, acetone- d_6)

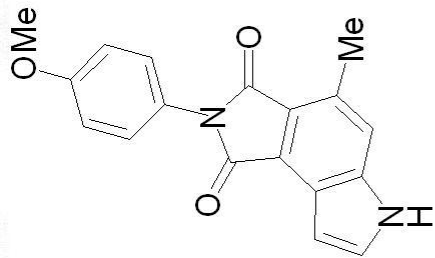




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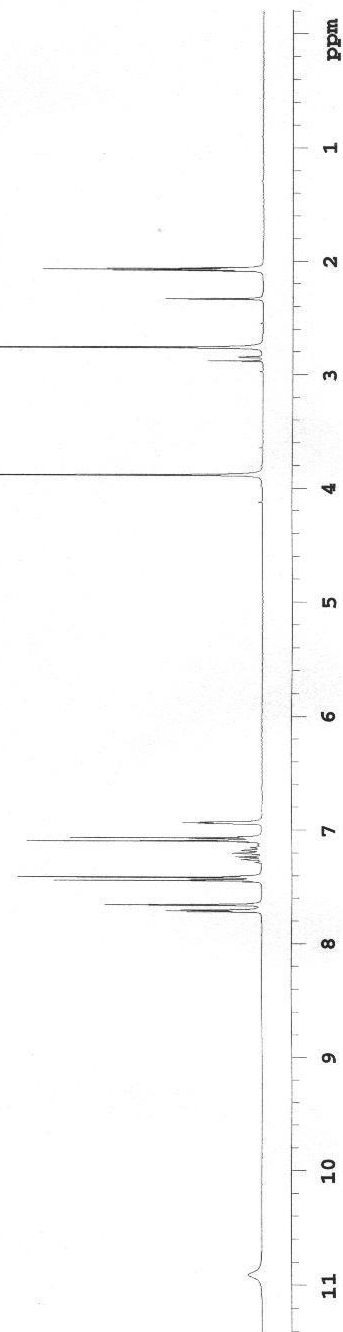
^{13}C NMR (75 MHz, DMSO-d_6)

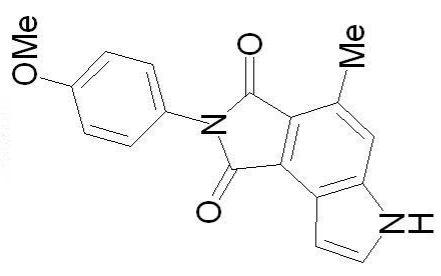




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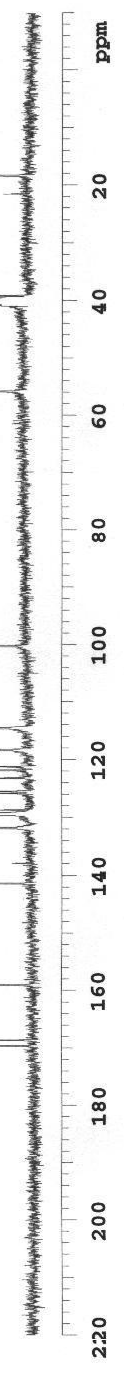
^1H NMR (300 MHz, acetone- d_6)

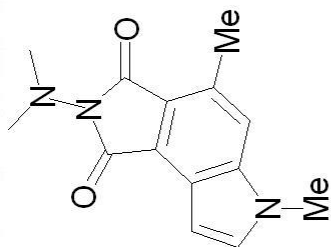




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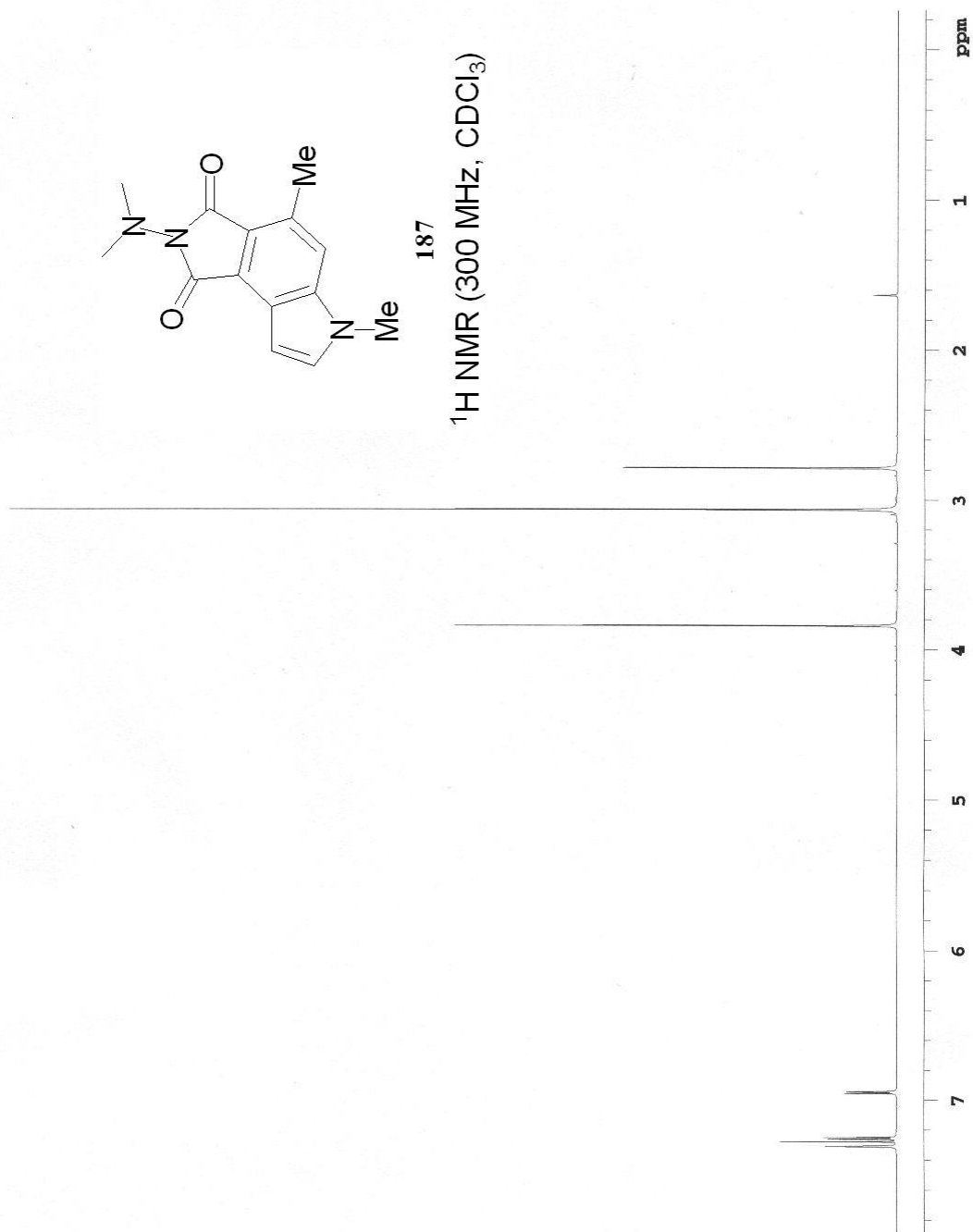
¹³C NMR (75 MHz, DMSO-d₆)

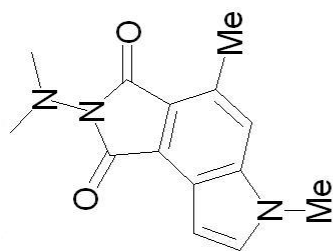




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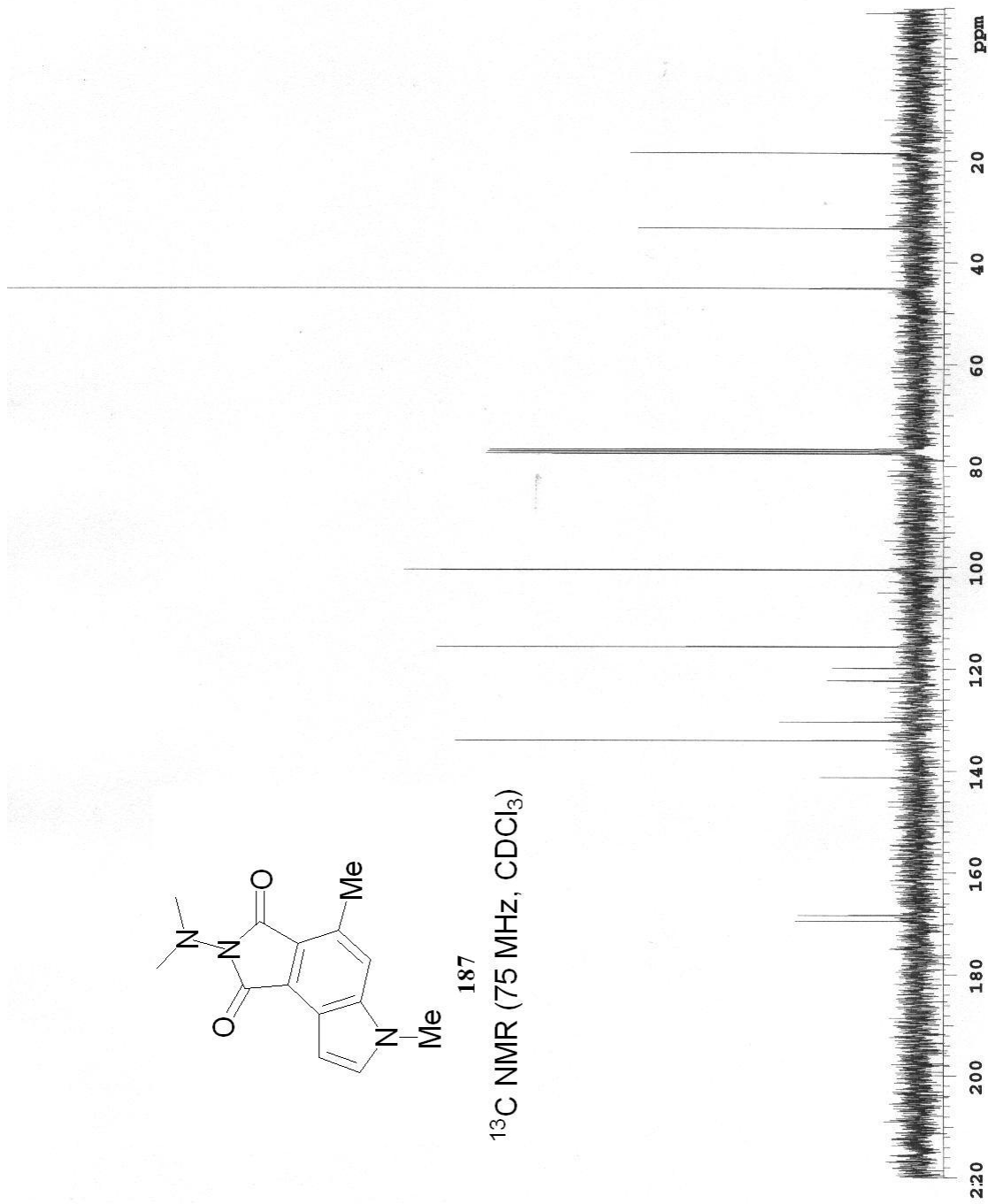
$^1\text{H NMR}$ (300 MHz, CDCl_3)

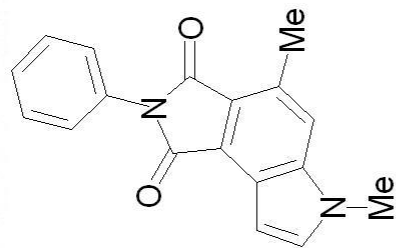




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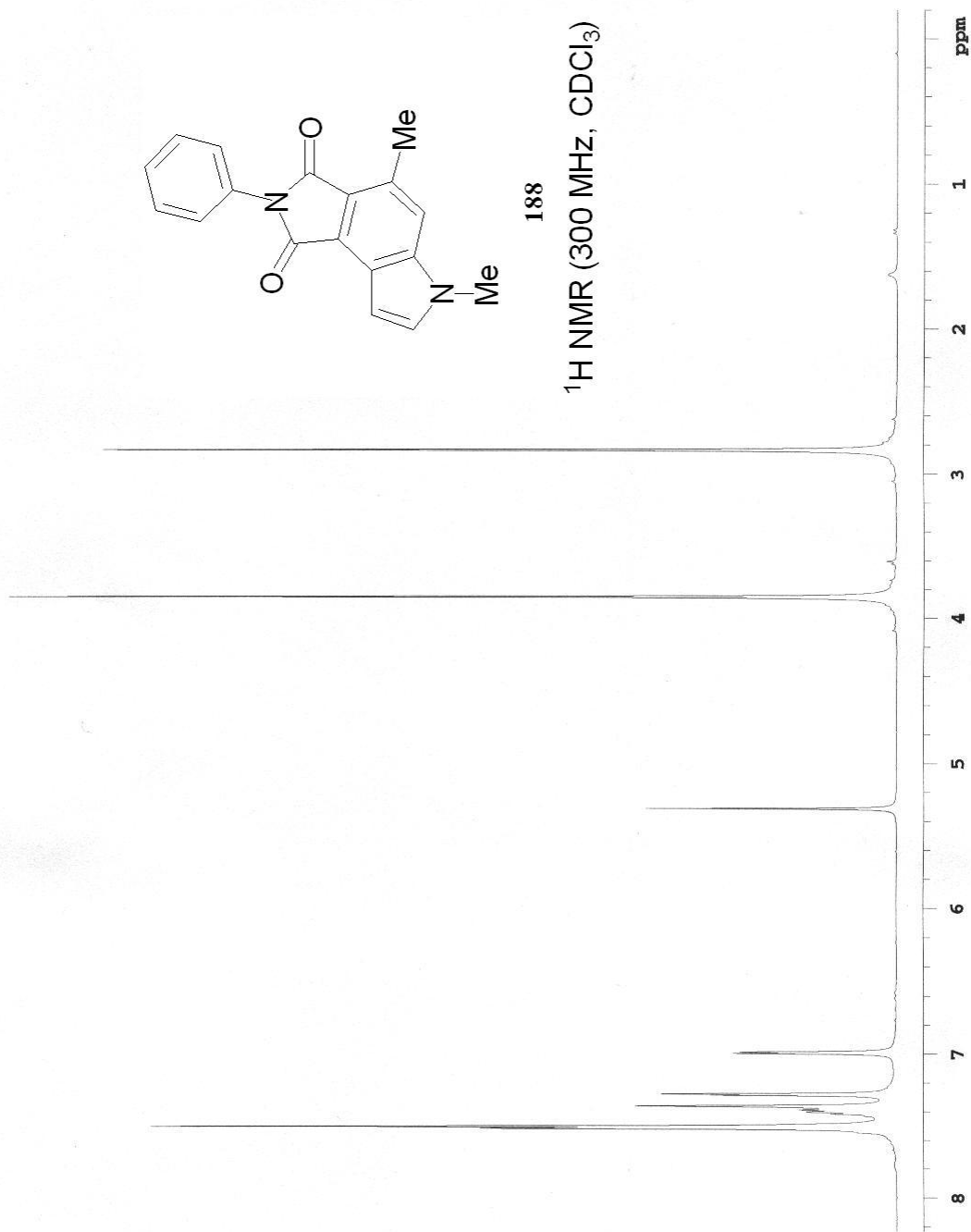
^{13}C NMR (75 MHz, CDCl_3)

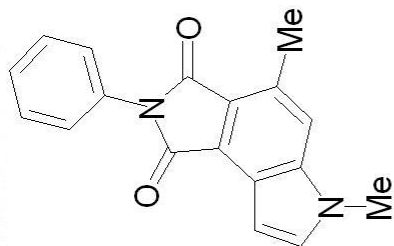




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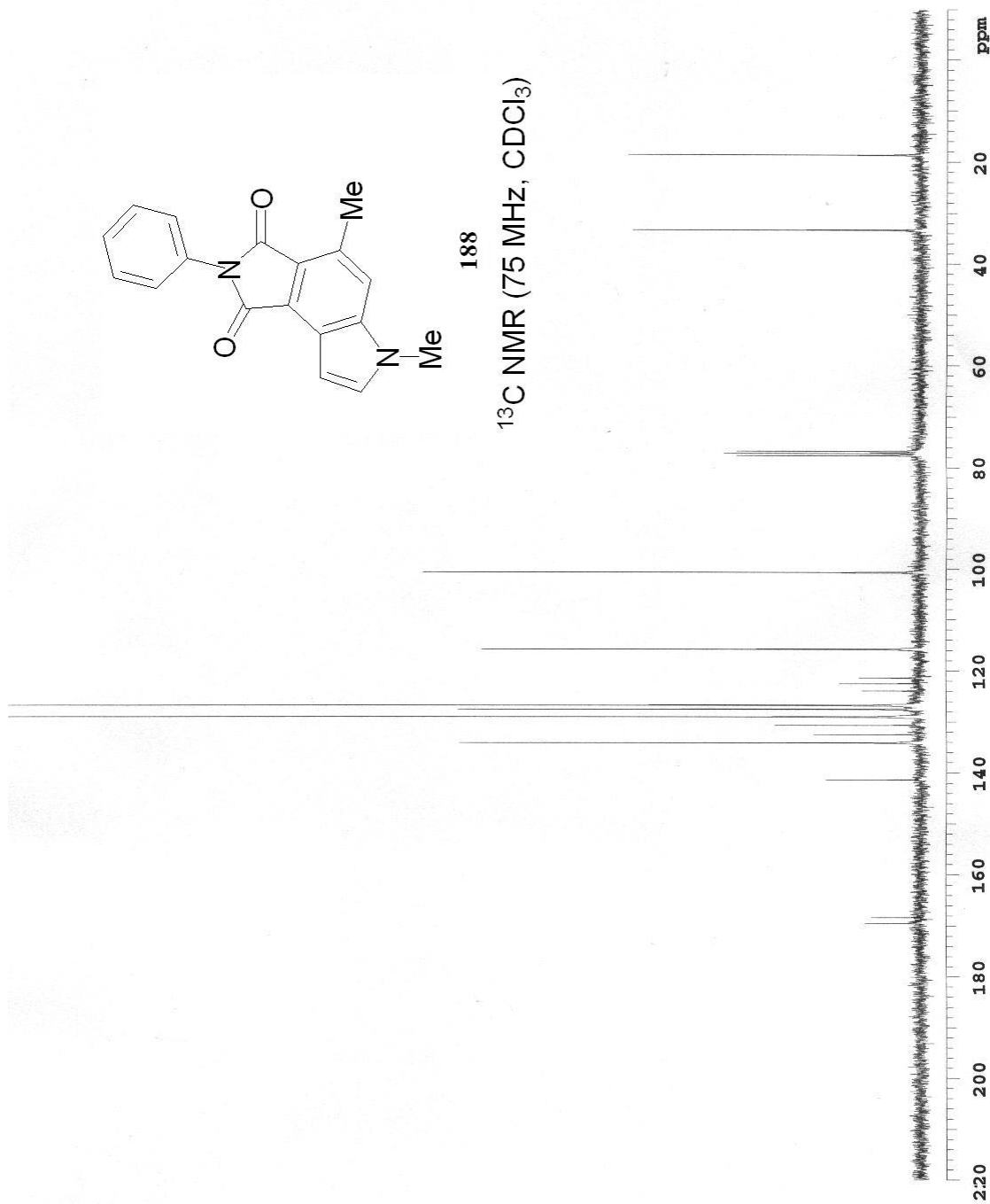
^1H NMR (300 MHz, CDCl_3)

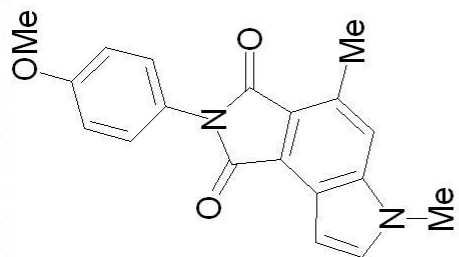




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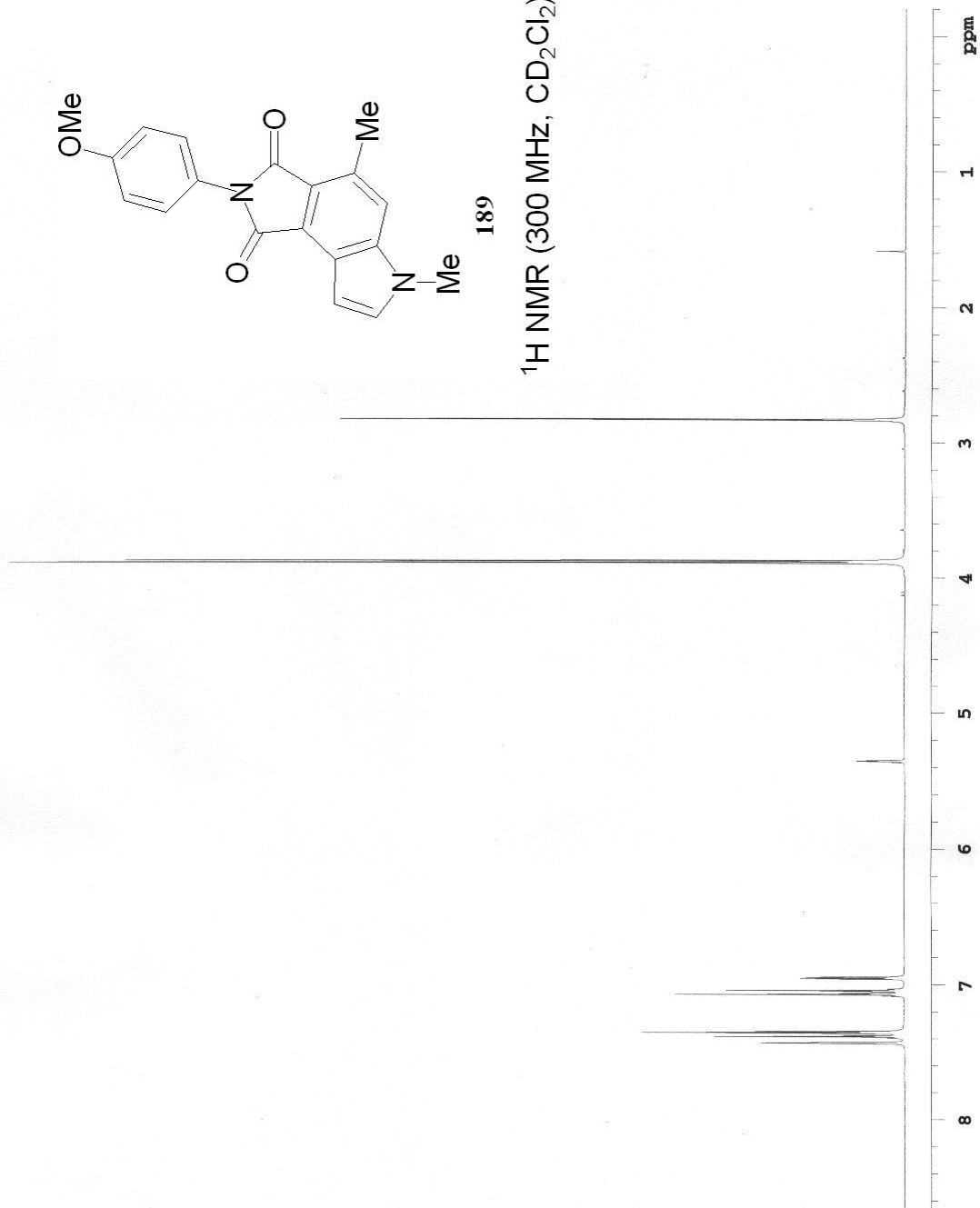
^{13}C NMR (75 MHz, CDCl_3)

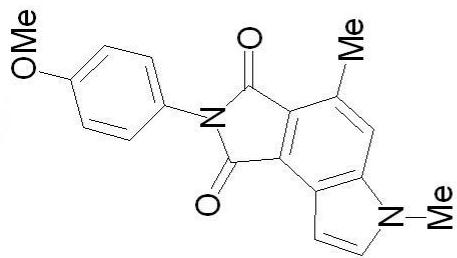




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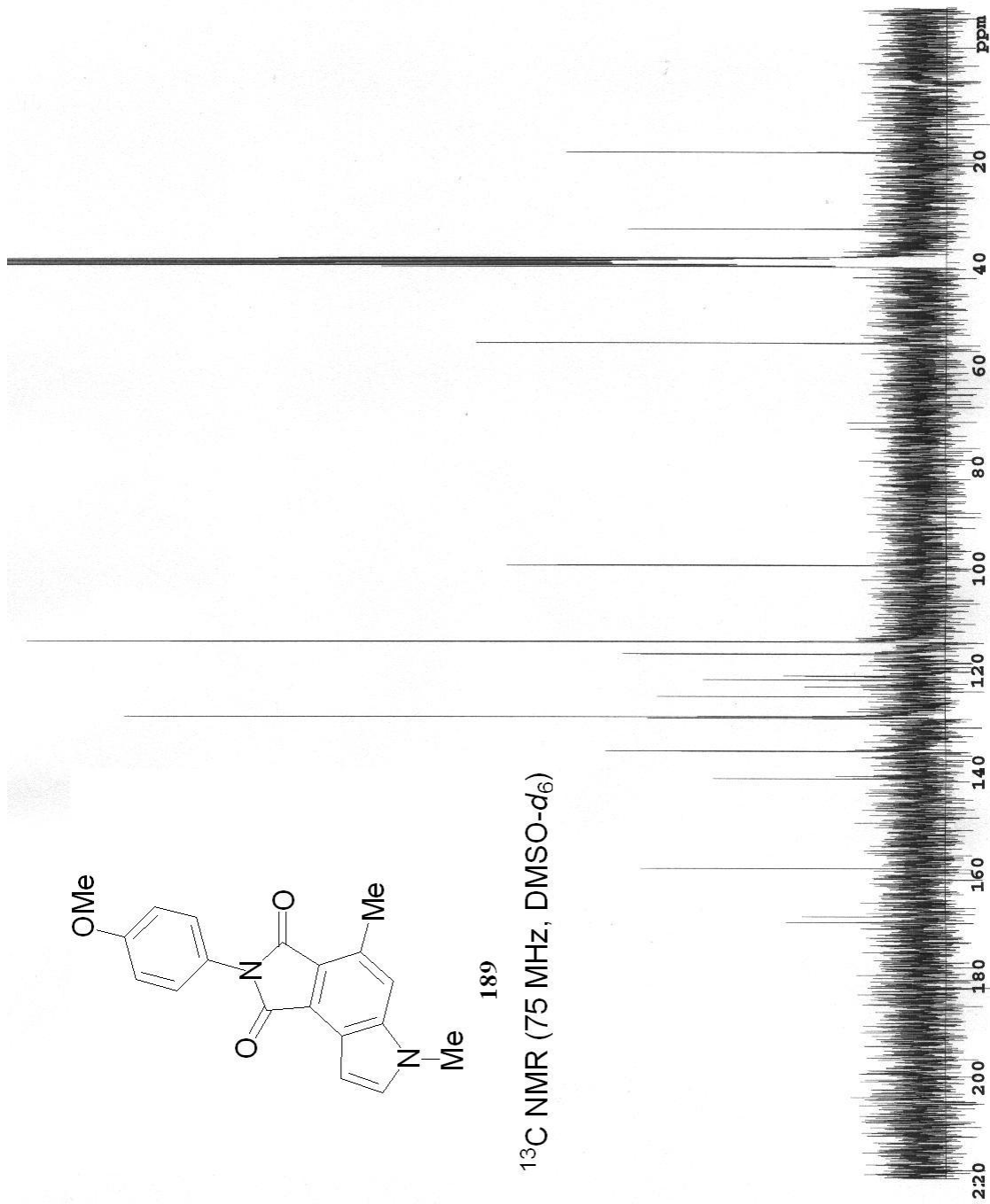
^1H NMR (300 MHz, CD_2Cl_2)

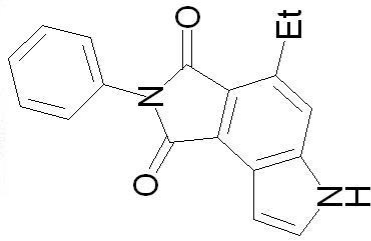




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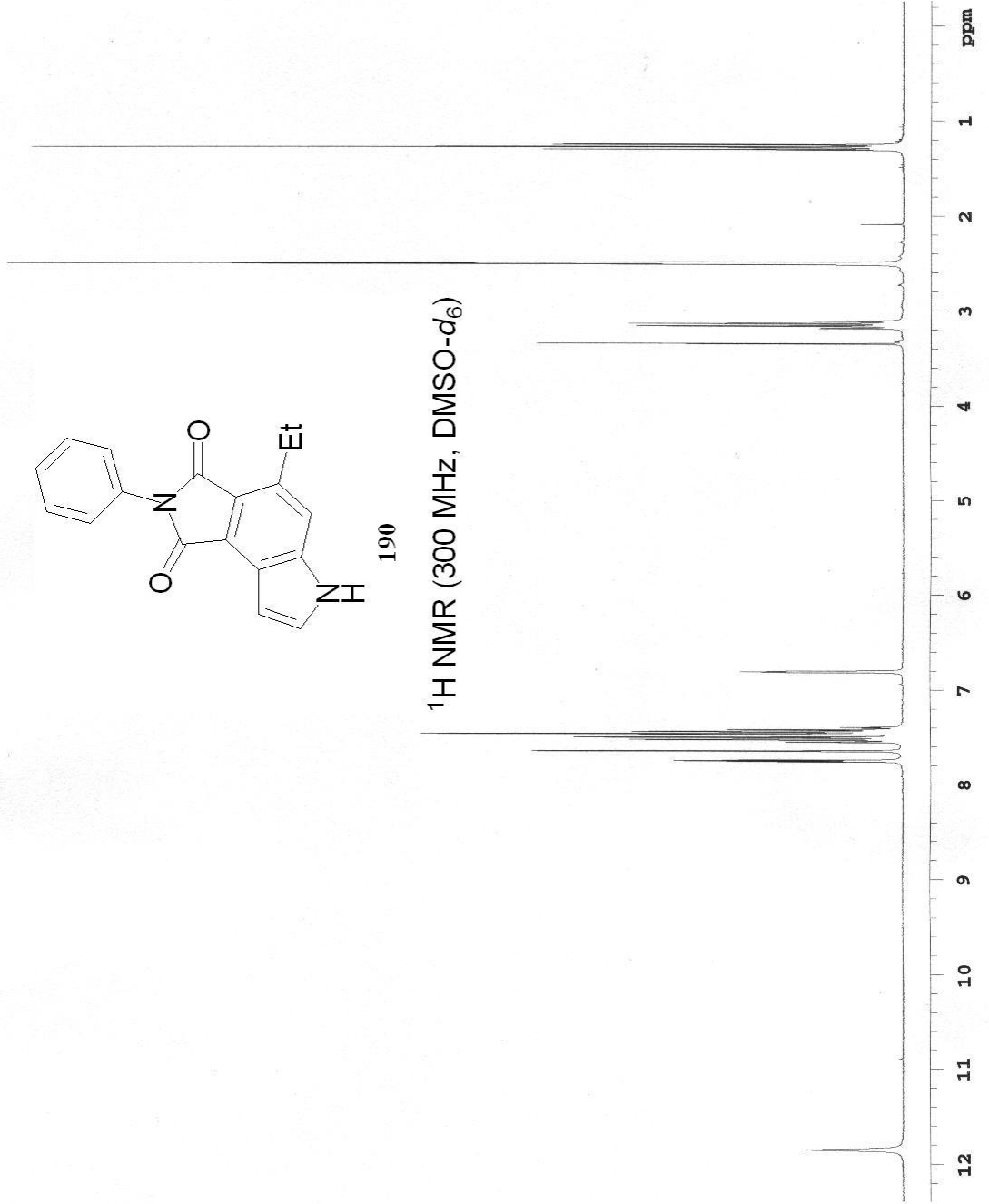
¹³C NMR (75 MHz, DMSO-d₆)

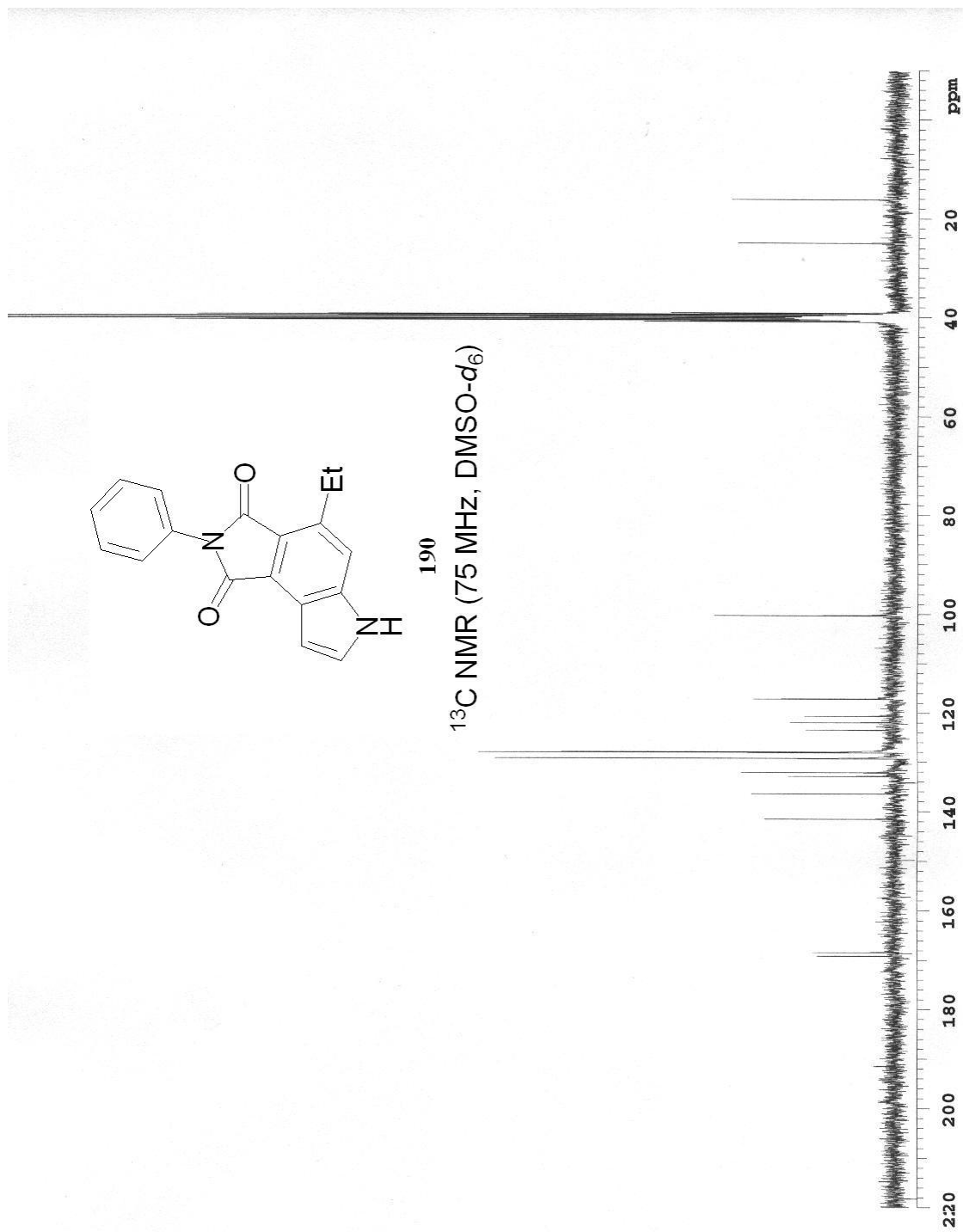


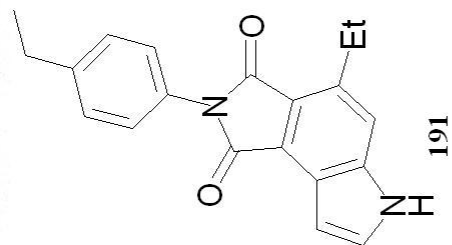


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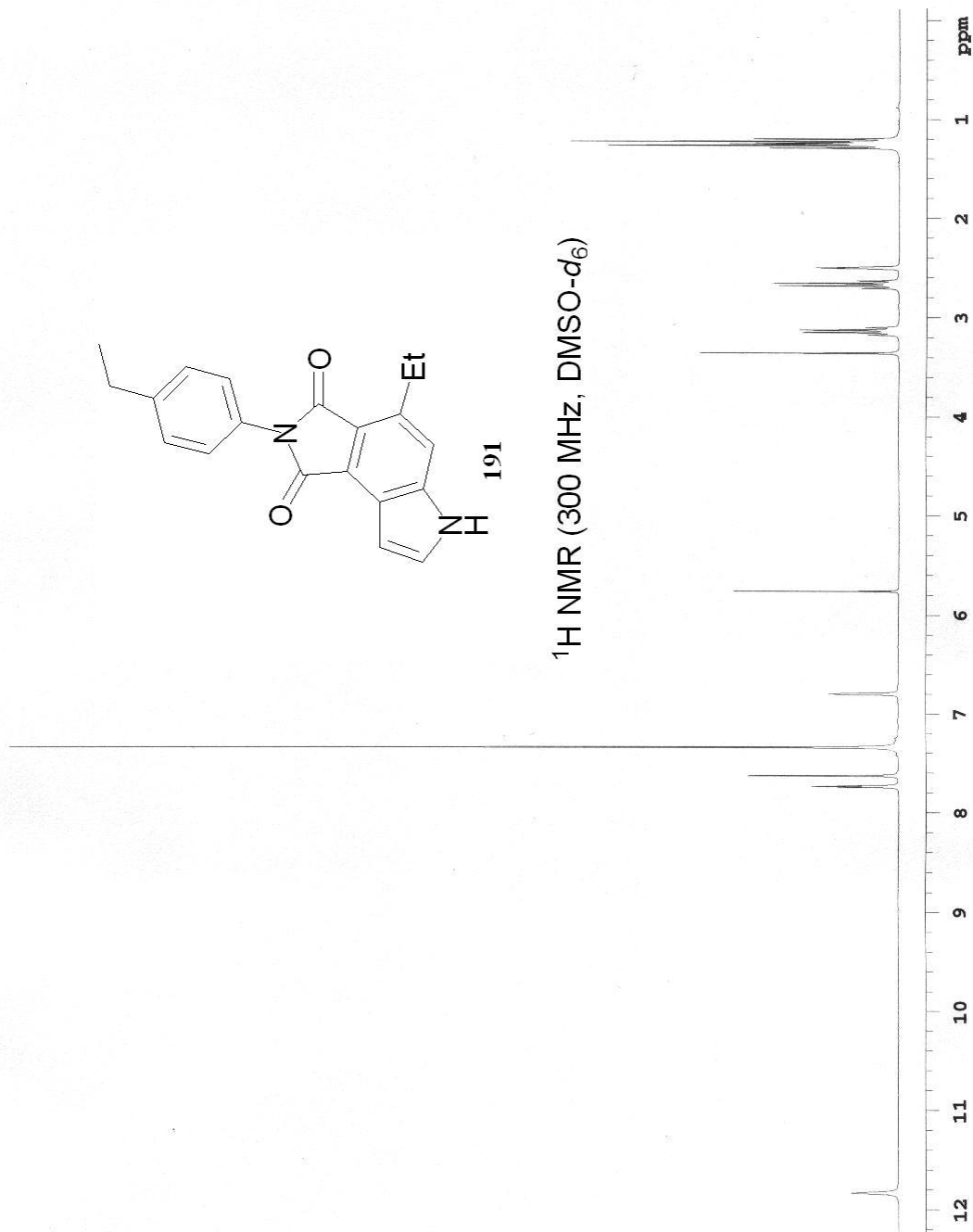
¹H NMR (300 MHz, DMSO-d₆)

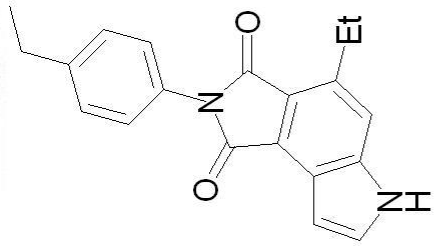






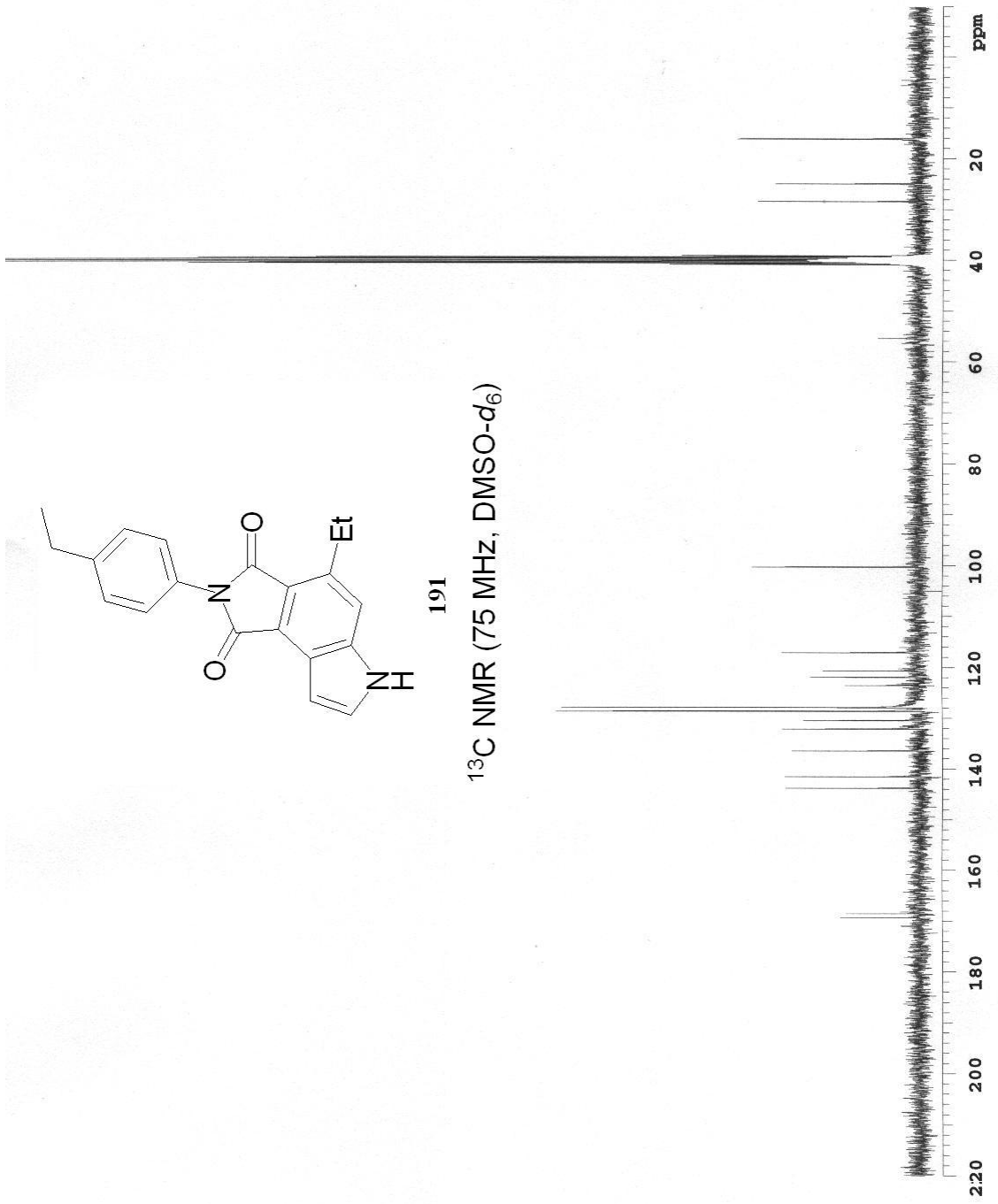
^1H NMR (300 MHz, DMSO- d_6)

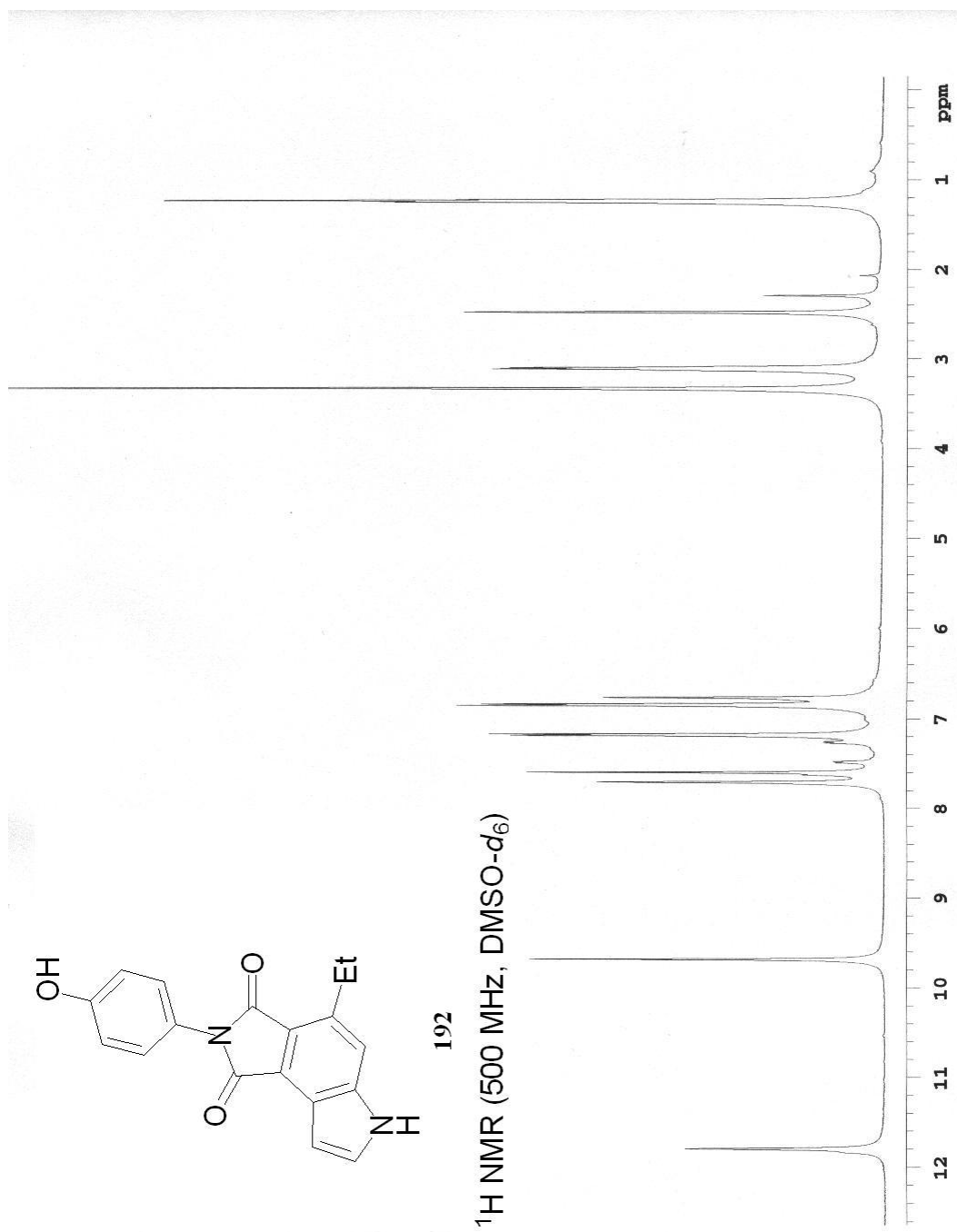


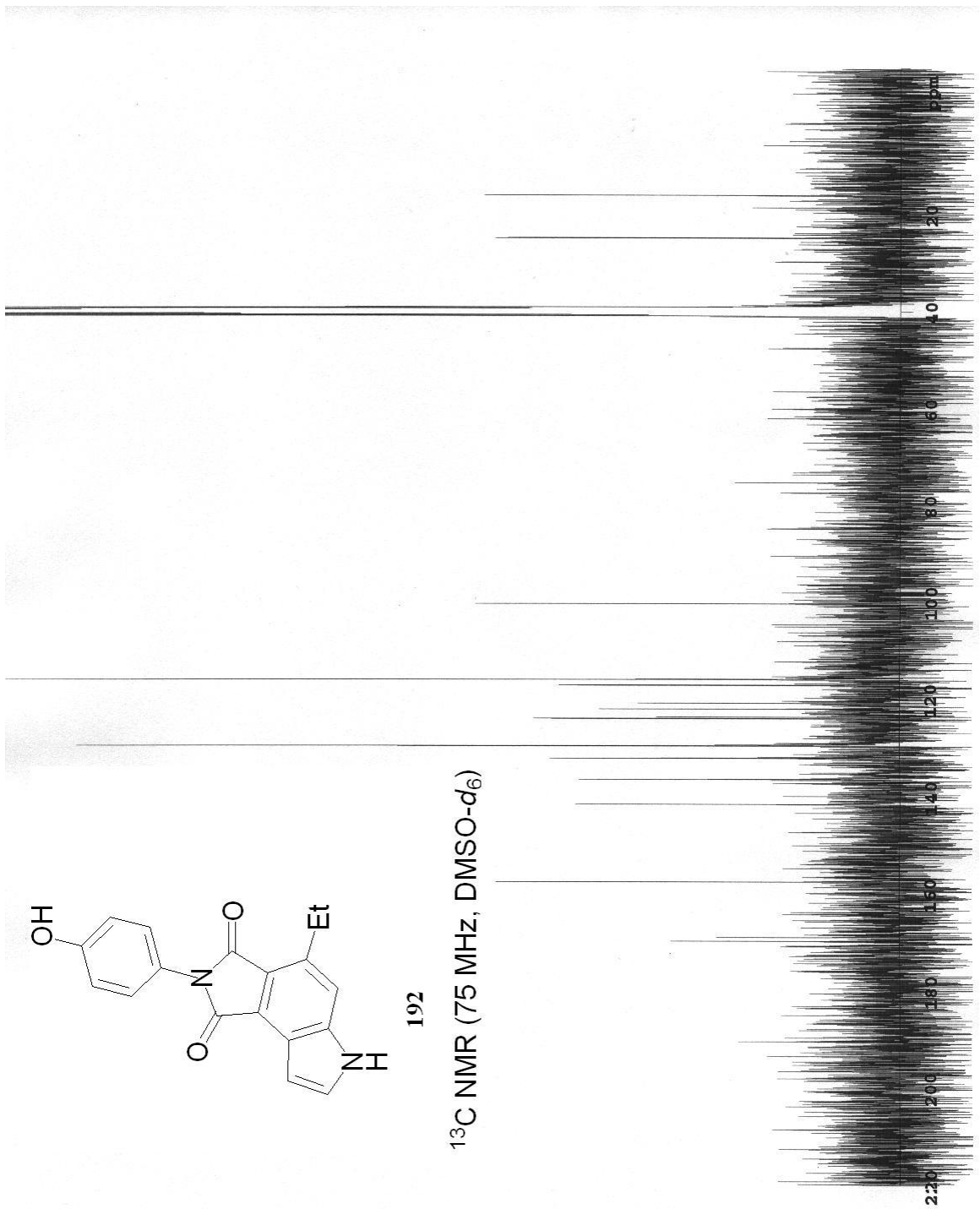


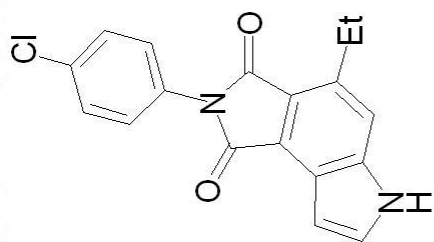
191

^{13}C NMR (75 MHz, DMSO- d_6)



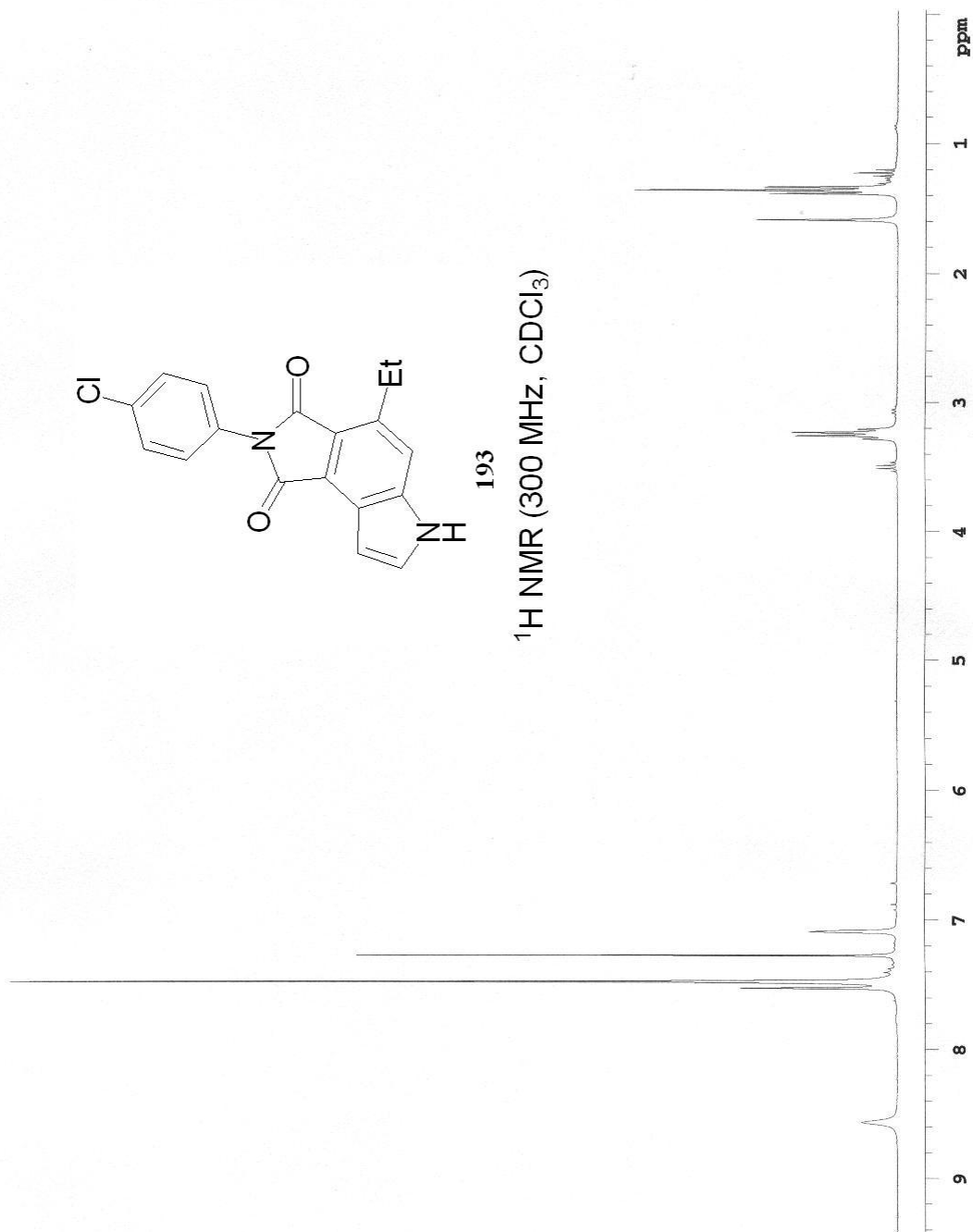


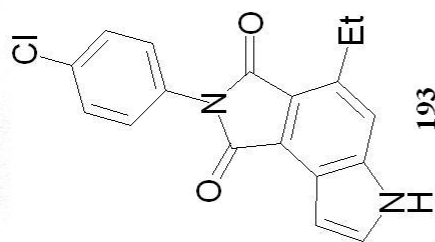




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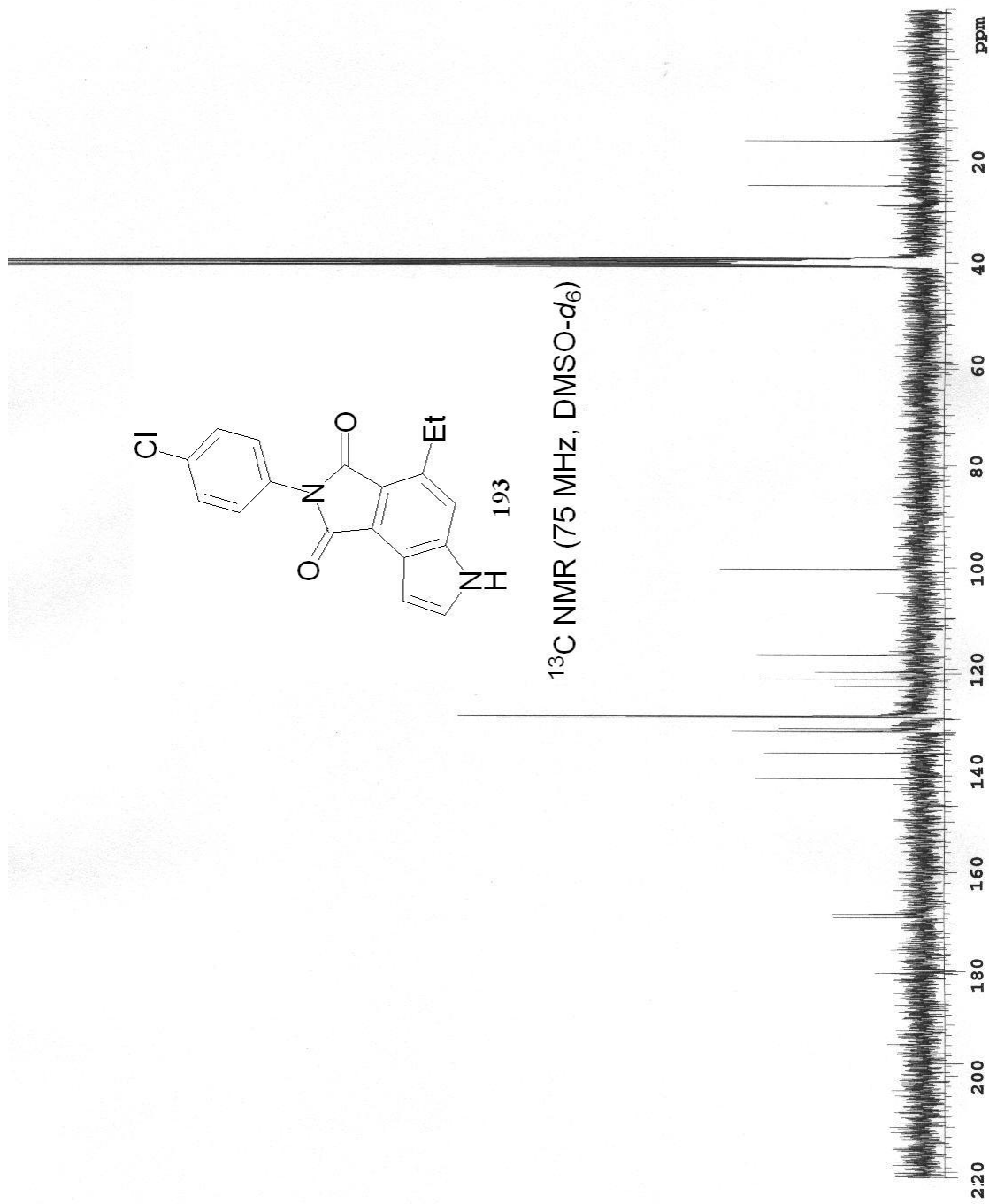
$^1\text{H NMR}$ (300 MHz, CDCl_3)

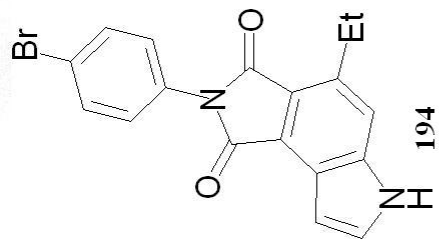




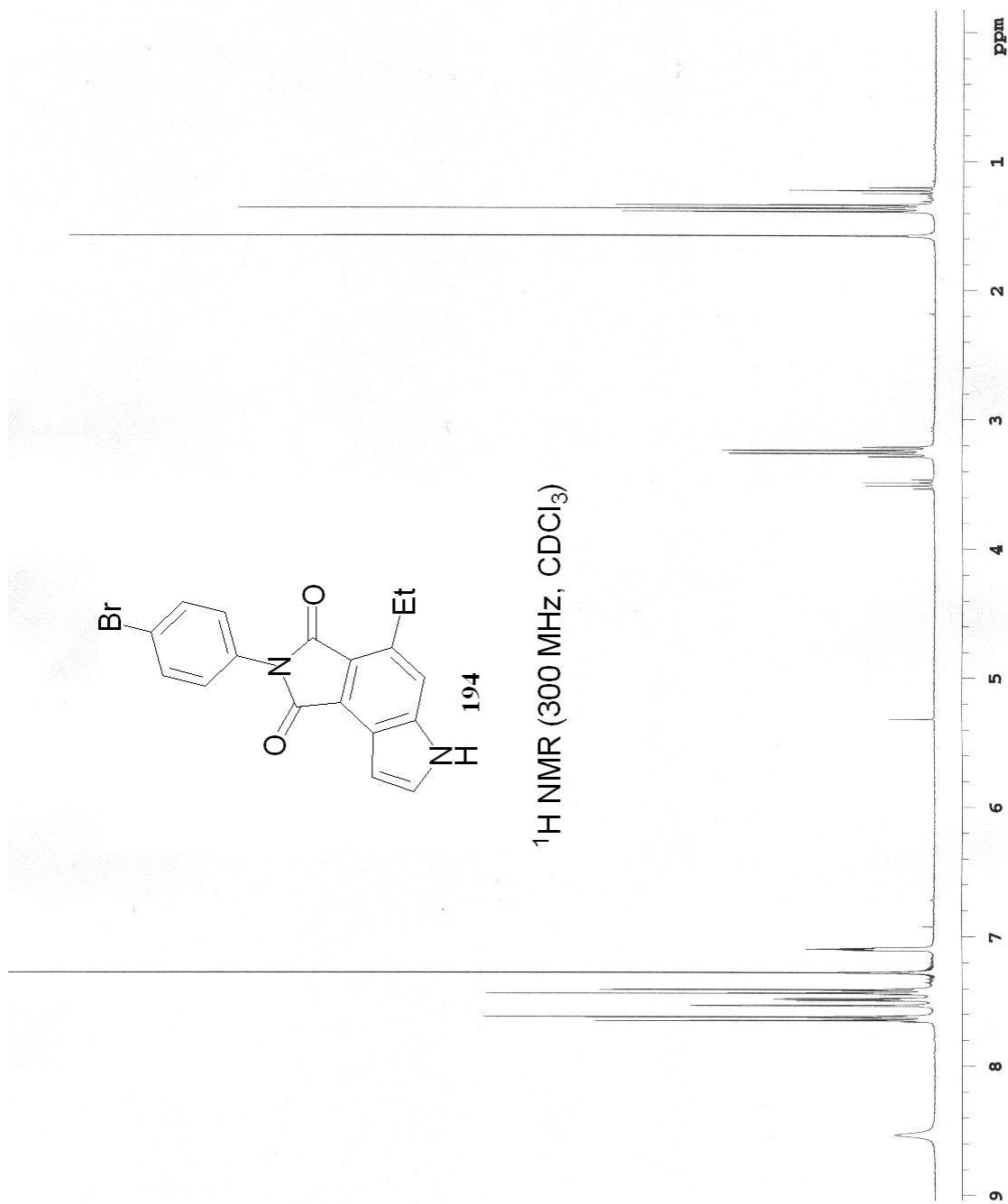
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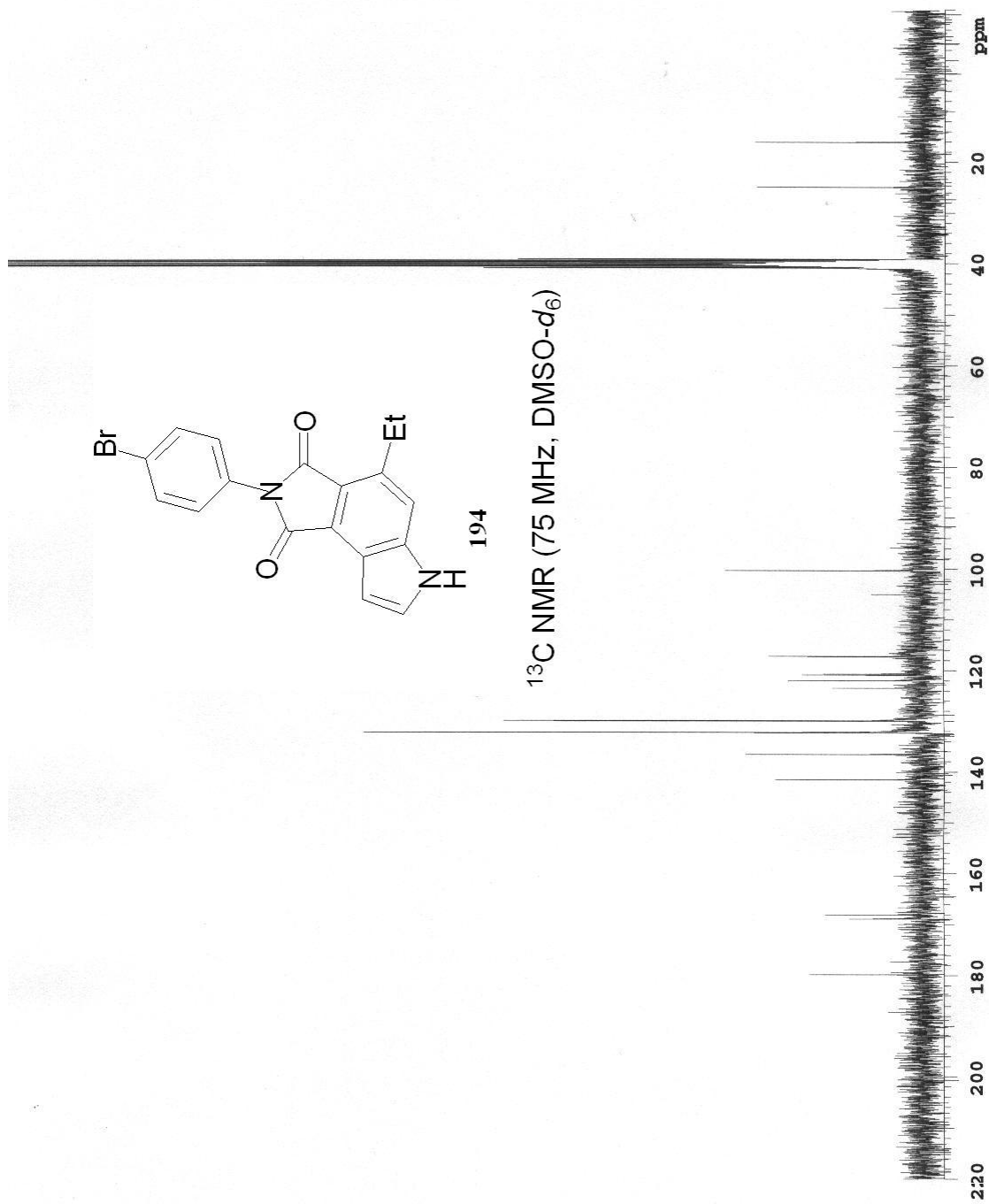
^{13}C NMR (75 MHz, DMSO- d_6)

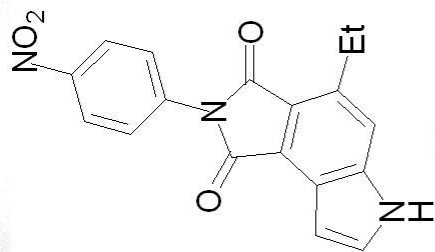




$^1\text{H NMR}$ (300 MHz, CDCl_3)

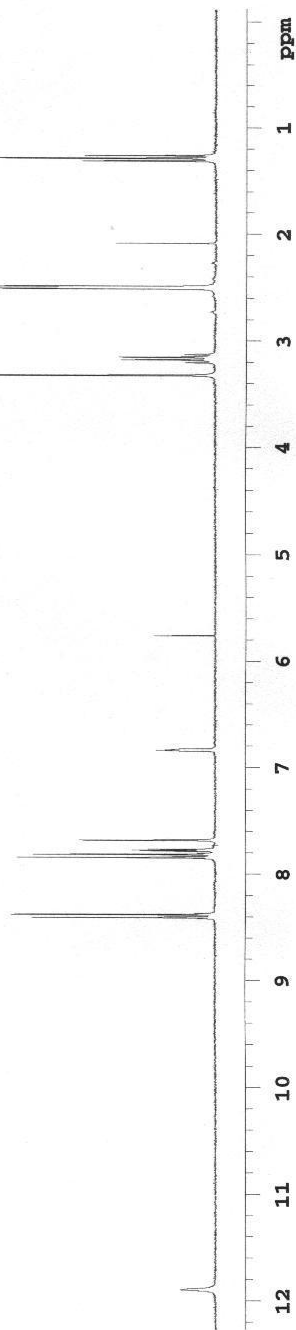


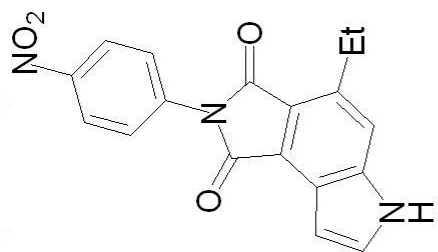




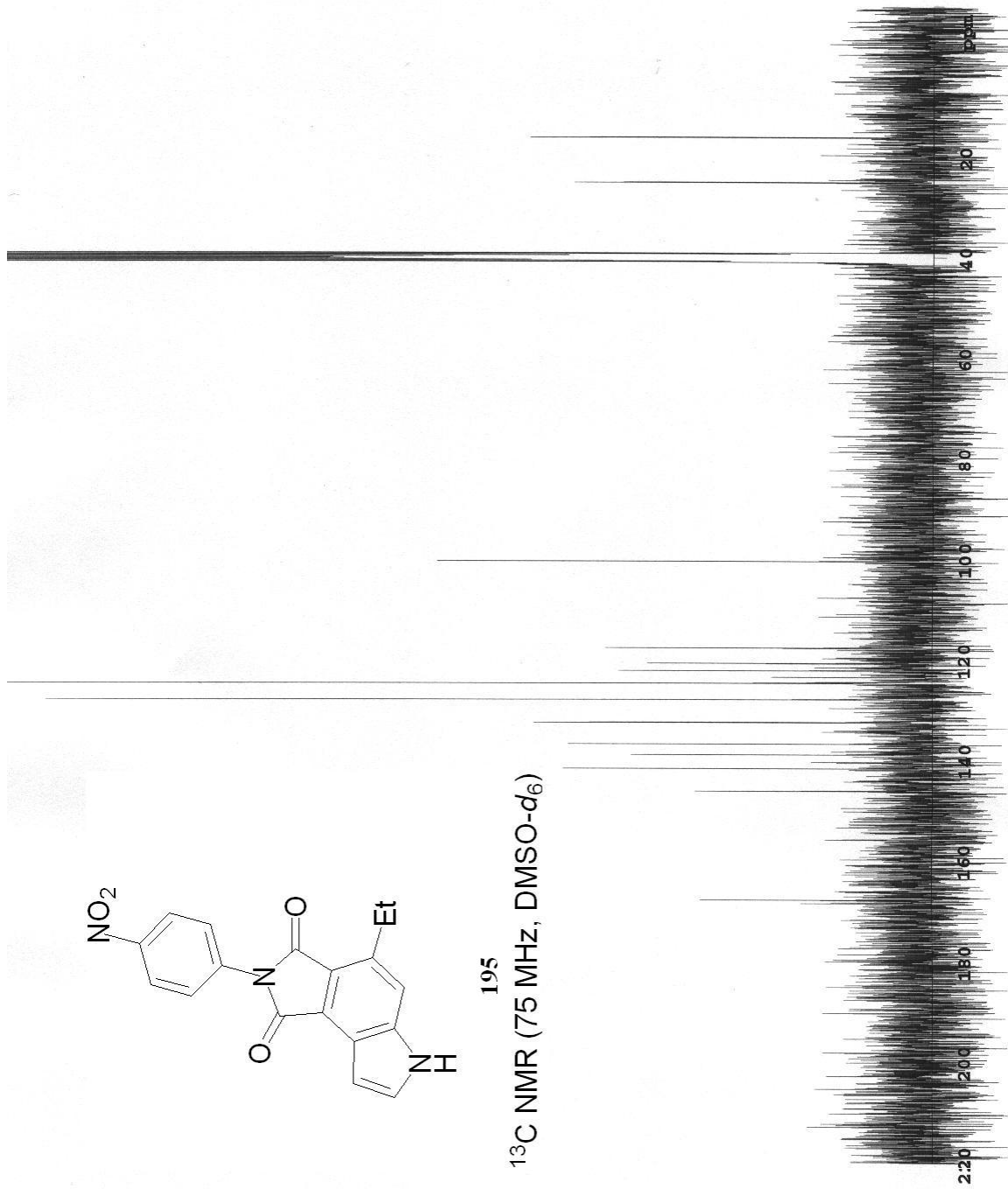
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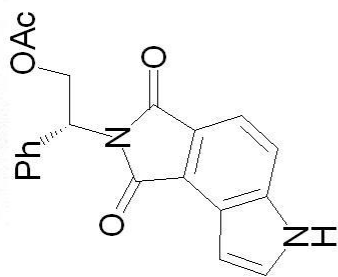
^1H NMR (300 MHz, $\text{DMSO}-d_6$)





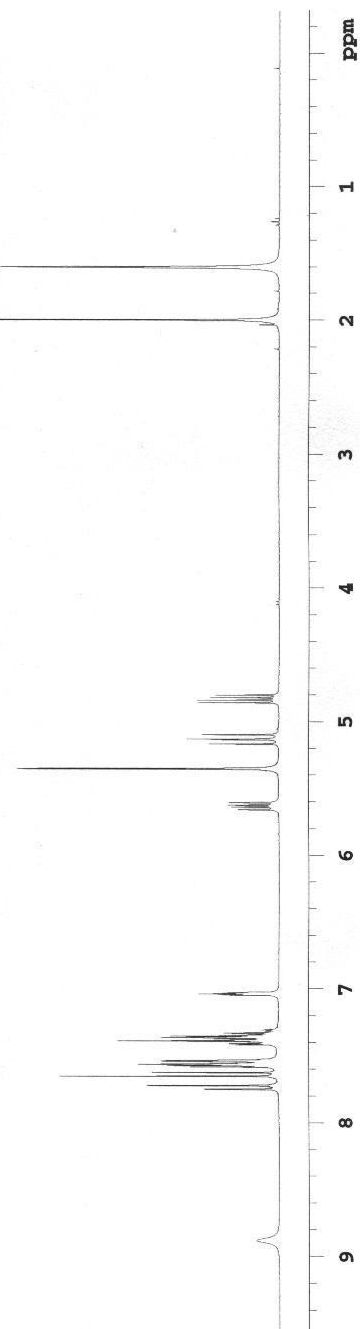
195
¹³C NMR (75 MHz, DMSO-d₆)

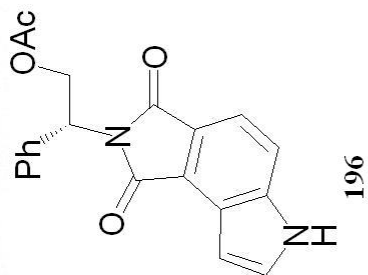




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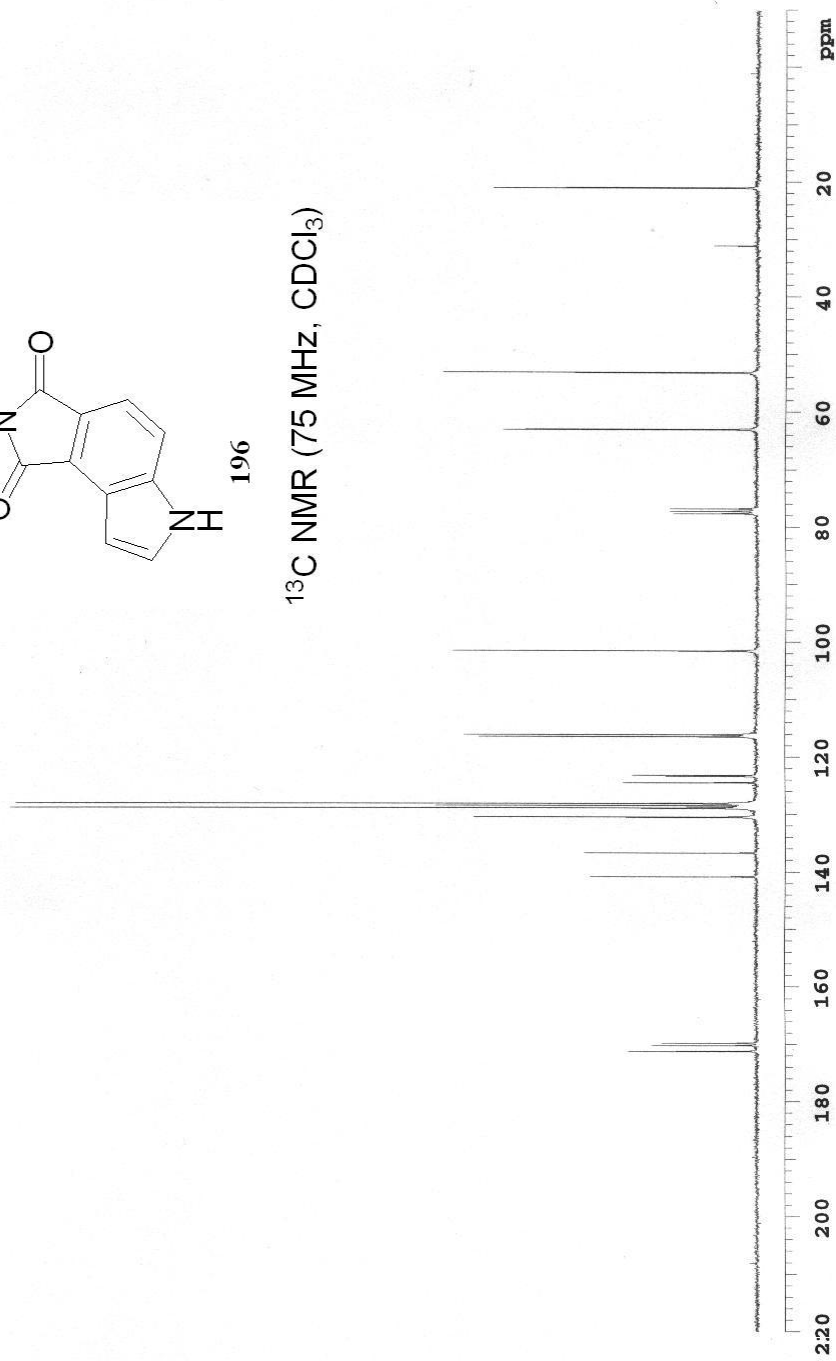
^1H NMR (300 MHz, CD_2Cl_2)

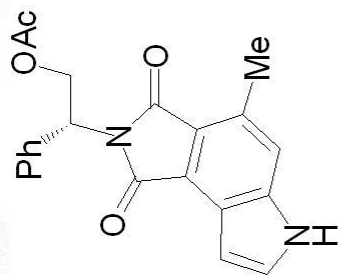




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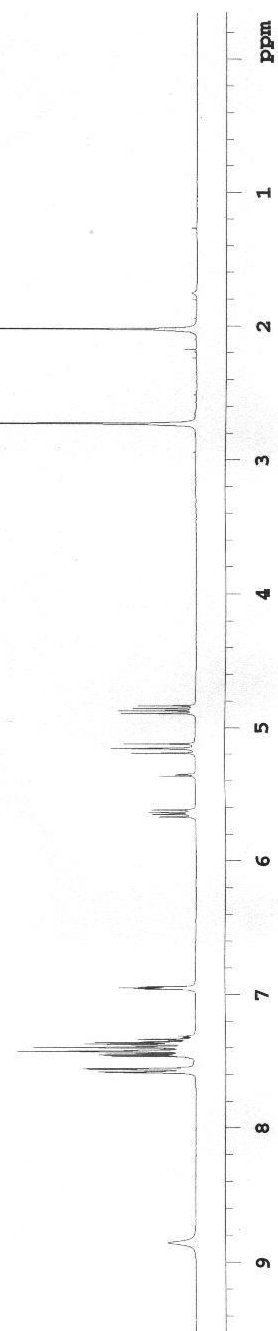
^{13}C NMR (75 MHz, CDCl_3)

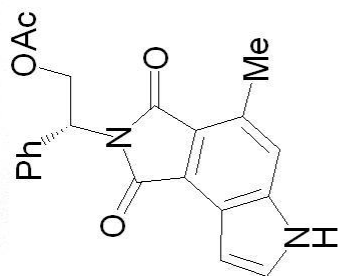




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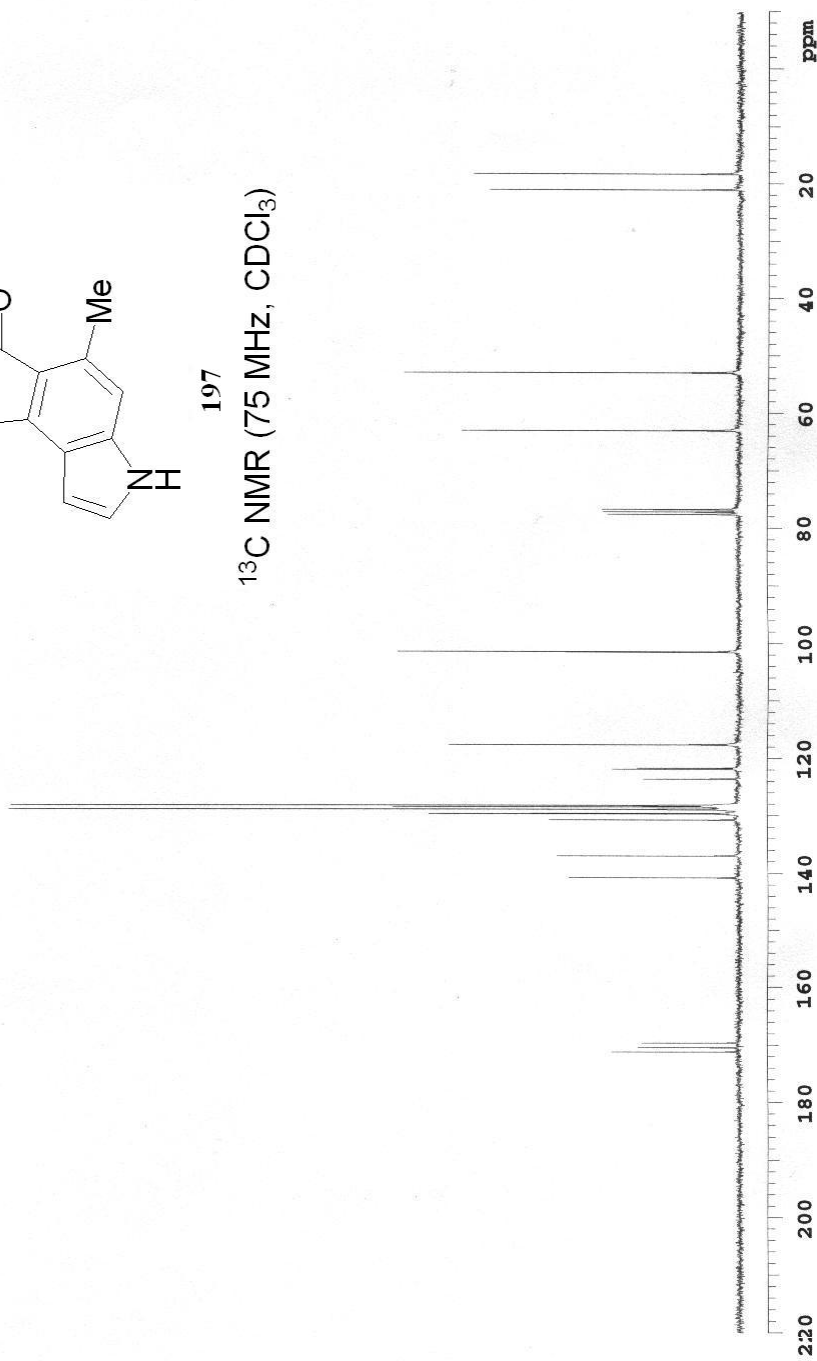
^1H NMR (300 MHz, CD_2Cl_2)

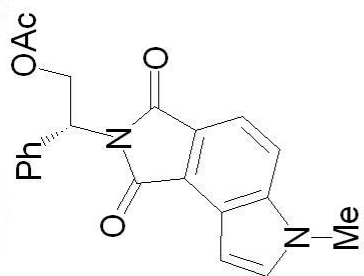




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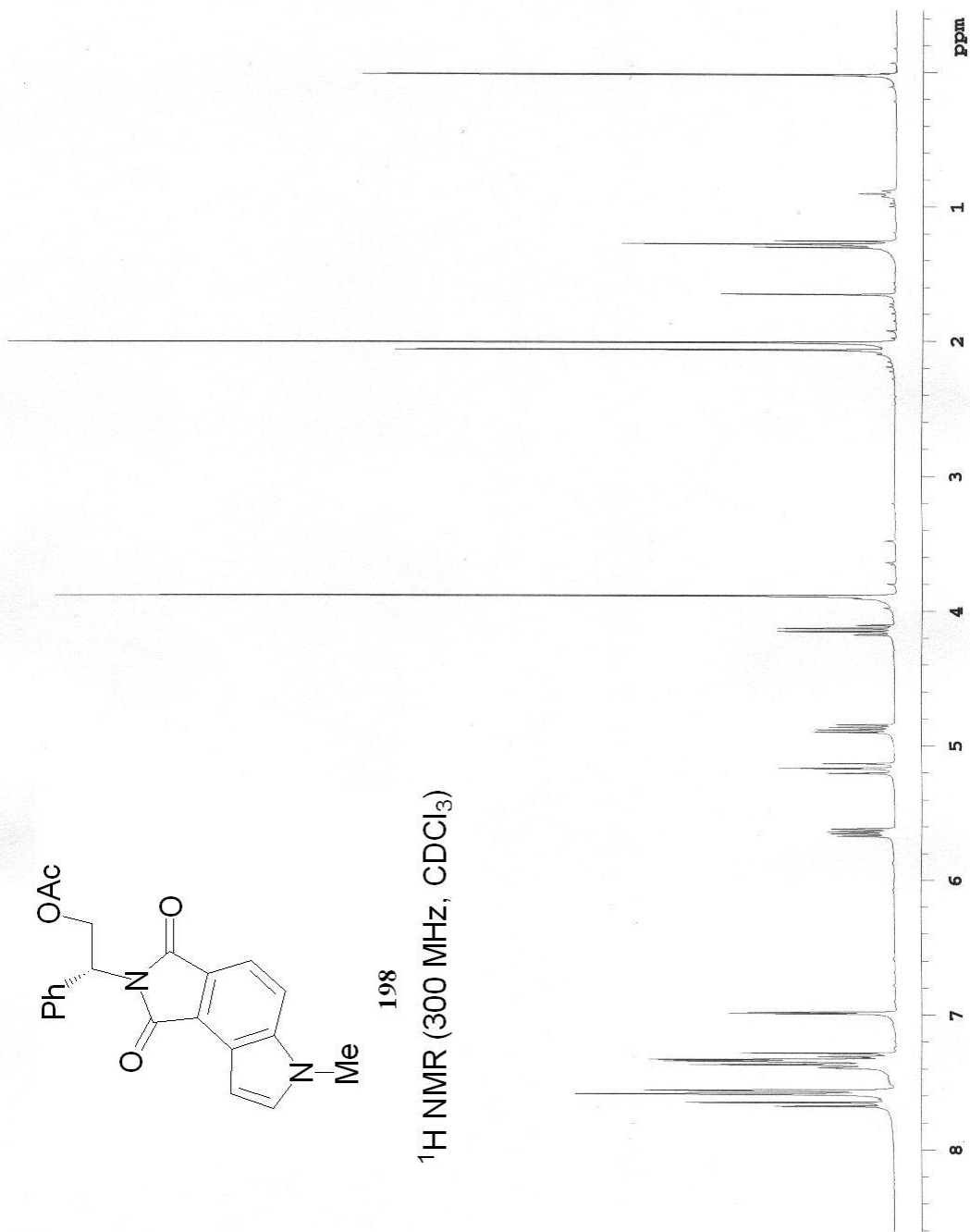
¹³C NMR (75 MHz, CDCl₃)

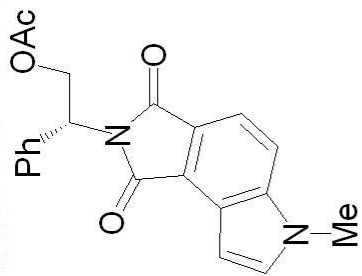




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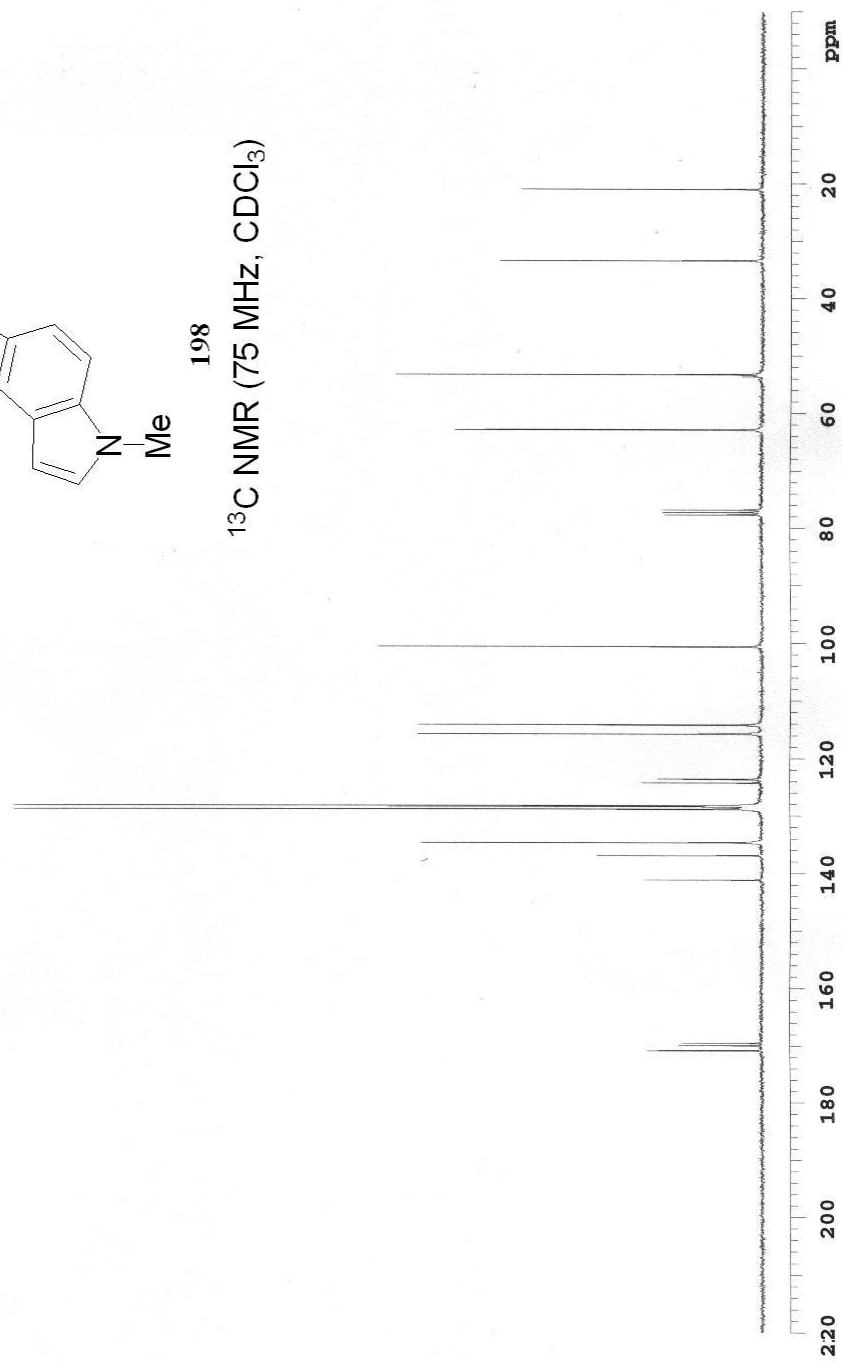
¹H NMR (300 MHz, CDCl₃)

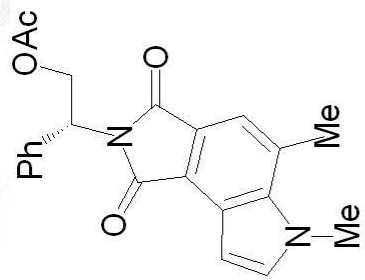




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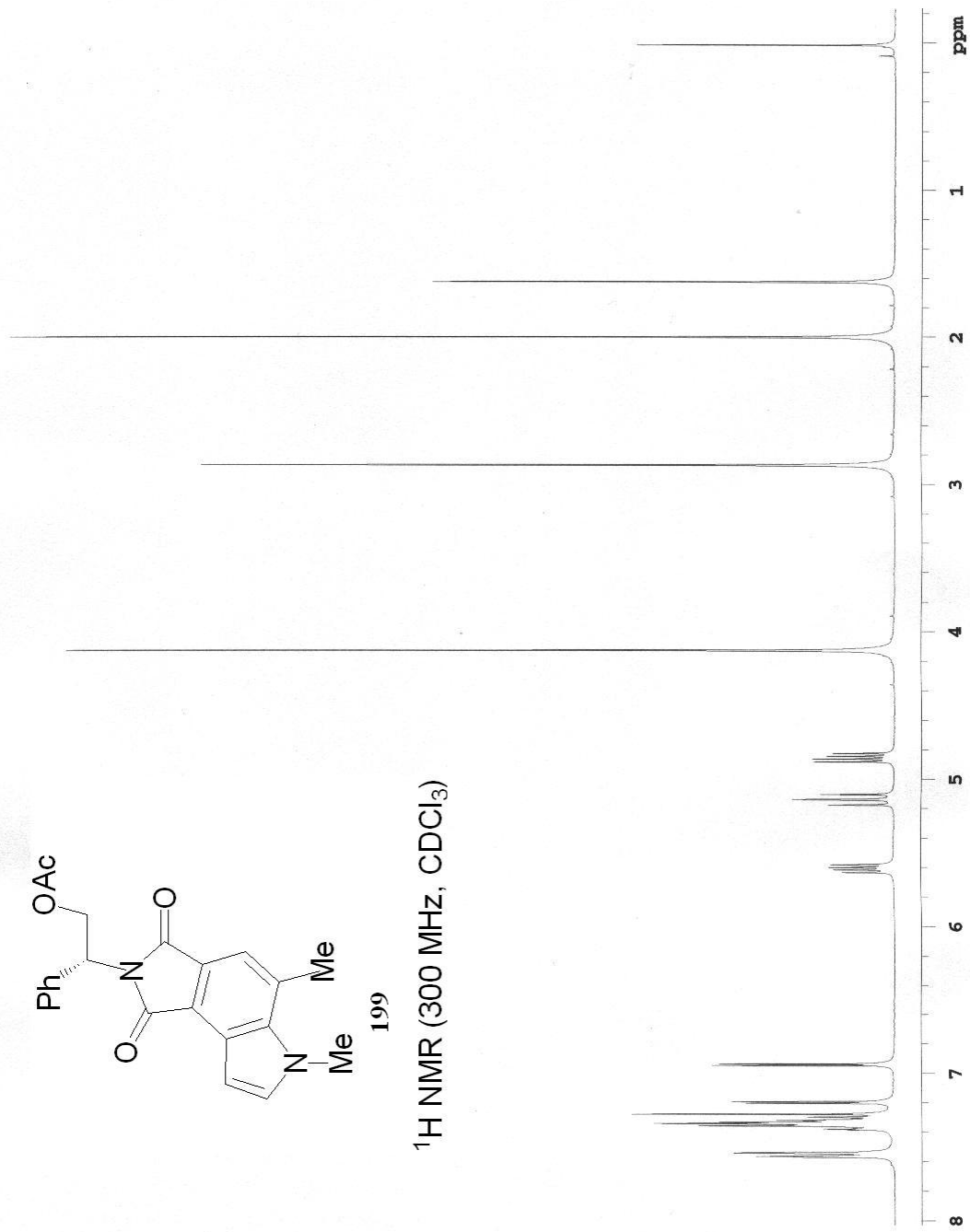
^{13}C NMR (75 MHz, CDCl_3)

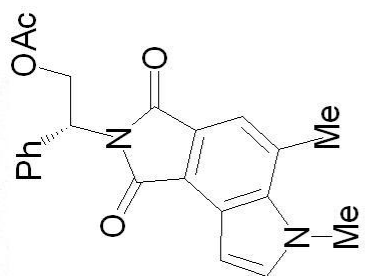




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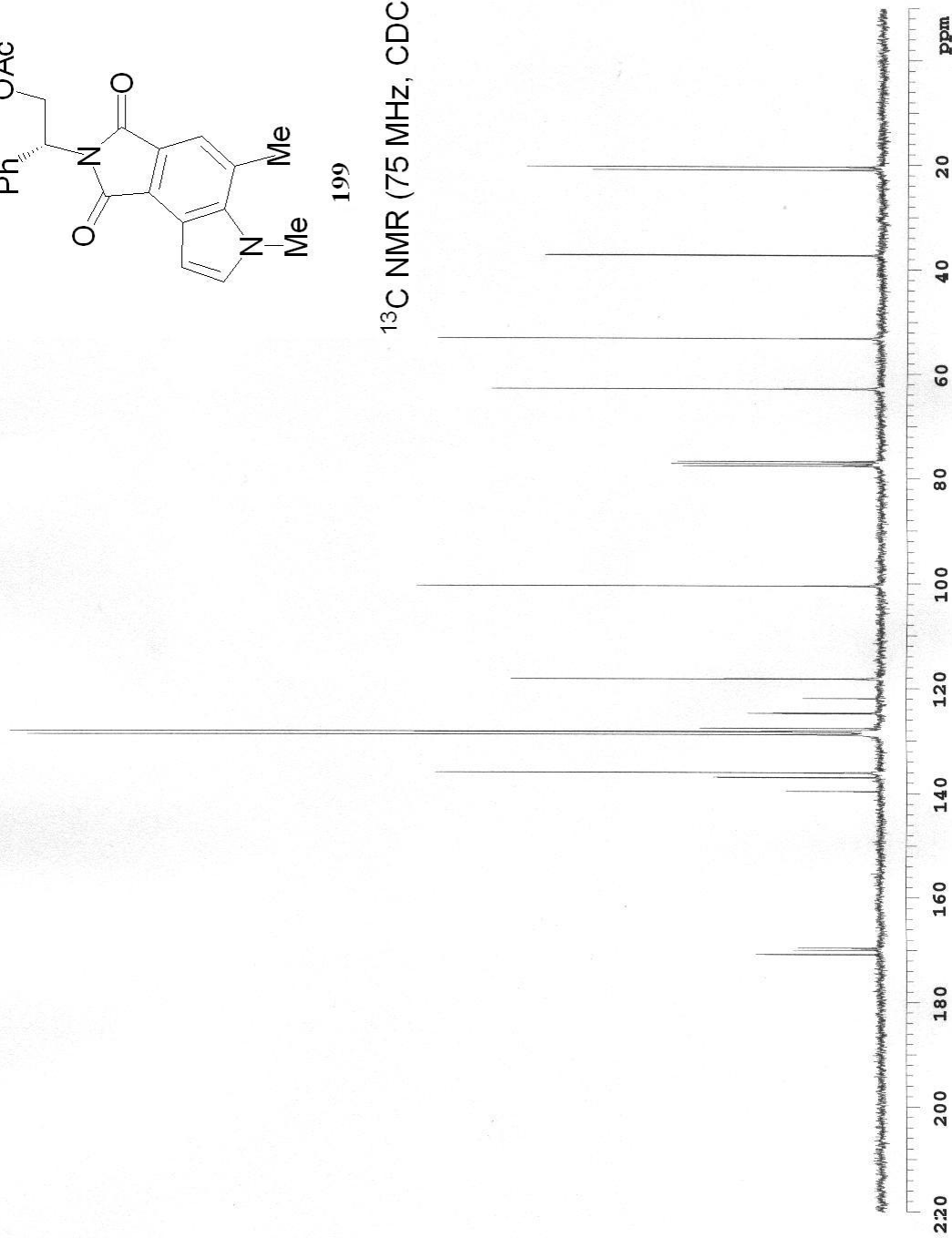
^1H NMR (300 MHz, CDCl_3)

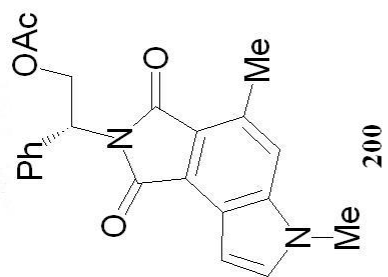




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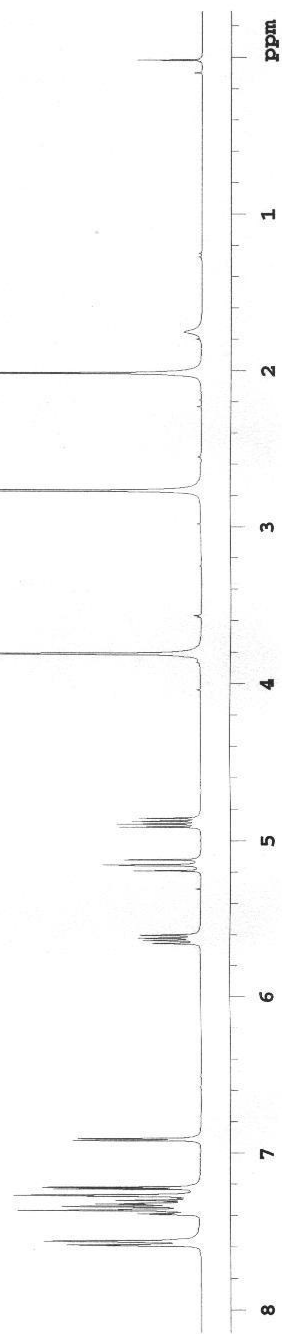
^{13}C NMR (75 MHz, CDCl_3)

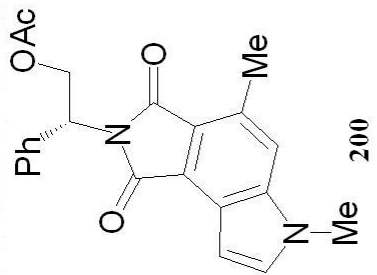




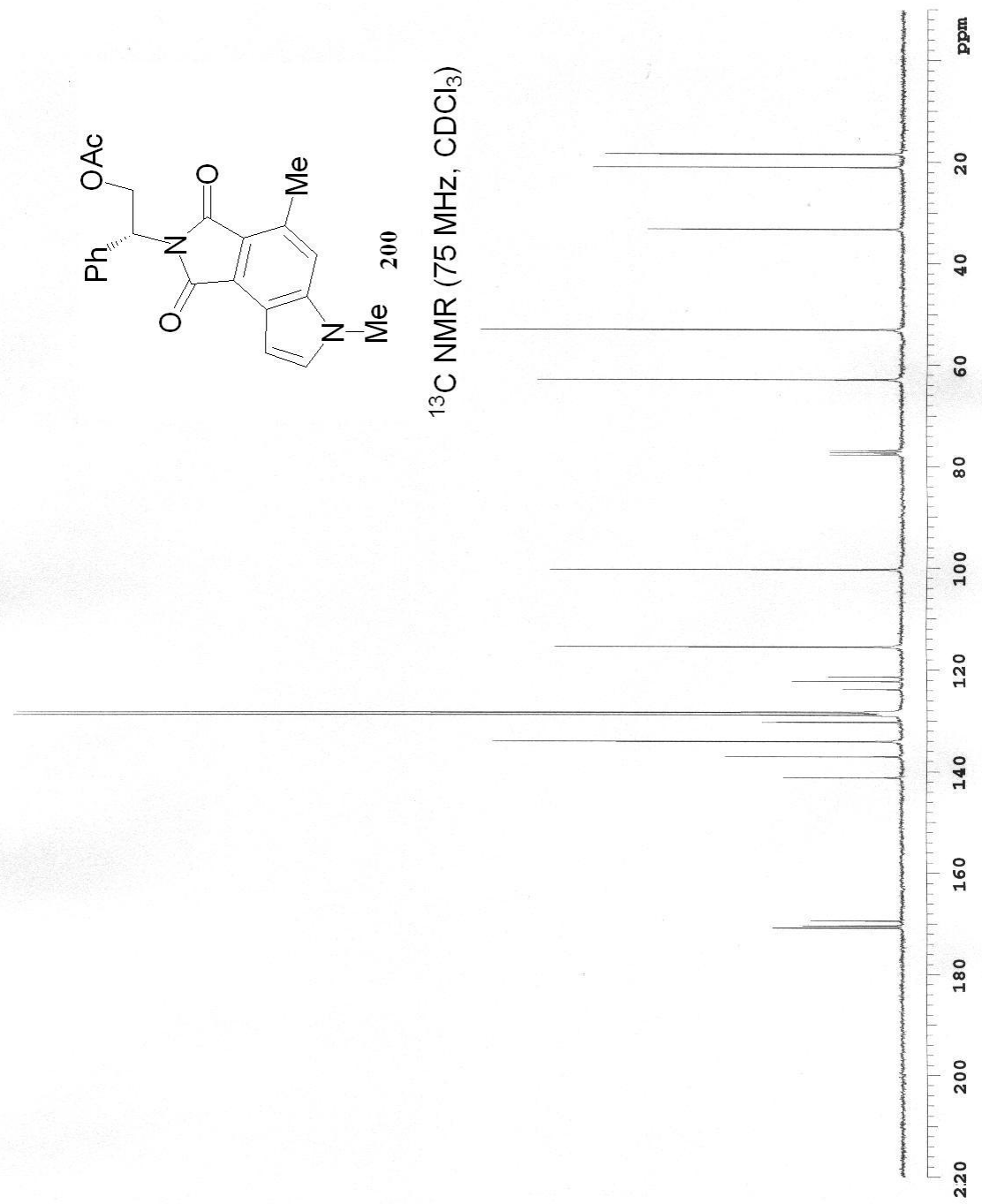
$^1\text{H NMR}$ (300 MHz, CDCl_3)

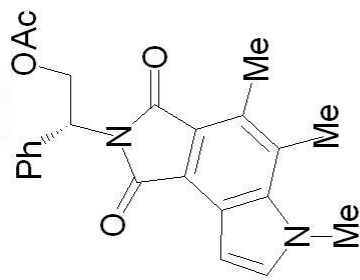
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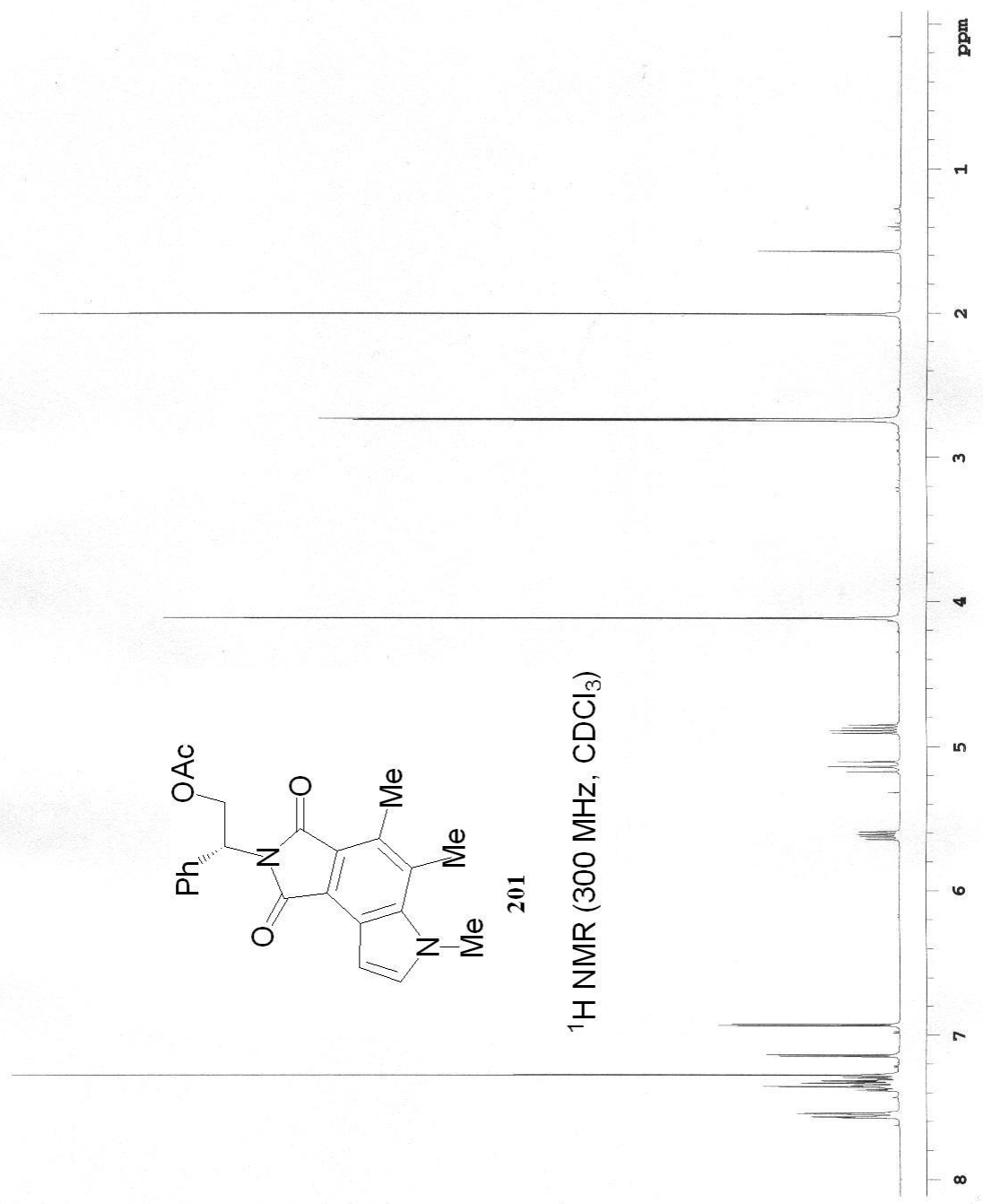
^{13}C NMR (75 MHz, CDCl_3)

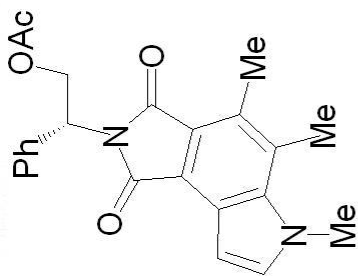




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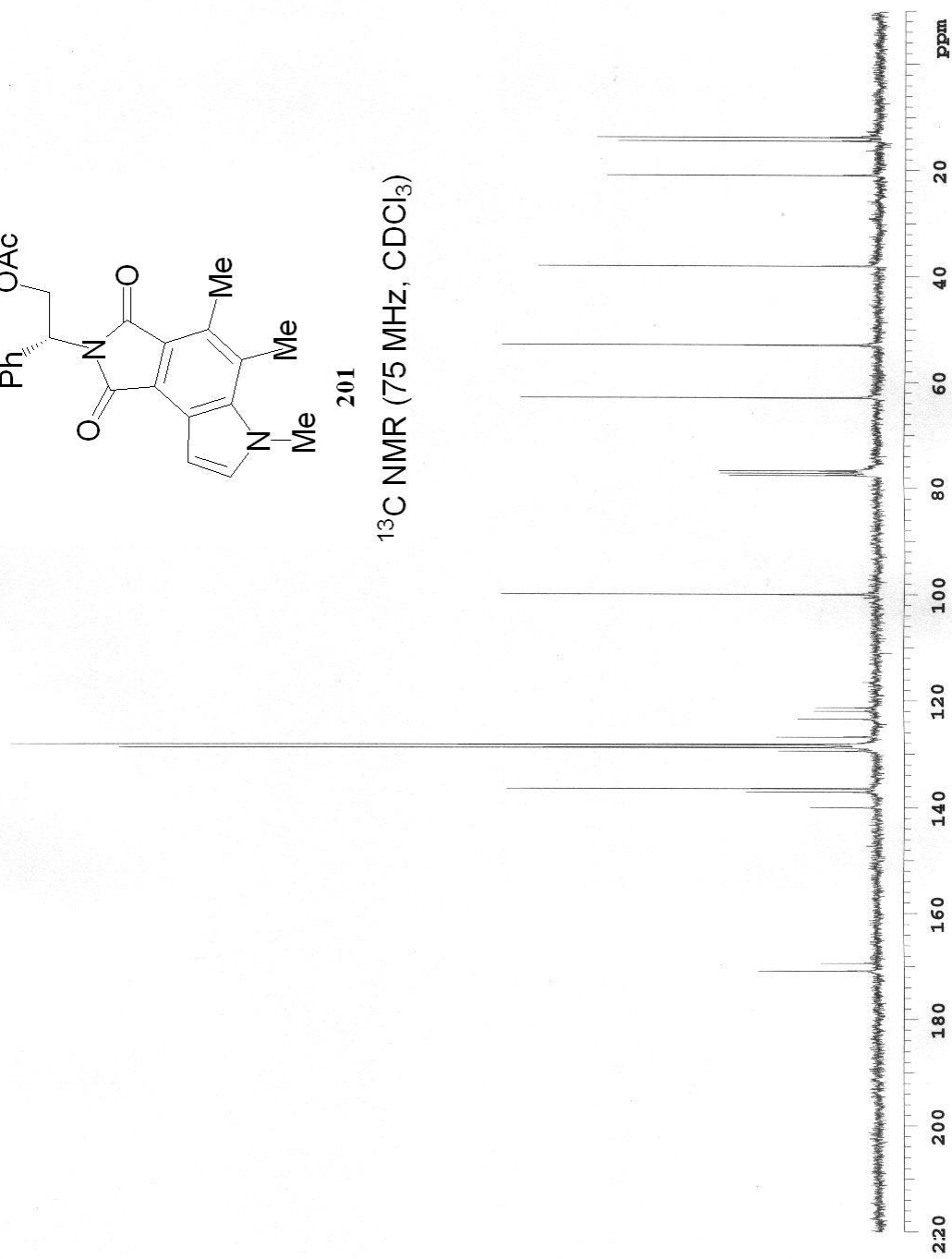
¹H NMR (300 MHz, CDCl₃)

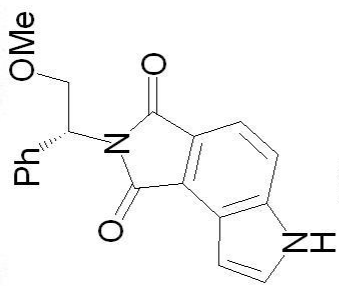




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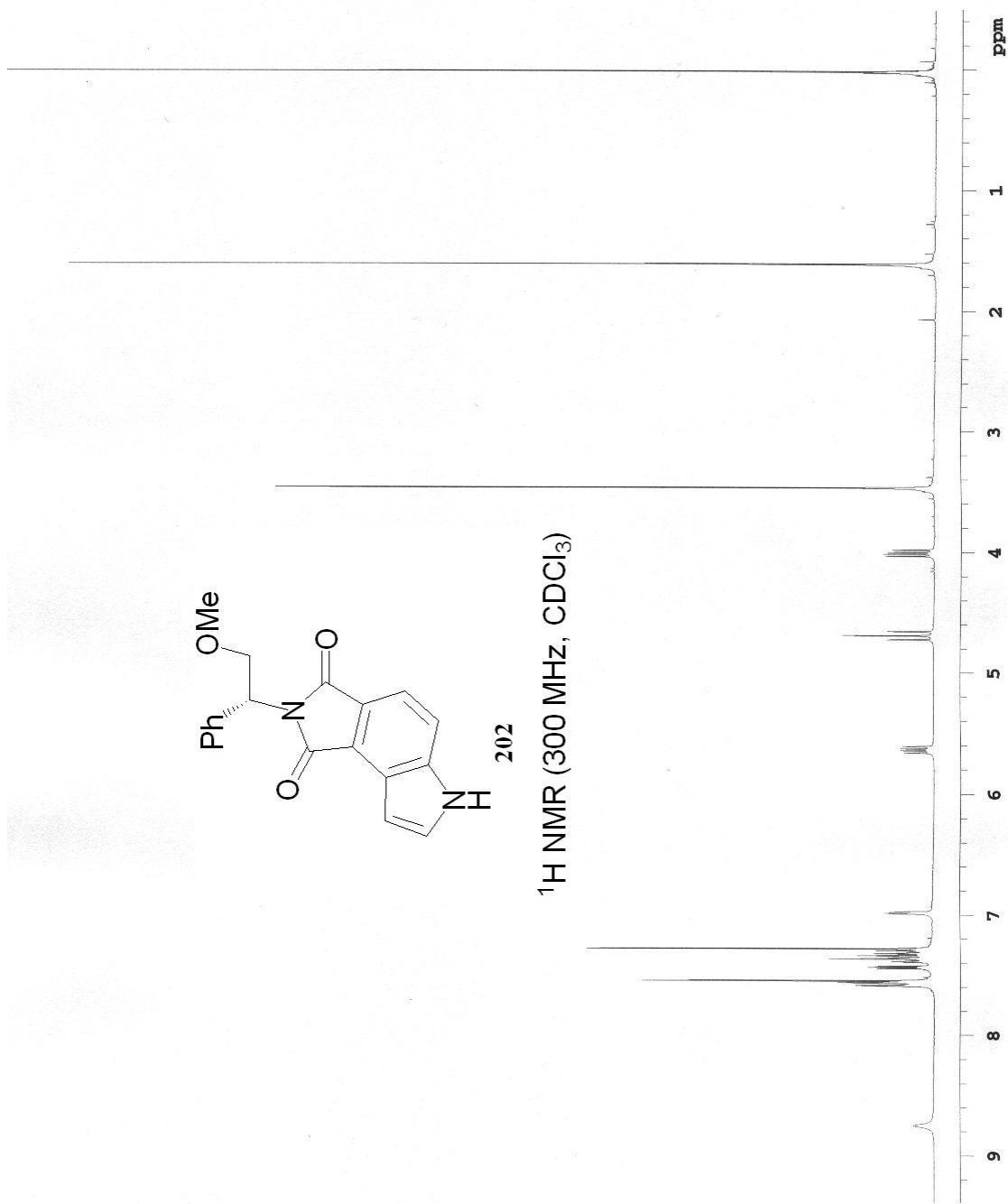
¹³C NMR (75 MHz, CDCl₃)

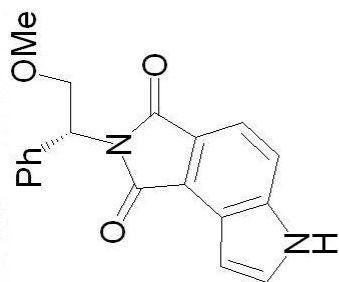




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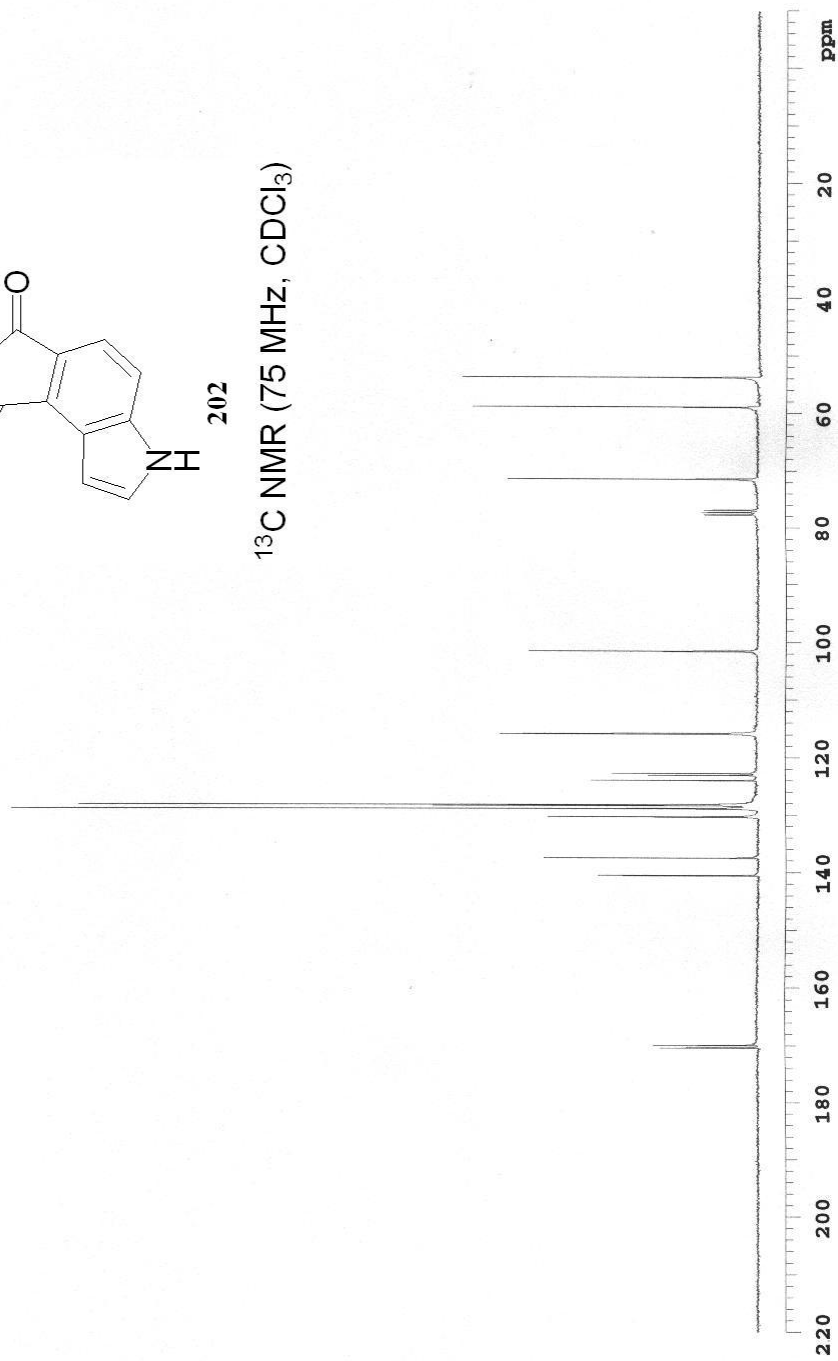
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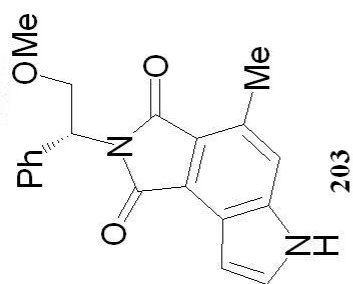




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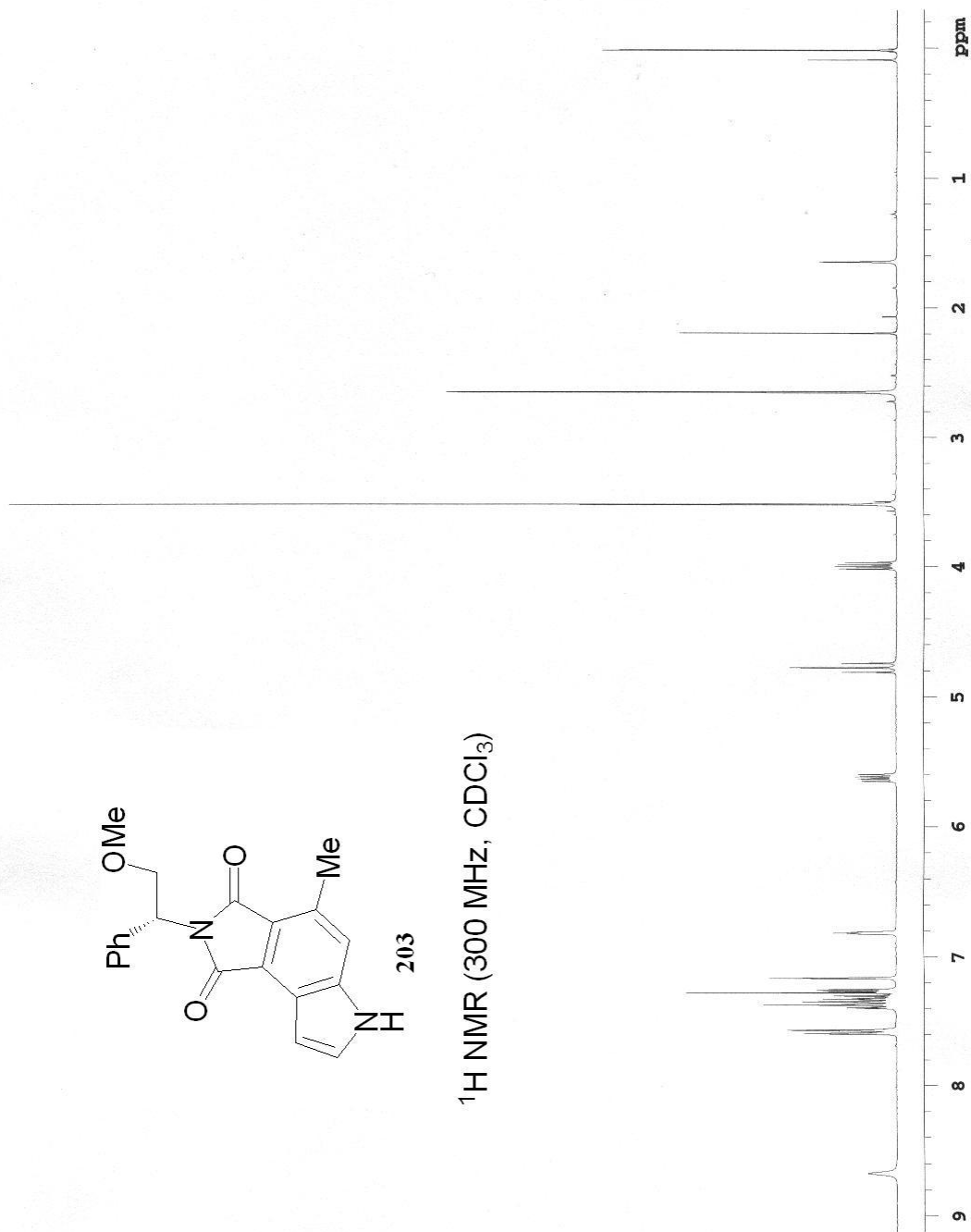
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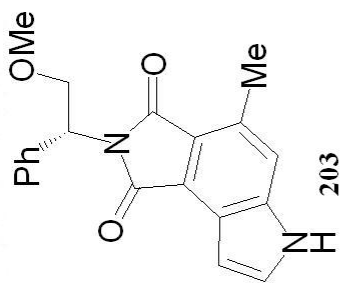




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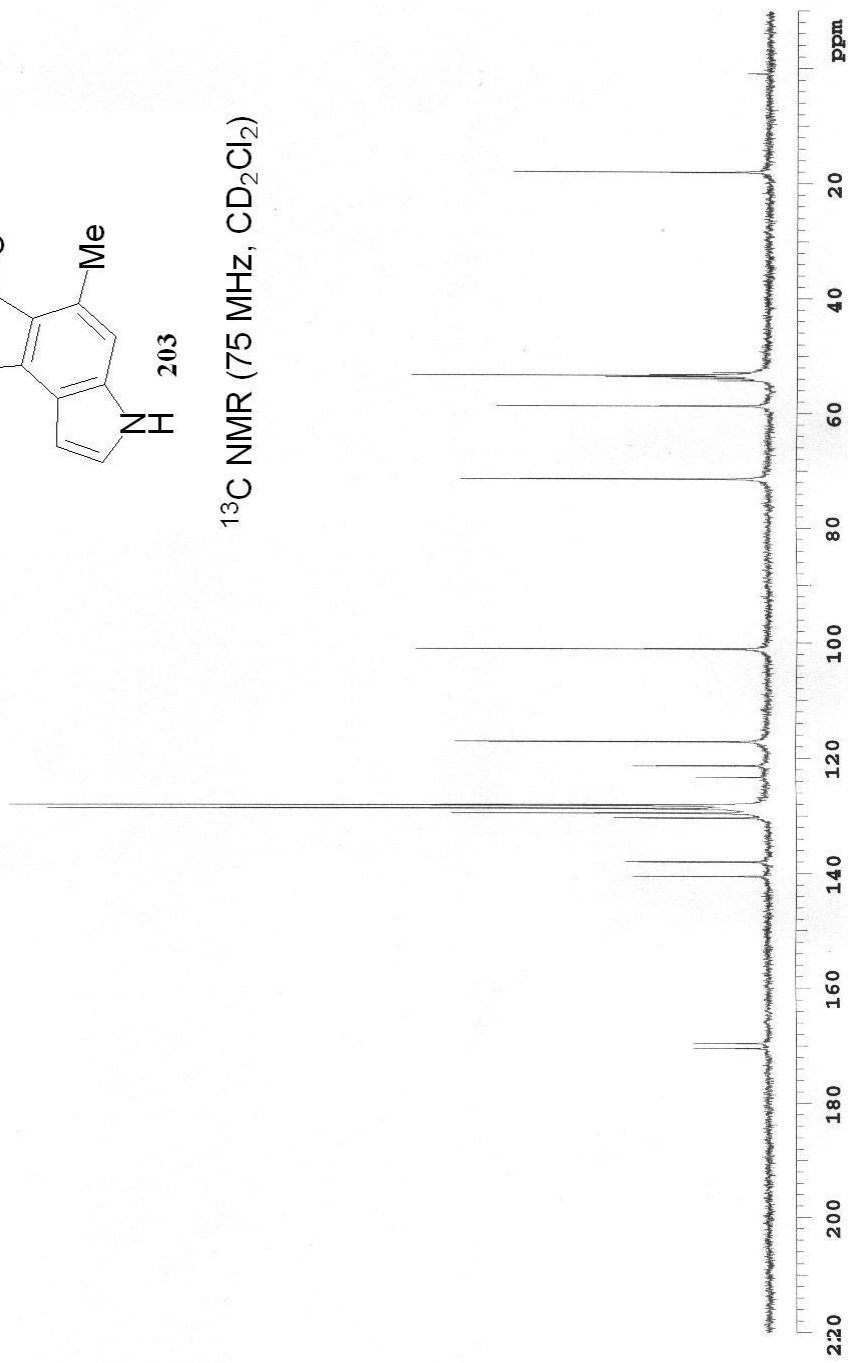
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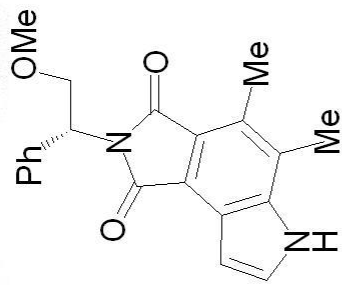




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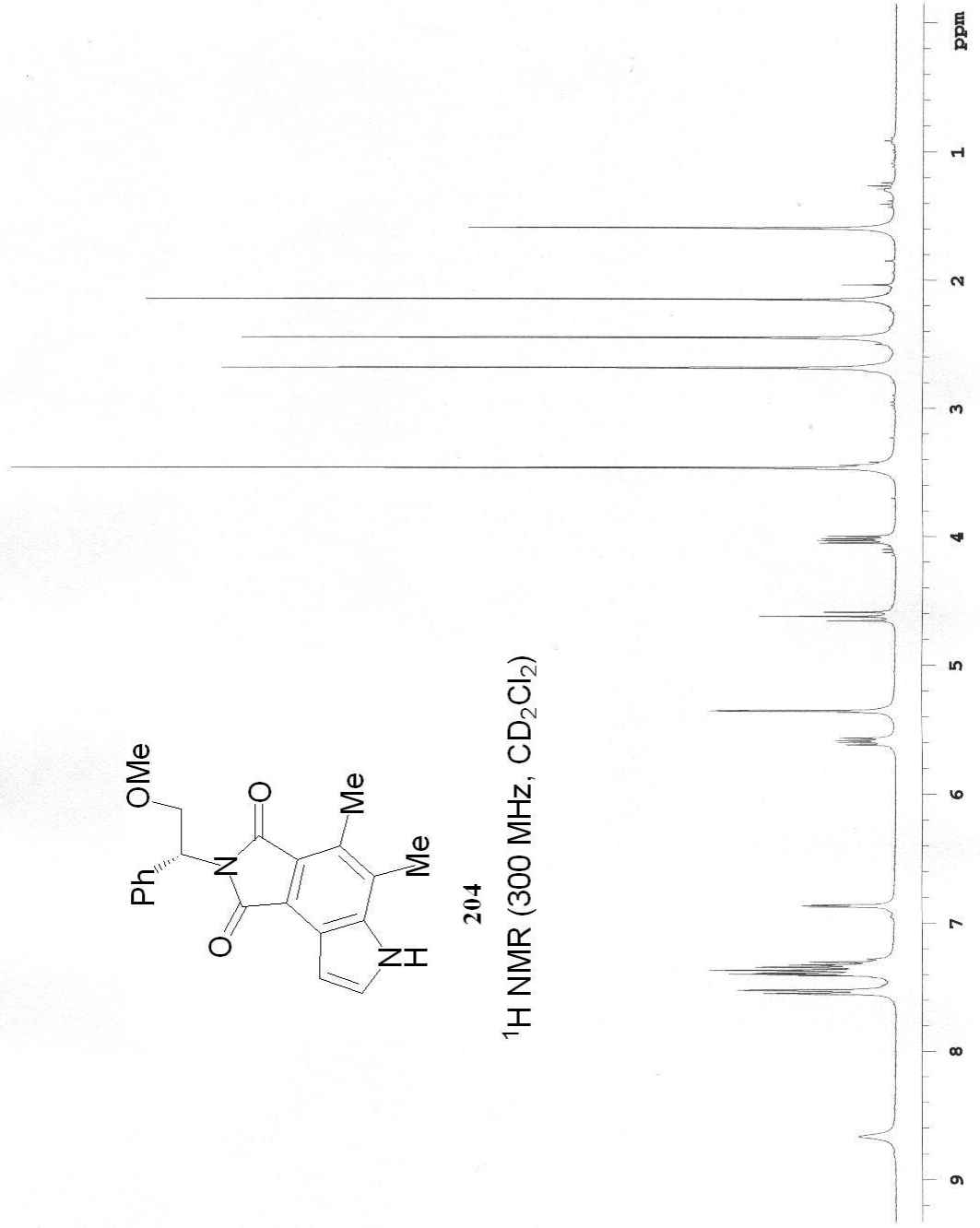
^{13}C NMR (75 MHz, CD_2Cl_2)

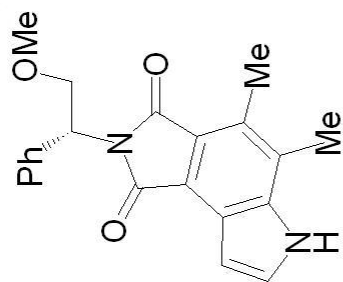




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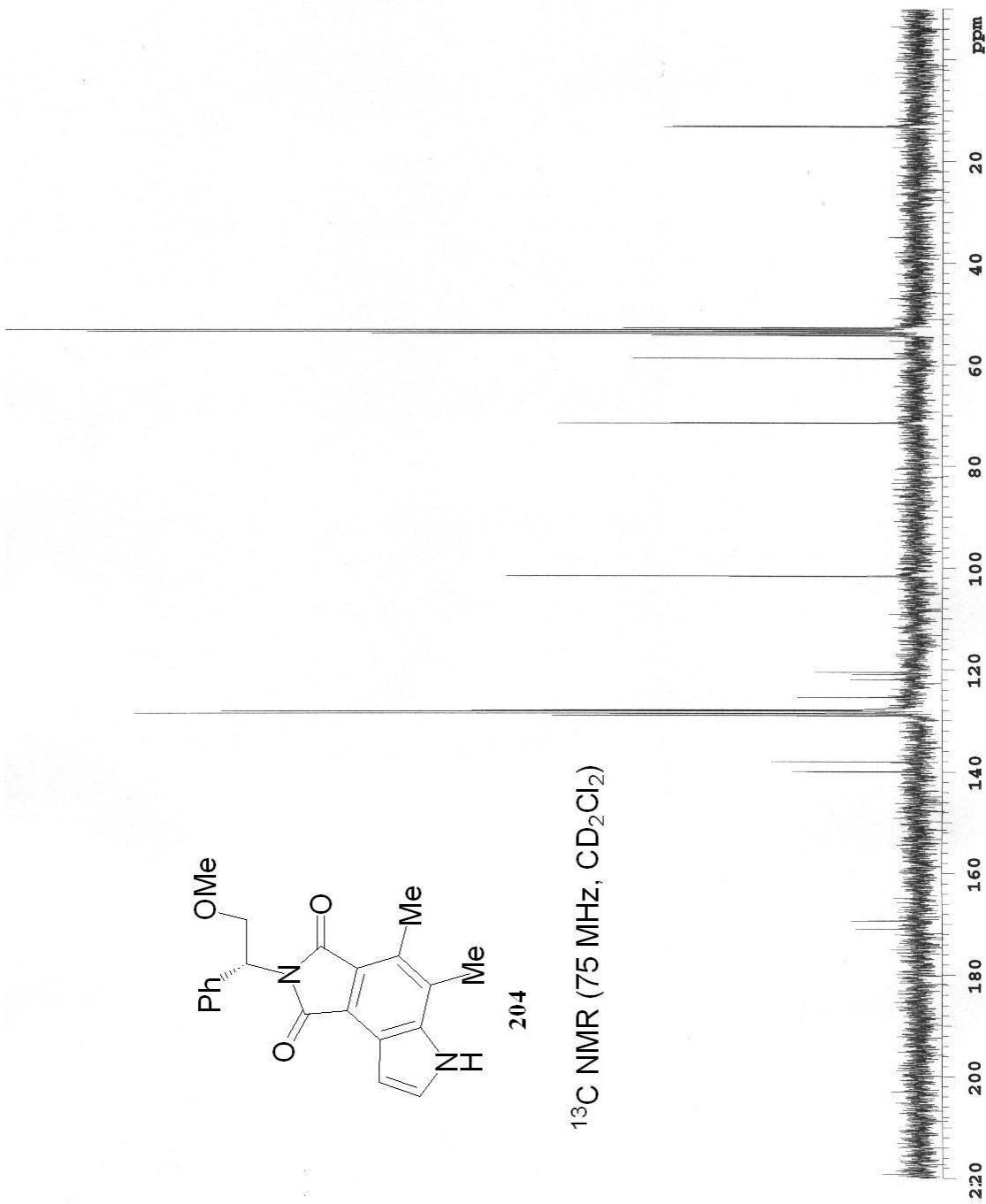
¹H NMR (300 MHz, CD₂Cl₂)

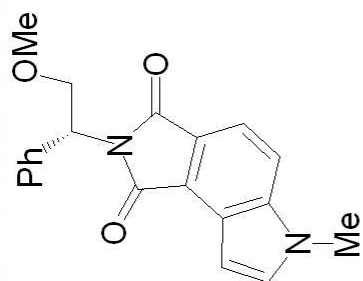




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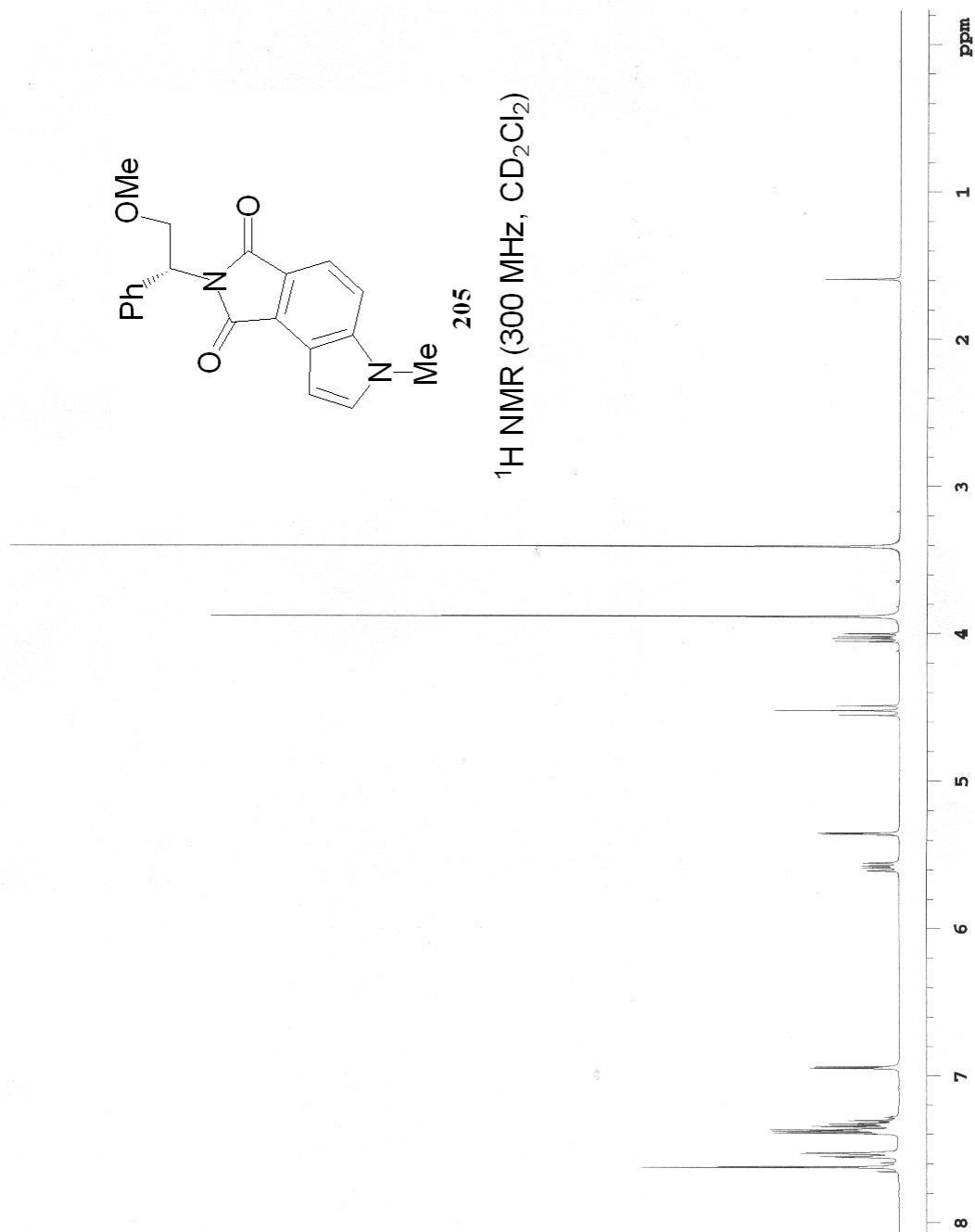
¹³C NMR (75 MHz, CD₂Cl₂)

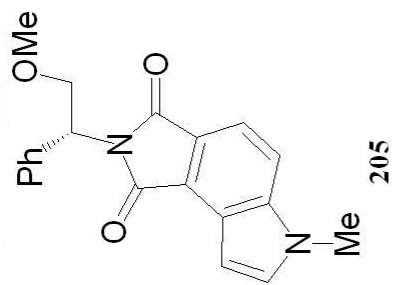




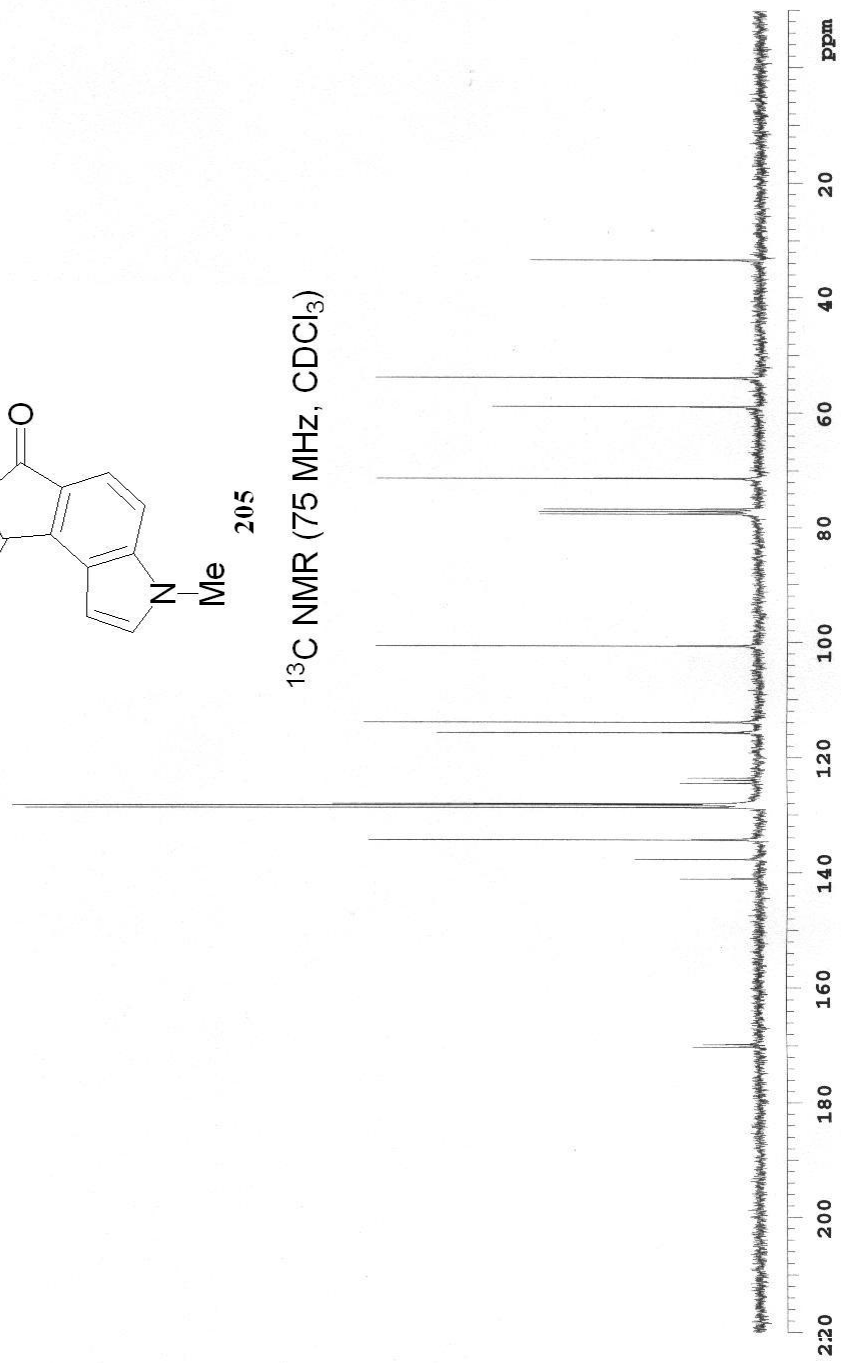
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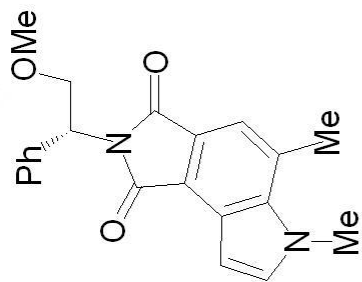
¹H NMR (300 MHz, CD₂Cl₂)





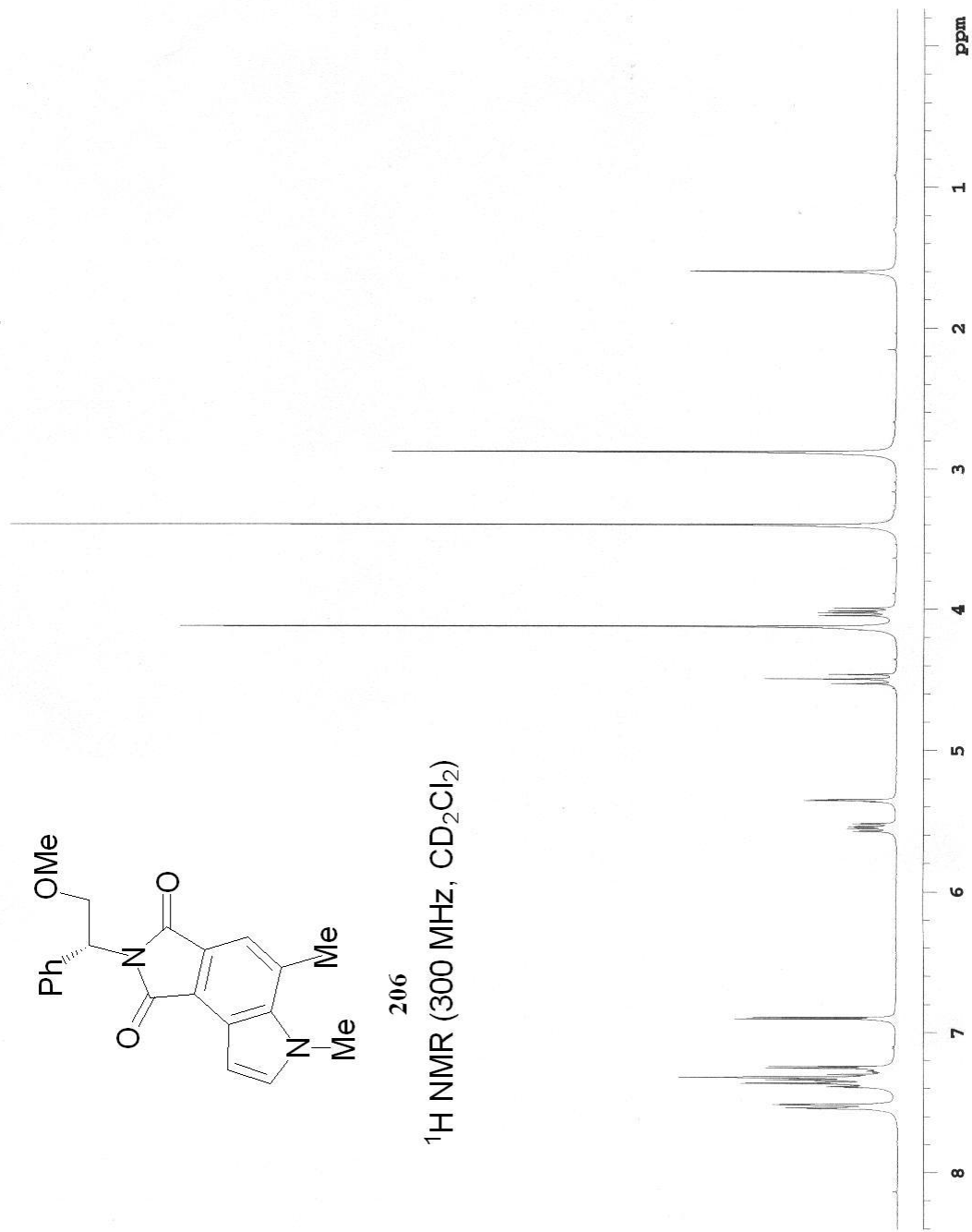
^{13}C NMR (75 MHz, CDCl_3)

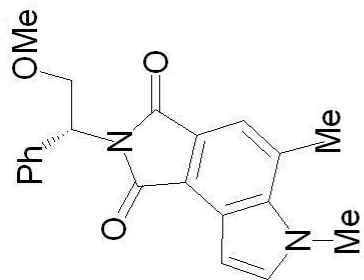




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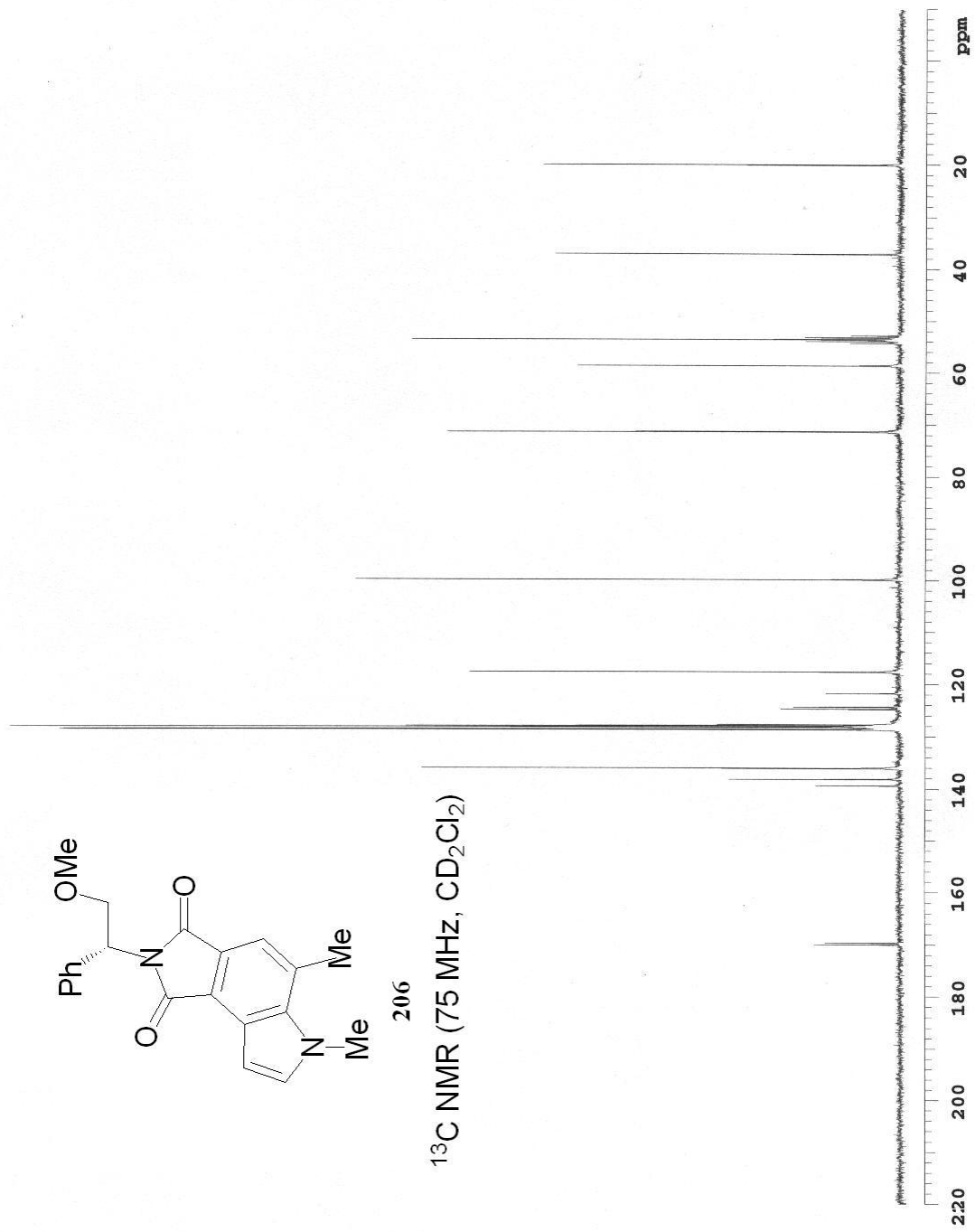
$^1\text{H NMR}$ (300 MHz, CD_2Cl_2)

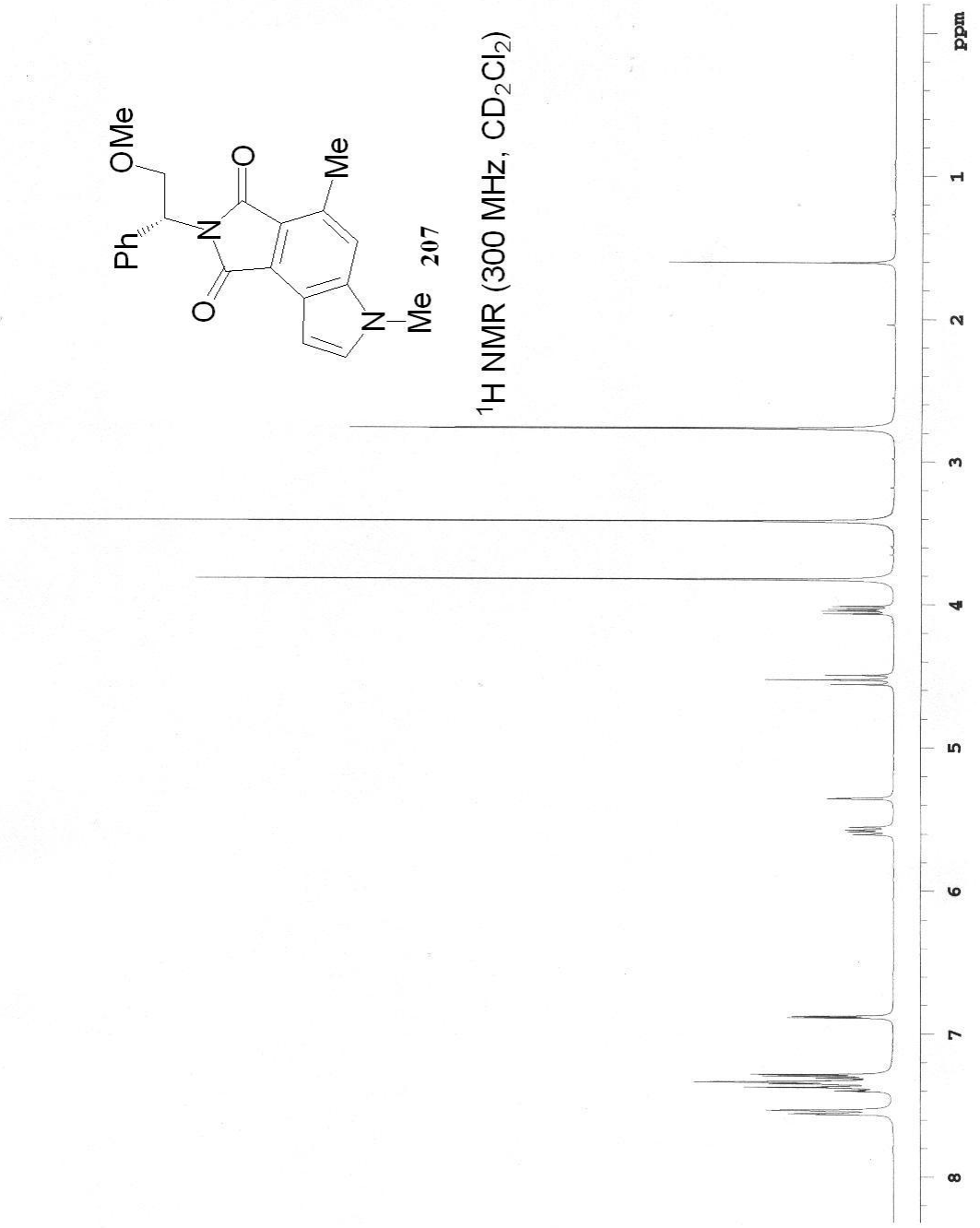


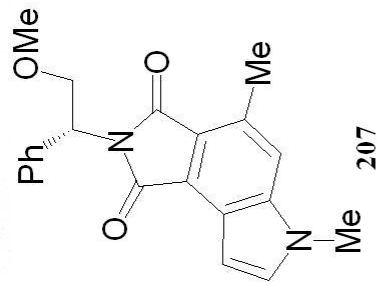


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^{13}C NMR (75 MHz, CD_2Cl_2)

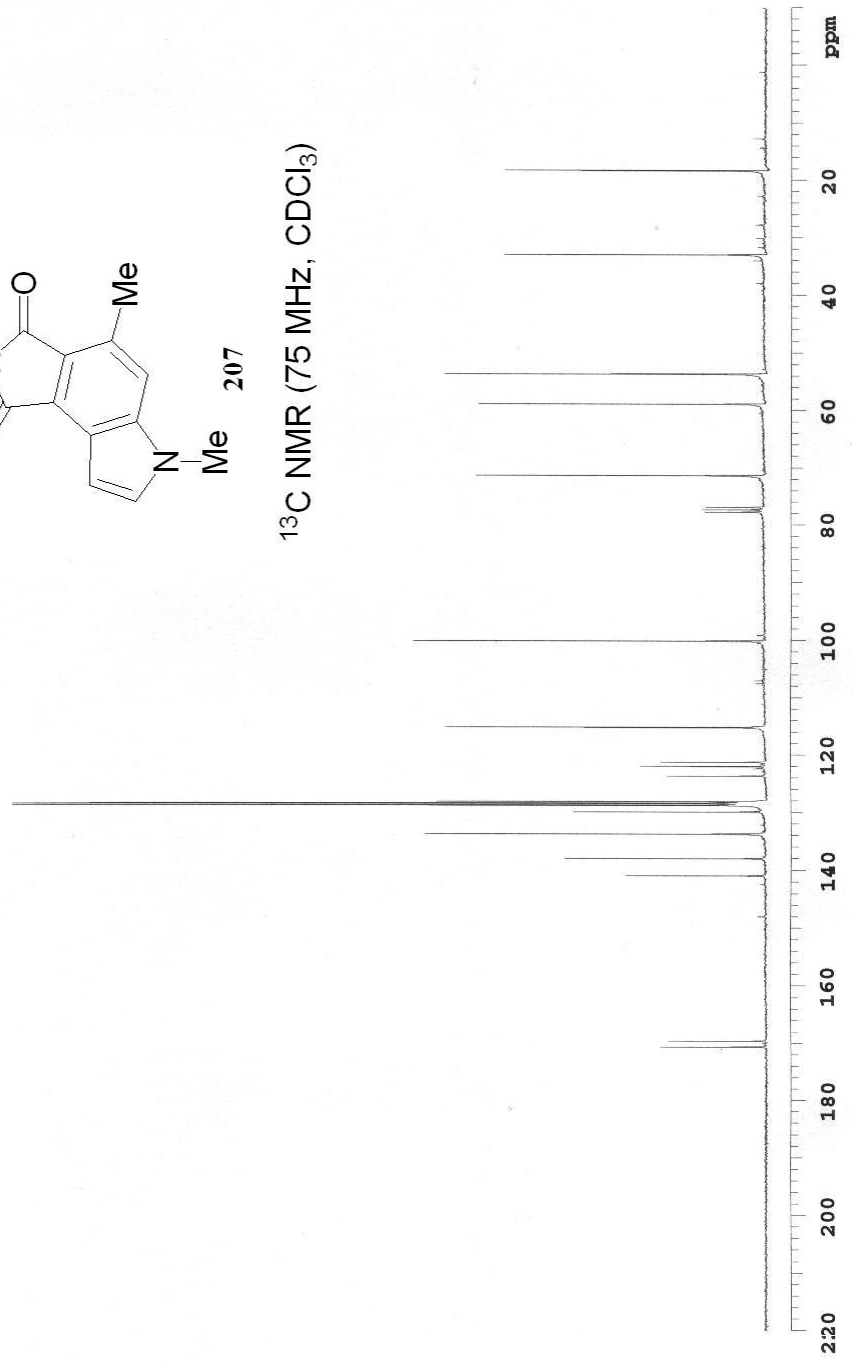


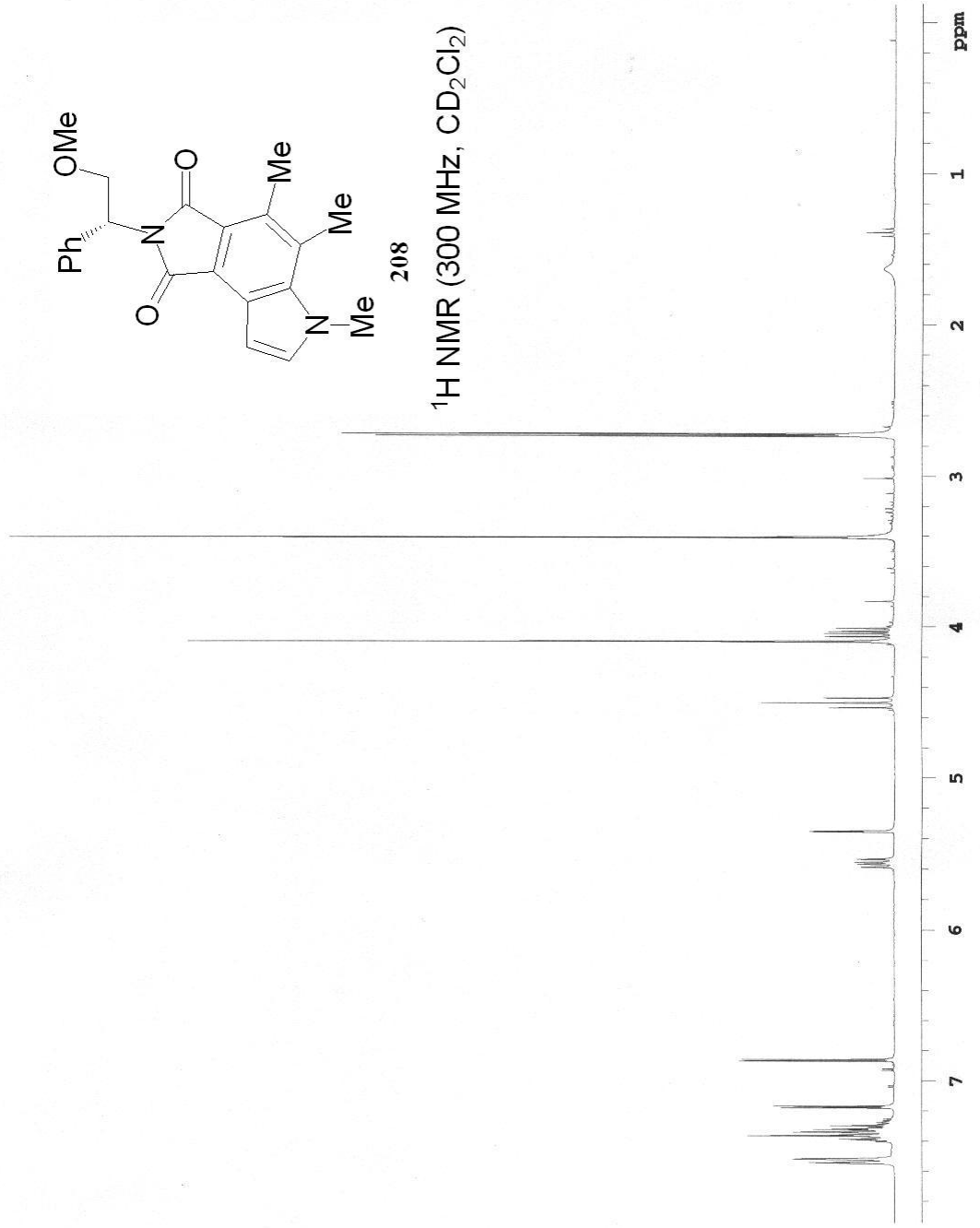


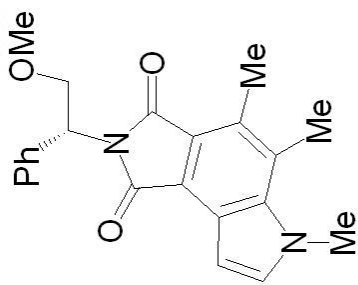


Me 207

^{13}C NMR (75 MHz, CDCl_3)

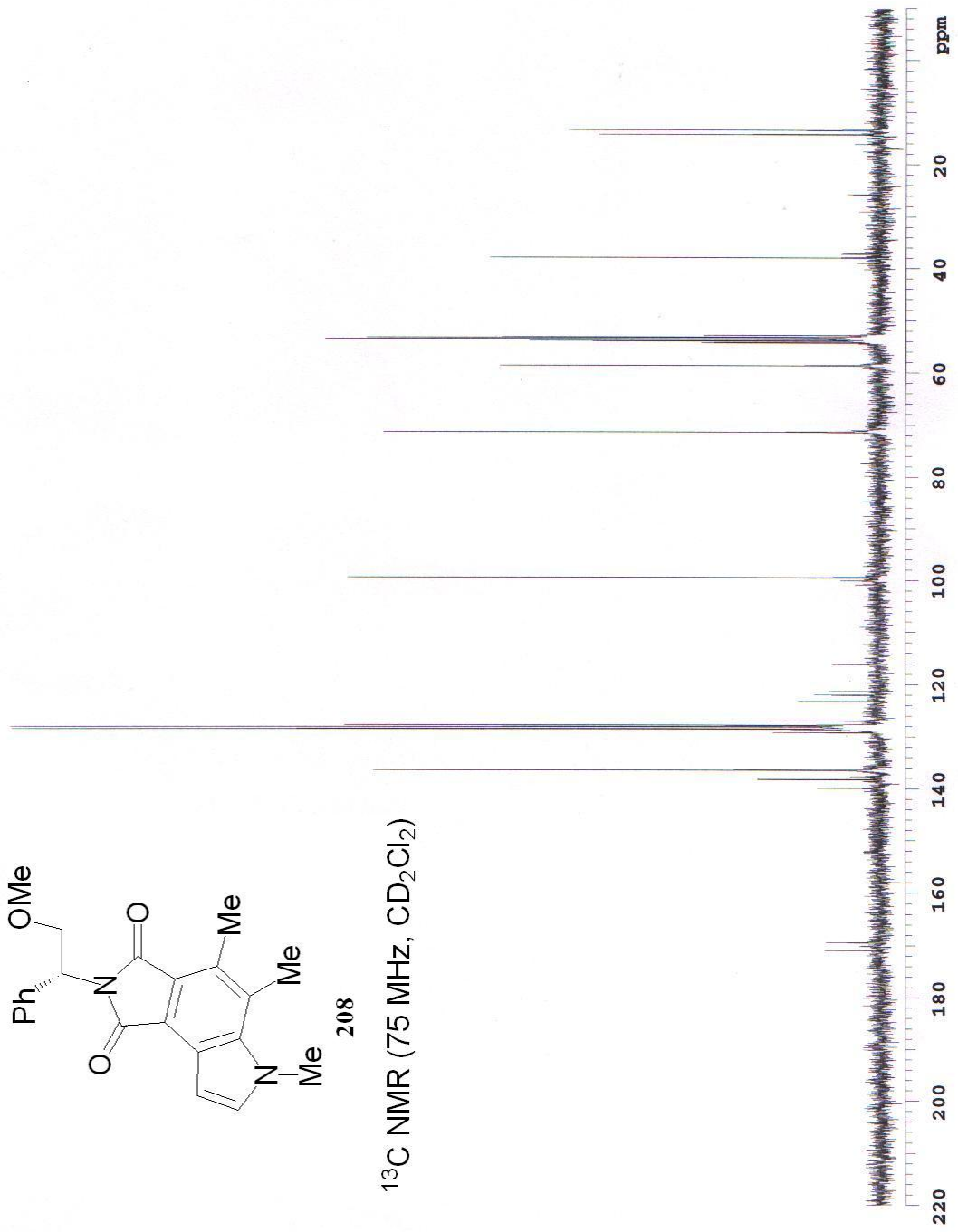


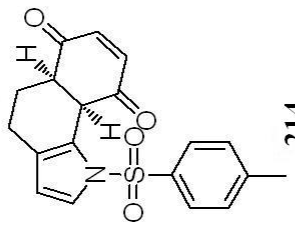




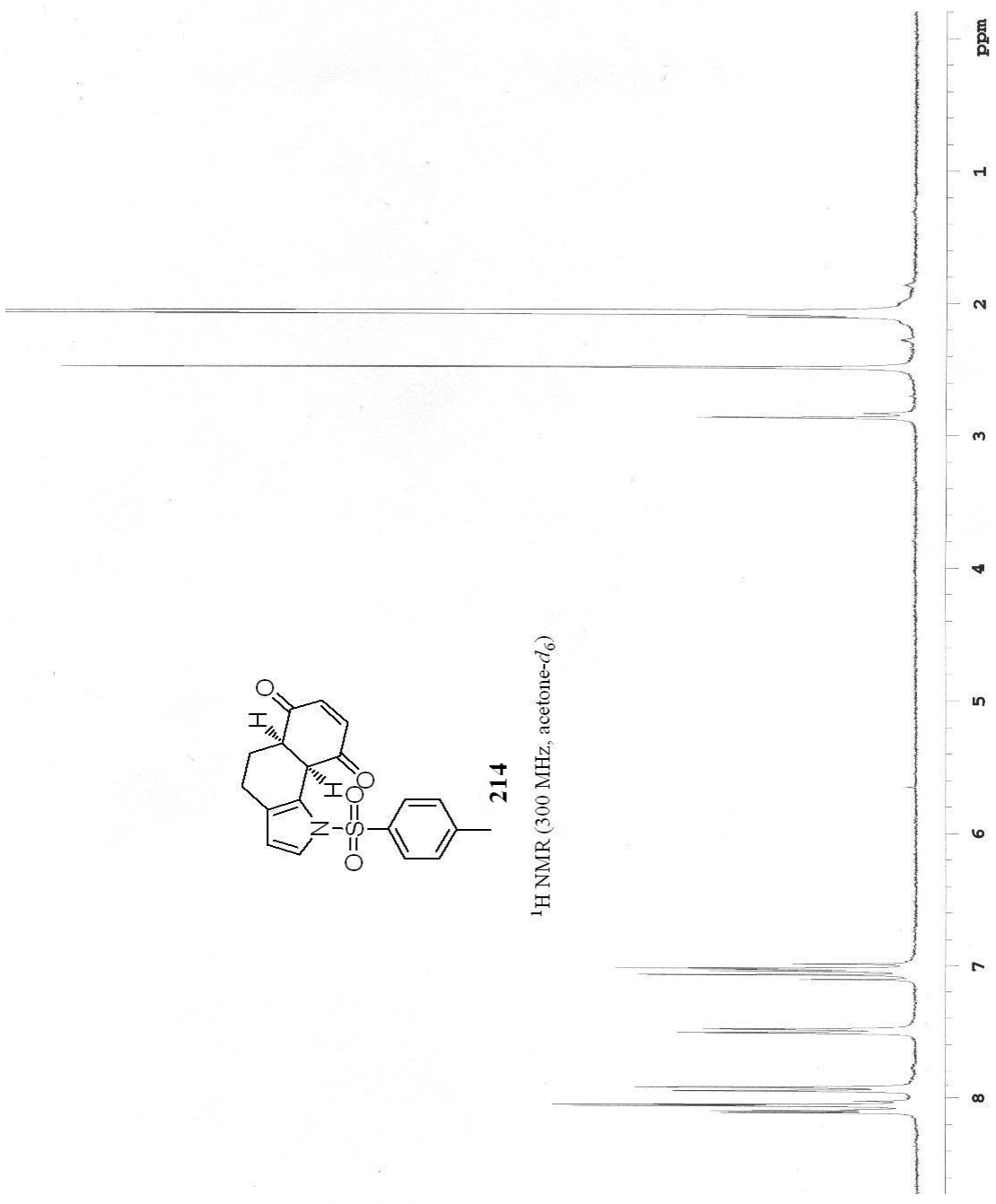
208

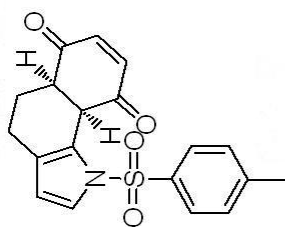
¹³C NMR (75 MHz, CD₂Cl₂)





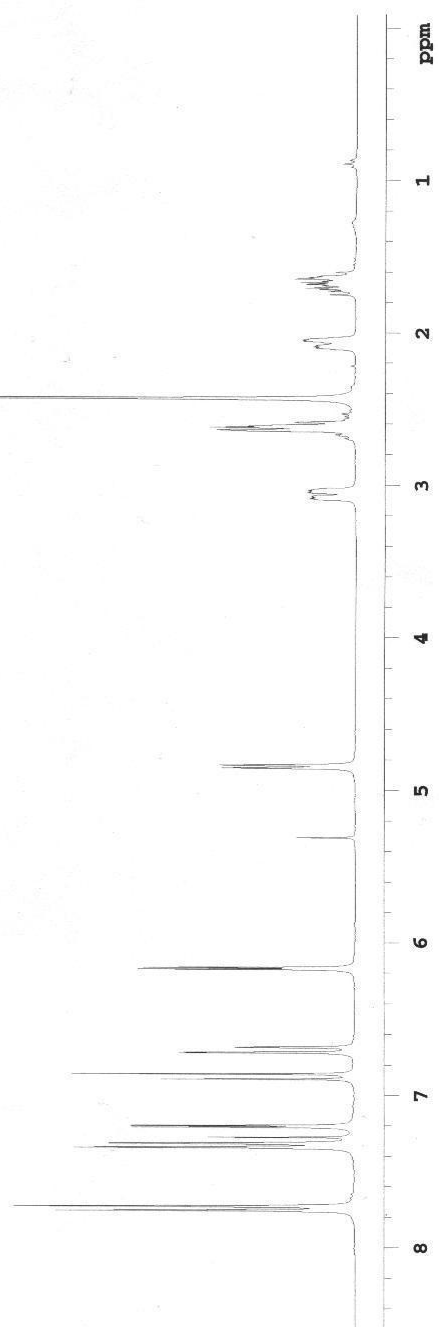
¹H NMR (300 MHz, acetone-d₆)

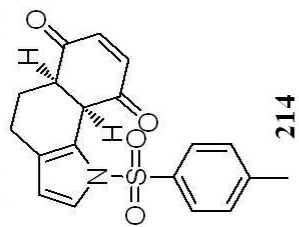




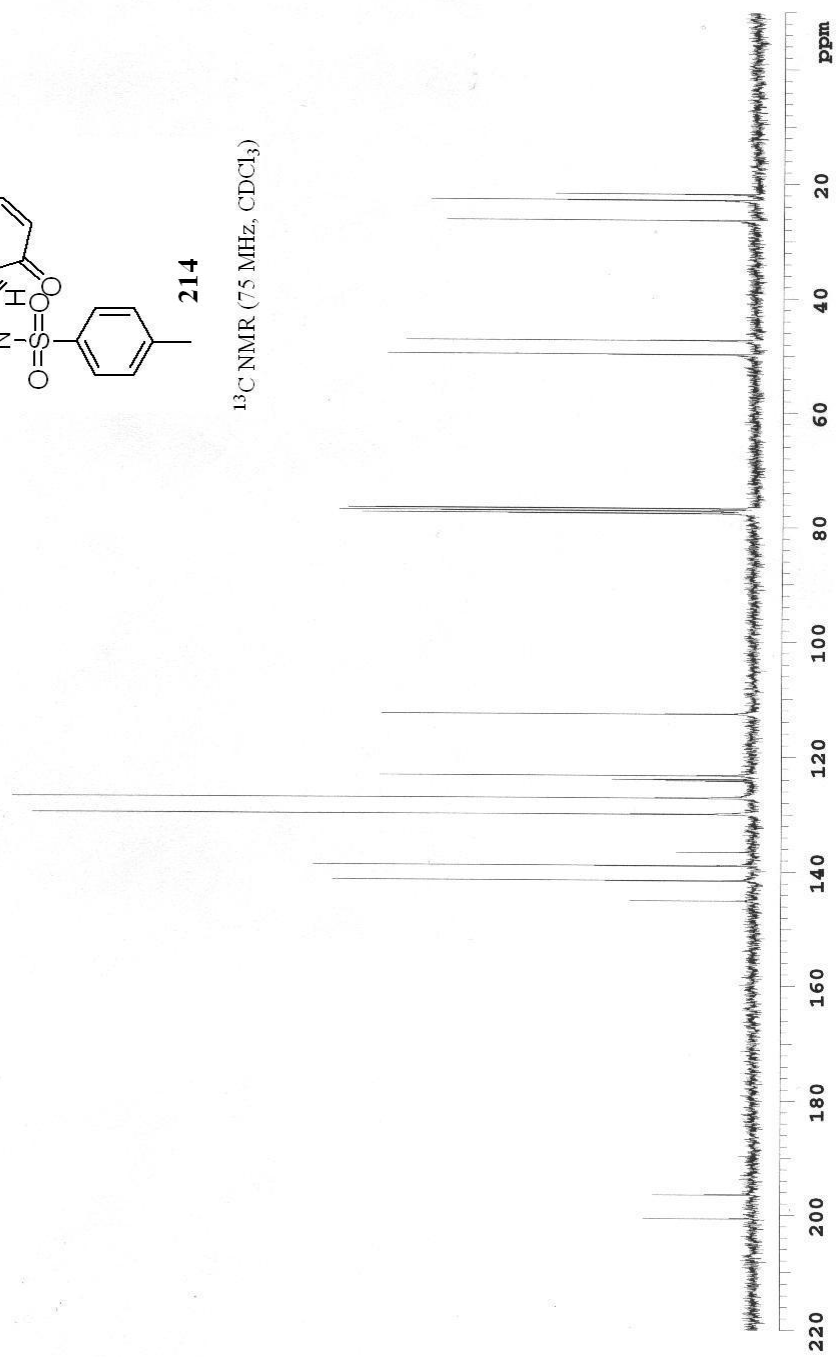
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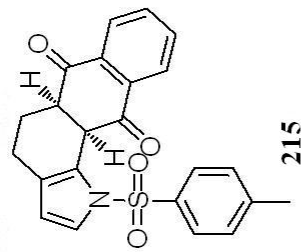
¹H NMR (300 MHz, CDCl₃)



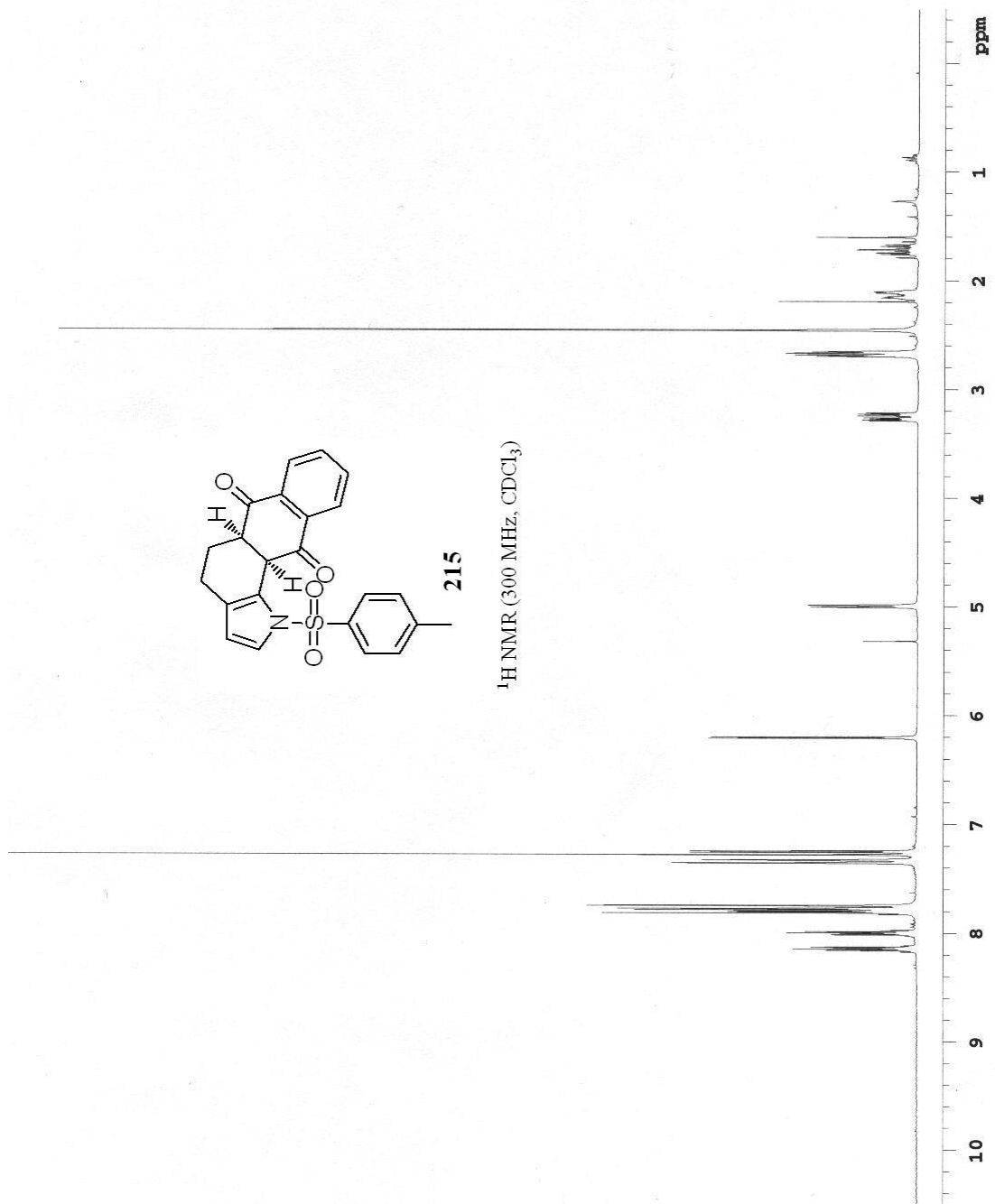


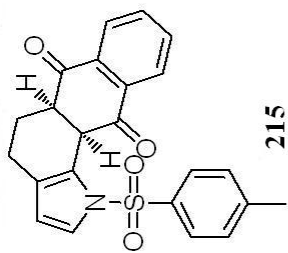
^{13}C NMR (75 MHz, CDCl_3)



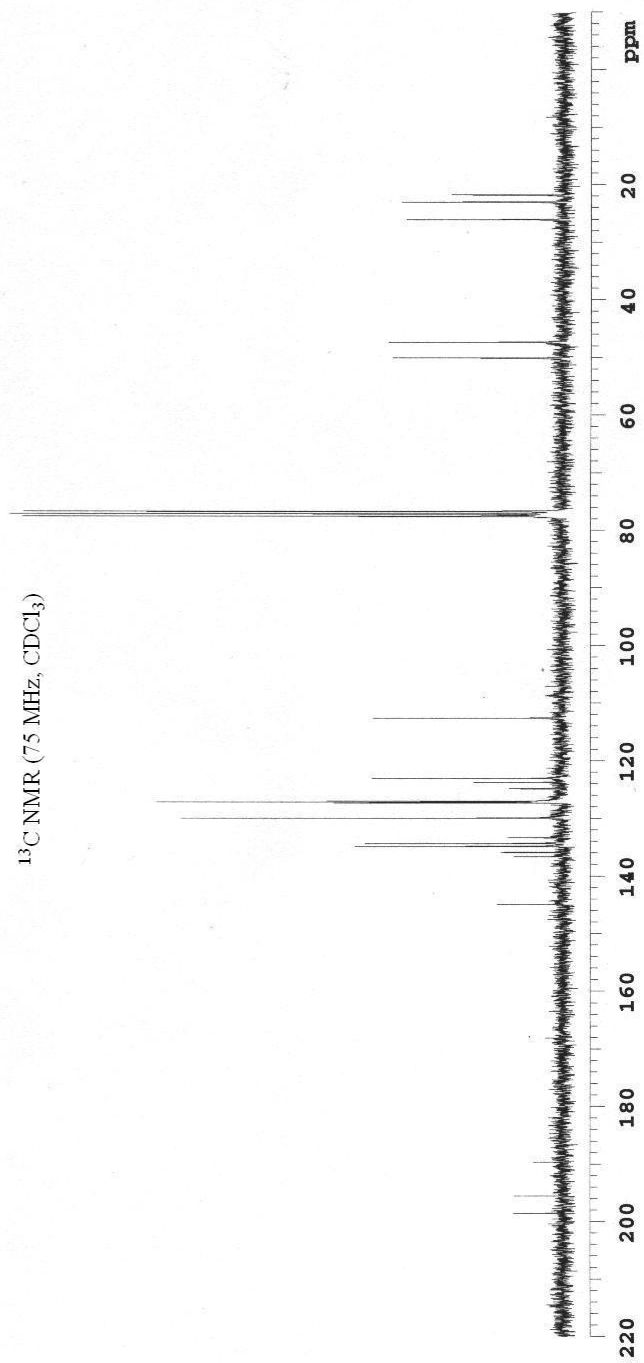


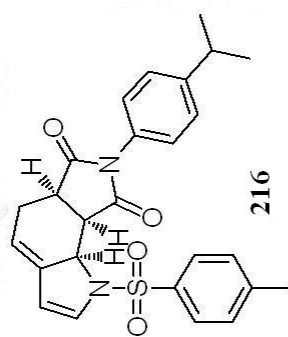
¹H NMR (300 MHz, CDCl₃)



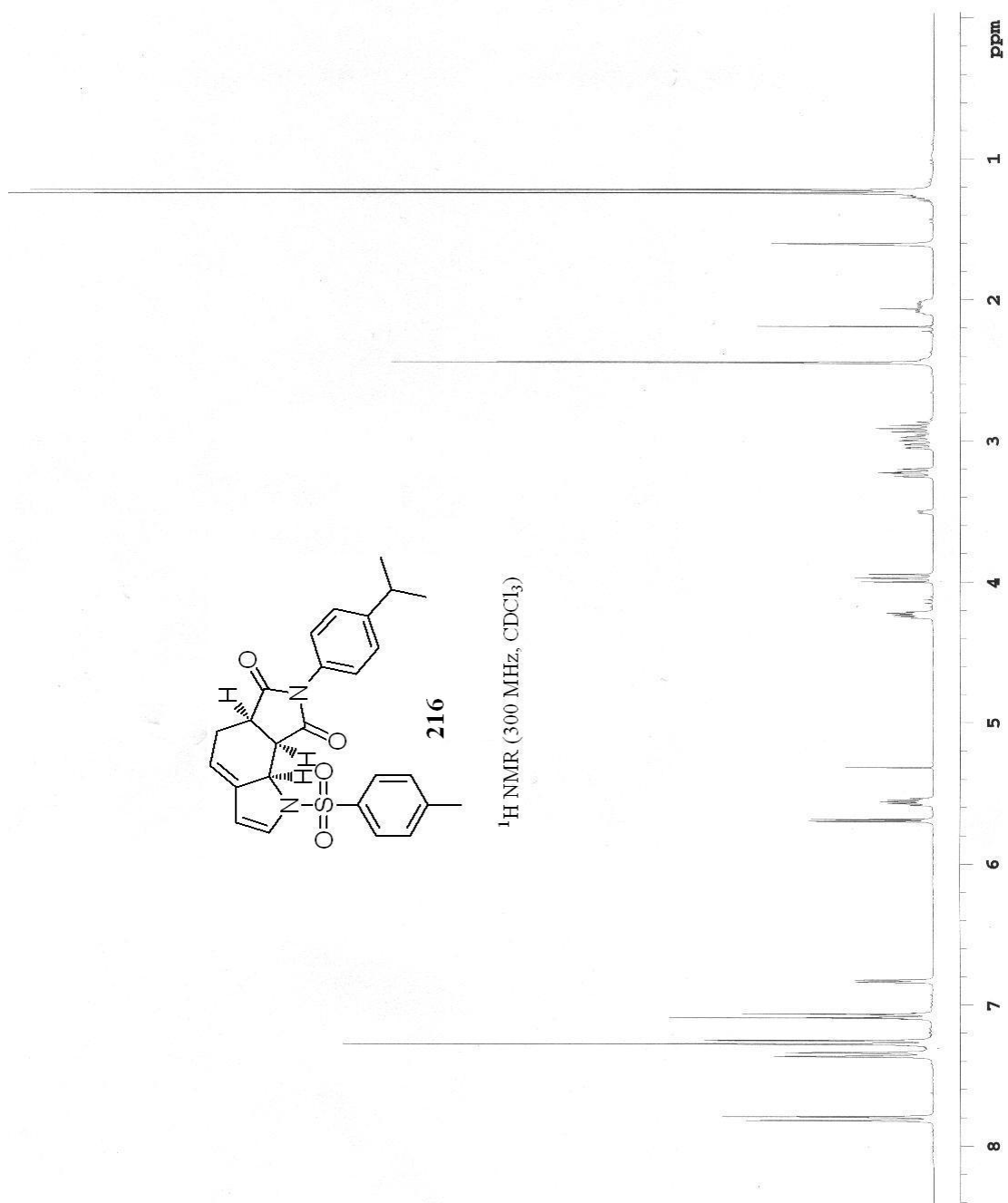


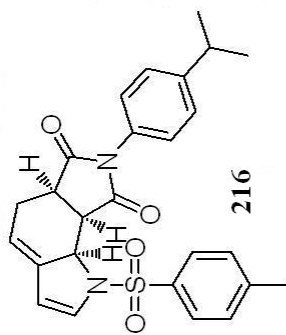
^{13}C NMR (75 MHz, CDCl_3)



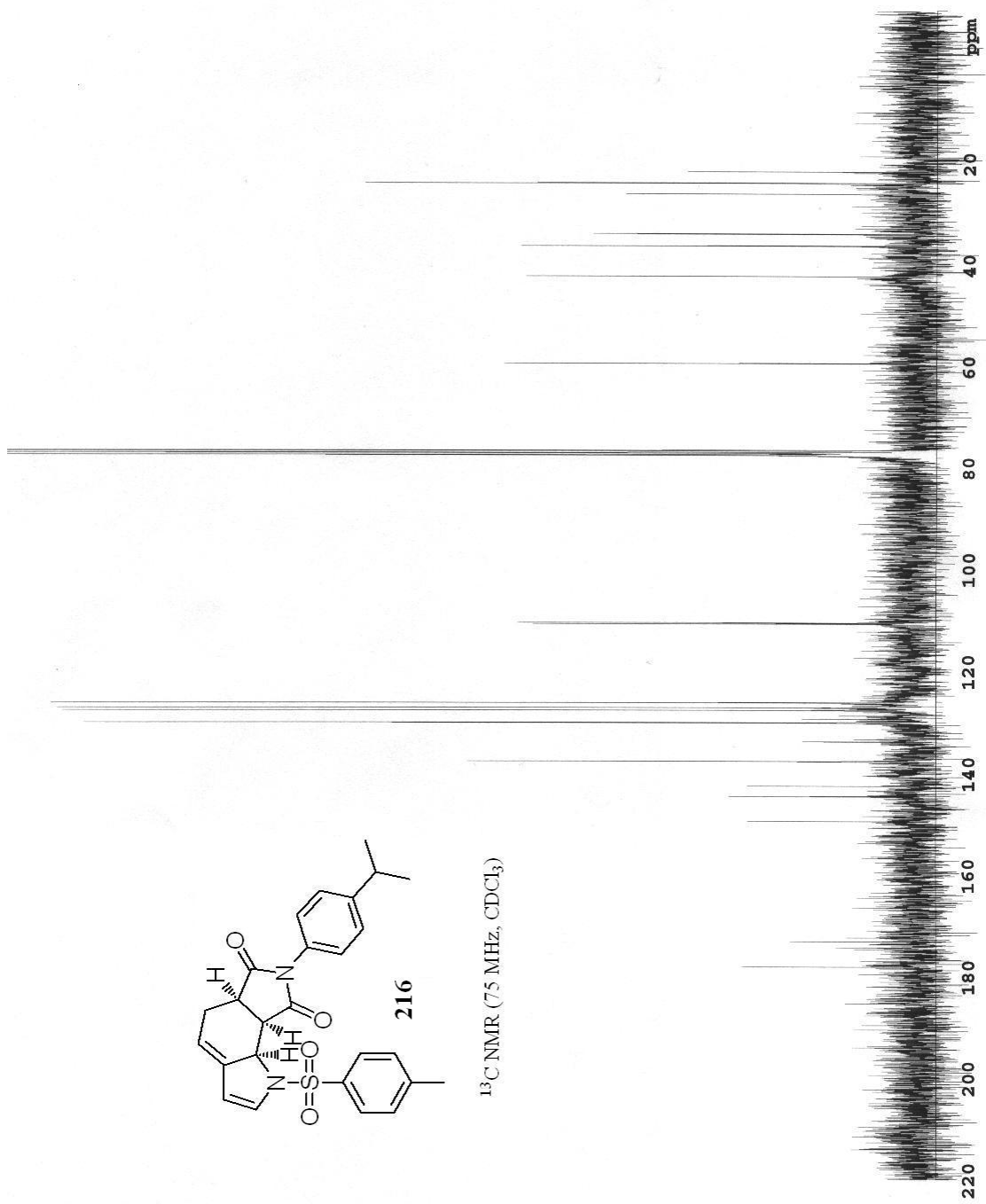


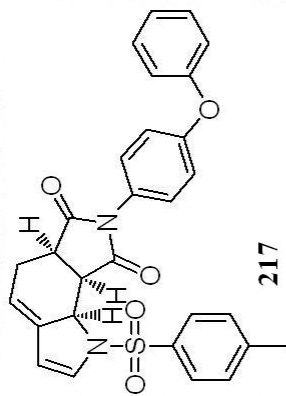
$^1\text{H NMR}$ (300 MHz, CDCl_3)



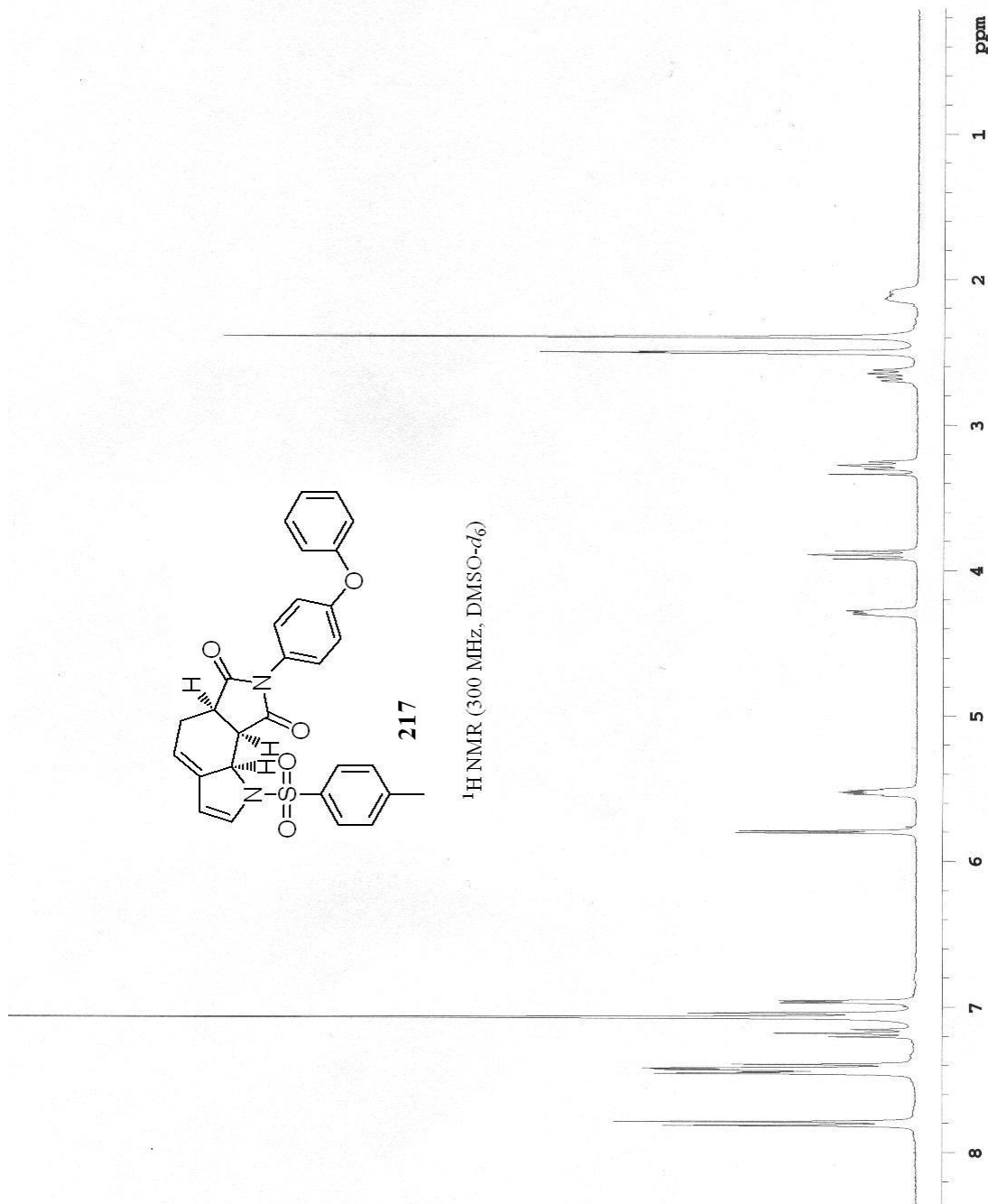


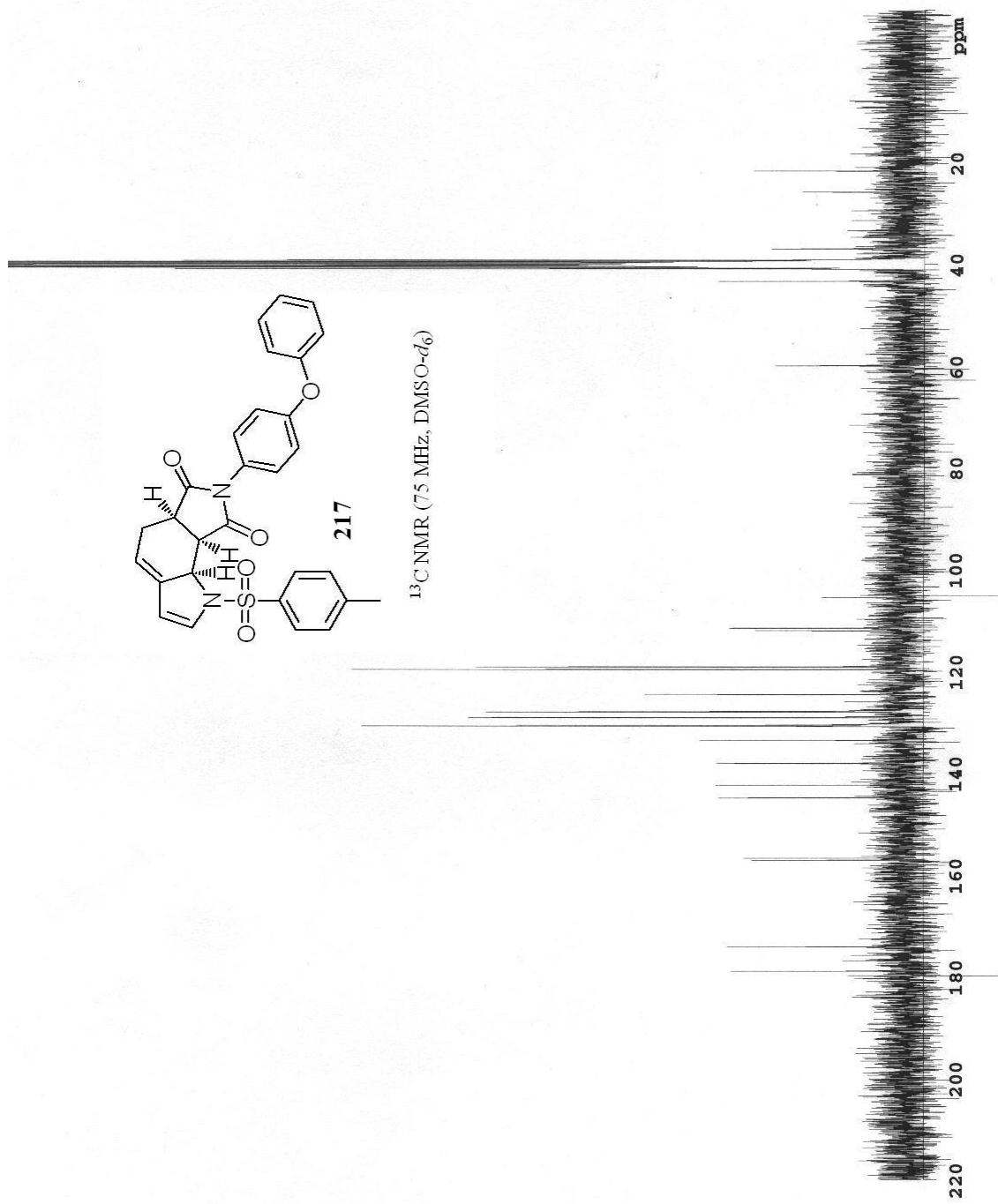
^{13}C NMR (75 MHz, CDCl_3)

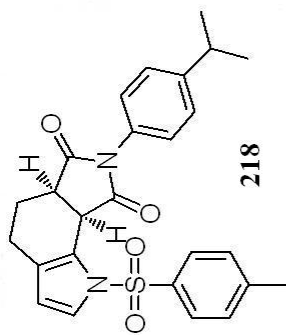




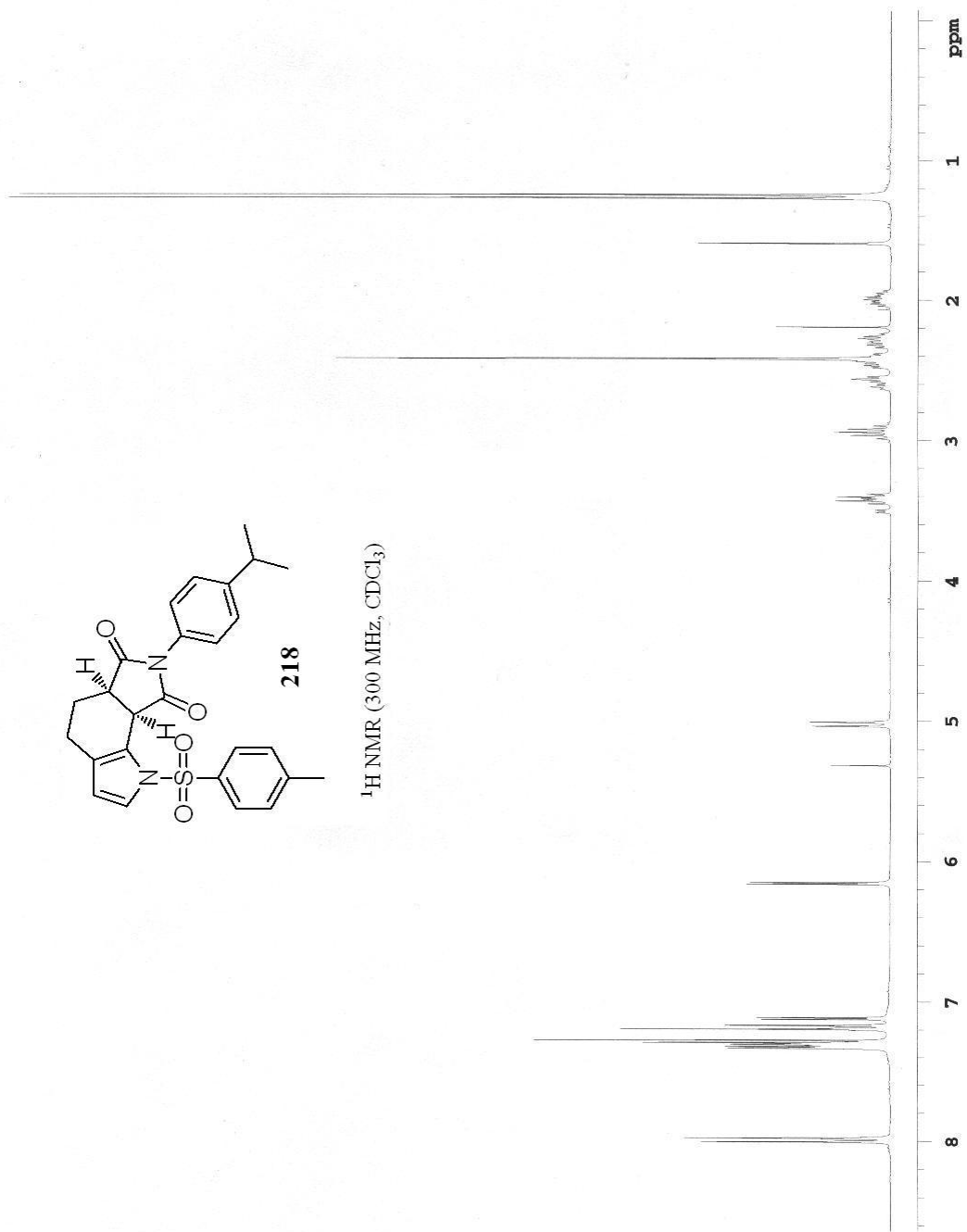
¹H NMR (300 MHz, DMSO-d₆)

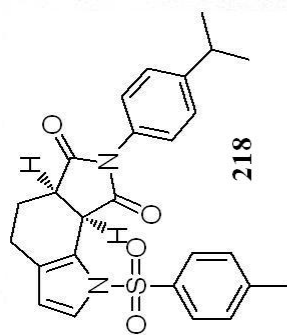




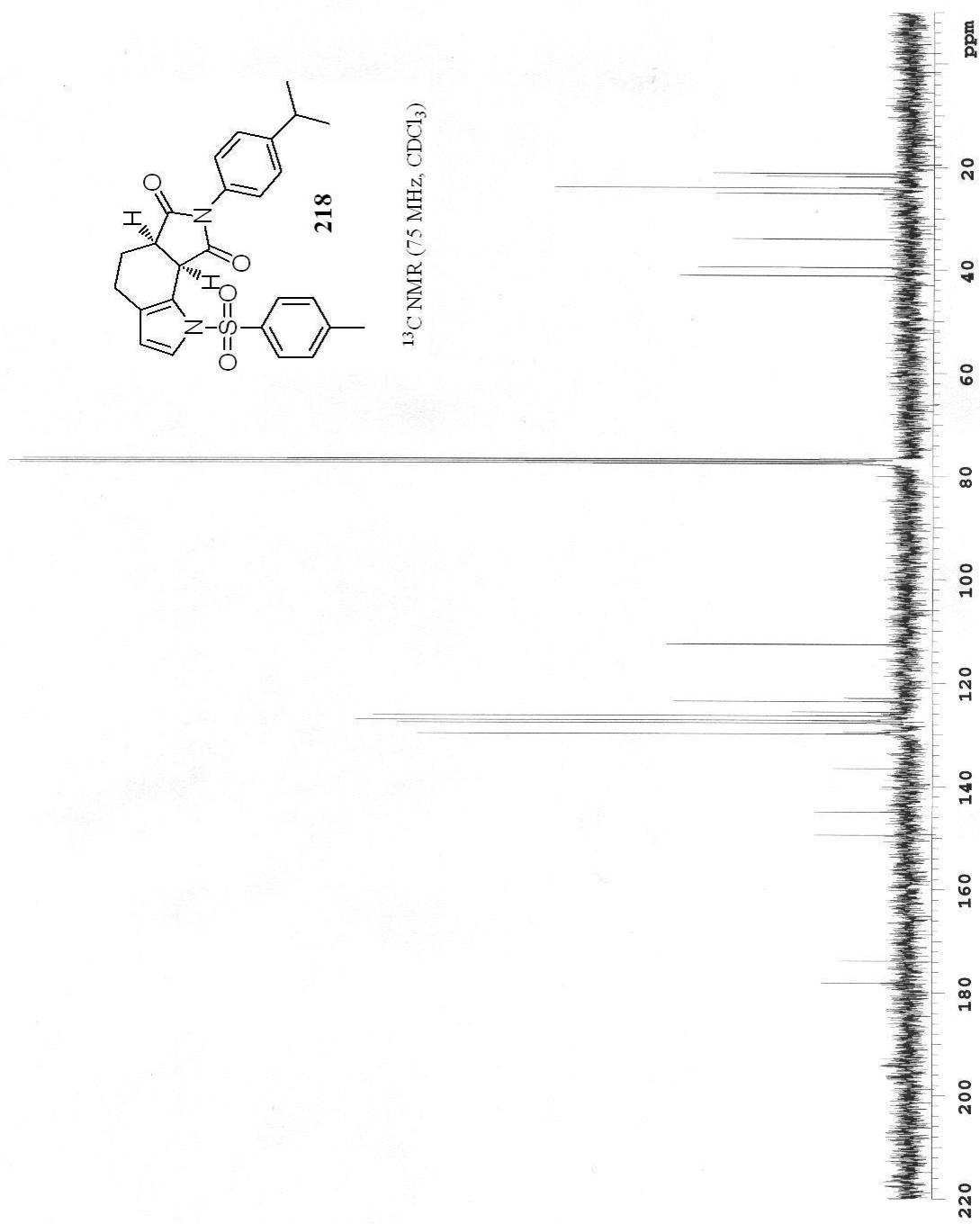


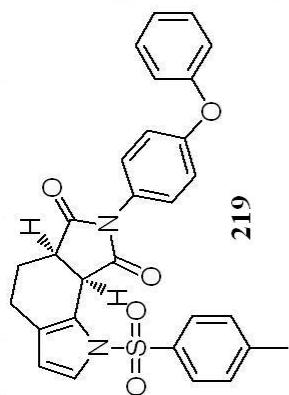
¹H NMR (300 MHz, CDCl₃)



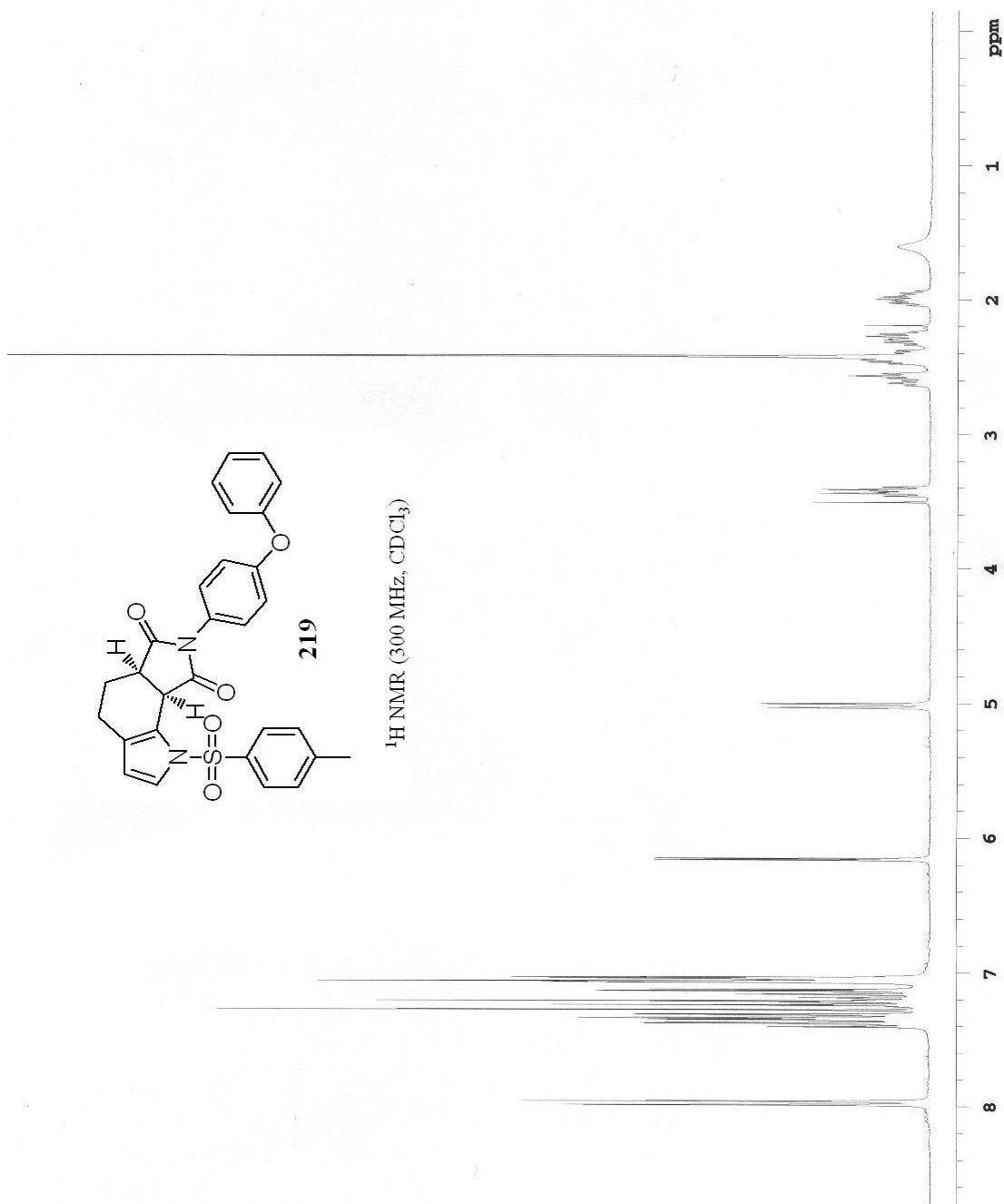


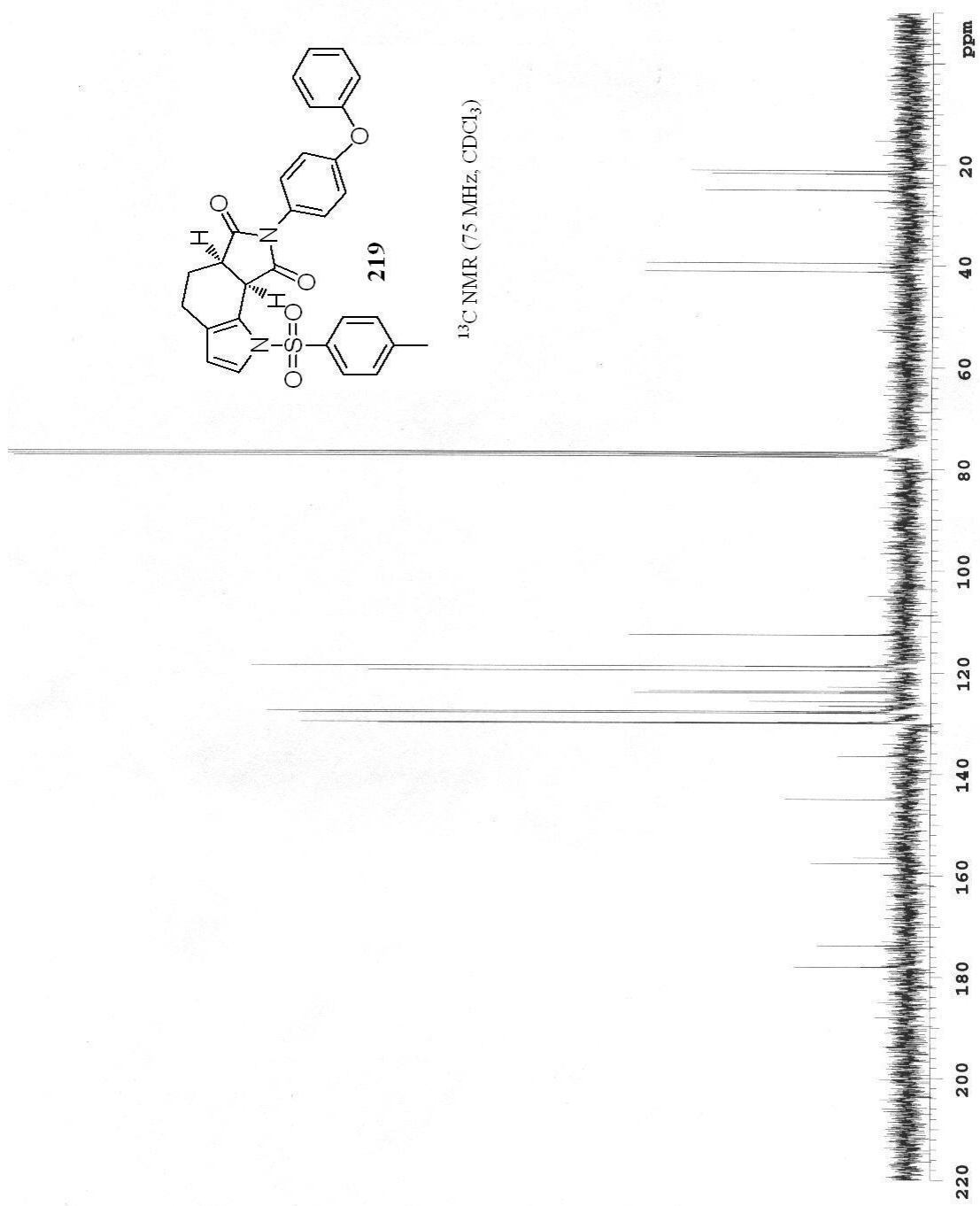
^{13}C NMR (75 MHz, CDCl_3)

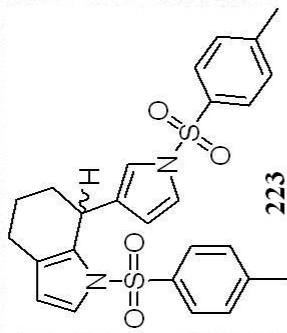




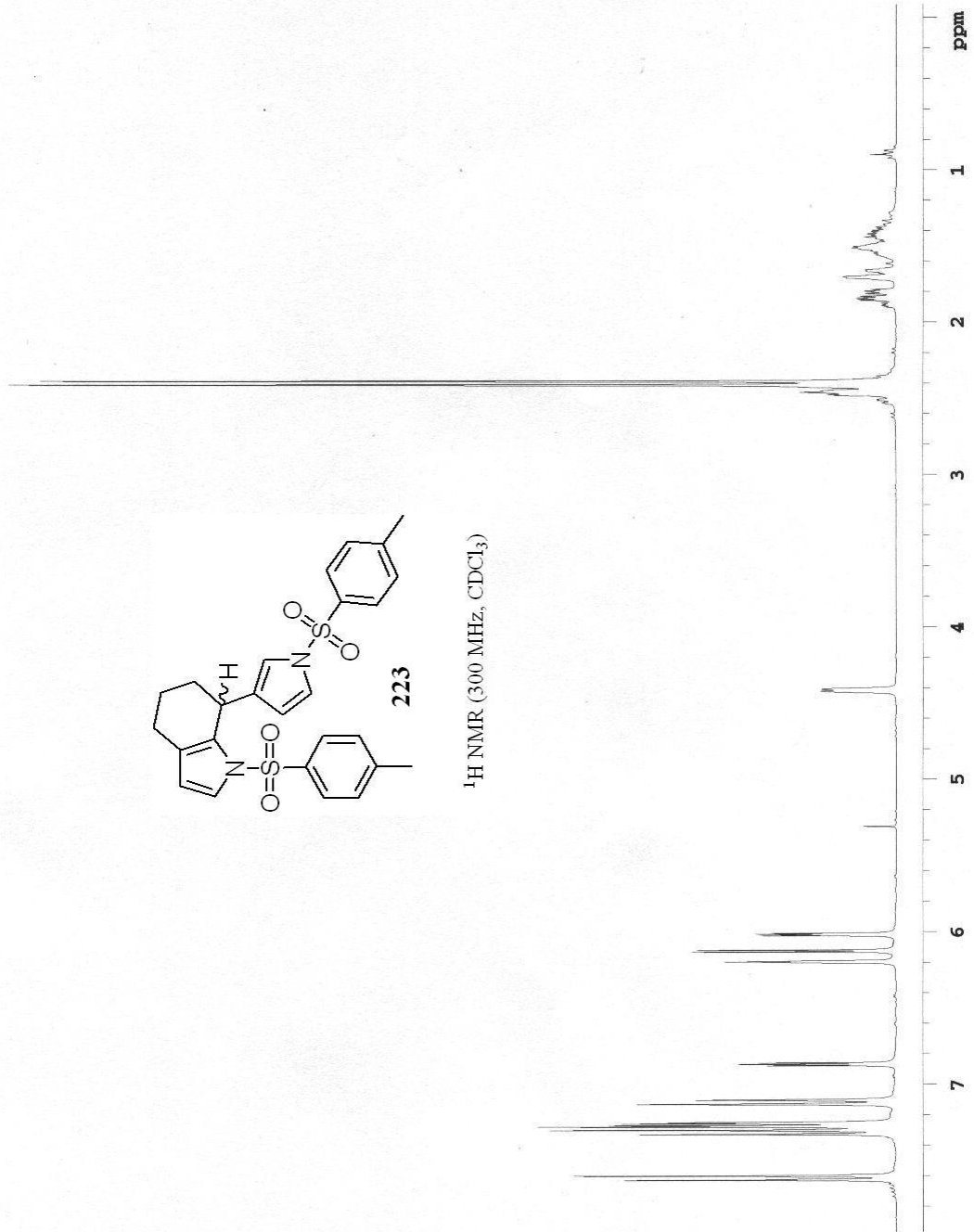
$^1\text{H NMR}$ (300 MHz, CDCl_3)

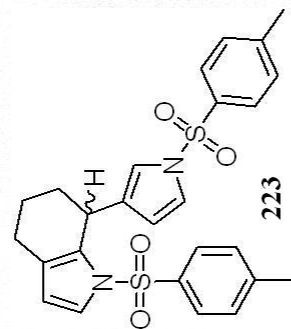




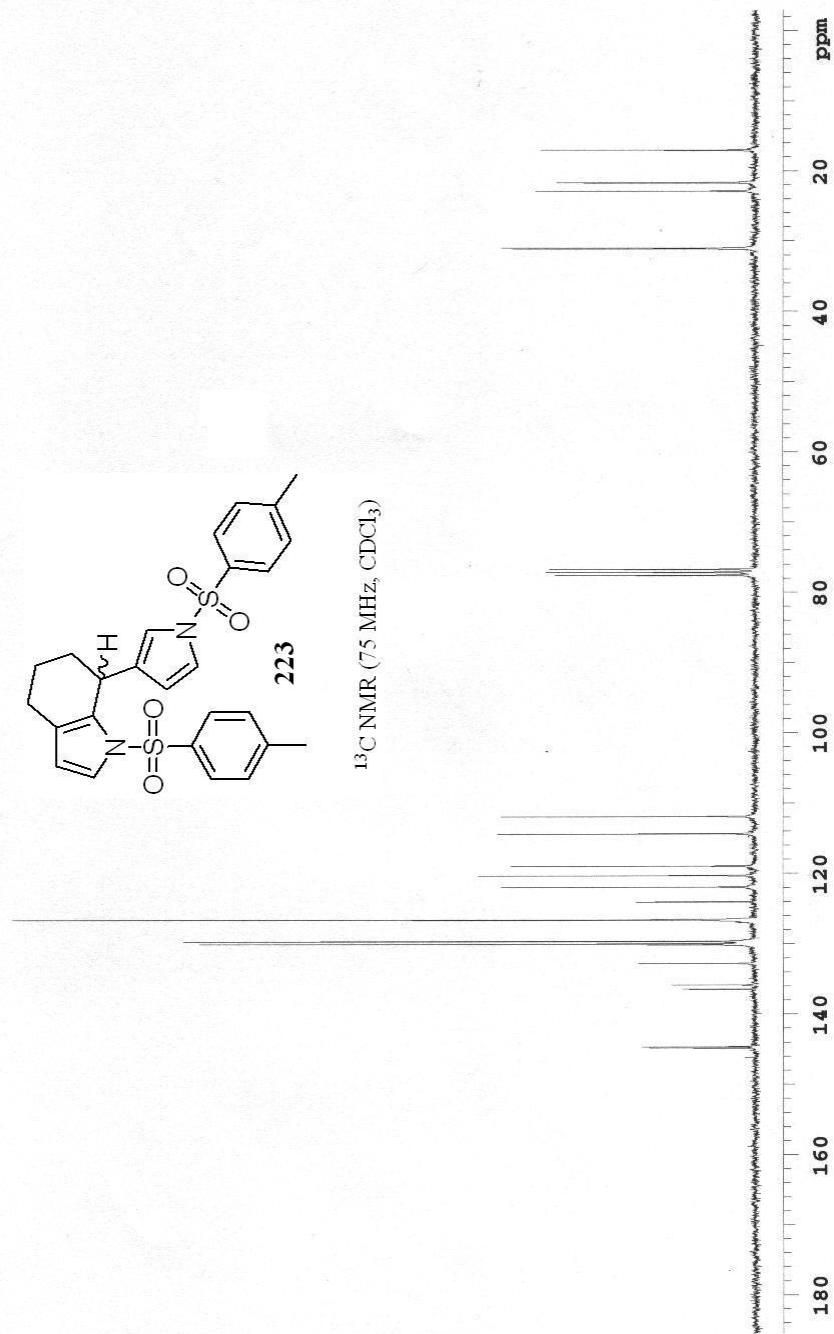


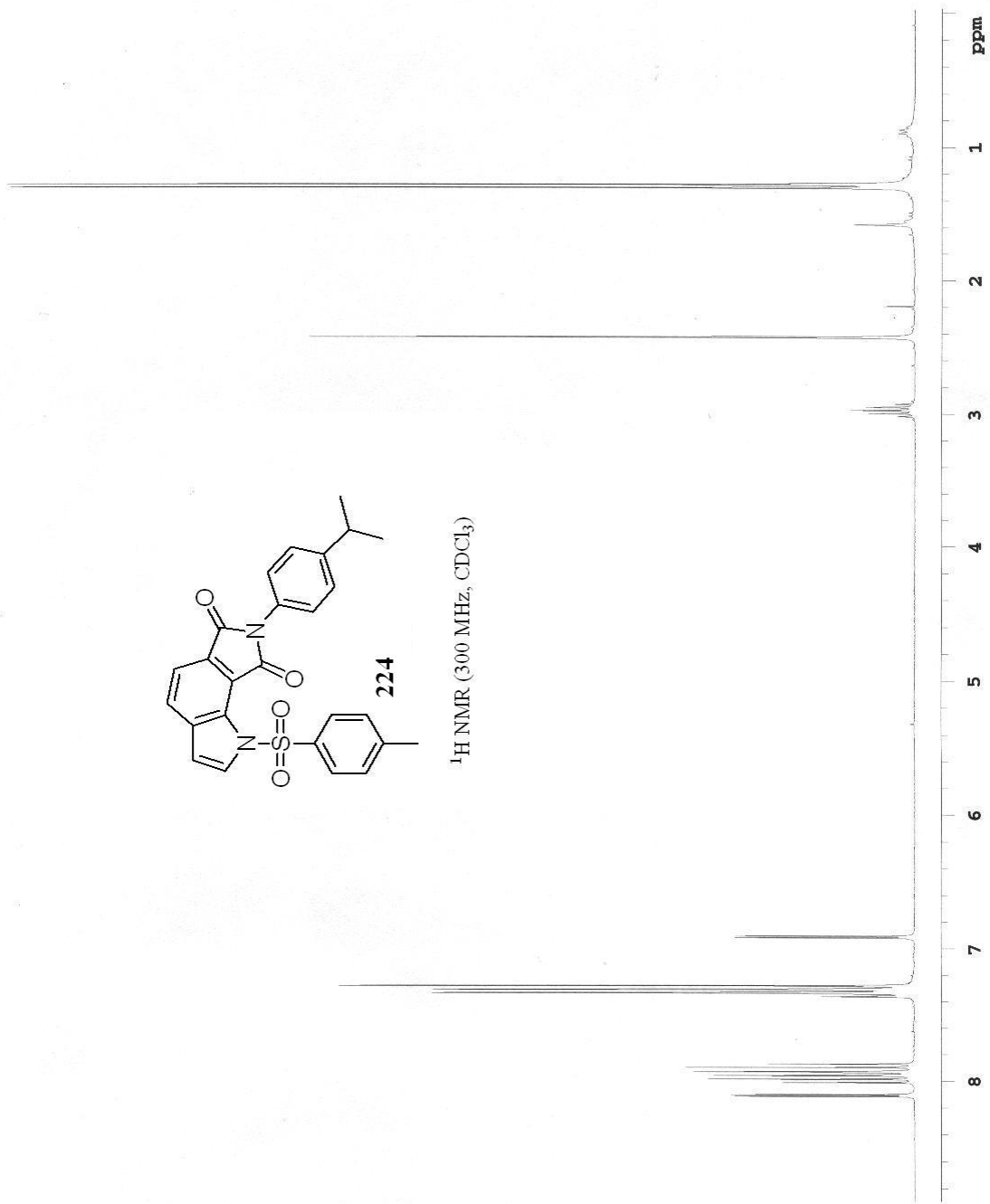
¹H NMR (300 MHz, CDCl₃)

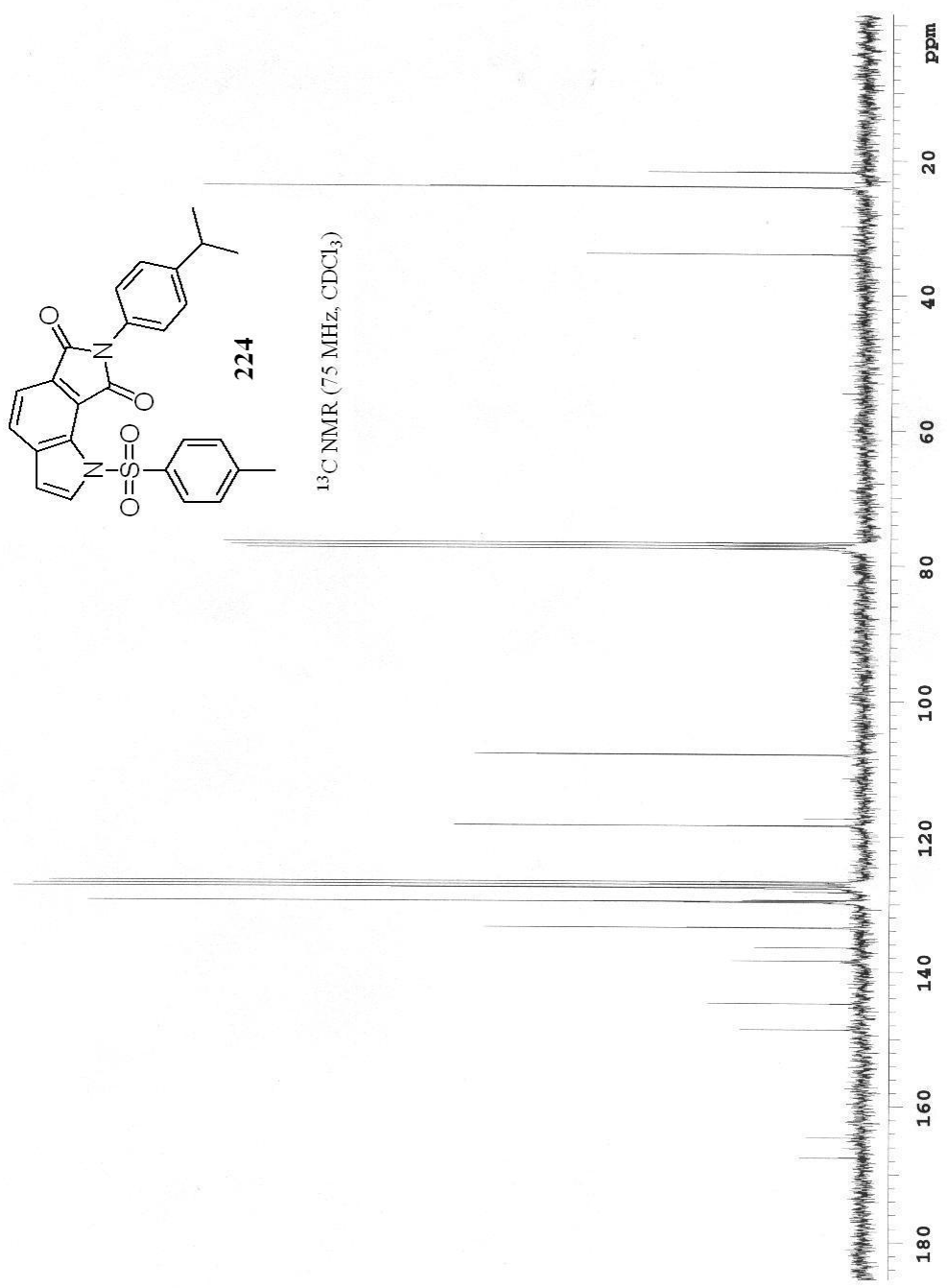


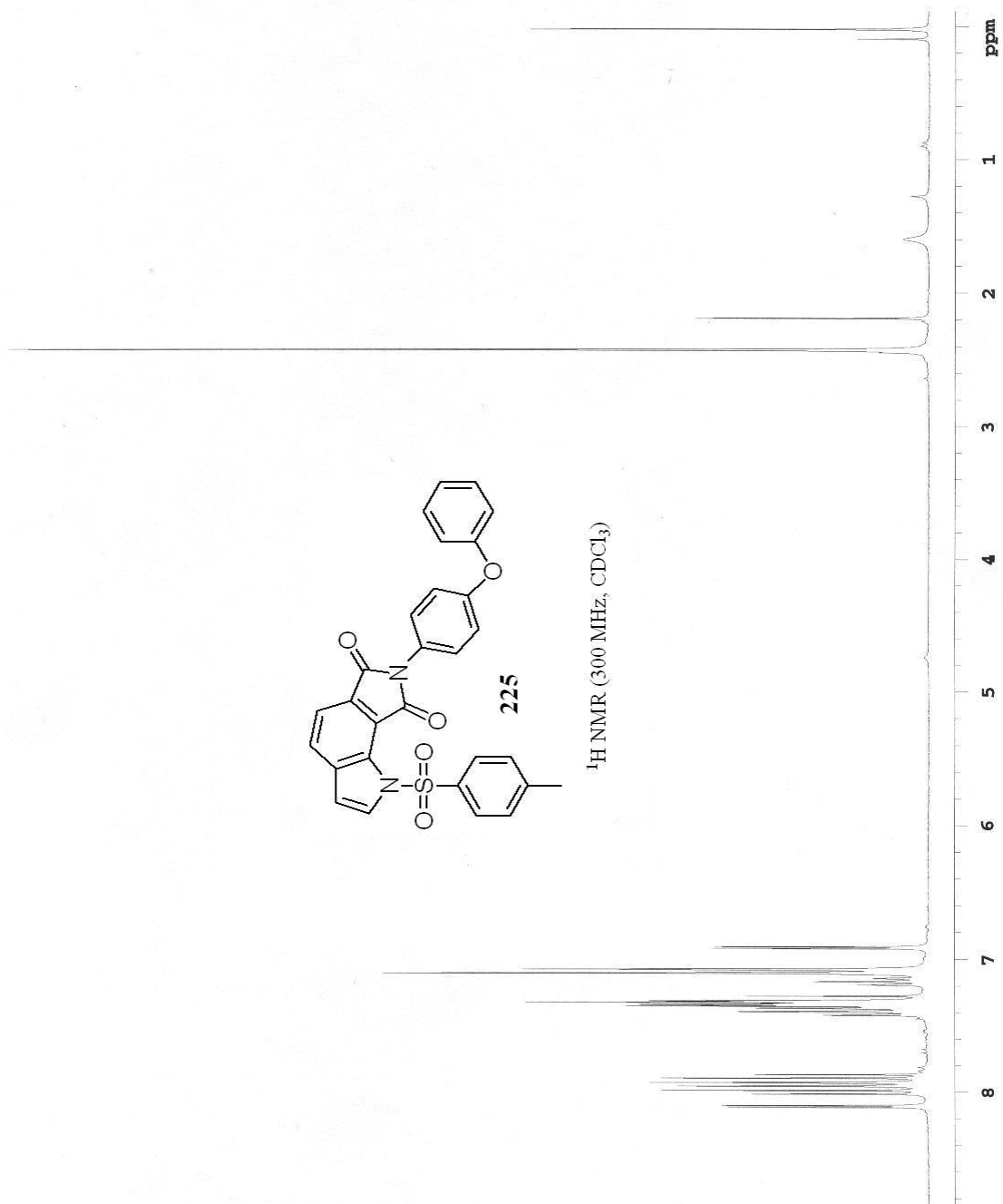


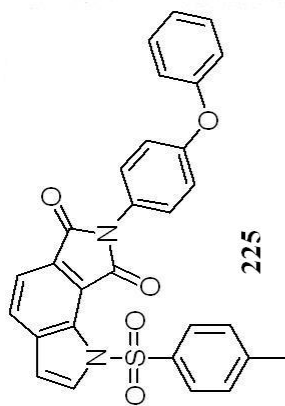
^{13}C NMR (75 MHz, CDCl_3)



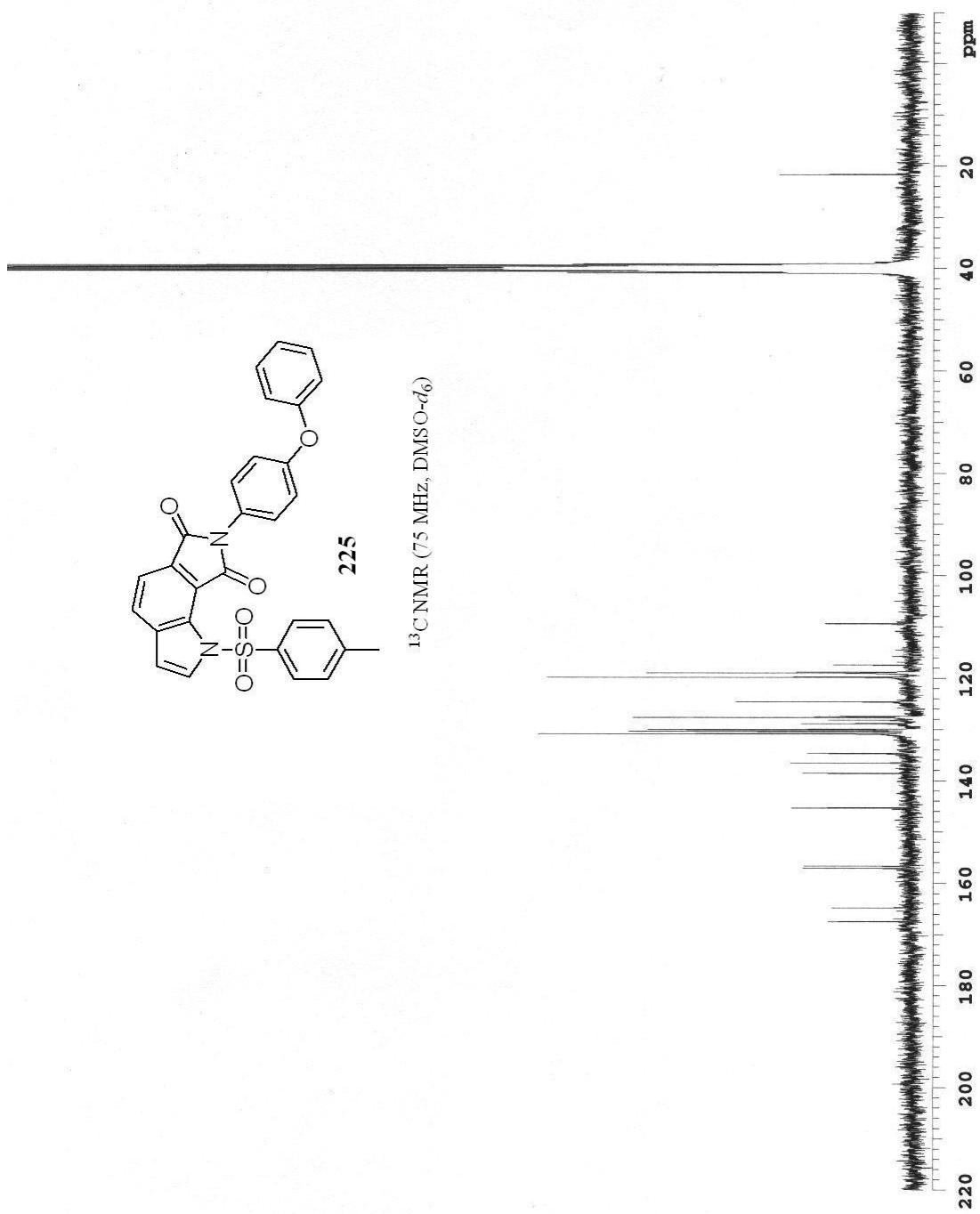


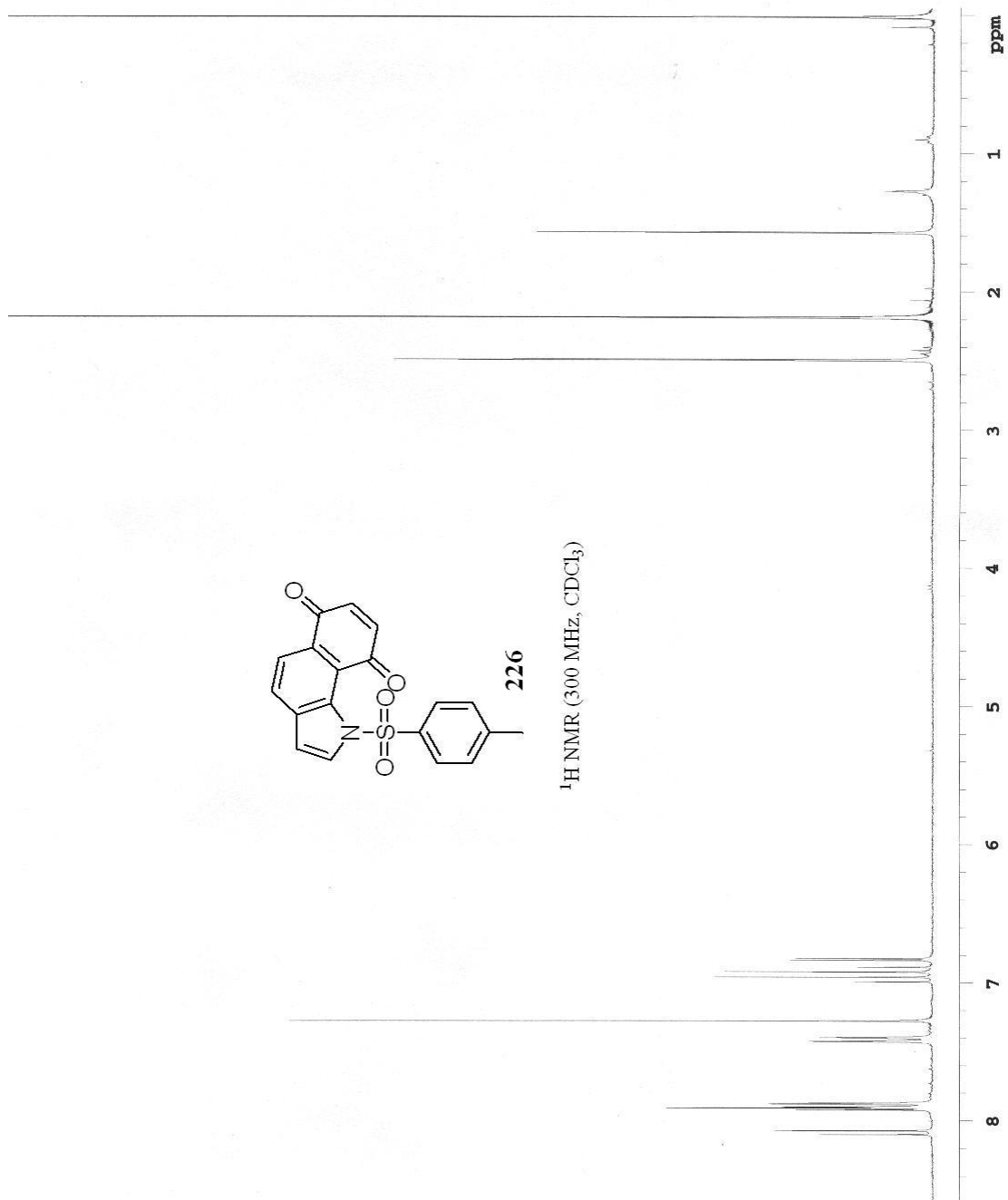


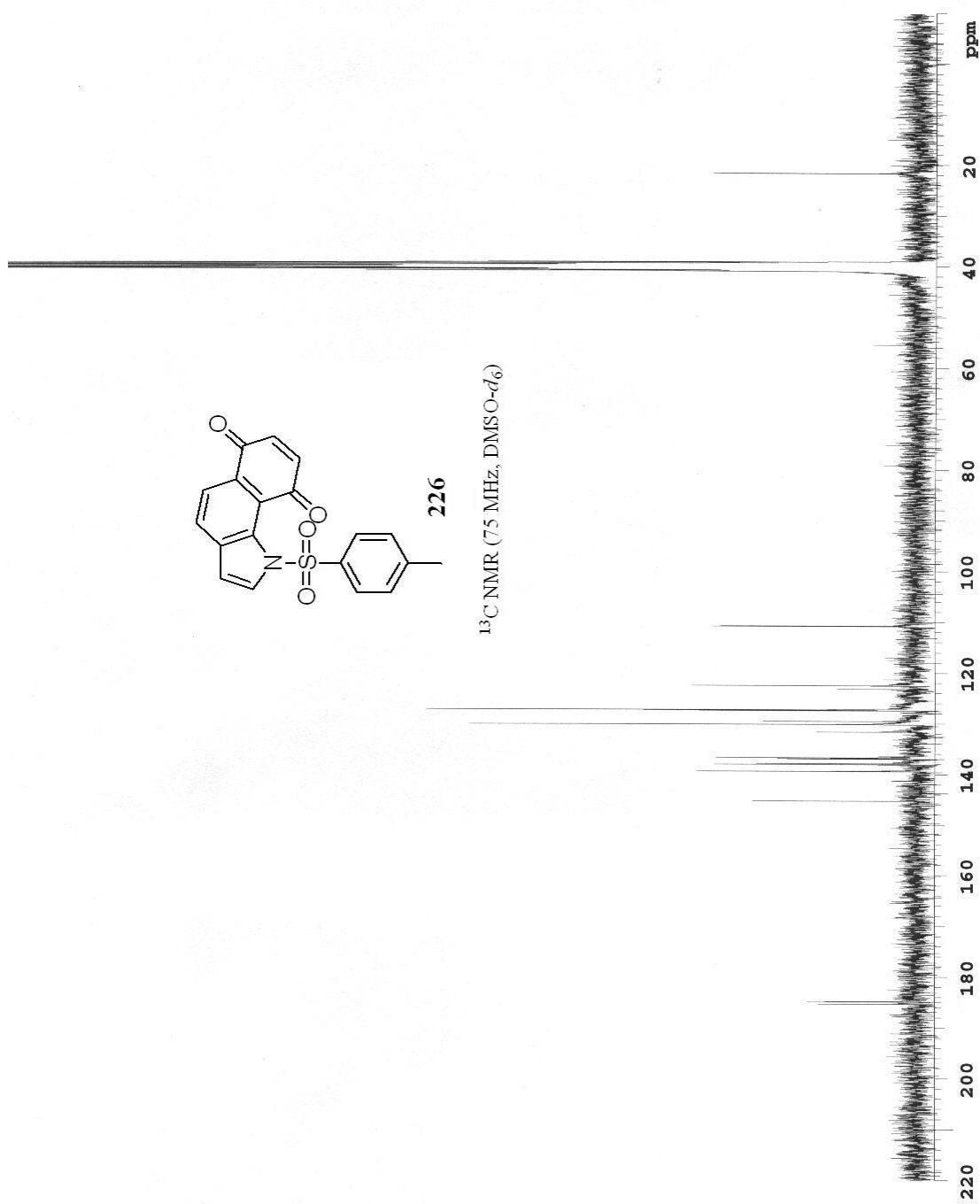


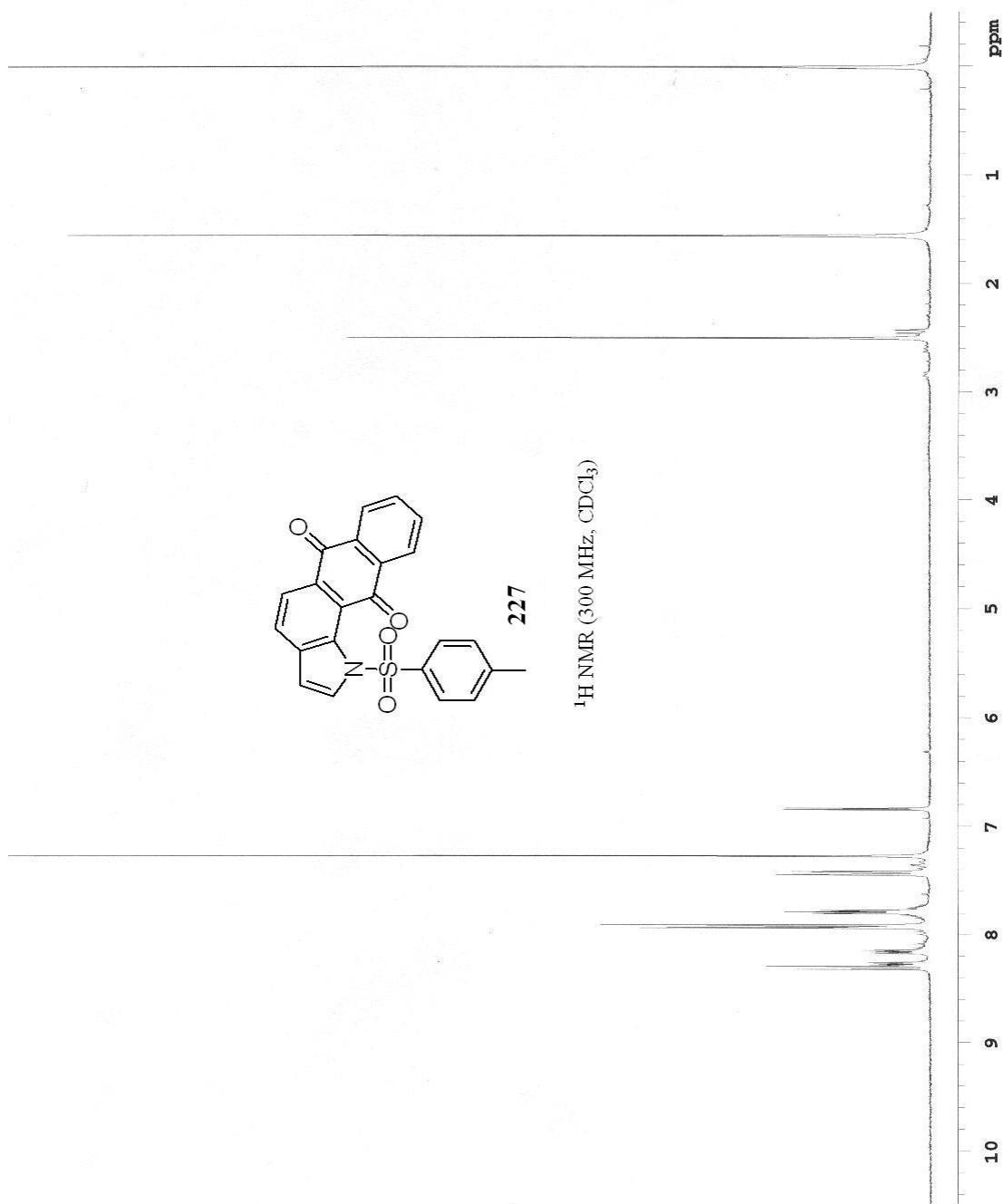


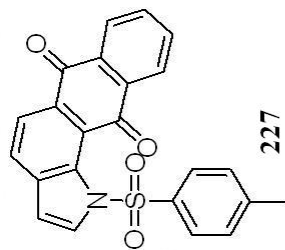
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)



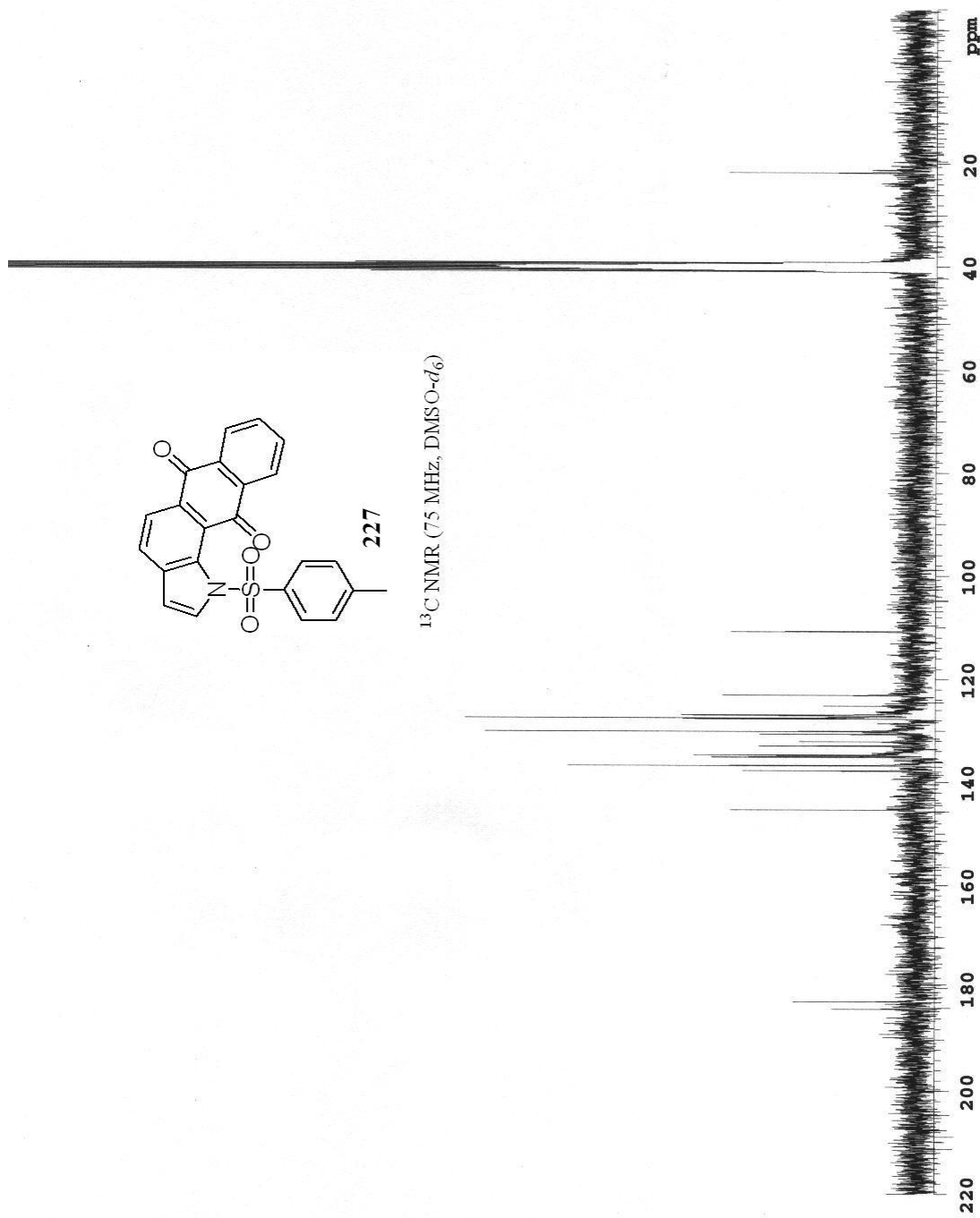


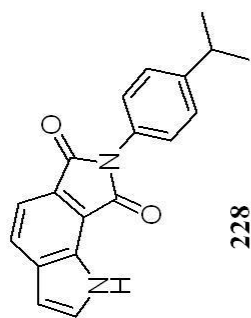






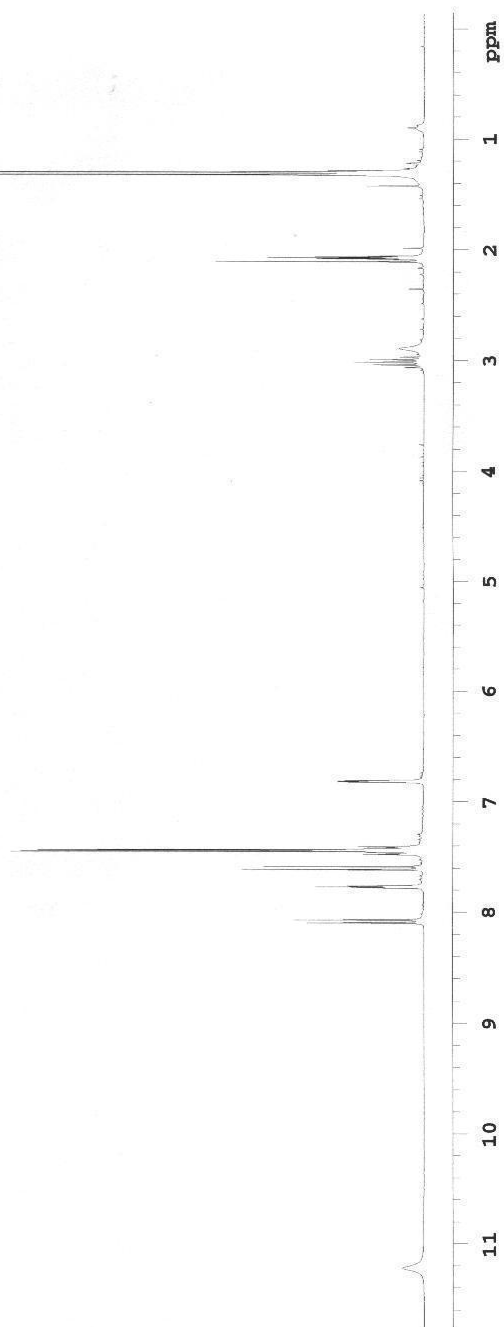
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)

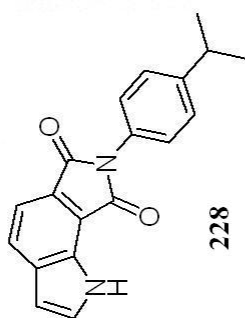




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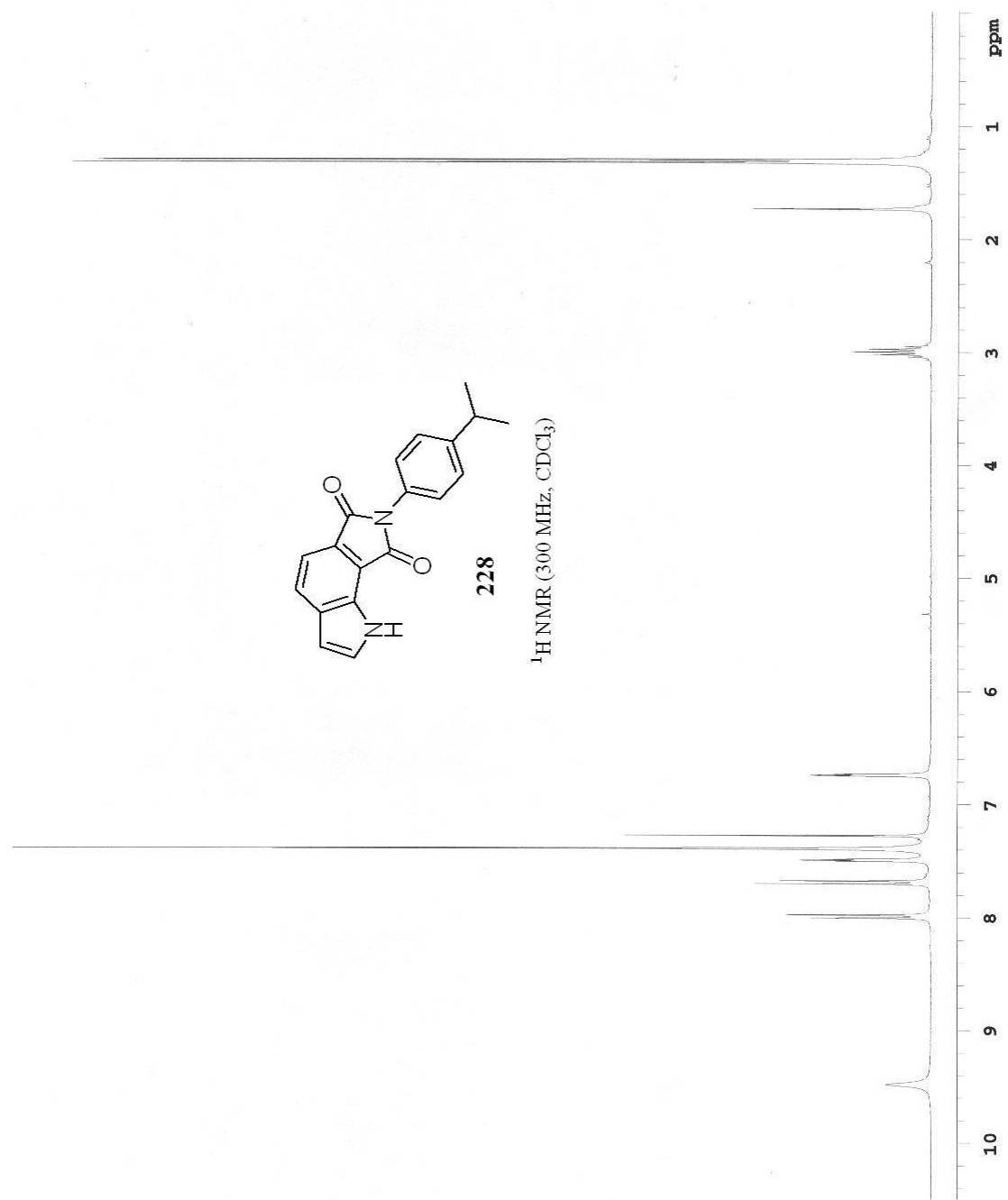
$^1\text{H NMR}$ (300 MHz, acetone- d_6)

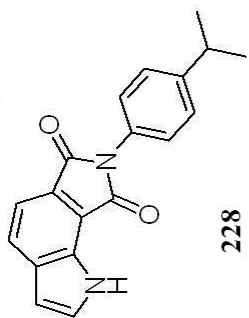




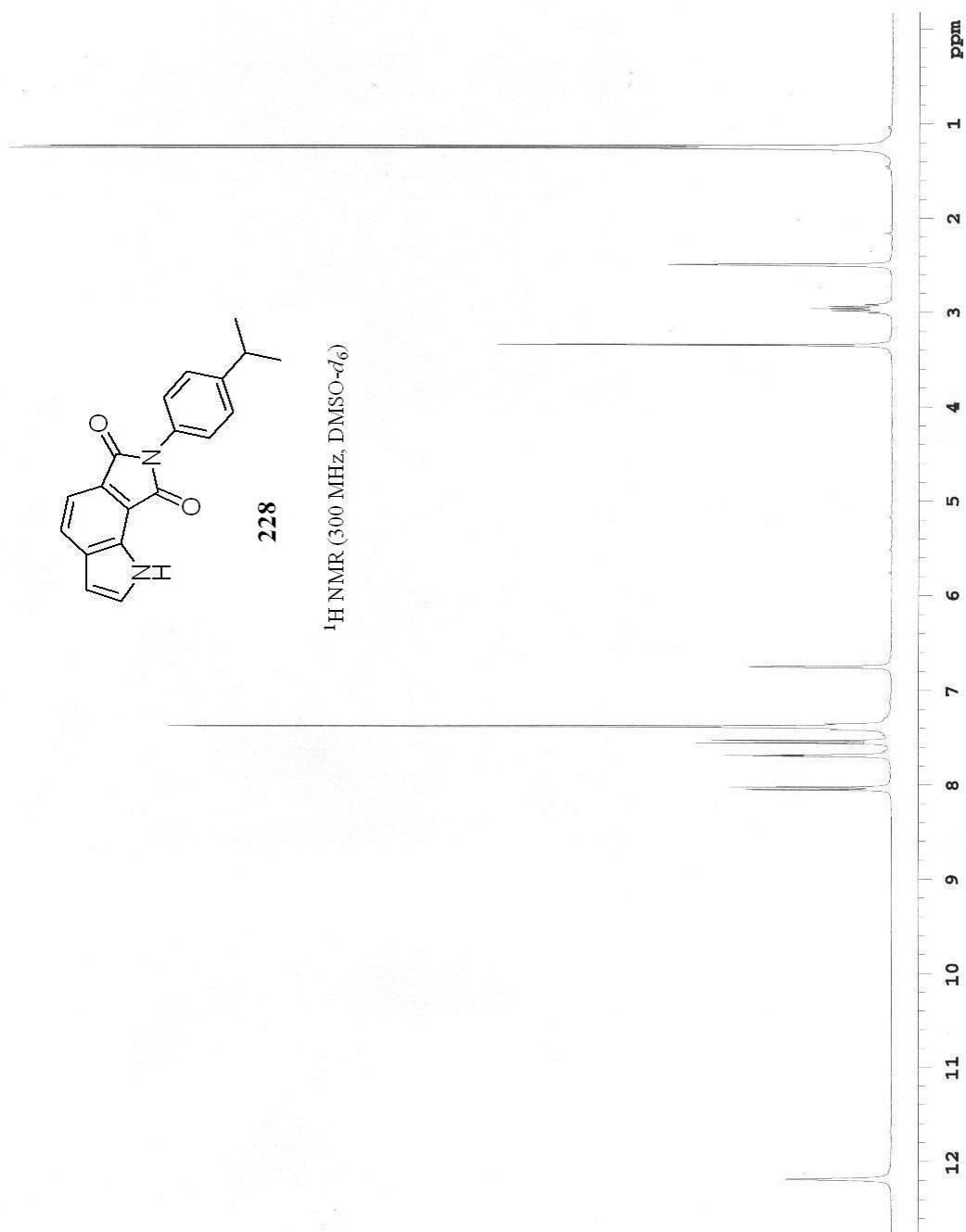
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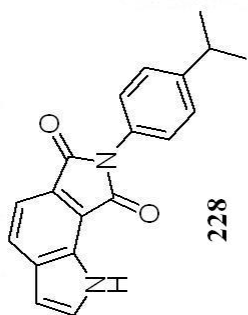
¹H NMR (300 MHz, CDCl₃)



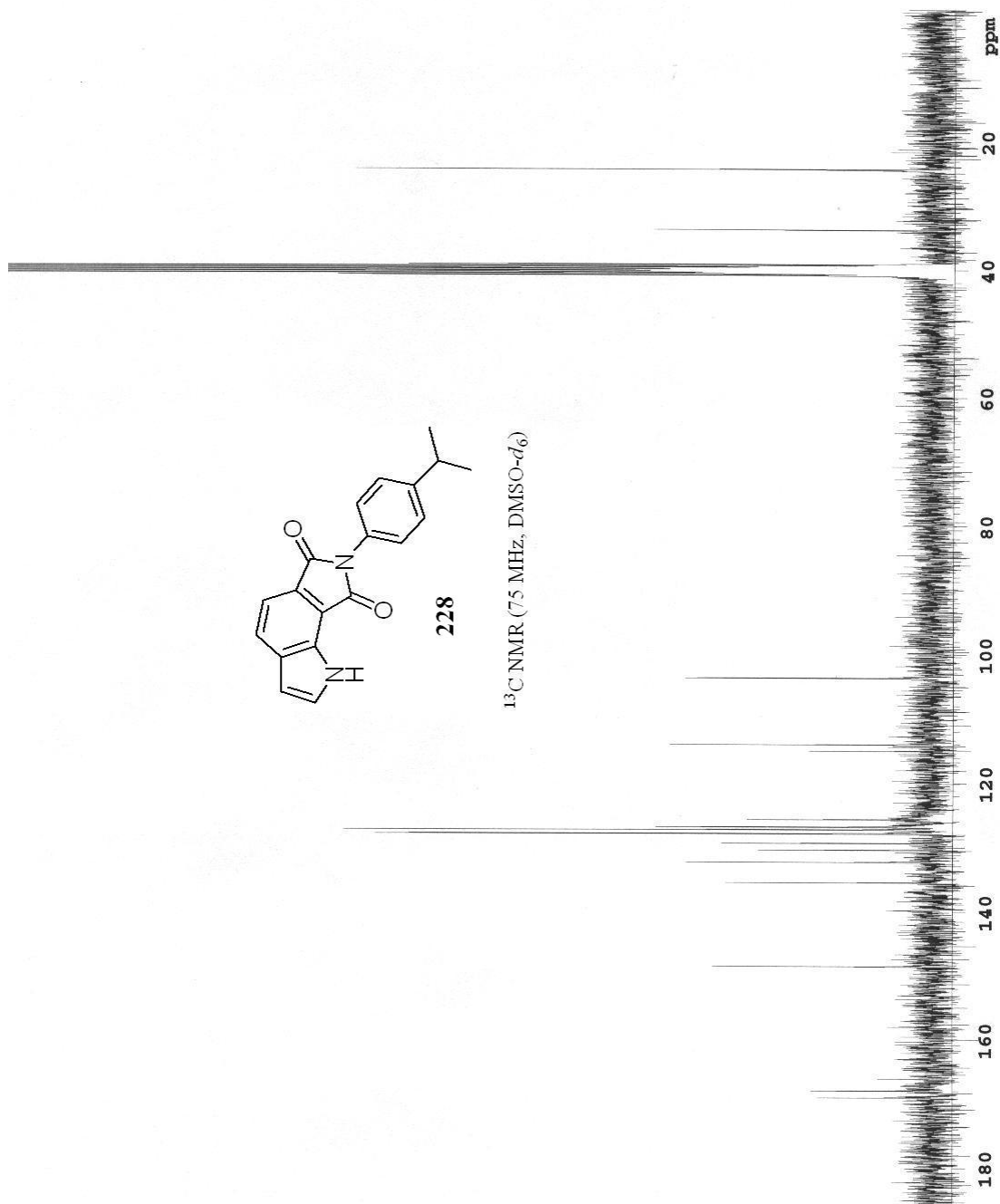


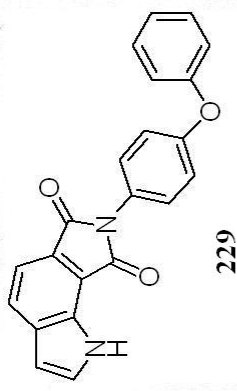
¹H NMR (300 MHz, DMSO-d₆)



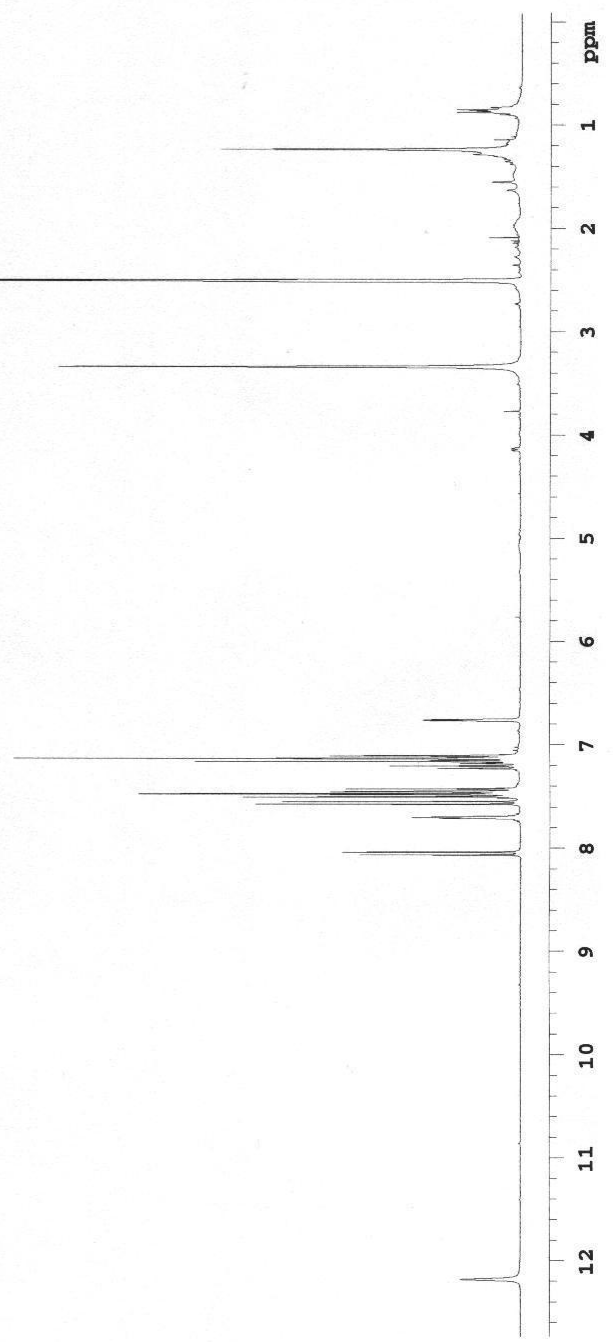


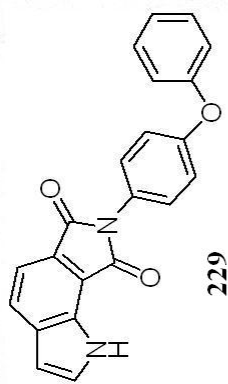
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)



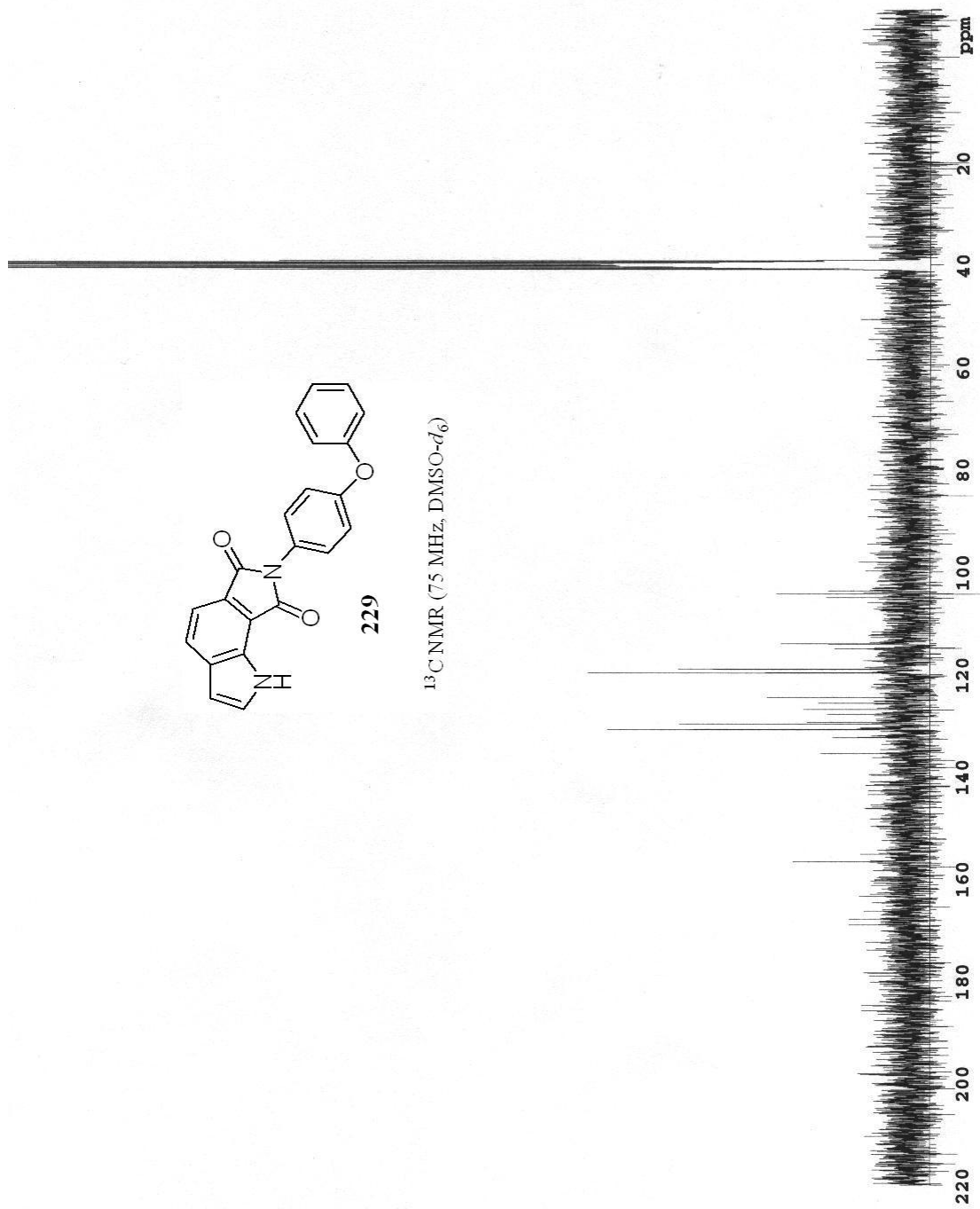


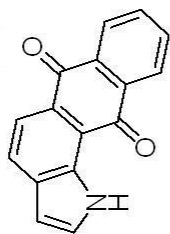
¹H NMR (300 MHz, DMSO-*d*₆)





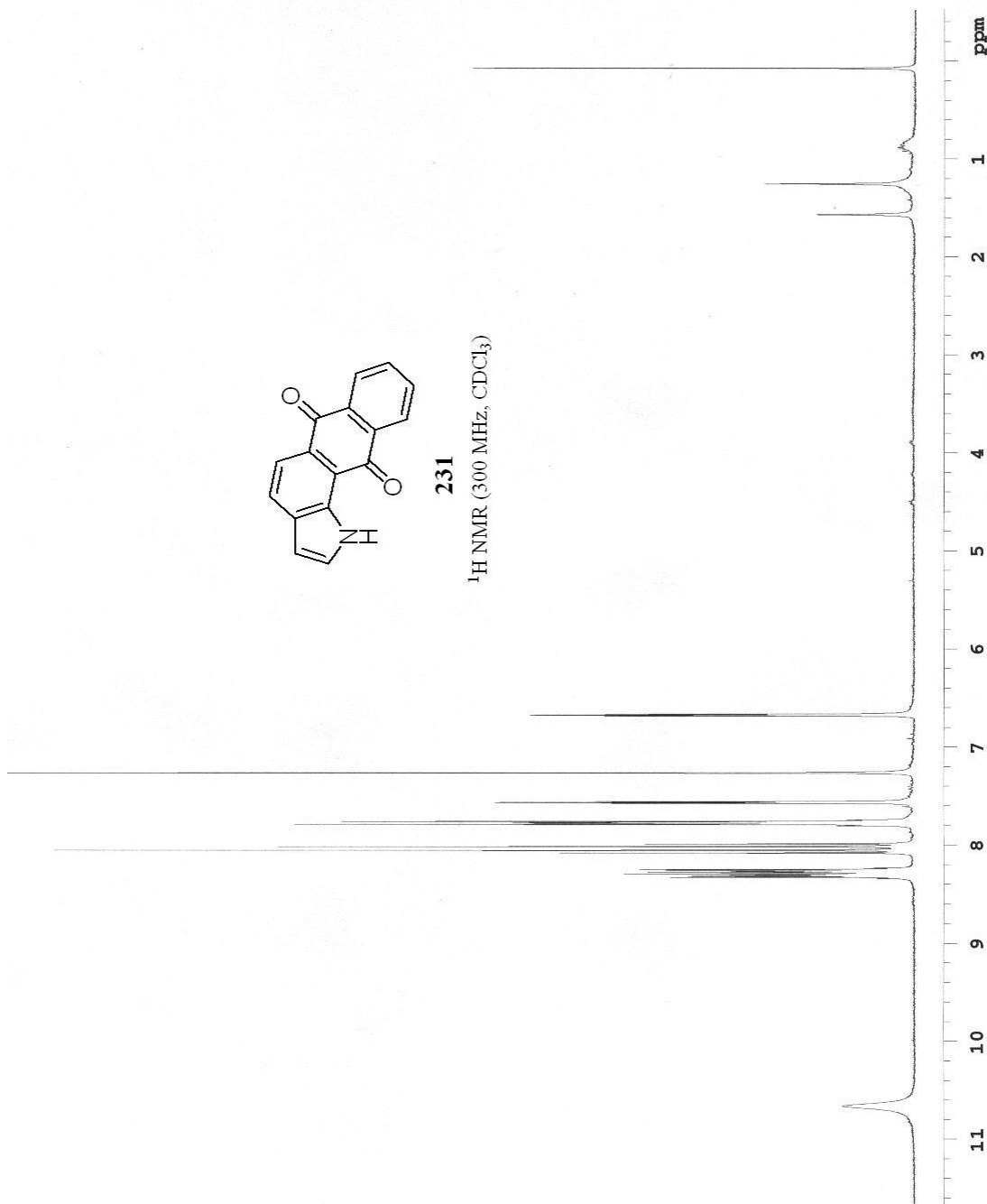
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)

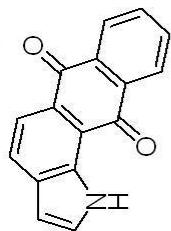




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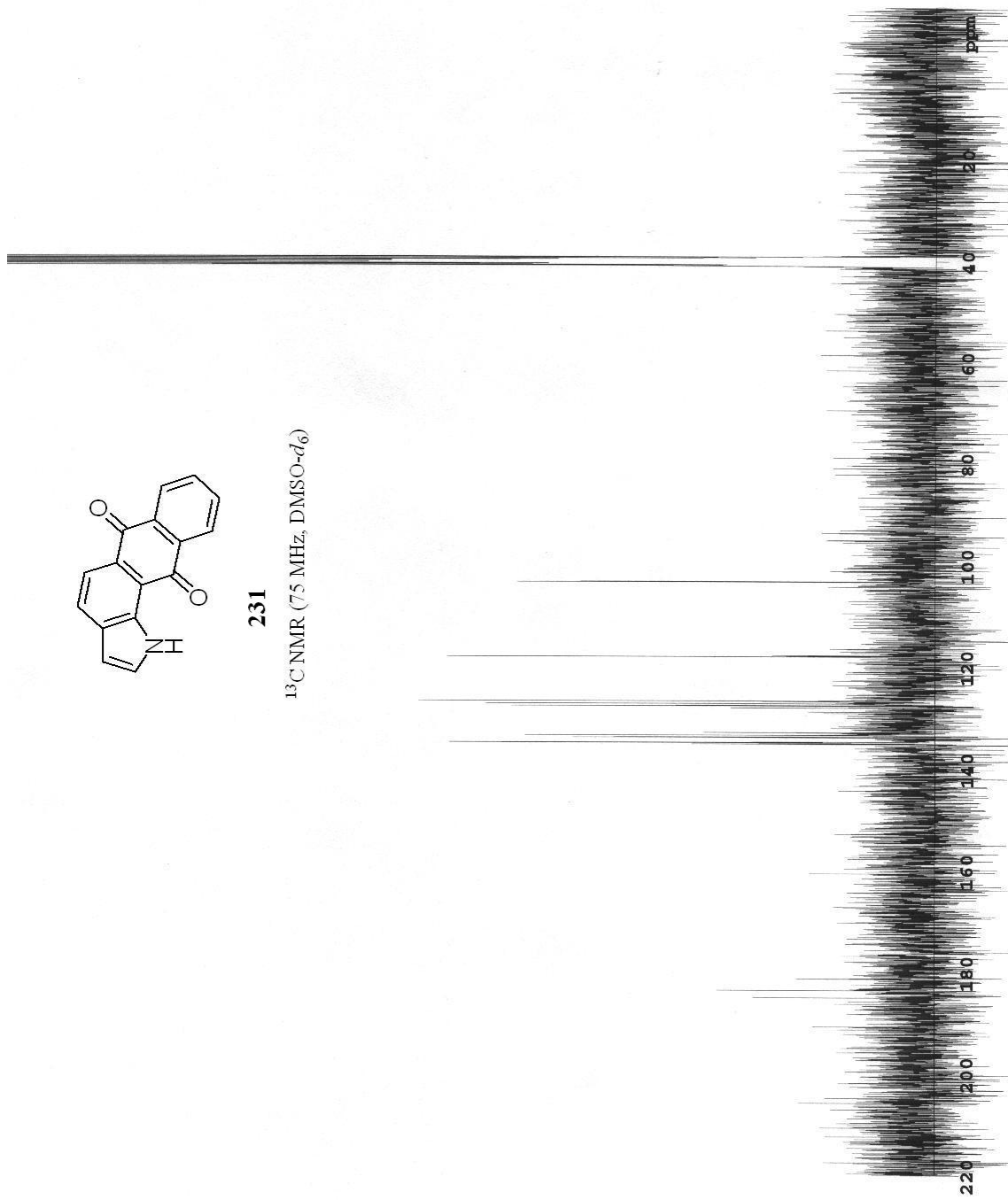
¹H NMR (300 MHz, CDCl₃)

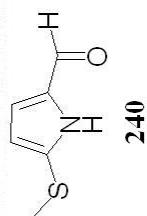




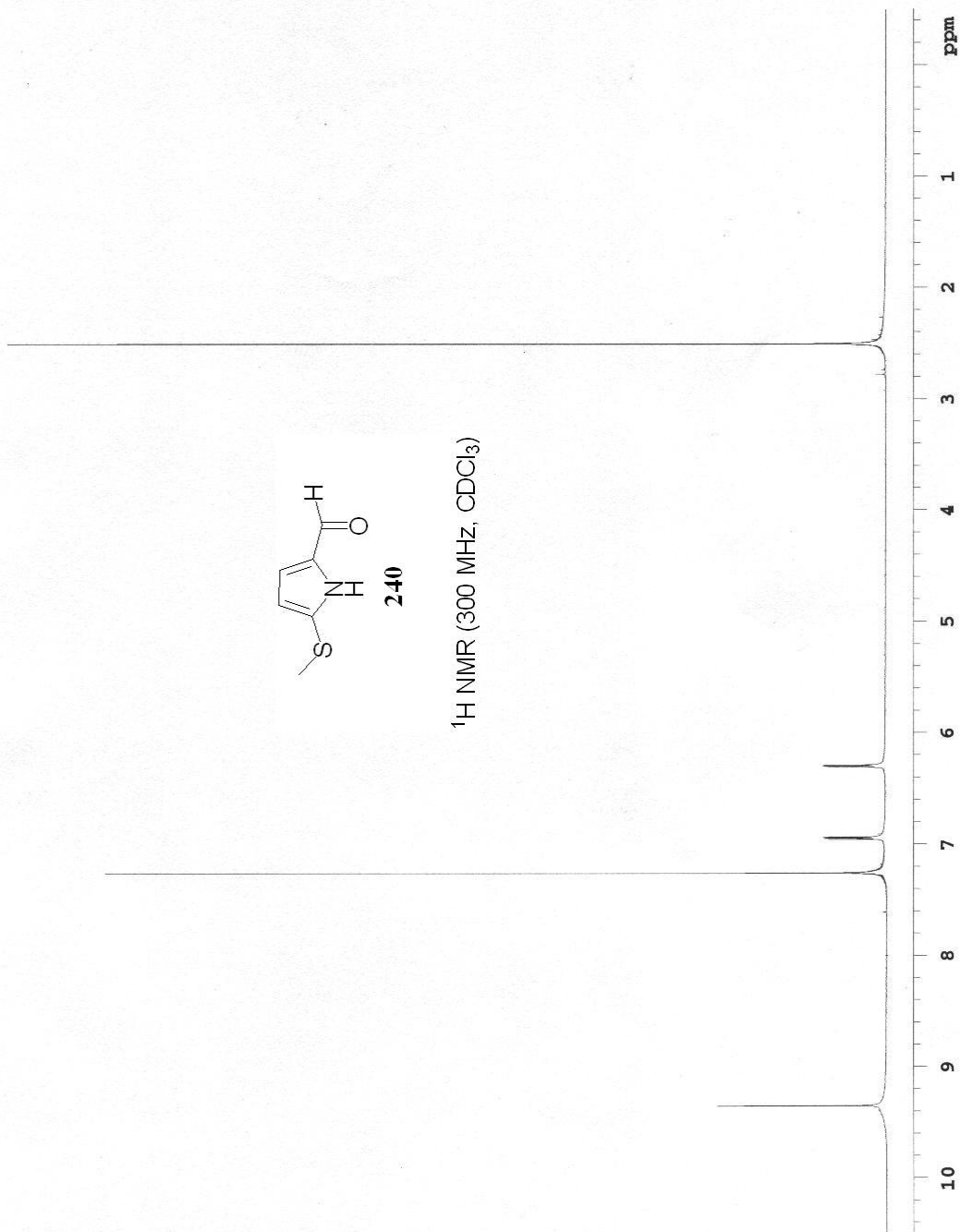
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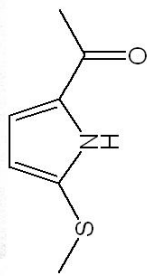
^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)





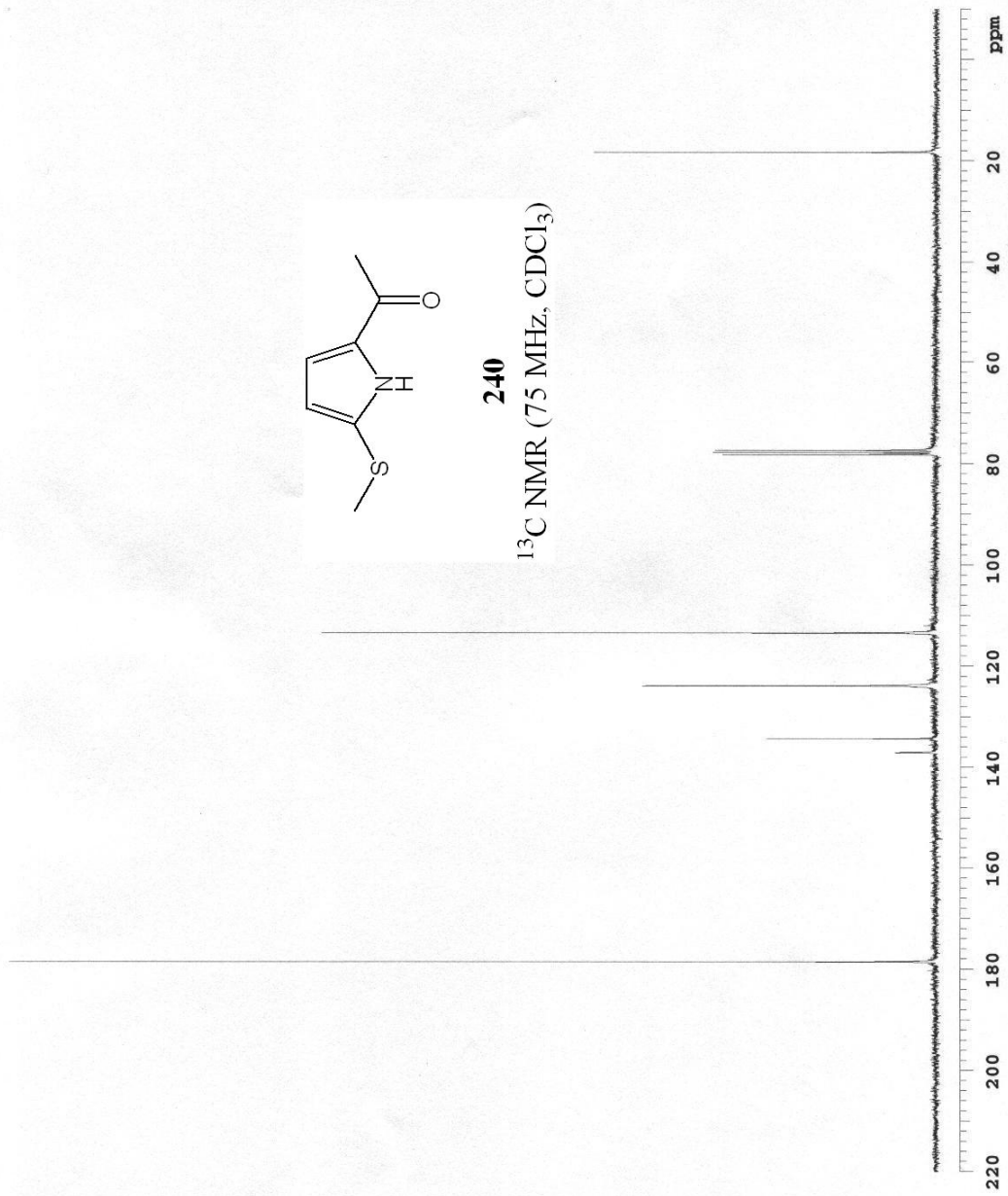
¹H NMR (300 MHz, CDCl₃)

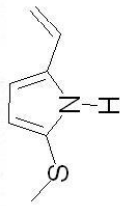




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^{13}C NMR (75 MHz, CDCl_3)

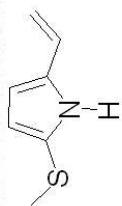




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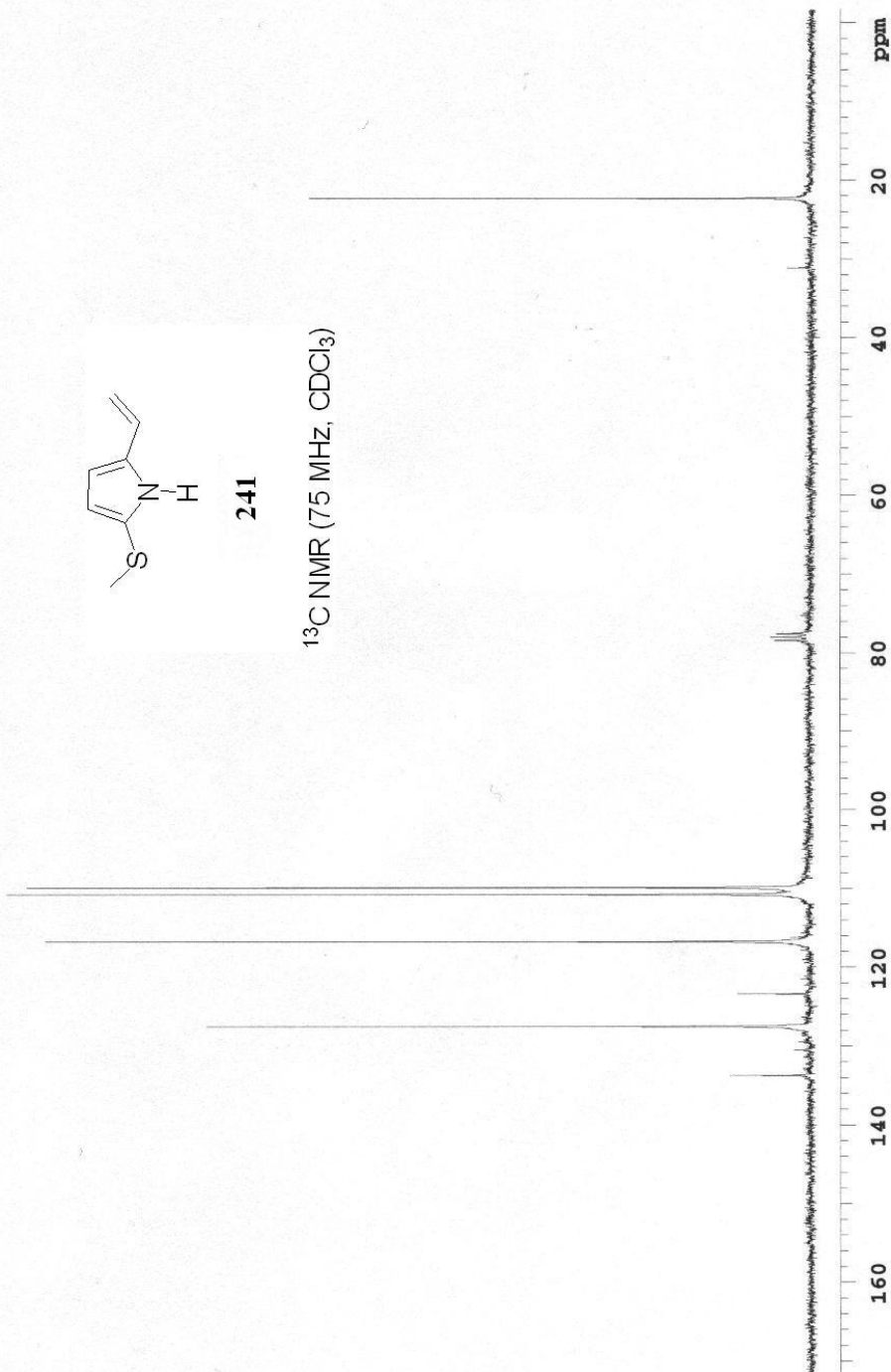
¹H NMR (300 MHz, CDCl₃)

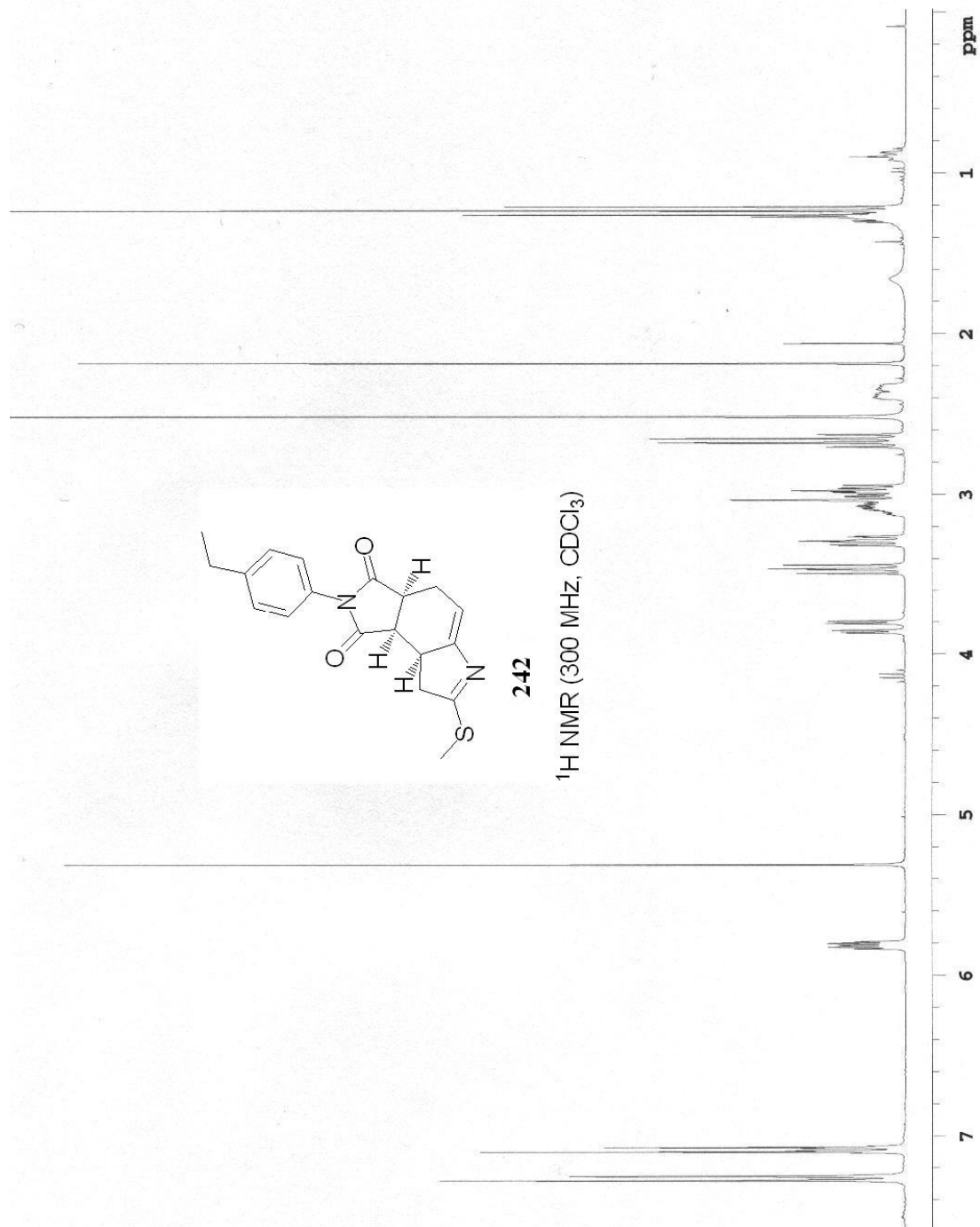


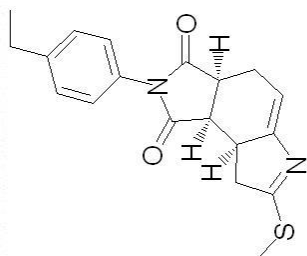


241

^{13}C NMR (75 MHz, CDCl_3)

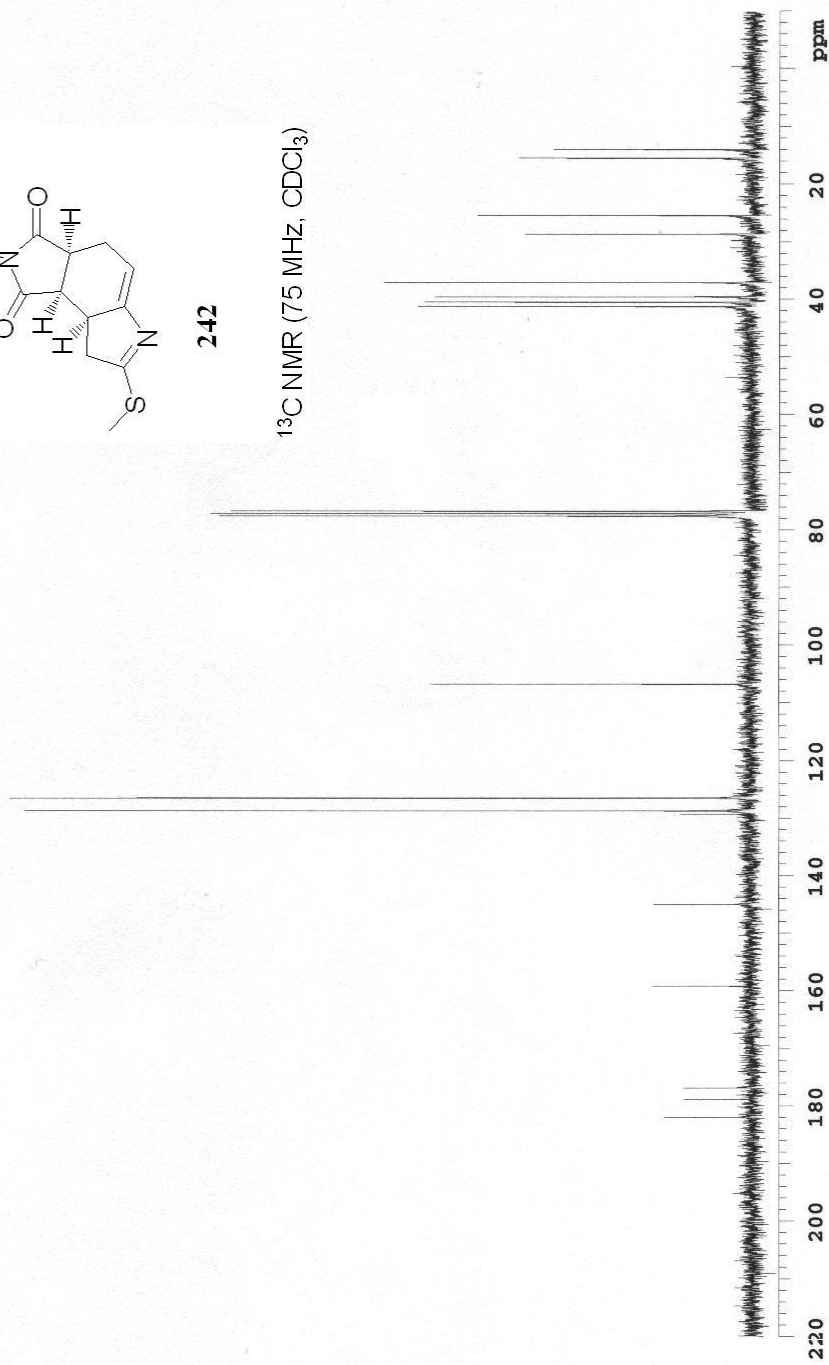


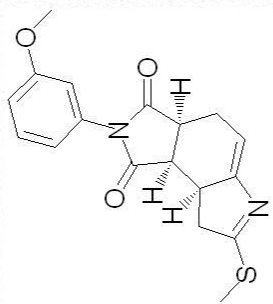




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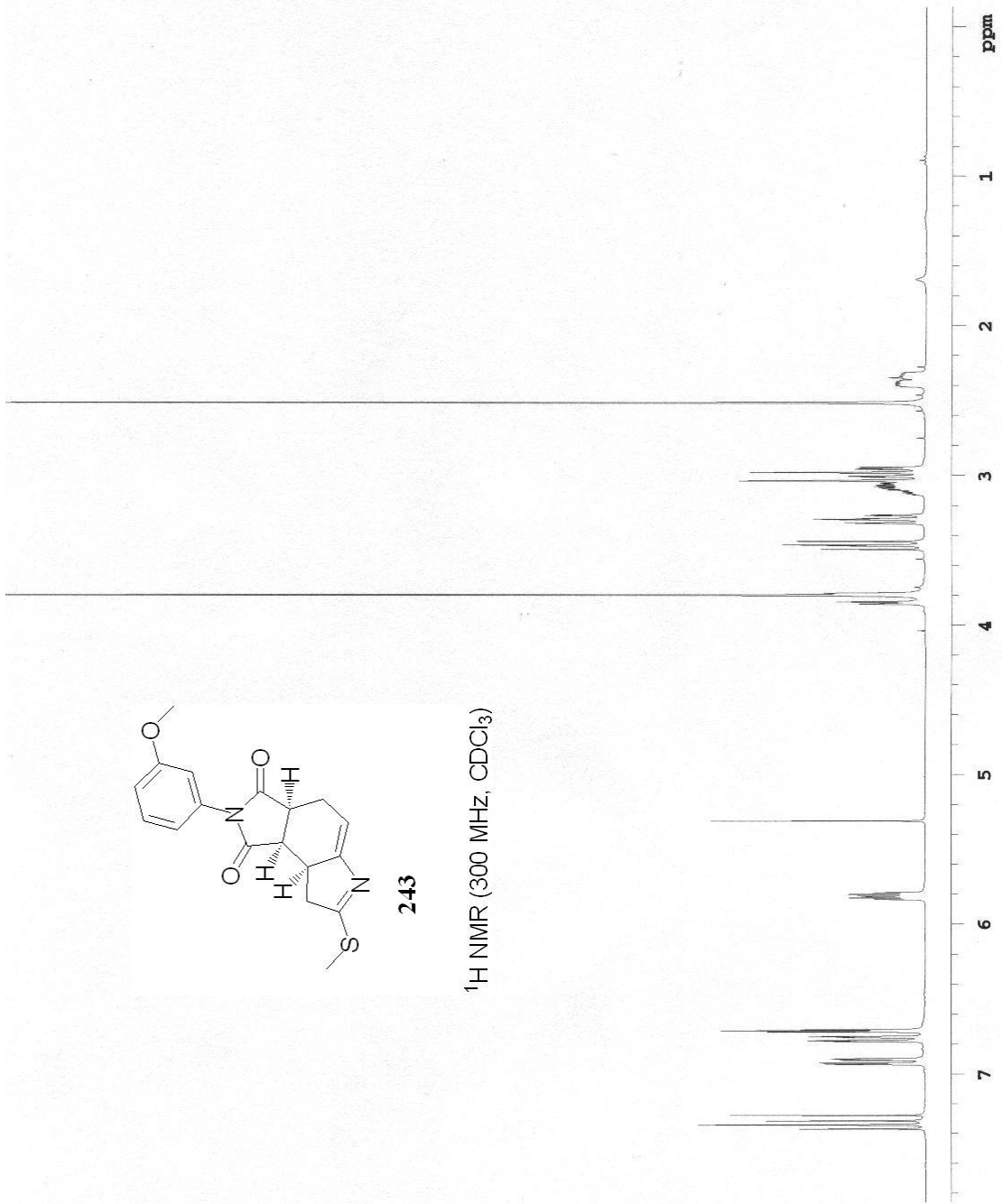
^{13}C NMR (75 MHz, CDCl_3)

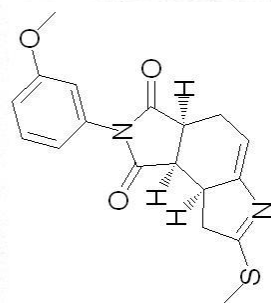




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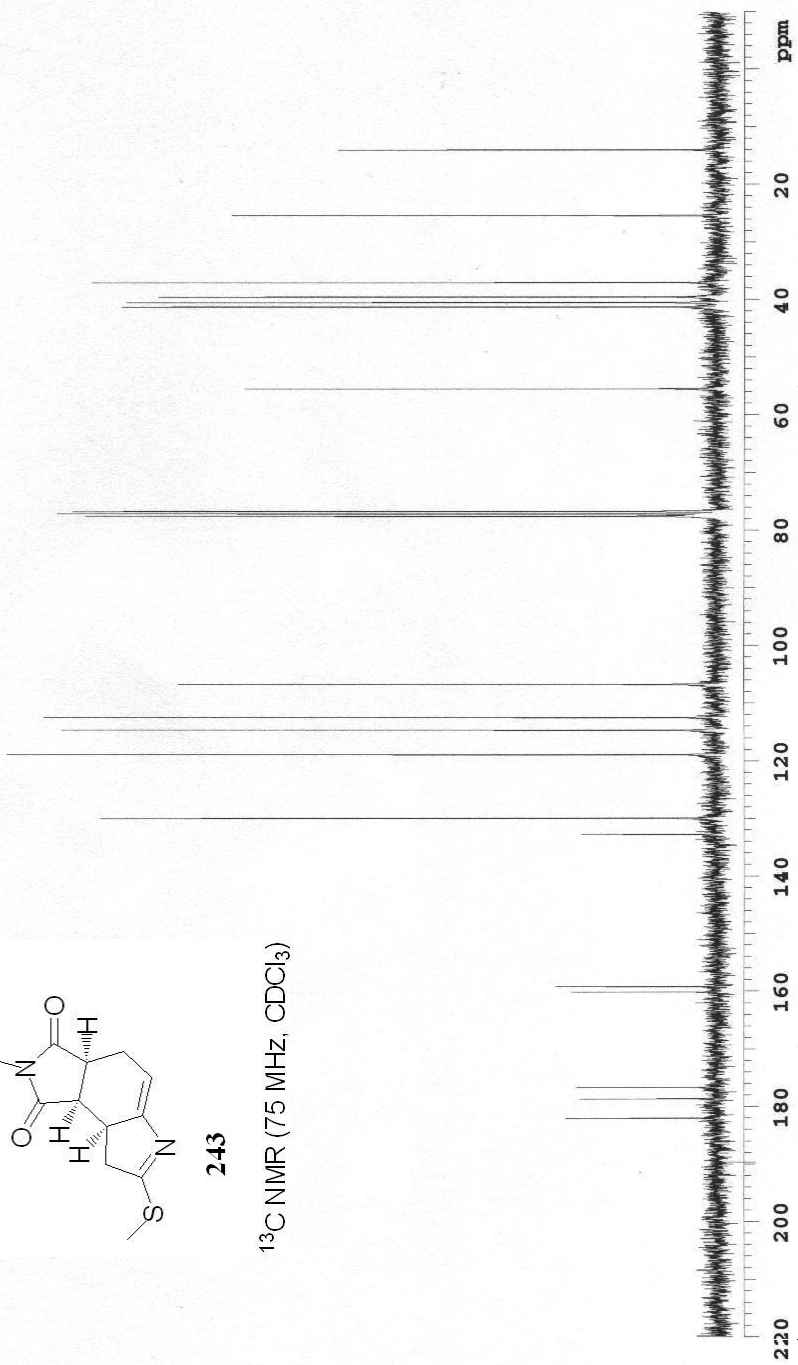
^1H NMR (300 MHz, CDCl_3)

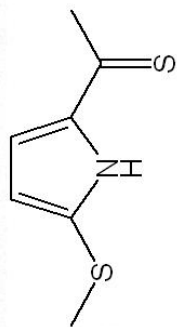




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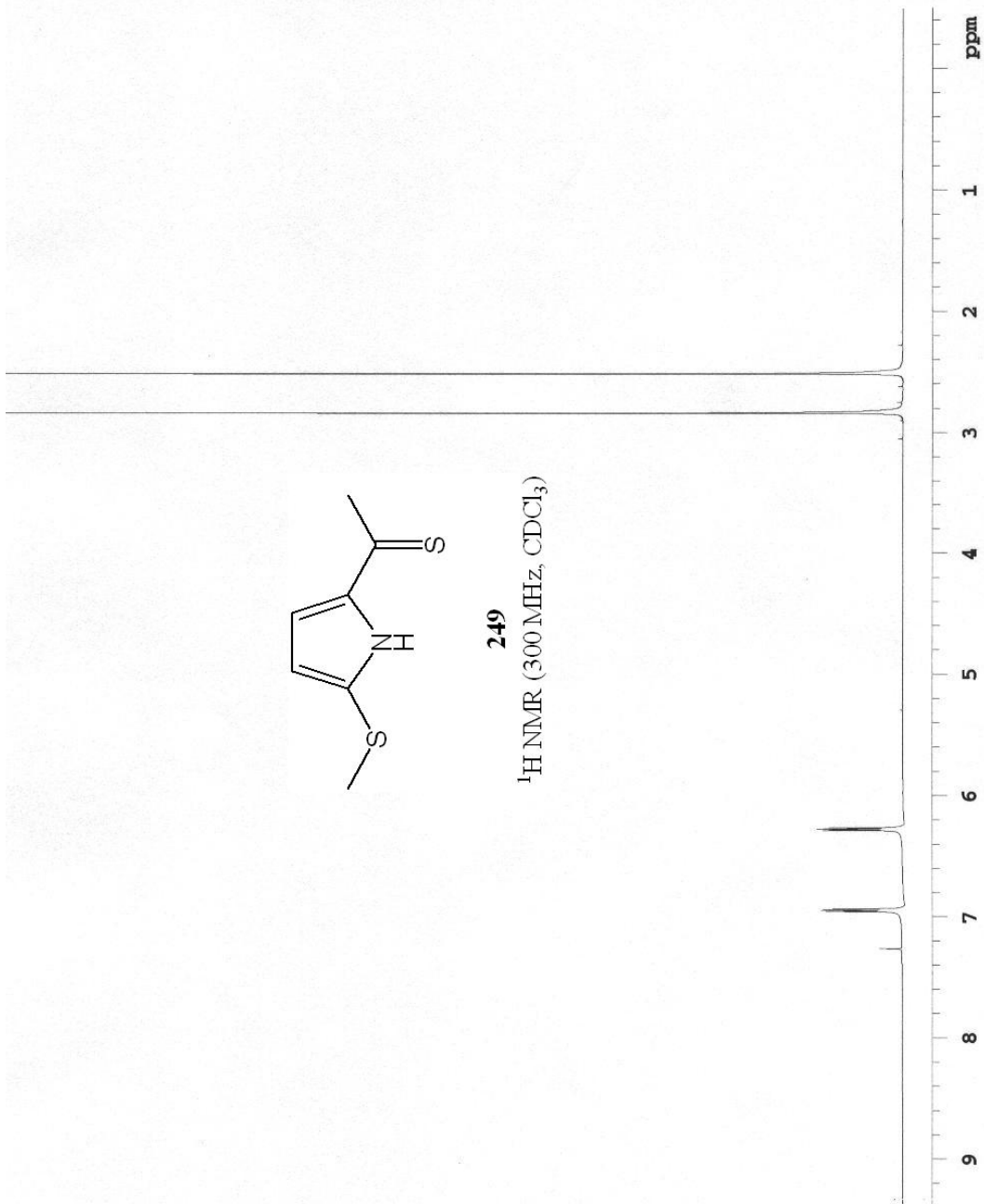
^{13}C NMR (75 MHz, CDCl_3)

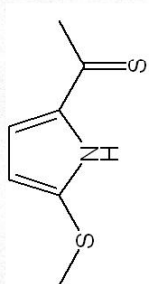




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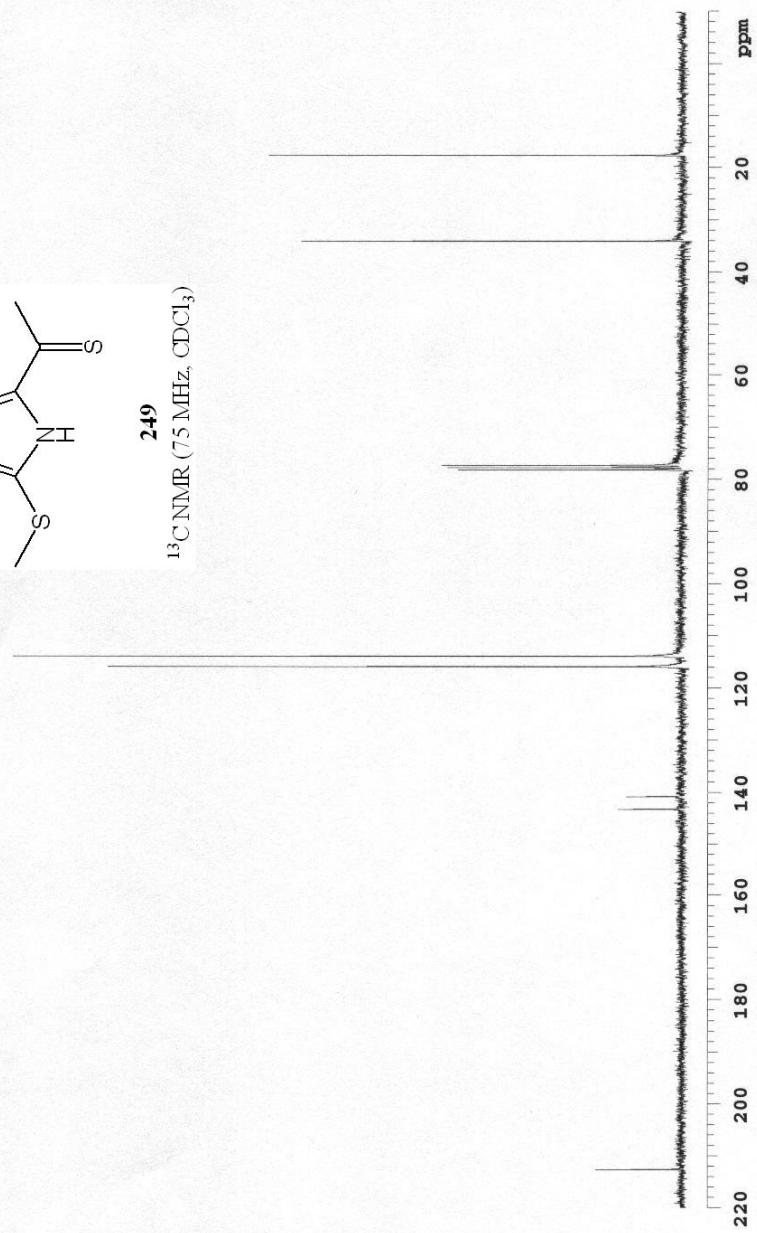
¹H NMR (300 MHz, CDCl₃)

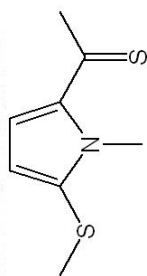




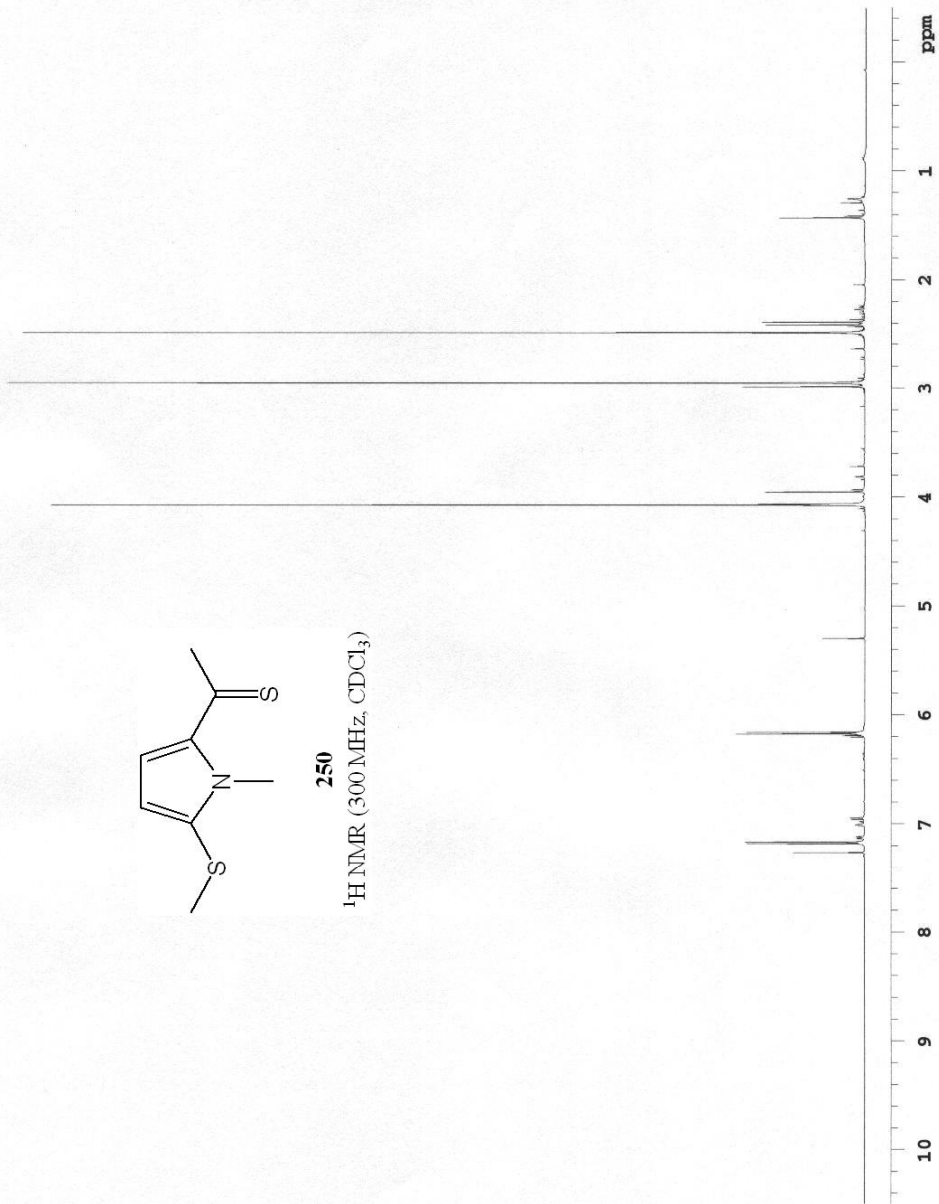
249

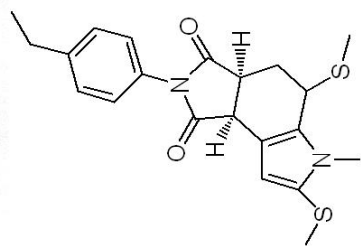
^{13}C NMR (75 MHz, CDCl_3)





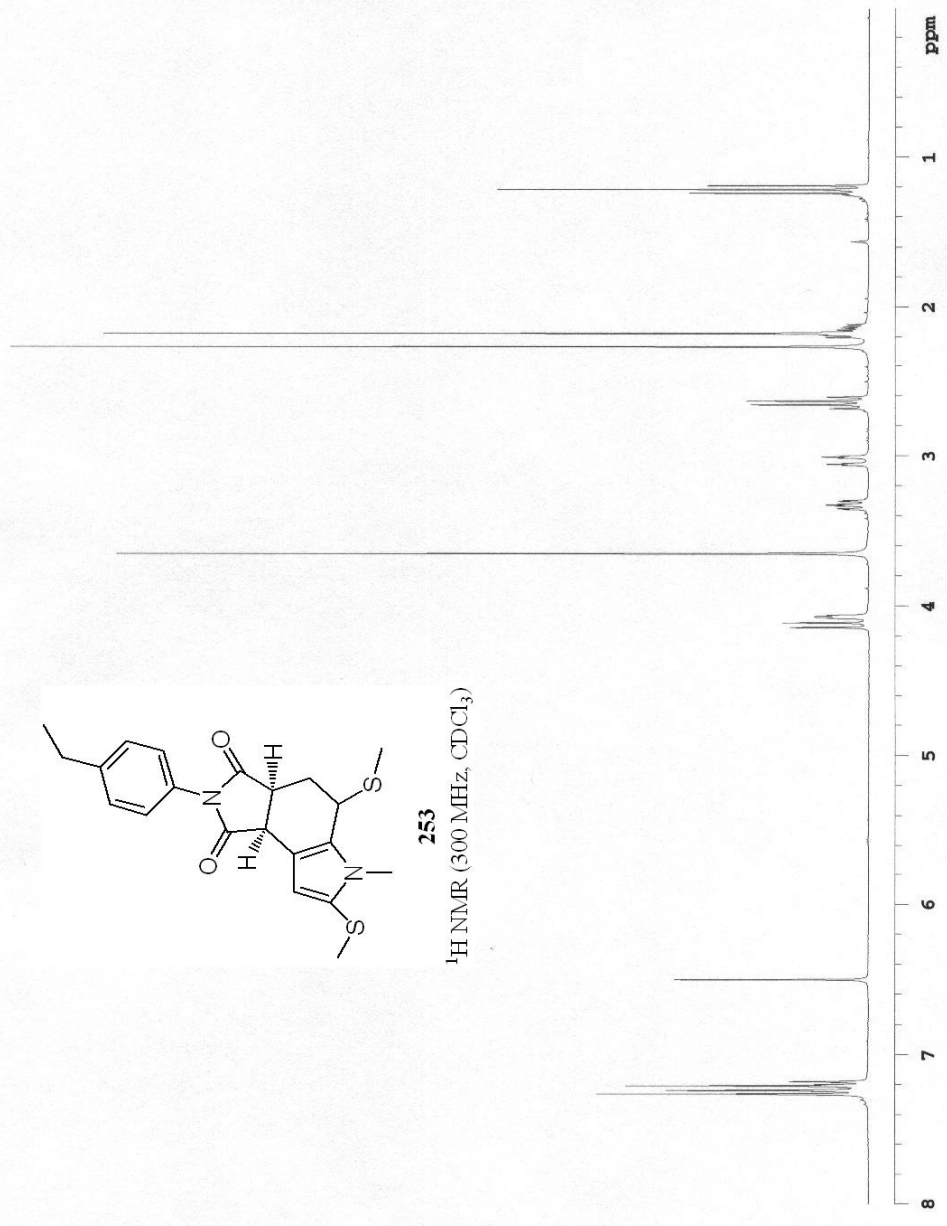
250
¹H NMR (300 MHz, CDCl₃)

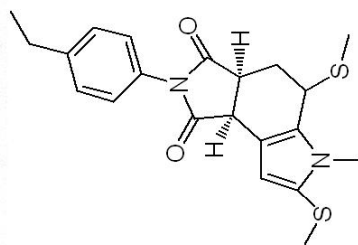




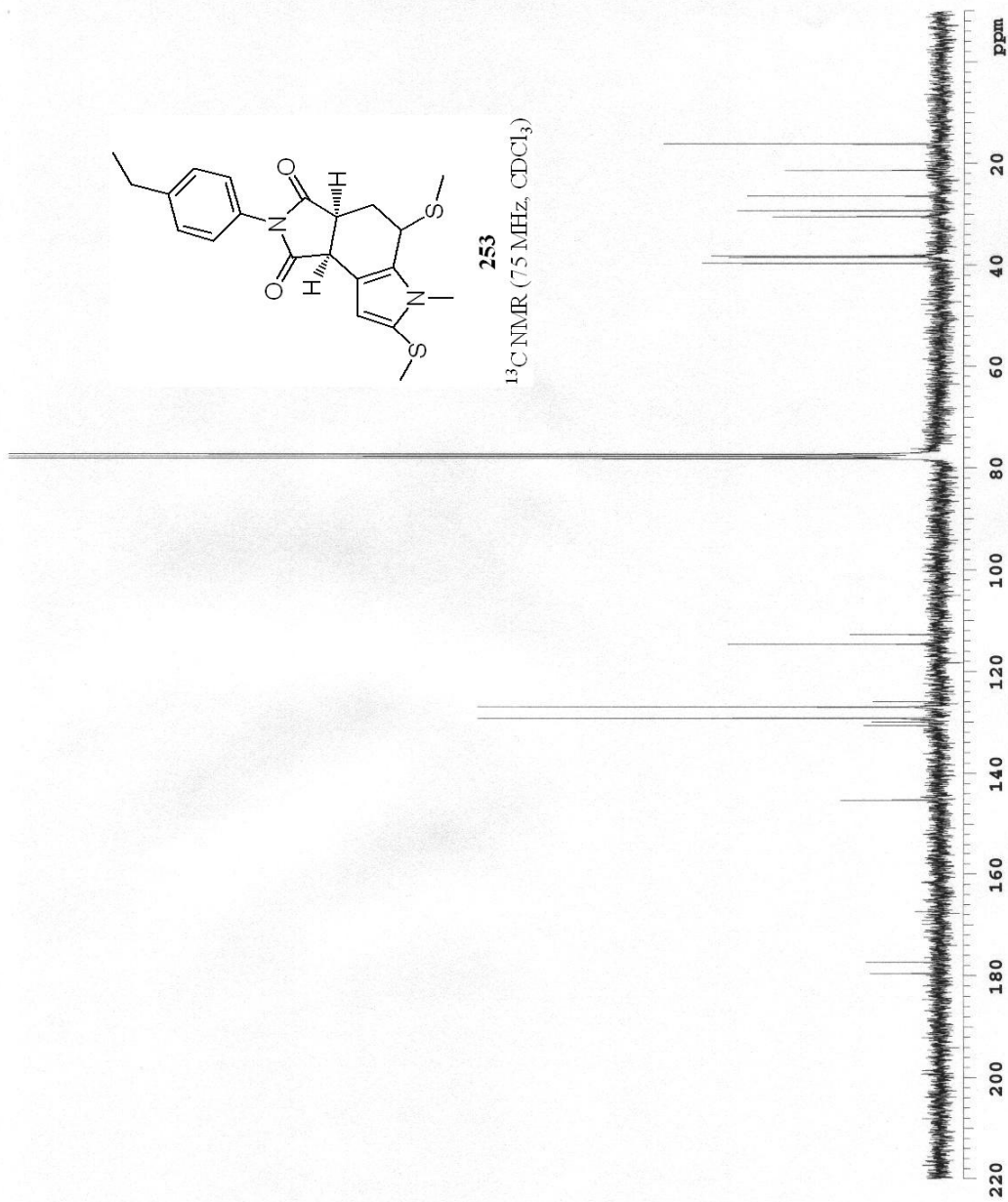
253

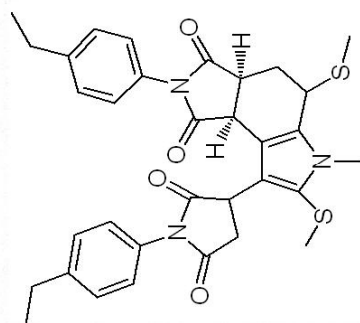
¹H NMR (300 MHz, CDCl₃)





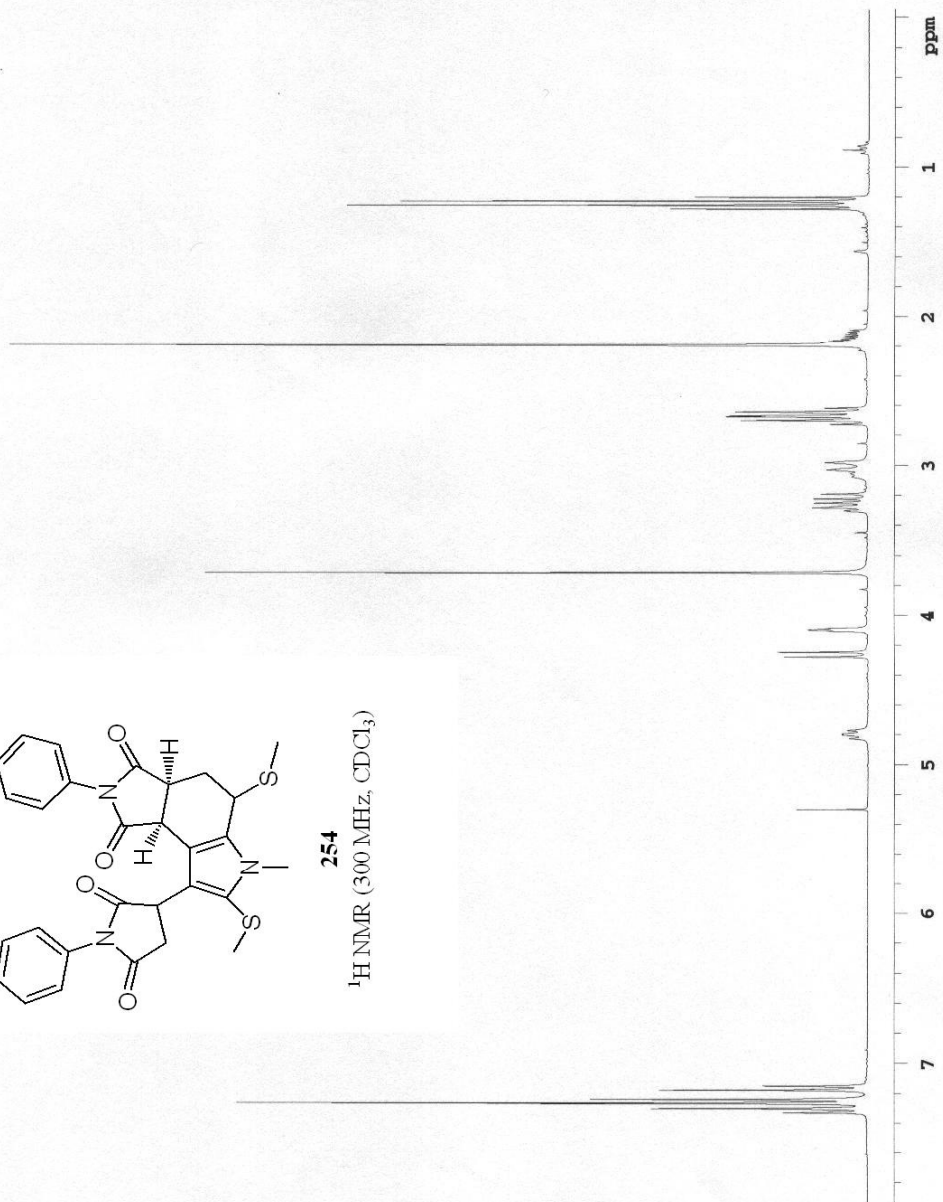
253
 ^{13}C NMR (75 MHz, CDCl_3)

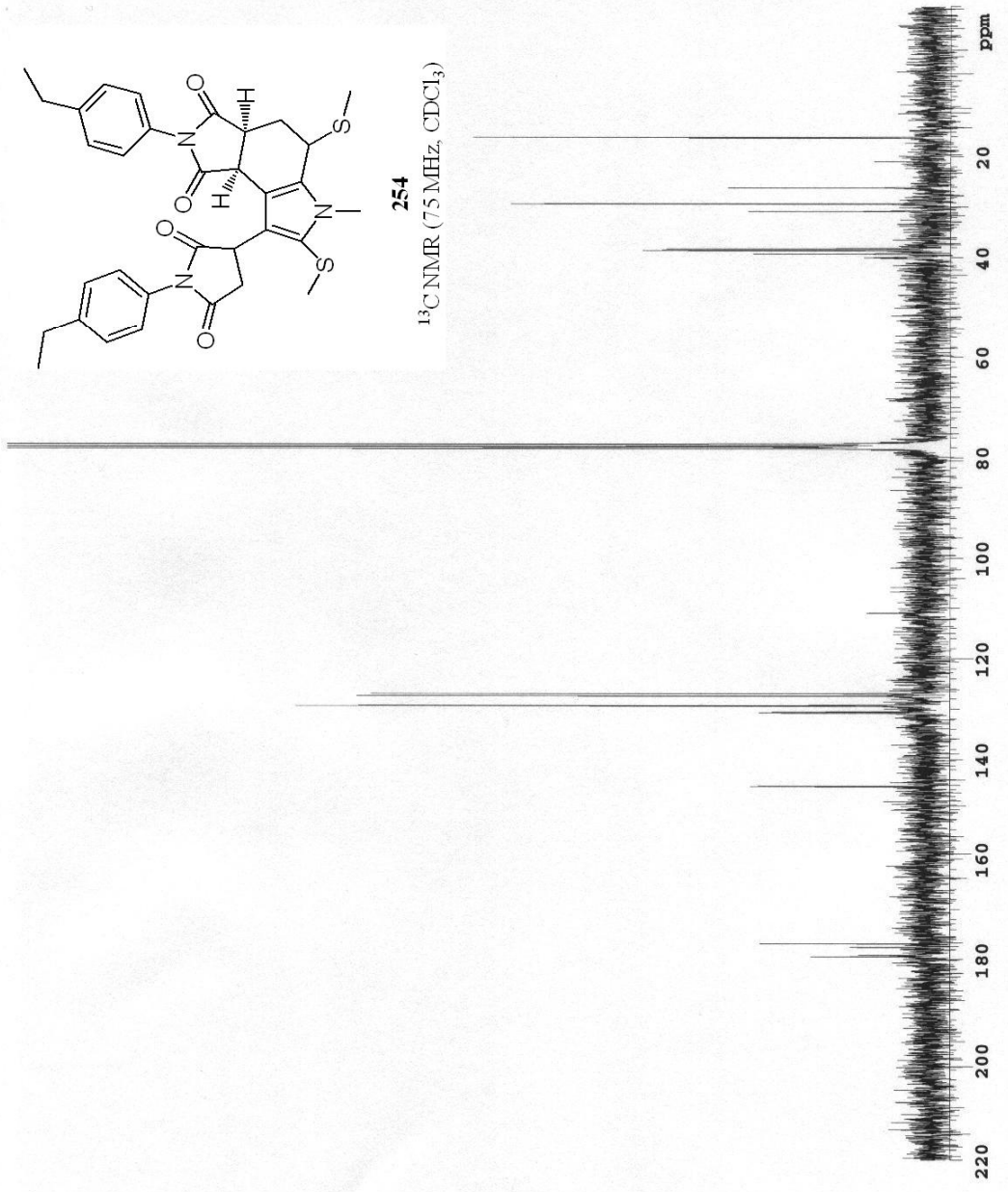


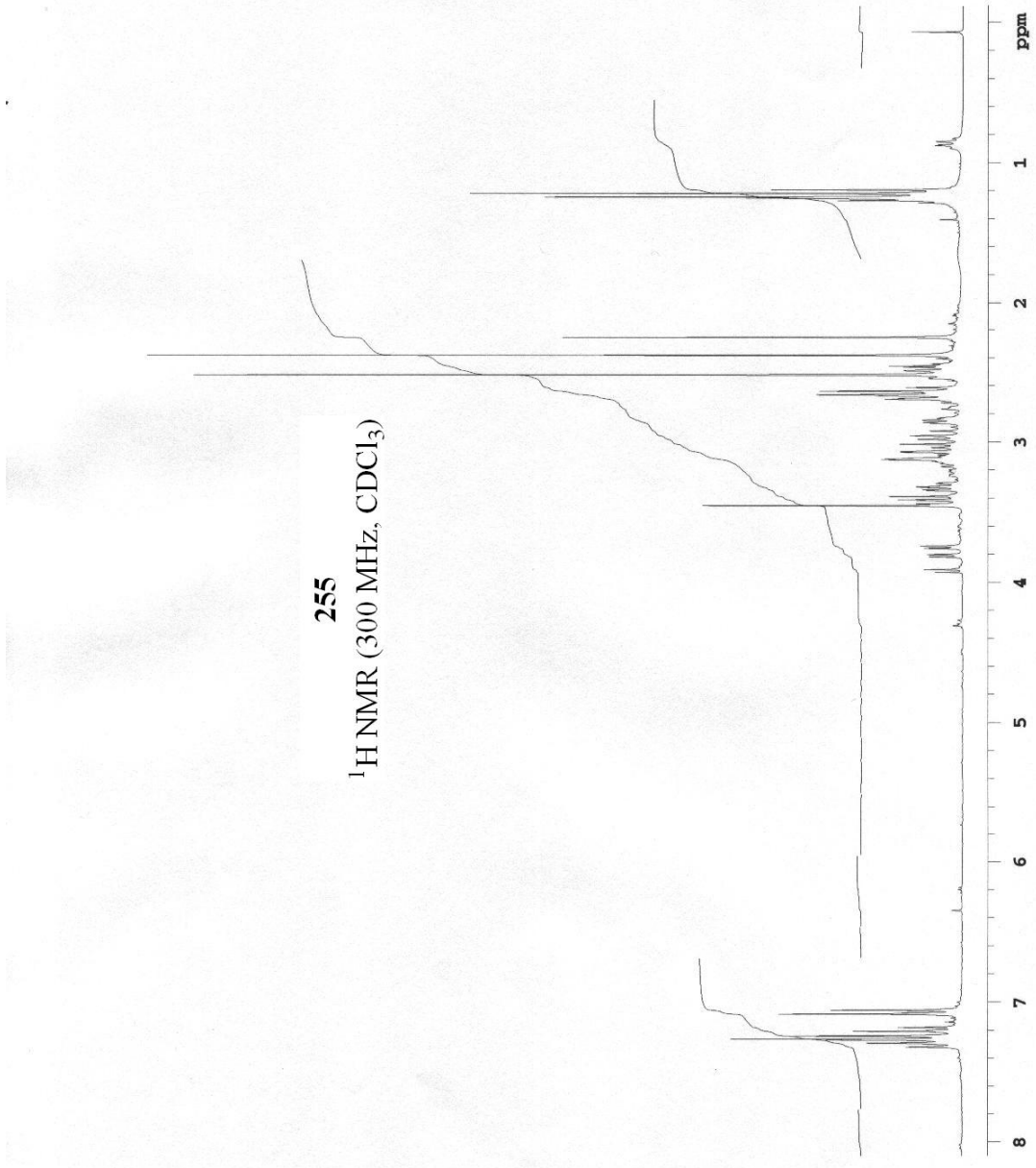


254

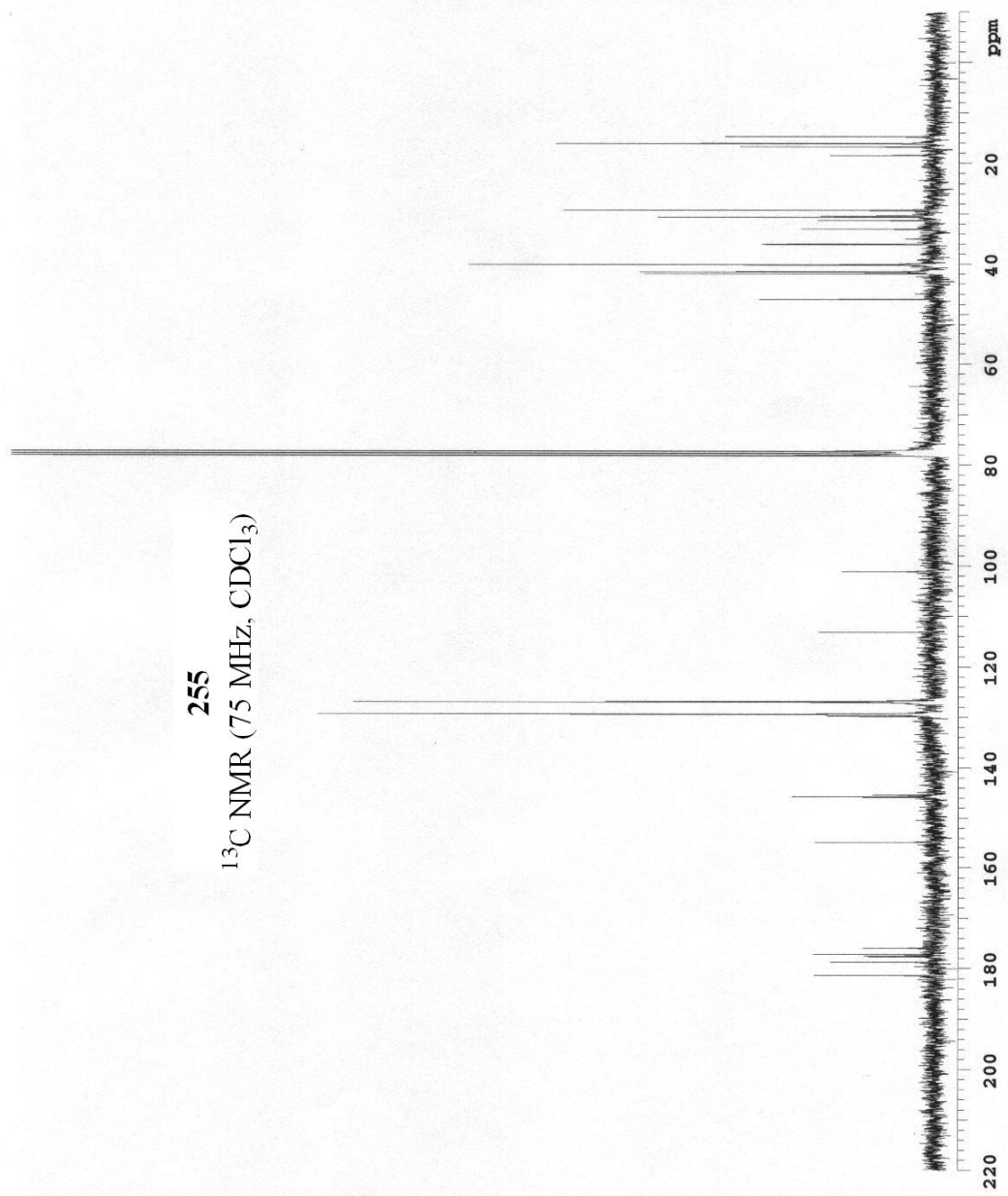
¹H NMR (300 MHz, CDCl₃)

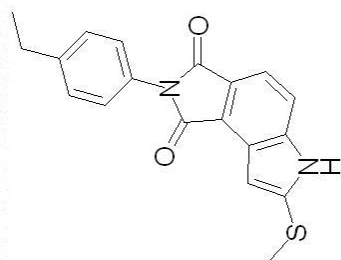






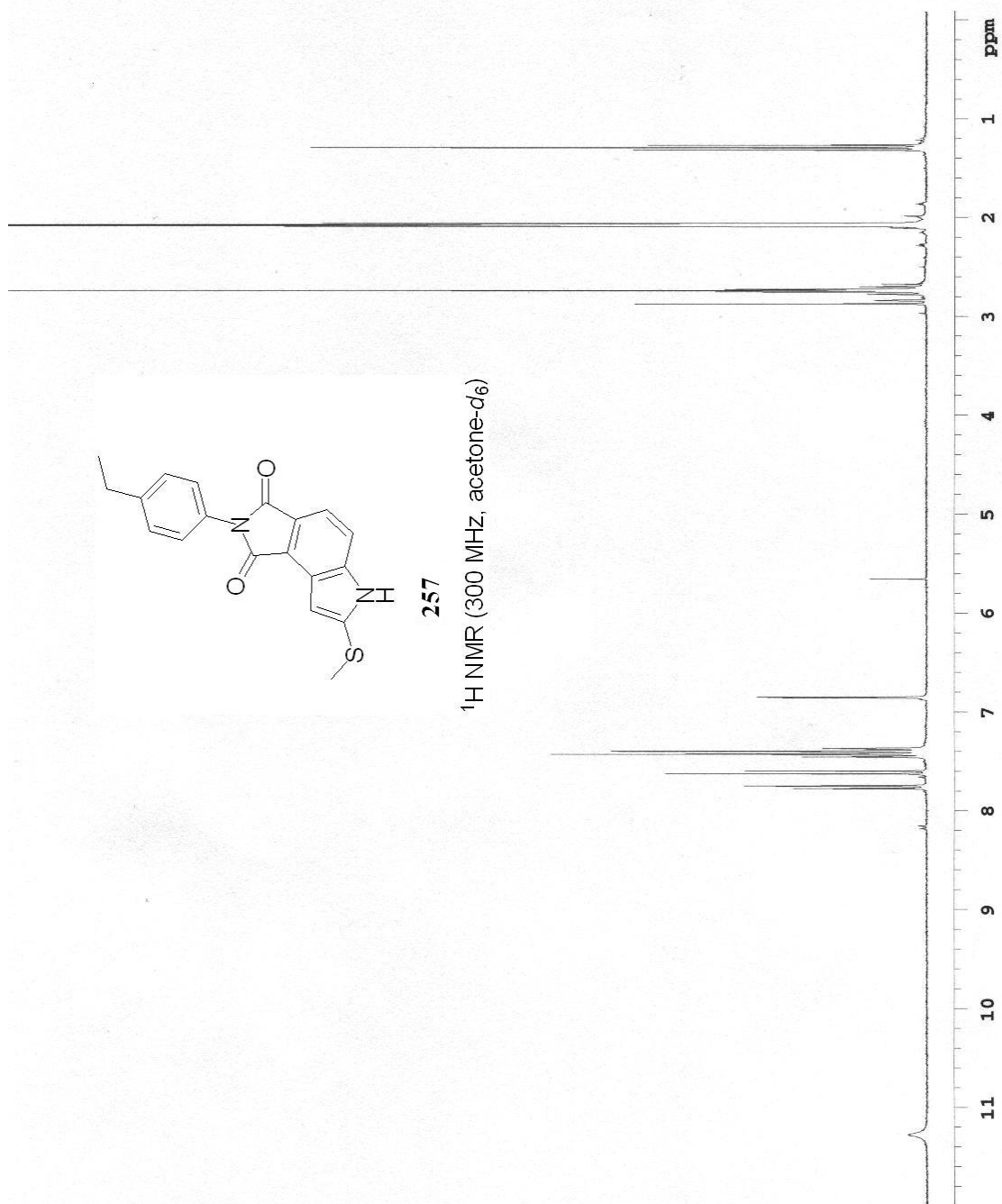
255
 ^1H NMR (300 MHz, CDCl_3)

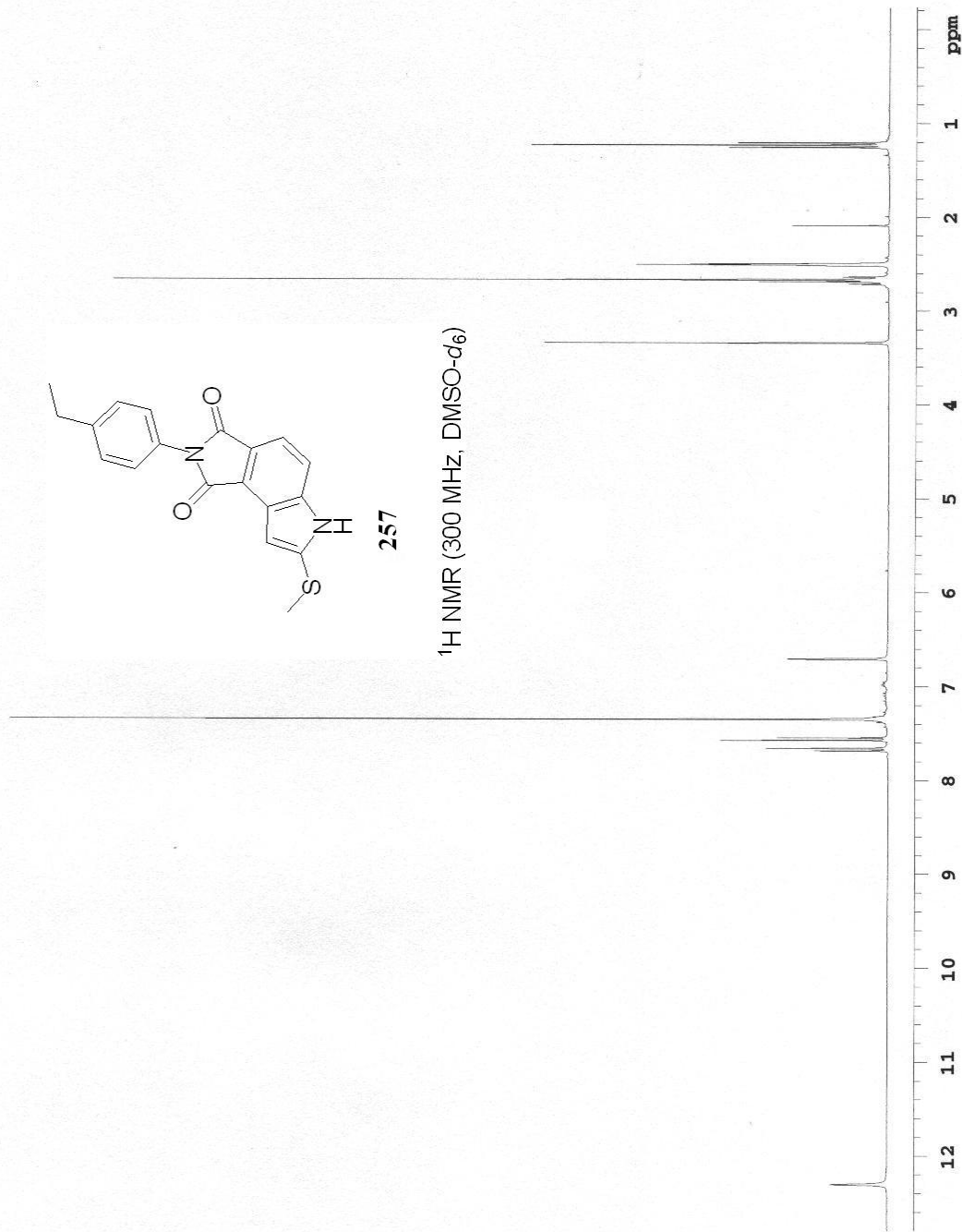


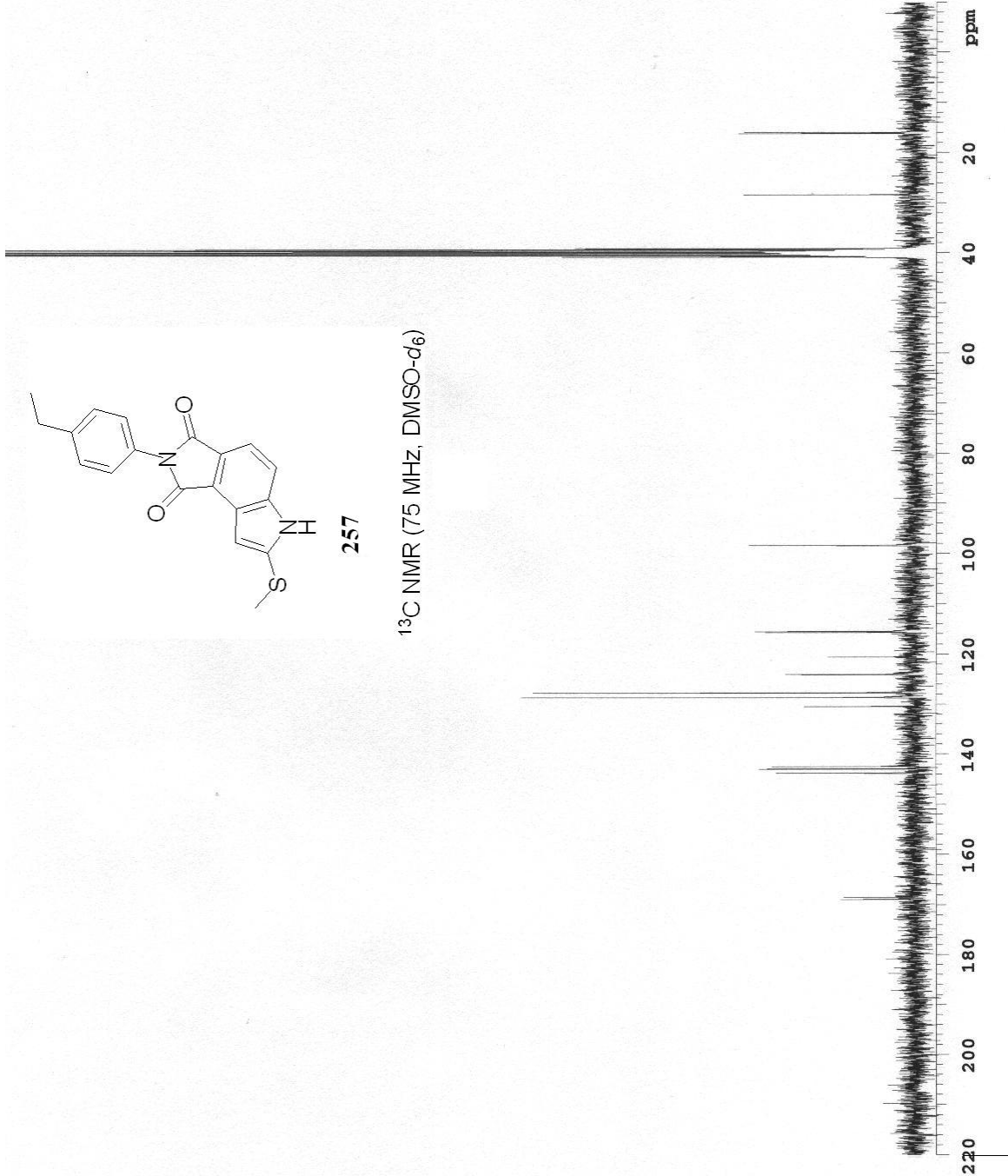


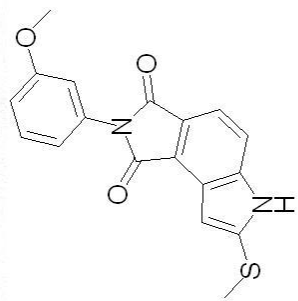
257

¹H NMR (300 MHz, acetone-d₆)



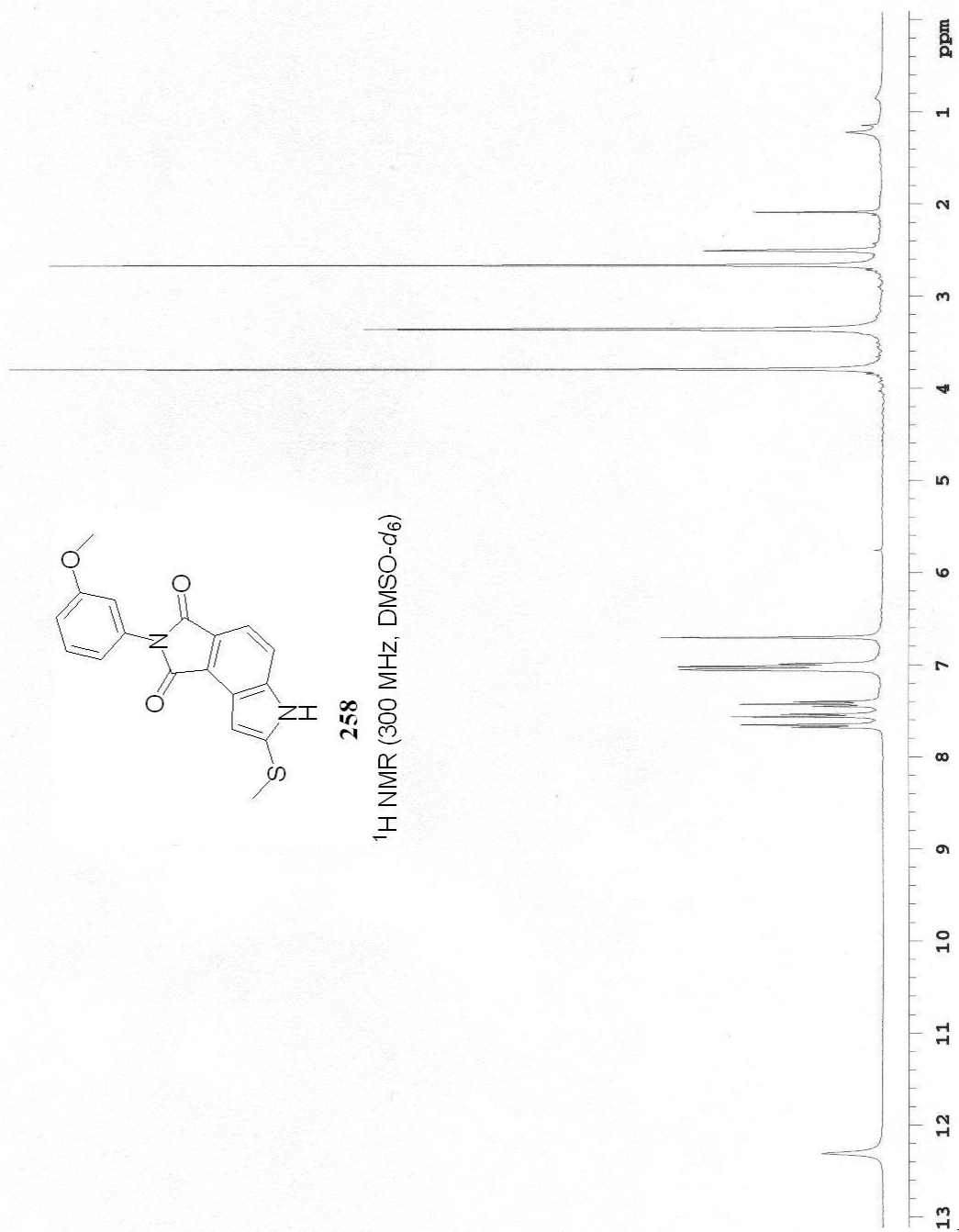


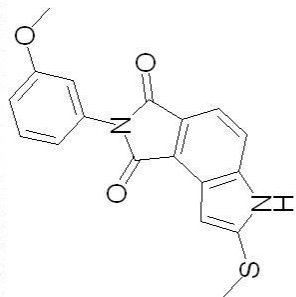




258

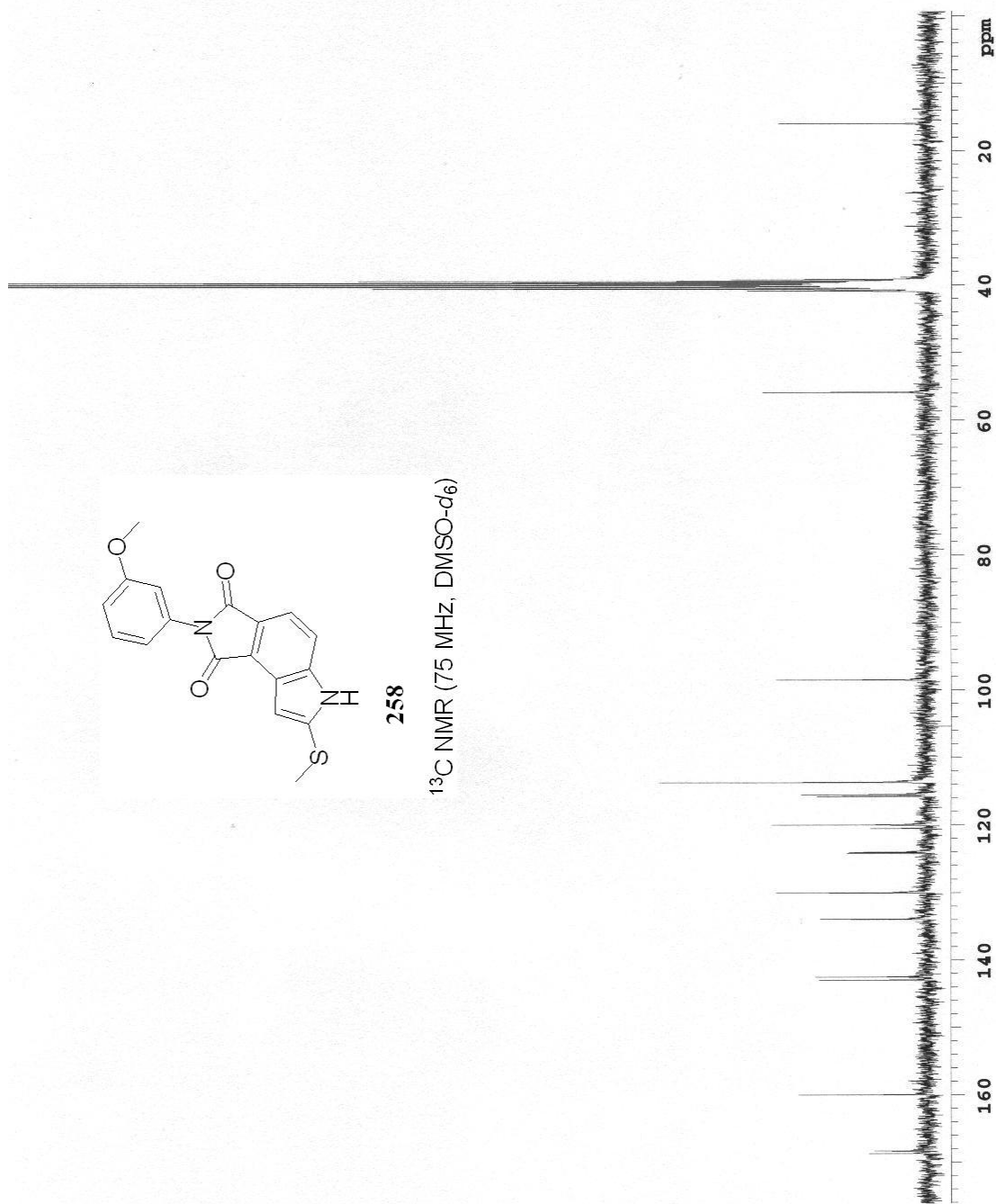
$^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$)

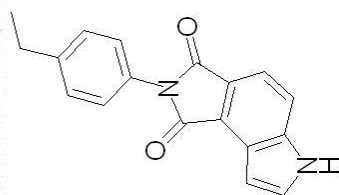




258

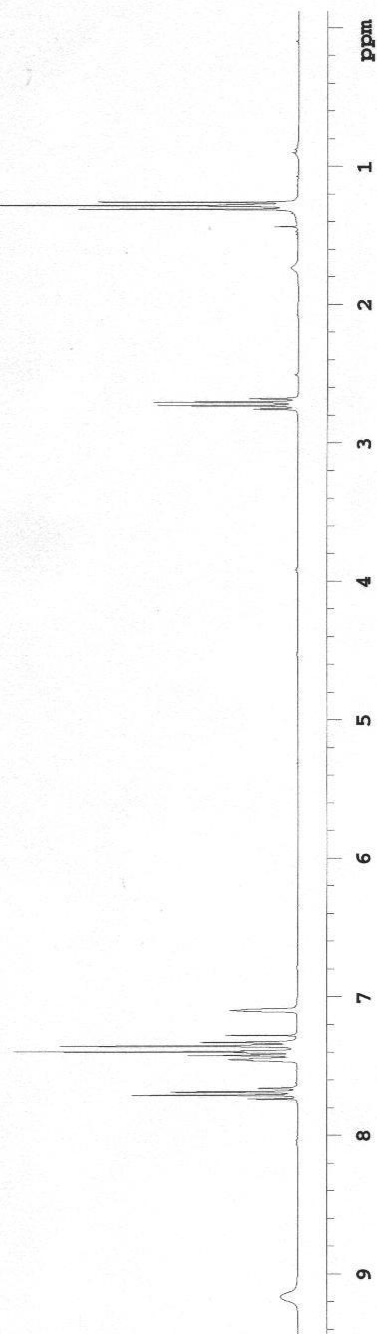
¹³C NMR (75 MHz, DMSO-d₆)

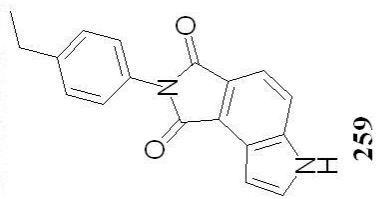




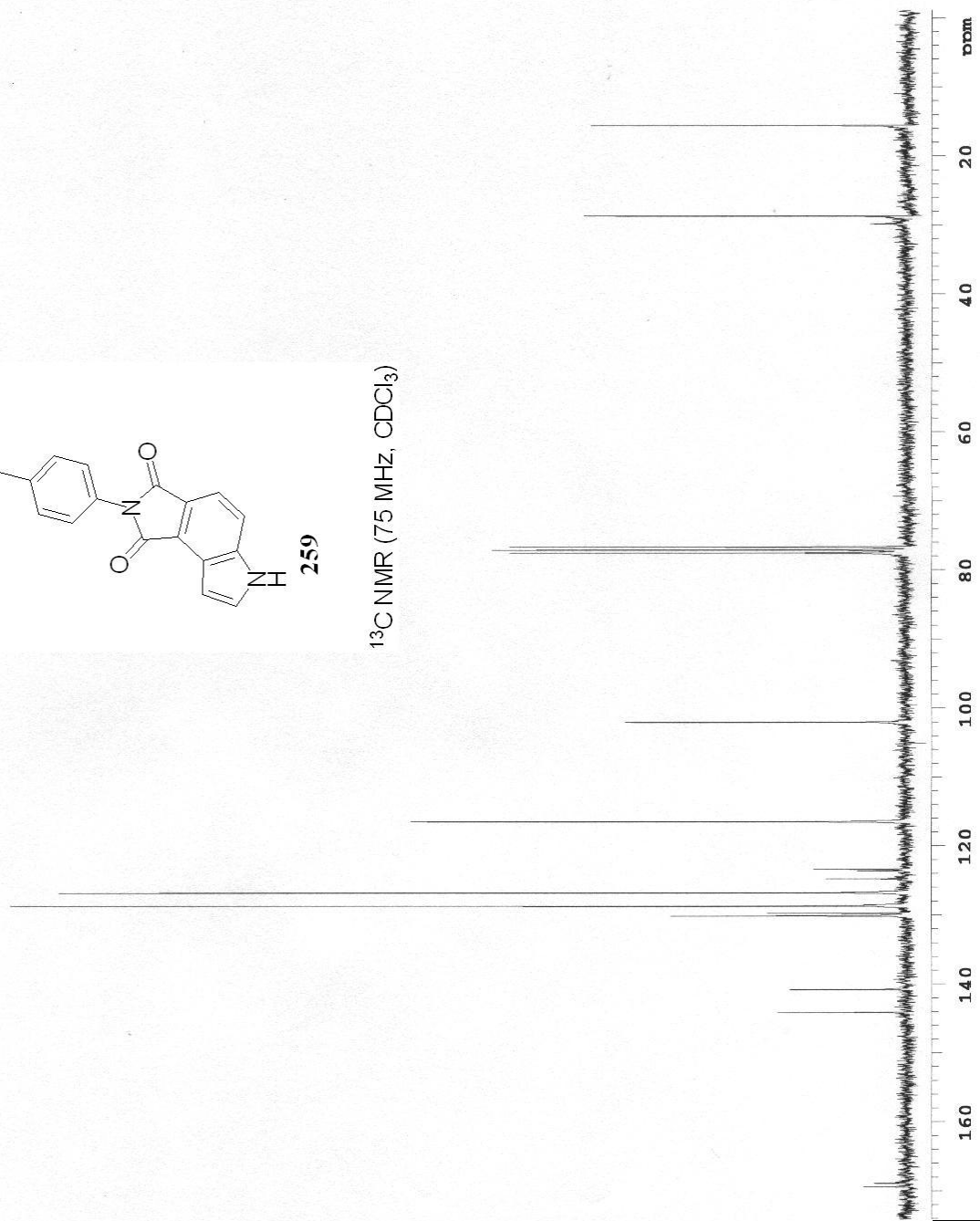
259

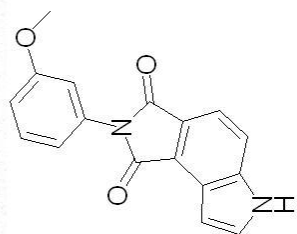
^1H NMR (300 MHz, CDCl_3)





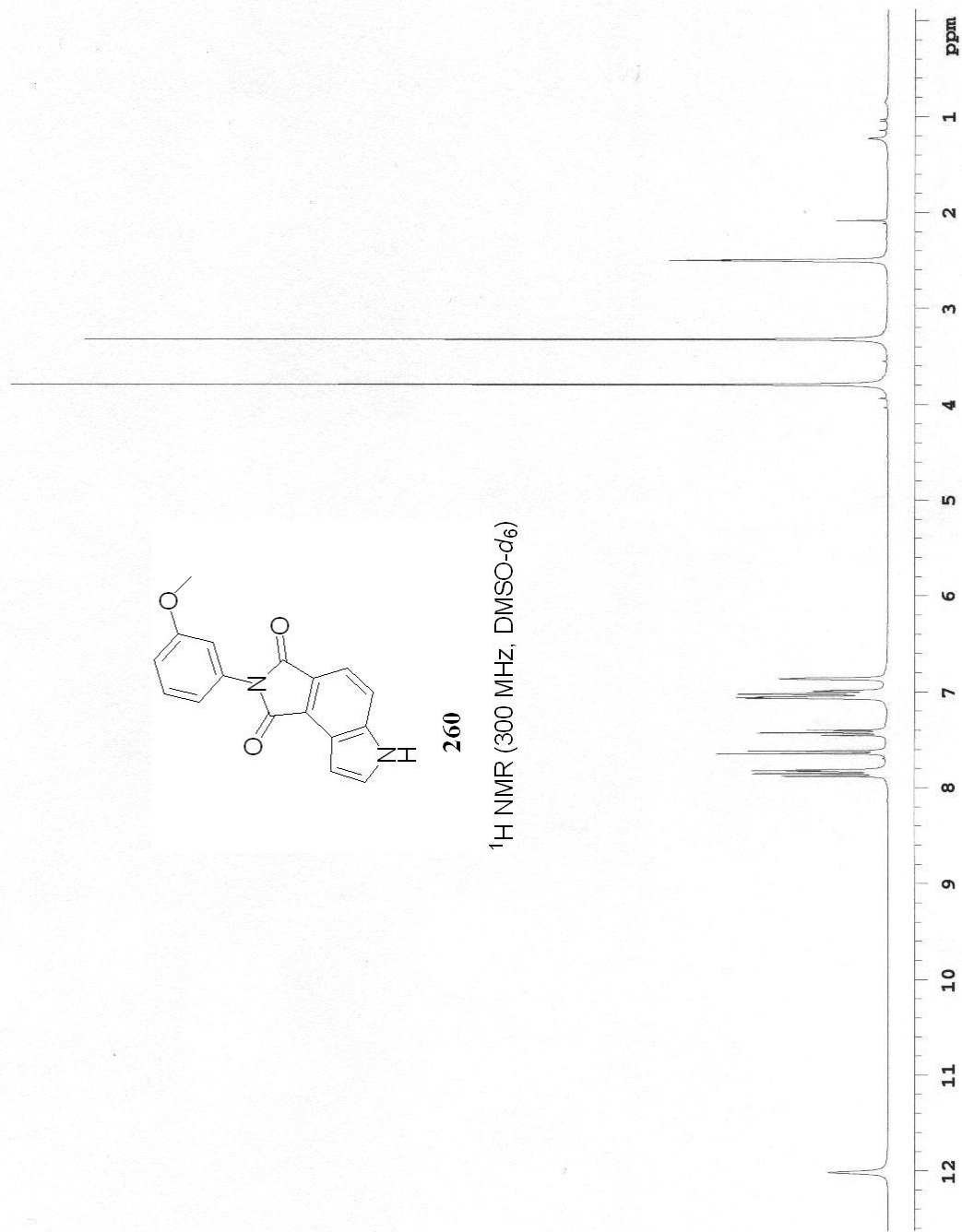
^{13}C NMR (75 MHz, CDCl_3)

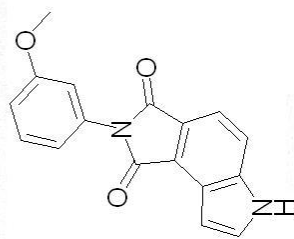




260

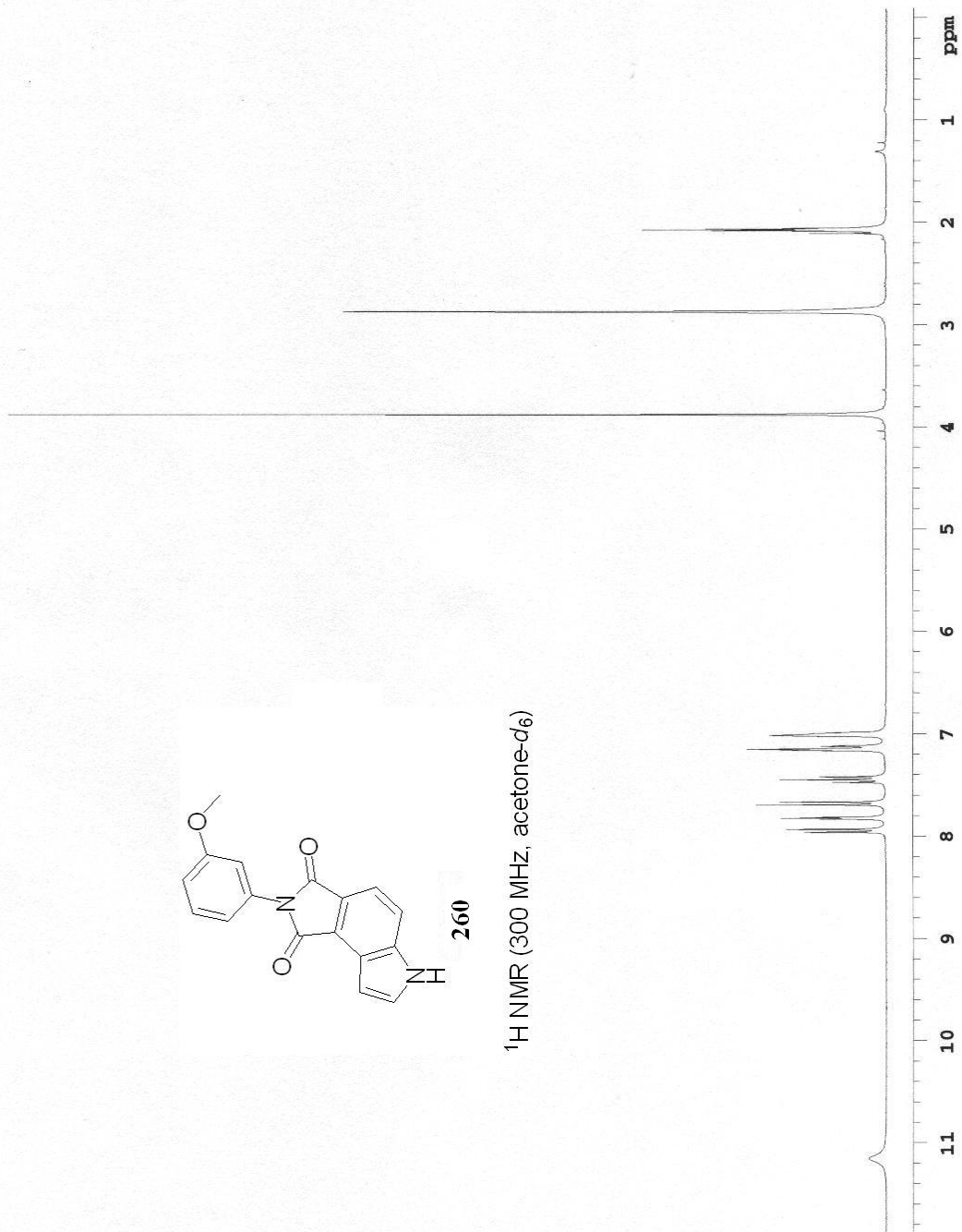
¹H NMR (300 MHz, DMSO-d₆)

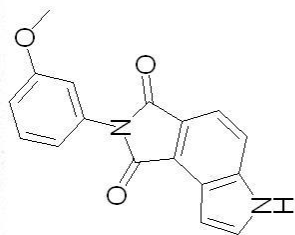




260

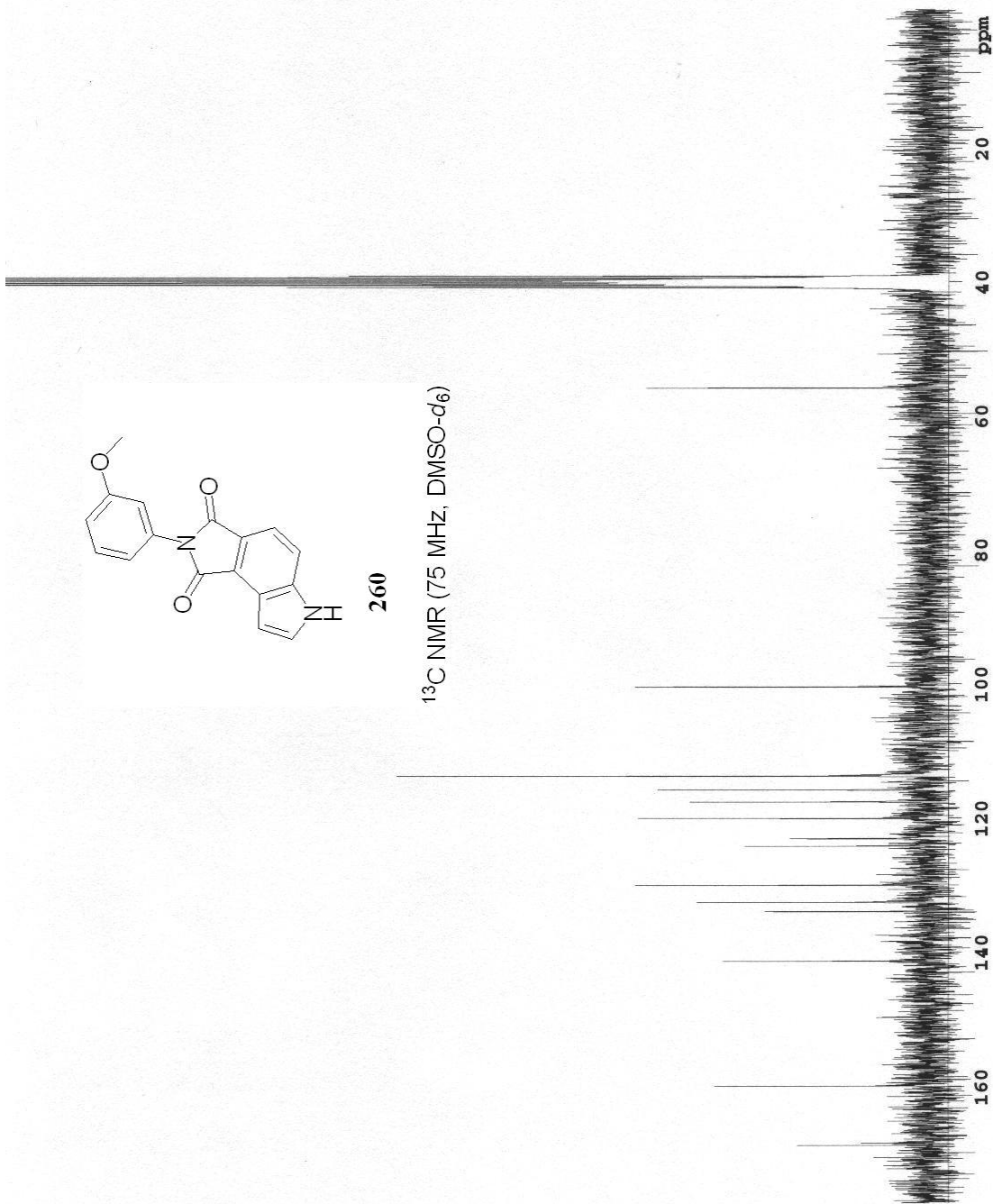
¹H NMR (300 MHz, acetone-d₆)





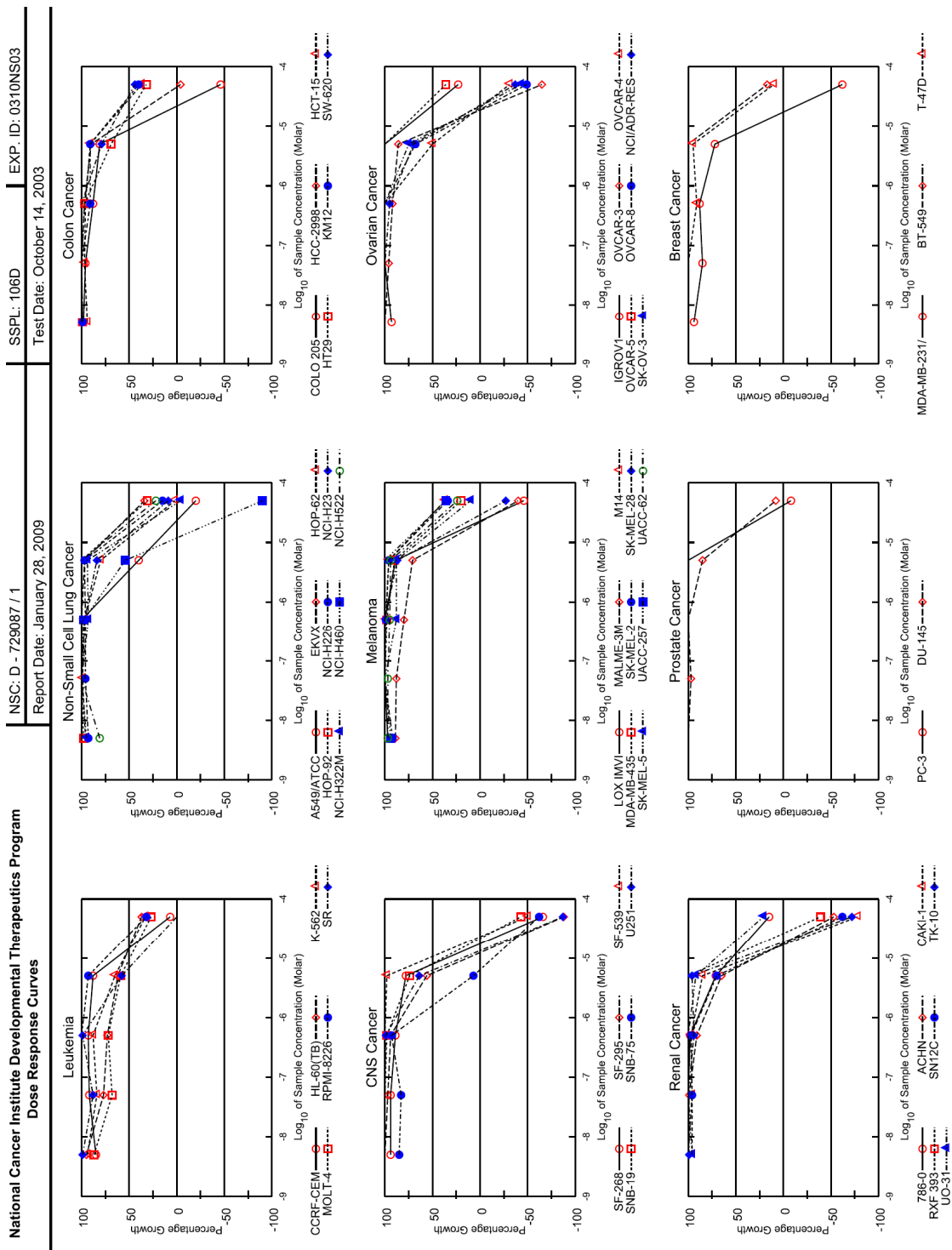
260

^{13}C NMR (75 MHz, $\text{DMSO-}d_6$)



Appendix 2. Biological Activity Data

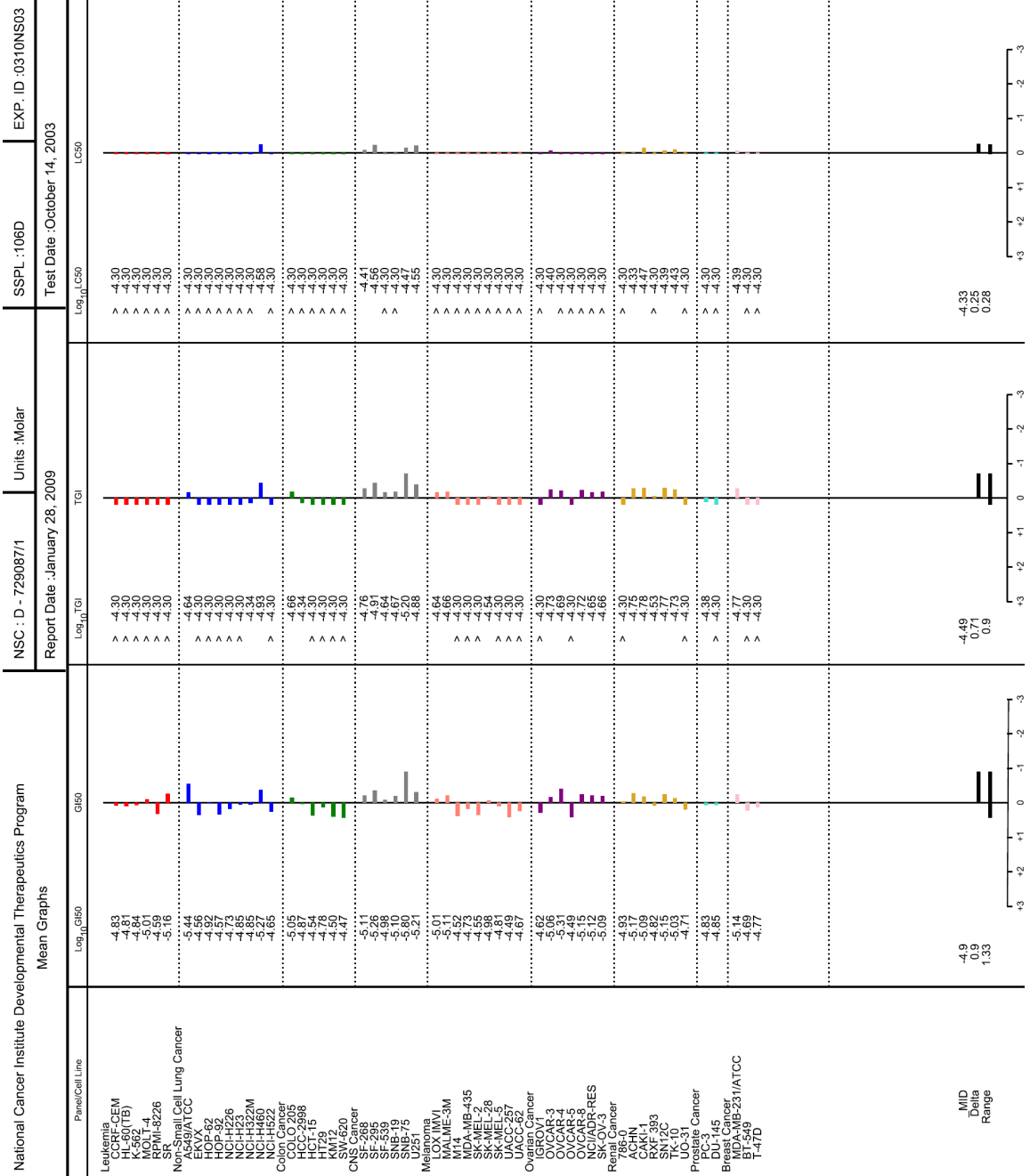
60 Human-Cancer Cell Line 5 Concentration Screen for Compound 79



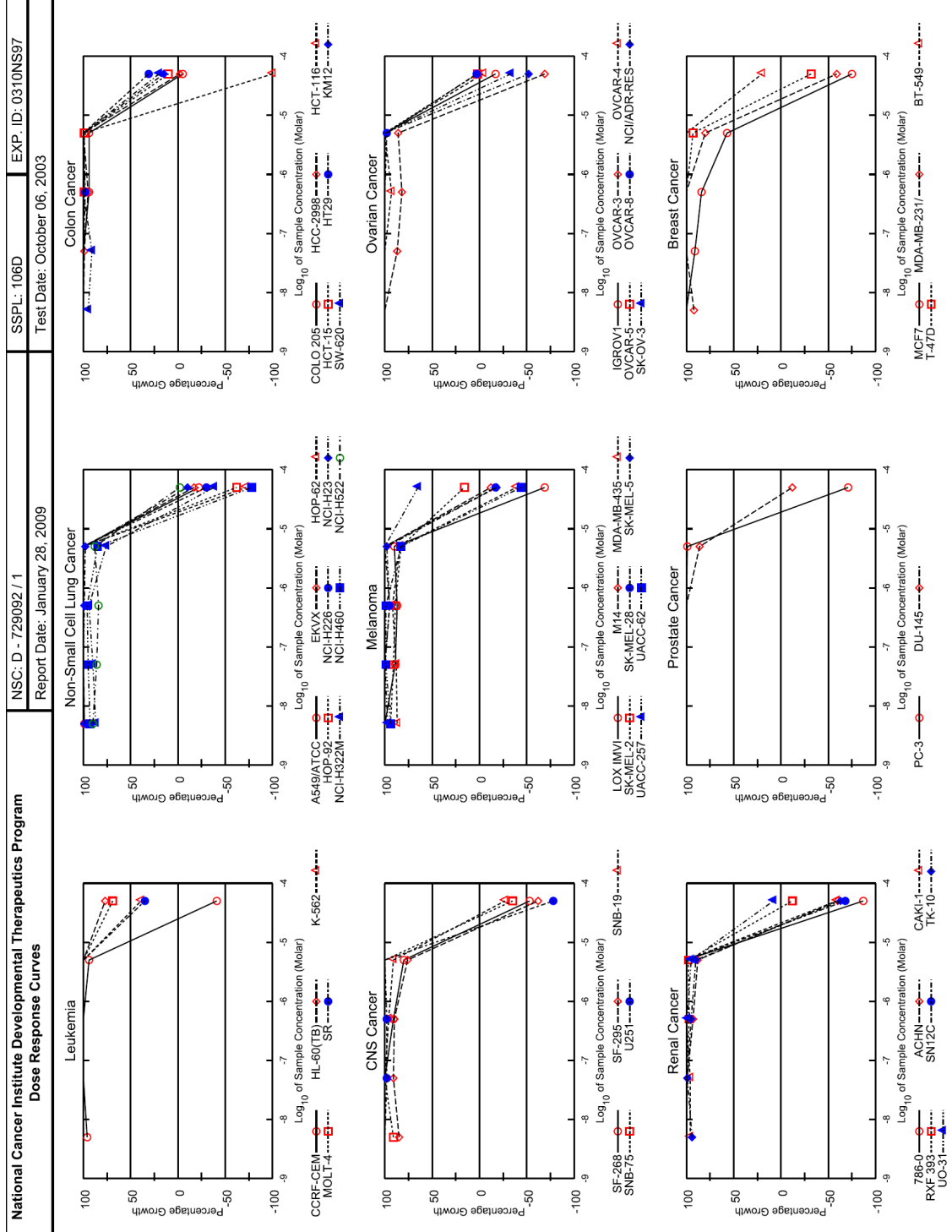
**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

NSC : D - 729087 / 1	Experiment ID : 0310NS03	Test Type : 08	Units : Molar
Report Date : January 28, 2009	Test Date : October 14, 2003	QNS :	MC :
COMI : 4987 (20429)	Stain Reagent : SRB Dual-Pass Related	SSPL : 106D	

Panel/Cell Line	Log10 Concentration														GI50	TGI	LC50
	Time Zero	Ctrl	Mean Optical Densities					Percent Growth									
			-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3	-4.3					
Leukemia																	
CCR5-CEM	0.198	0.619	0.557	0.587	0.589	0.570	0.227	85	92	93	88	7	1.47E-5	> 5.00E-5	> 5.00E-5		
HL-60(TB)	0.323	1.655	1.586	1.345	1.300	1.155	0.815	95	77	73	62	37	1.53E-5	> 5.00E-5	> 5.00E-5		
K-562	0.216	1.291	1.224	1.115	1.167	0.915	0.568	84	84	88	65	33	1.46E-5	> 5.00E-5	> 5.00E-5		
MOLT-4	0.137	0.848	0.754	0.622	0.646	0.560	0.330	87	68	72	59	27	9.79E-6	> 5.00E-5	> 5.00E-5		
RPMI-8226	0.278	0.733	0.781	0.758	0.742	0.702	0.426	110	105	102	93	32	2.57E-5	> 5.00E-5	> 5.00E-5		
SR	0.226	0.976	0.972	0.884	0.971	0.664	0.227	99	88	99	58	.	6.95E-6	> 5.00E-5	> 5.00E-5		
Non-Small Cell Lung Cancer																	
A549/ATCC	0.162	0.812	0.815	0.818	0.882	0.422	0.129	100	101	111	40	-20	3.60E-6	2.30E-5	> 5.00E-5		
EKVX	0.715	1.719	1.825	1.777	1.760	1.685	1.055	110	106	104	97	34	2.76E-5	> 5.00E-5	> 5.00E-5		
HOP-62	0.143	1.022	0.985	1.018	0.997	0.845	0.157	96	99	97	80	2	1.20E-5	> 5.00E-5	> 5.00E-5		
HOP-92	0.391	1.240	1.224	1.259	1.255	1.264	0.655	98	102	102	103	31	2.72E-5	> 5.00E-5	> 5.00E-5		
NCI-H226	0.527	1.636	1.562	1.589	1.593	1.606	0.696	93	96	96	97	15	1.88E-5	> 5.00E-5	> 5.00E-5		
NCI-H23	0.252	0.855	0.876	0.906	0.840	0.759	0.304	103	108	97	84	9	1.41E-5	> 5.00E-5	> 5.00E-5		
NCI-H322M	0.837	1.391	1.362	1.417	1.352	1.356	0.804	95	105	93	94	-4	1.40E-5	4.56E-5	> 5.00E-5		
NCI-H460	0.170	1.114	1.168	1.183	1.093	0.682	0.017	106	107	98	54	-90	5.35E-6	1.19E-5	2.63E-5		
NCI-H522	0.561	1.533	1.349	1.600	1.659	1.548	0.779	81	107	113	101	22	2.24E-5	> 5.00E-5	> 5.00E-5		
Colon Cancer																	
COLO 205	0.910	2.861	2.831	2.782	2.625	2.496	0.494	98	96	88	81	-46	8.81E-6	2.18E-5	> 5.00E-5		
HCC-2998	0.237	0.875	0.946	0.927	0.853	0.812	0.229	111	108	97	90	-4	1.34E-5	4.58E-5	> 5.00E-5		
HCT-15	0.230	1.294	1.228	1.267	1.257	1.198	0.622	94	97	96	91	37	2.85E-5	> 5.00E-5	> 5.00E-5		
HT29	0.098	0.858	0.850	0.861	0.837	0.626	0.345	99	100	97	69	32	1.67E-5	> 5.00E-5	> 5.00E-5		
KM12	0.388	1.458	1.451	1.476	1.359	1.360	0.814	99	102	91	91	40	3.16E-5	> 5.00E-5	> 5.00E-5		
SW-620	0.141	0.587	0.629	0.588	0.590	0.494	0.337	109	100	101	79	44	3.35E-5	> 5.00E-5	> 5.00E-5		
CNS Cancer																	
SF-268	0.703	1.264	1.229	1.229	1.202	1.140	0.236	94	94	89	78	-66	7.79E-6	1.73E-5	3.85E-5		
SF-295	0.527	0.905	0.921	0.894	0.882	0.738	0.065	104	97	94	56	-88	5.49E-6	1.22E-5	2.73E-5		
SF-539	0.596	1.444	1.564	1.498	1.518	1.423	0.298	114	106	109	98	-50	1.05E-5	2.29E-5	> 5.00E-5		
SNB-19	0.360	1.073	1.100	1.081	1.057	0.887	0.207	104	101	98	74	-43	8.02E-6	2.15E-5	> 5.00E-5		
SNB-75	0.479	0.826	0.773	0.766	0.803	0.504	0.184	85	83	93	7	-62	1.59E-6	6.36E-6	3.38E-5		
U251	0.163	0.835	0.858	0.837	0.829	0.593	0.022	103	100	99	64	-87	6.18E-6	1.33E-5	2.85E-5		
Melanoma																	
LOX IMVI	0.301	1.216	1.187	1.237	1.231	1.113	0.162	97	102	102	89	-46	9.69E-6	2.27E-5	> 5.00E-5		
MALME-3M	0.891	1.124	1.099	1.096	1.078	1.056	0.532	89	88	80	71	-40	7.69E-6	2.17E-5	> 5.00E-5		
M14	0.075	0.873	0.869	0.899	0.865	0.844	0.368	100	103	99	96	37	2.99E-5	> 5.00E-5	> 5.00E-5		
MDA-MB-435	0.632	1.980	1.981	1.987	1.957	1.846	0.904	100	100	98	90	20	1.87E-5	> 5.00E-5	> 5.00E-5		
SK-MEL-2	0.262	1.258	1.184	1.286	1.250	1.223	0.604	92	103	99	96	34	2.80E-5	> 5.00E-5	> 5.00E-5		
SK-MEL-28	0.369	0.554	0.577	0.618	0.567	0.530	0.268	113	135	107	87	-27	1.06E-5	2.88E-5	> 5.00E-5		
SK-MEL-5	0.325	1.463	1.522	1.495	1.325	1.327	0.442	105	103	88	88	10	1.54E-5	> 5.00E-5	> 5.00E-5		
UACC-257	0.975	1.733	1.690	1.785	1.826	1.819	1.246	94	107	112	111	36	3.23E-5	> 5.00E-5	> 5.00E-5		
UACC-62	0.514	1.808	1.772	1.775	1.746	1.732	0.824	97	97	95	94	24	2.13E-5	> 5.00E-5	> 5.00E-5		
Ovarian Cancer																	
IGROV1	0.183	0.580	0.552	0.621	0.600	0.613	0.274	93	110	105	108	23	2.41E-5	> 5.00E-5	> 5.00E-5		
OVCAR-3	0.816	1.484	1.530	1.454	1.433	1.388	0.287	107	96	92	86	-65	8.63E-6	1.85E-5	3.99E-5		
OVCAR-4	0.243	1.093	1.144	1.112	1.123	0.666	0.167	106	102	103	50	-31	4.95E-6	2.05E-5	> 5.00E-5		
OVCAR-5	0.529	1.049	1.067	1.076	1.066	1.111	0.715	104	105	103	112	36	3.24E-5	> 5.00E-5	> 5.00E-5		
OVCAR-8	0.398	1.117	1.163	1.167	1.156	0.889	0.203	106	107	105	68	-49	7.15E-6	1.91E-5	> 5.00E-5		
NCI/ADR-RES	0.209	0.710	0.739	0.729	0.685	0.557	0.133	106	104	95	70	-37	7.64E-6	2.26E-5	> 5.00E-5		
SK-OV-3	0.355	1.042	1.086	1.066	1.051	0.870	0.203	106	103	101	75	-43	8.13E-6	2.16E-5	> 5.00E-5		
Renal Cancer																	
786-0	0.111	1.234	1.338	1.260	1.207	0.906	0.274	109	102	98	71	15	1.17E-5	> 5.00E-5	> 5.00E-5		
ACHN	0.343	1.154	1.153	1.142	1.083	0.870	0.161	100	99	91	65	-53	6.69E-6	1.78E-5	4.71E-5		
CAKI-1	0.857	1.677	1.641	1.649	1.657	1.552	0.188	96	96	97	85	-78	8.17E-6	1.66E-5	3.36E-5		
RXF 393	0.614	0.879	0.901	0.897	0.938	0.963	0.377	108	107	122	132	-39	1.51E-5	2.96E-5	> 5.00E-5		
SN12C	0.476	1.151	1.177	1.125	1.131	0.952	0.180	104	96	97	70	-62	7.13E-6	1.70E-5	4.04E-5		
TK-10	0.766	1.613	1.609	1.701	1.566	1.580	0.215	99	110	94	96	-72	9.40E-6	1.86E-5	3.70E-5		
UO-31	0.158	1.307	1.261	1.346	1.381	1.216	0.395	96	103	106	92	21	1.94E-5	> 5.00E-5	> 5.00E-5		
Prostate Cancer																	
PC-3	0.523	1.498	1.528	1.556	1.558	1.509	0.480	103	106	106	101	-8	1.47E-5	4.20E-5	> 5.00E-5		
DU-145	0.323	1.244	1.287	1.220	1.272	1.110	0.394	105	97	103	85	8	1.43E-5	> 5.00E-5	> 5.00E-5		
Breast Cancer																	
MDA-MB-231/ATCC	0.436	0.799	0.779	0.745	0.755	0.696	0.165	94	85	88	72	-62	7.25E-6	1.72E-5	4.06E-5		
BT-549	0.696	1.155	1.212	1.245	1.183	1.170	0.773	112	120	106	103	17	2.06E-5	> 5.00E-5	> 5.00E-5		
T-47D	0.850	2.875	2.885	2.969	2.697	2.767	1.055	100	105	91	95	10	1.69E-5	> 5.00E-5	> 5.00E-5		



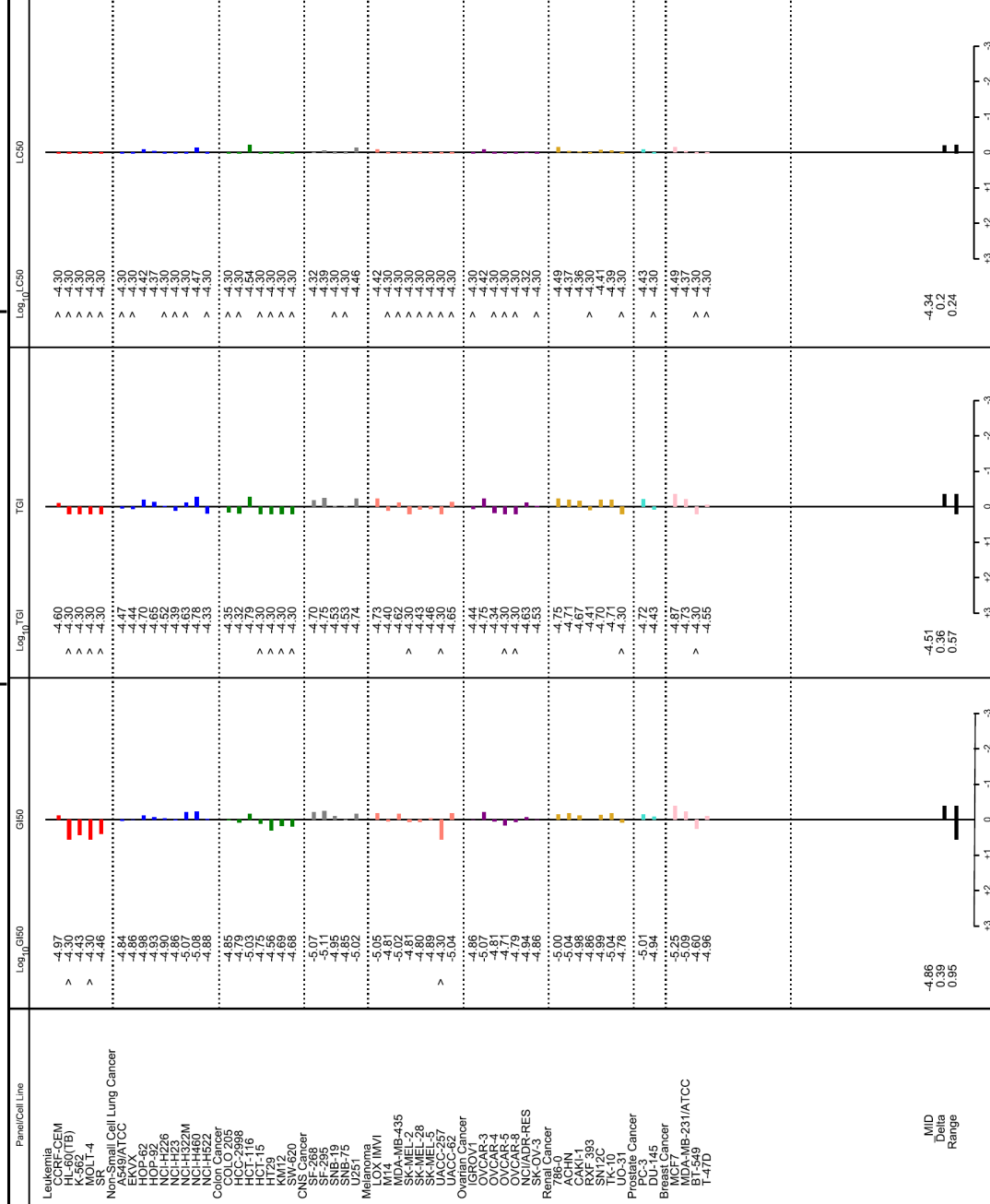
60 Human-Cancer Cell Line 5 Concentration Screen for Compound 101



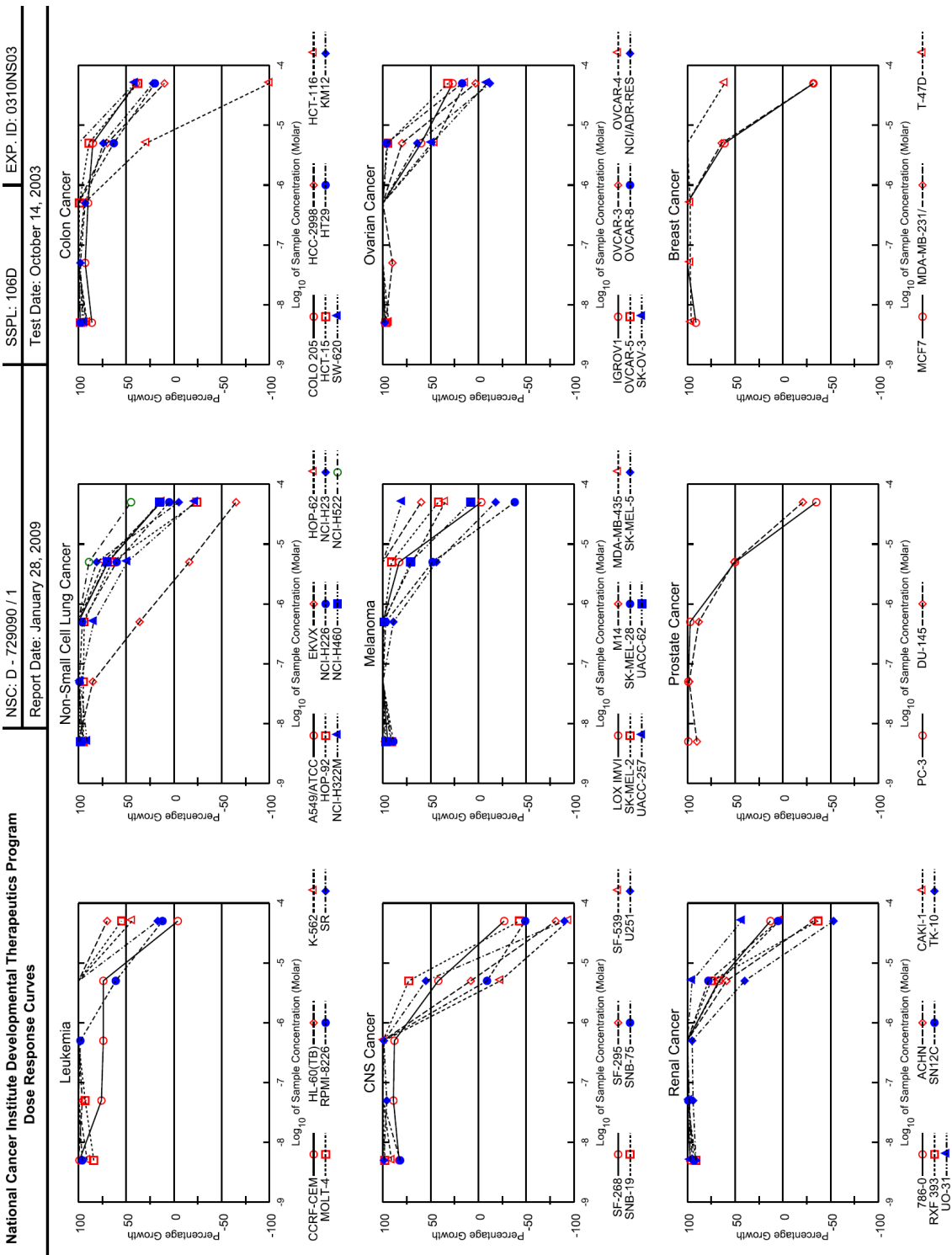
**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

NSC : D - 729092 / 1	Experiment ID : 0310NS97	Test Type : 08	Units : Molar
Report Date : January 28, 2009	Test Date : October 06, 2003	QNS :	MC :
COMI : 5000 (20531)	Stain Reagent : SRB Dual-Pass Related	SSPL : 106D	

Panel/Cell Line	Log10 Concentration											G150	TGI	LC50	
	Time	Mean Optical Densities						Percent Growth							
	Zero	Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3				-4.3
Leukemia															
CCRF-CEM	0.286	0.712	0.695	0.714	0.749	0.687	0.169	96	100	109	94	-41	1.06E-5	2.49E-5	> 5.00E-5
HL-60(TB)	0.493	2.029	2.145	2.179	2.295	2.300	1.683	108	110	117	118	77	> 5.00E-5	> 5.00E-5	> 5.00E-5
K-562	0.249	1.064	1.115	1.276	1.301	1.232	0.571	106	126	129	121	39	3.71E-5	> 5.00E-5	> 5.00E-5
MOLT-4	0.205	0.899	0.910	0.974	0.992	0.958	0.683	102	111	113	109	69	> 5.00E-5	> 5.00E-5	> 5.00E-5
SR	0.421	1.251	1.326	1.366	1.756	1.492	0.710	109	114	161	129	35	3.45E-5	> 5.00E-5	> 5.00E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.368	1.395	1.389	1.424	1.500	1.519	0.287	99	103	110	112	-22	1.45E-5	3.42E-5	> 5.00E-5
EKVX	0.697	1.355	1.399	1.405	1.440	1.369	0.578	107	108	113	102	-17	1.37E-5	3.59E-5	> 5.00E-5
HOP-62	0.440	1.023	1.055	1.037	1.088	1.071	0.122	105	102	111	108	-72	1.05E-5	1.99E-5	3.76E-5
HOP-92	0.660	0.941	0.987	0.997	0.954	0.988	0.253	116	120	105	117	-62	1.18E-5	2.26E-5	4.30E-5
NCI-H226	1.239	1.901	1.912	1.934	1.943	1.931	0.866	102	105	106	105	-30	1.27E-5	2.99E-5	> 5.00E-5
NCI-H23	0.530	1.537	1.527	1.538	1.525	1.520	0.476	99	100	99	98	-10	1.39E-5	4.03E-5	> 5.00E-5
NCI-H322M	0.614	0.902	0.865	0.874	0.886	0.834	0.383	87	90	94	76	-38	8.48E-6	2.33E-5	> 5.00E-5
NCI-H460	0.097	0.686	0.645	0.660	0.663	0.601	0.021	93	95	96	85	-78	8.23E-6	1.66E-5	3.36E-5
NCI-H522	0.212	0.863	0.798	0.773	0.759	0.788	0.207	90	86	84	88	-2	1.32E-5	4.71E-5	> 5.00E-5
Colon Cancer															
COLO 205	0.538	2.272	2.376	2.359	2.174	2.173	0.514	106	105	94	94	-5	1.40E-5	4.50E-5	> 5.00E-5
HCC-2998	0.435	1.428	1.447	1.421	1.383	1.479	0.425	102	99	95	105	-2	1.63E-5	4.76E-5	> 5.00E-5
HCT-116	0.199	1.062	1.077	1.084	1.096	1.108	-0.002	102	103	104	105	-100	9.30E-6	1.63E-5	2.85E-5
HCT-15	0.231	1.036	1.045	1.072	1.027	1.026	0.313	101	105	99	99	10	1.78E-5	> 5.00E-5	> 5.00E-5
HT29	0.214	1.106	1.168	1.111	1.086	1.132	0.493	107	101	98	103	31	2.73E-5	> 5.00E-5	> 5.00E-5
KM12	0.601	1.745	1.829	1.759	1.755	1.801	0.770	107	101	101	105	15	2.03E-5	> 5.00E-5	> 5.00E-5
SW-620	0.157	0.656	0.630	0.611	0.688	0.655	0.256	95	91	106	100	20	2.09E-5	> 5.00E-5	> 5.00E-5
CNS Cancer															
SF-268	0.405	0.793	0.816	0.794	0.758	0.717	0.192	106	100	91	80	-53	8.46E-6	2.01E-5	4.77E-5
SF-295	0.365	0.745	0.689	0.709	0.705	0.654	0.138	85	91	90	76	-62	7.72E-6	1.78E-5	4.08E-5
SNB-19	0.578	1.349	1.412	1.414	1.321	1.281	0.423	108	108	96	91	-27	1.12E-5	2.96E-5	> 5.00E-5
SNB-75	0.773	0.944	0.929	1.005	0.968	0.978	0.503	91	136	114	120	-35	1.42E-5	2.98E-5	> 5.00E-5
U251	0.211	0.882	0.879	0.865	0.870	0.881	0.046	100	98	98	100	-78	9.52E-6	1.82E-5	3.46E-5
Melanoma															
LOX IMVI	0.297	1.089	1.087	1.003	0.988	1.013	0.093	100	89	87	90	-69	8.96E-6	1.85E-5	3.81E-5
M14	0.307	0.765	0.763	0.801	0.814	0.812	0.269	100	108	111	110	-12	1.55E-5	3.96E-5	> 5.00E-5
MDA-MB-435	0.423	1.034	0.953	0.964	0.985	0.938	0.257	87	88	92	84	-39	9.46E-6	2.40E-5	> 5.00E-5
SK-MEL-2	0.119	0.774	0.733	0.717	0.701	0.663	0.226	94	91	89	83	16	1.56E-5	> 5.00E-5	> 5.00E-5
SK-MEL-28	0.492	0.976	1.045	1.032	0.951	1.066	0.406	114	112	95	119	-17	1.60E-5	3.72E-5	> 5.00E-5
SK-MEL-5	0.405	1.146	1.184	1.153	1.109	1.129	0.333	105	101	95	98	-18	1.29E-5	3.50E-5	> 5.00E-5
UACC-257	1.071	2.175	2.137	2.257	2.212	2.195	1.784	97	107	103	102	65	> 5.00E-5	> 5.00E-5	> 5.00E-5
UACC-62	0.700	1.606	1.553	1.596	1.594	1.452	0.393	94	99	99	83	-44	9.09E-6	2.25E-5	> 5.00E-5
Ovarian Cancer															
IGROV1	0.214	0.487	0.521	0.546	0.543	0.493	0.178	112	121	120	102	-17	1.37E-5	3.59E-5	> 5.00E-5
OVCA3-3	0.755	1.404	1.431	1.321	1.289	1.315	0.234	104	87	82	86	-69	8.56E-6	1.80E-5	3.77E-5
OVCA3-4	0.610	1.224	1.307	1.261	1.178	1.236	0.584	114	106	93	102	-4	1.54E-5	4.56E-5	> 5.00E-5
OVCA3-5	0.434	0.879	0.966	0.941	0.945	0.967	0.442	119	114	115	120	2	1.95E-5	> 5.00E-5	> 5.00E-5
OVCA3-8	0.414	1.302	1.324	1.349	1.399	1.285	0.442	102	105	111	98	3	1.60E-5	> 5.00E-5	> 5.00E-5
NCI/ADR-RES	0.270	0.839	0.894	0.877	0.857	0.890	0.129	110	107	103	109	-52	1.16E-5	2.37E-5	4.83E-5
SK-OV-3	0.721	1.075	1.086	1.126	1.087	1.126	0.483	103	114	103	114	-33	1.37E-5	2.98E-5	> 5.00E-5
Renal Cancer															
786-0	0.497	1.296	1.366	1.398	1.392	1.363	0.064	109	113	112	108	-87	9.95E-6	1.79E-5	3.23E-5
ACHN	0.241	0.853	0.876	0.846	0.812	0.781	0.096	104	99	93	88	-60	9.05E-6	1.96E-5	4.26E-5
CAKI-1	0.780	1.355	1.330	1.330	1.368	1.360	0.323	96	96	102	101	-59	1.04E-5	2.14E-5	4.41E-5
RXF 393	0.802	1.421	1.434	1.430	1.402	1.410	0.706	102	102	97	98	-12	1.37E-5	3.89E-5	> 5.00E-5
SN12C	0.622	1.176	1.195	1.208	1.237	1.197	0.198	103	106	111	104	-68	1.03E-5	2.01E-5	3.92E-5
TK-10	0.746	1.441	1.402	1.434	1.407	1.374	0.276	94	99	95	90	-63	9.16E-6	1.94E-5	4.11E-5
UC-31	0.068	0.948	0.968	0.963	0.938	0.904	0.138	102	102	99	95	8	1.64E-5	> 5.00E-5	> 5.00E-5
Prostate Cancer															
PC-3	0.208	0.845	0.859	0.876	0.915	0.841	0.060	102	105	111	99	-71	9.73E-6	1.91E-5	3.76E-5
DU-145	0.186	0.723	0.753	0.725	0.750	0.646	0.163	105	100	105	86	-12	1.15E-5	3.74E-5	> 5.00E-5
Breast Cancer															
MCF7	0.156	0.482	0.535	0.454	0.429	0.343	0.039	116	91	84	57	-75	5.68E-6	1.36E-5	3.24E-5
MDA-MB-231/ATCC	0.623	0.863	0.844	0.870	0.963	0.815	0.255	92	103	142	80	-59	8.18E-6	1.87E-5	4.30E-5
BT-549	0.647	1.056	1.106	1.139	1.146	1.139	0.727	112	120	122	120	20	2.50E-5	> 5.00E-5	> 5.00E-5
T-47D	0.560	2.193	2.312	2.260	2.219	2.079	0.384	107	104	102	93	-32	1.11E-5	2.79E-5	> 5.00E-5



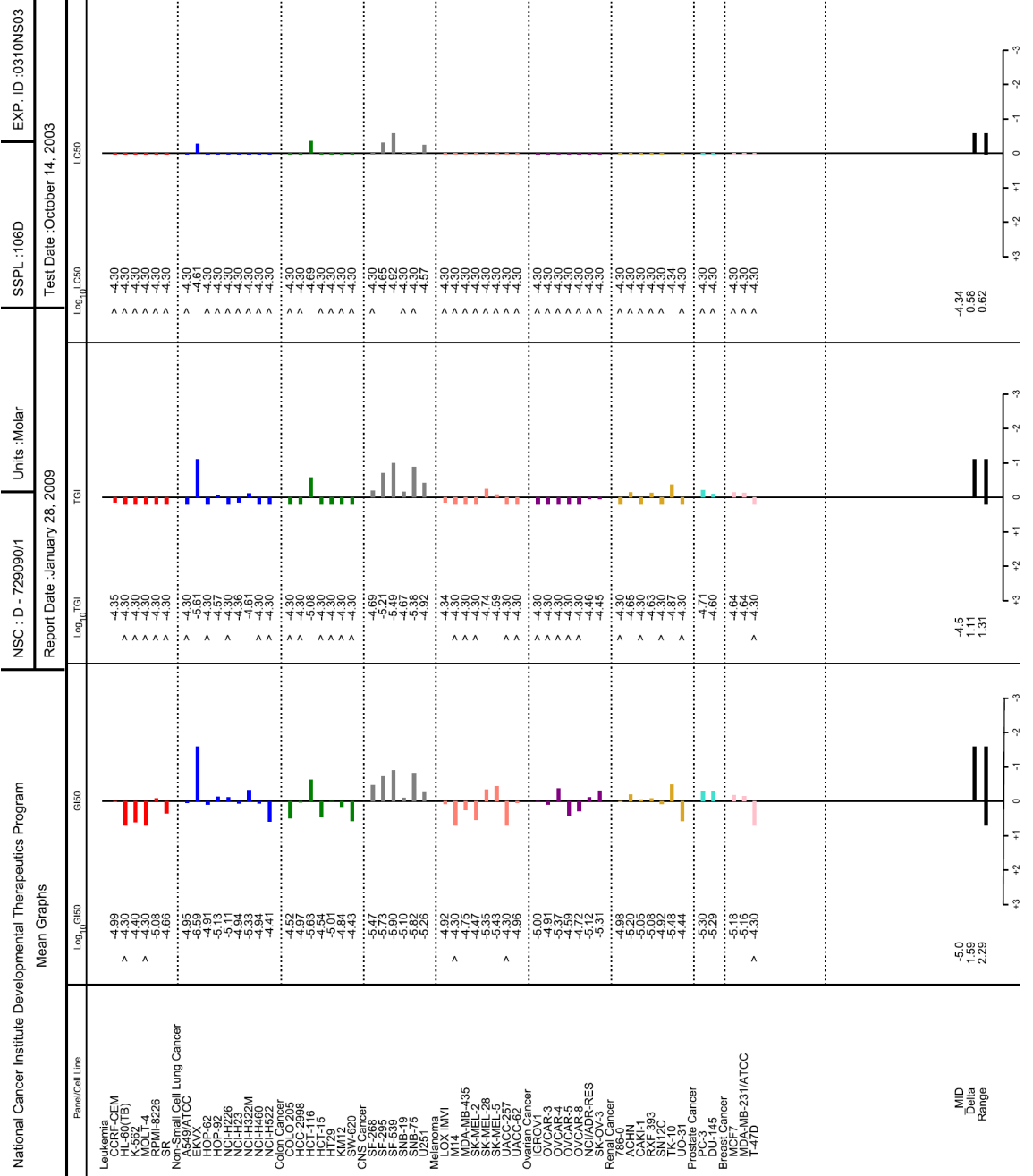
60 Human-Cancer Cell Line 5 Concentration Screen for Compound 103



**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

NSC : D - 729090 / 1	Experiment ID : 0310NS03	Test Type : 08	Units : Molar
Report Date : January 28, 2009	Test Date : October 14, 2003	QNS :	MC :
COMI : 4993 (20435)	Stain Reagent : SRB Dual-Pass Related	SSPL : 106D	

Panel/Cell Line	Log10 Concentration														GI50	TGI	LC50
	Time Zero	Mean Optical Densities						Percent Growth									
		Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3	-4.3					
Leukemia																	
CCR5-CEM	0.198	0.518	0.516	0.440	0.435	0.435	0.190	99	76	74	74	-4	1.02E-5	4.44E-5	> 5.00E-5		
HL-60(TB)	0.323	1.158	1.211	1.124	1.315	1.261	0.911	106	96	119	112	70	> 5.00E-5	> 5.00E-5	> 5.00E-5		
K-562	0.216	1.090	1.011	1.183	1.203	1.117	0.602	91	111	113	103	44	3.97E-5	> 5.00E-5	> 5.00E-5		
MOLT-4	0.137	0.738	0.640	0.699	0.791	0.811	0.467	84	93	109	112	55	> 5.00E-5	> 5.00E-5	> 5.00E-5		
RPMI-8226	0.278	0.869	0.845	0.885	0.858	0.636	0.348	96	103	98	61	12	8.24E-6	> 5.00E-5	> 5.00E-5		
SR	0.226	0.893	0.897	0.973	1.012	0.960	0.337	101	112	118	110	17	2.19E-5	> 5.00E-5	> 5.00E-5		
Non-Small Cell Lung Cancer																	
A549(ATCC)	0.162	0.874	0.902	0.909	0.948	0.653	0.265	104	105	110	69	14	1.11E-5	> 5.00E-5	> 5.00E-5		
EKVX	0.715	0.872	0.898	0.849	0.772	0.598	0.251	116	85	36	-16	-65	2.58E-7	2.43E-6	2.47E-5		
HOP-62	0.143	1.175	1.127	1.211	1.226	0.911	0.273	95	104	105	74	13	1.24E-5	> 5.00E-5	> 5.00E-5		
HOP-92	0.391	1.156	1.114	1.118	1.108	0.887	0.298	95	95	94	65	-24	7.34E-6	2.69E-5	> 5.00E-5		
NCI-H226	0.527	1.770	1.720	1.761	1.716	1.278	0.593	96	99	96	60	5	7.72E-6	> 5.00E-5	> 5.00E-5		
NCI-H23	0.252	0.861	0.854	0.973	1.046	0.762	0.239	96	115	126	81	-5	1.14E-5	4.34E-5	> 5.00E-5		
NCI-H322M	0.837	1.134	1.108	1.128	1.088	0.982	0.650	91	98	84	49	-22	4.68E-6	2.43E-5	> 5.00E-5		
NCI-H460	0.170	1.008	0.994	1.022	1.012	0.756	0.298	98	102	100	70	15	1.16E-5	> 5.00E-5	> 5.00E-5		
NCI-H522	0.561	1.547	1.601	1.660	1.608	1.442	1.006	105	111	106	89	45	3.88E-5	> 5.00E-5	> 5.00E-5		
Colon Cancer																	
COLO 205	0.910	3.111	2.804	2.949	2.897	2.786	1.797	86	93	90	85	40	3.04E-5	> 5.00E-5	> 5.00E-5		
HCC-2998	0.237	0.872	0.823	0.911	0.927	0.684	0.298	92	106	109	70	10	1.08E-5	> 5.00E-5	> 5.00E-5		
HCT-116	0.006	0.466	0.423	0.468	0.438	0.138	-0.005	91	100	94	29	-100	2.36E-6	8.35E-6	2.04E-5		
HCT-15	0.230	1.201	1.180	1.266	1.193	1.091	0.599	98	107	99	89	38	2.90E-5	> 5.00E-5	> 5.00E-5		
HT29	0.098	0.848	0.831	0.890	0.891	0.567	0.247	98	105	106	63	20	9.82E-6	> 5.00E-5	> 5.00E-5		
KM12	0.388	1.261	1.228	1.246	1.198	1.032	0.578	96	98	93	74	22	1.43E-5	> 5.00E-5	> 5.00E-5		
SW-620	0.141	0.431	0.413	0.473	0.472	0.459	0.261	94	114	114	110	41	3.72E-5	> 5.00E-5	> 5.00E-5		
CNS Cancer																	
SF-268	0.703	1.295	1.197	1.229	1.221	0.953	0.513	83	89	88	42	-27	3.36E-6	2.03E-5	> 5.00E-5		
SF-295	0.527	0.911	0.945	0.967	0.934	0.558	0.103	109	115	106	8	-81	1.86E-6	6.15E-6	2.26E-5		
SF-539	0.596	0.798	0.779	0.813	0.795	0.460	0.036	91	108	99	-23	-94	1.26E-6	3.25E-6	1.20E-5		
SNB-19	0.360	1.052	1.035	1.138	1.061	0.864	0.207	98	112	101	73	-43	7.89E-6	2.14E-5	> 5.00E-5		
SNB-75	0.479	0.754	0.705	0.771	0.771	0.434	0.245	82	106	106	-9	-49	1.53E-6	4.14E-6	> 5.00E-5		
U251	0.163	0.763	0.756	0.737	0.757	0.495	0.017	99	96	99	55	-90	5.44E-6	1.20E-5	2.67E-5		
Melanoma																	
LOX IMVI	0.301	1.042	1.009	1.092	1.101	0.913	0.291	95	107	108	83	-3	1.20E-5	4.57E-5	> 5.00E-5		
M14	0.075	0.965	0.946	1.044	1.036	0.980	0.610	98	109	108	102	60	> 5.00E-5	> 5.00E-5	> 5.00E-5		
MDA-MB-435	0.632	1.806	1.877	1.868	1.850	1.439	1.042	106	105	104	69	35	1.79E-5	> 5.00E-5	> 5.00E-5		
SK-MEL-2	0.262	1.435	1.332	1.444	1.426	1.324	0.755	91	101	99	91	42	3.42E-5	> 5.00E-5	> 5.00E-5		
SK-MEL-28	0.369	0.646	0.615	0.681	0.637	0.501	0.231	89	113	97	48	-38	4.50E-6	1.81E-5	> 5.00E-5		
SK-MEL-5	0.325	0.784	0.745	0.829	0.735	0.527	0.268	92	110	89	44	-18	3.70E-6	2.60E-5	> 5.00E-5		
UACC-257	0.975	2.128	2.214	2.236	2.415	2.347	1.894	107	109	125	119	80	> 5.00E-5	> 5.00E-5	> 5.00E-5		
UACC-62	0.514	1.834	1.797	1.868	1.817	1.457	0.618	97	103	99	71	8	1.09E-5	> 5.00E-5	> 5.00E-5		
Ovarian Cancer																	
IGROV1	0.183	0.665	0.656	0.707	0.727	0.471	0.312	98	109	113	60	27	9.89E-6	> 5.00E-5	> 5.00E-5		
OVCAR-3	0.816	1.539	1.520	1.470	1.600	1.396	0.840	97	90	108	80	3	1.23E-5	> 5.00E-5	> 5.00E-5		
OVCAR-4	0.243	1.230	1.169	1.259	1.243	0.698	0.384	94	103	101	46	14	4.24E-6	> 5.00E-5	> 5.00E-5		
OVCAR-5	0.529	1.122	1.101	1.262	1.235	1.095	0.716	97	124	119	95	32	2.57E-5	> 5.00E-5	> 5.00E-5		
OVCAR-8	0.398	1.273	1.275	1.393	1.407	1.238	0.547	100	114	115	96	17	1.91E-5	> 5.00E-5	> 5.00E-5		
NCI/ADR-RES	0.209	0.730	0.720	0.771	0.731	0.540	0.184	98	108	100	64	-12	7.55E-6	3.47E-5	> 5.00E-5		
SK-OV-3	0.355	1.097	1.102	1.173	1.168	0.721	0.325	101	110	110	49	-9	4.86E-6	3.55E-5	> 5.00E-5		
Renal Cancer																	
786-0	0.111	1.303	1.266	1.350	1.362	0.910	0.268	97	104	105	67	13	1.04E-5	> 5.00E-5	> 5.00E-5		
ACHN	0.343	1.071	1.032	1.058	1.073	0.776	0.235	95	98	100	59	-32	6.36E-6	2.25E-5	> 5.00E-5		
CAKI-1	0.857	1.795	1.891	1.902	1.921	1.474	0.894	110	111	113	66	4	8.99E-6	> 5.00E-5	> 5.00E-5		
RXF 393	0.614	1.045	1.006	1.063	1.173	0.936	0.385	91	104	130	75	-37	8.30E-6	2.32E-5	> 5.00E-5		
SN12C	0.476	1.141	1.095	1.136	1.188	0.994	0.510	93	99	107	78	5	1.21E-5	> 5.00E-5	> 5.00E-5		
TK-10	0.766	1.285	1.236	1.256	1.260	0.975	0.358	91	94	95	40	-53	3.33E-6	1.35E-5	4.61E-5		
UO-31	0.158	1.437	1.394	1.412	1.463	1.374	0.708	97	98	102	95	43	3.67E-5	> 5.00E-5	> 5.00E-5		
Prostate Cancer																	
PC-3	0.523	1.276	1.268	1.267	1.251	0.903	0.339	99	99	97	50	-35	5.06E-6	1.94E-5	> 5.00E-5		
DU-145	0.323	0.807	0.757	0.796	0.750	0.569	0.254	90	98	88	51	-21	5.11E-6	2.53E-5	> 5.00E-5		
Breast Cancer																	
MCF7	0.185	0.433	0.412	0.446	0.472	0.338	0.126	91	105	115	61	-32	6.63E-6	2.28E-5	> 5.00E-5		
MDA-MB-231(ATCC)	0.436	0.906	0.904	0.930	0.915	0.737	0.296	100	105	102	64	-32	6.98E-6	2.31E-5	> 5.00E-5		
T-47D	0.850	3.109	3.021	3.052	3.040	3.131	2.238	96	97	97	101	61	> 5.00E-5	> 5.00E-5	> 5.00E-5		



60 Human-Cancer Cell Line 5 Concentration Screen for Compound 104

National Cancer Institute Developmental Therapeutics Program
 Dose Response Curves

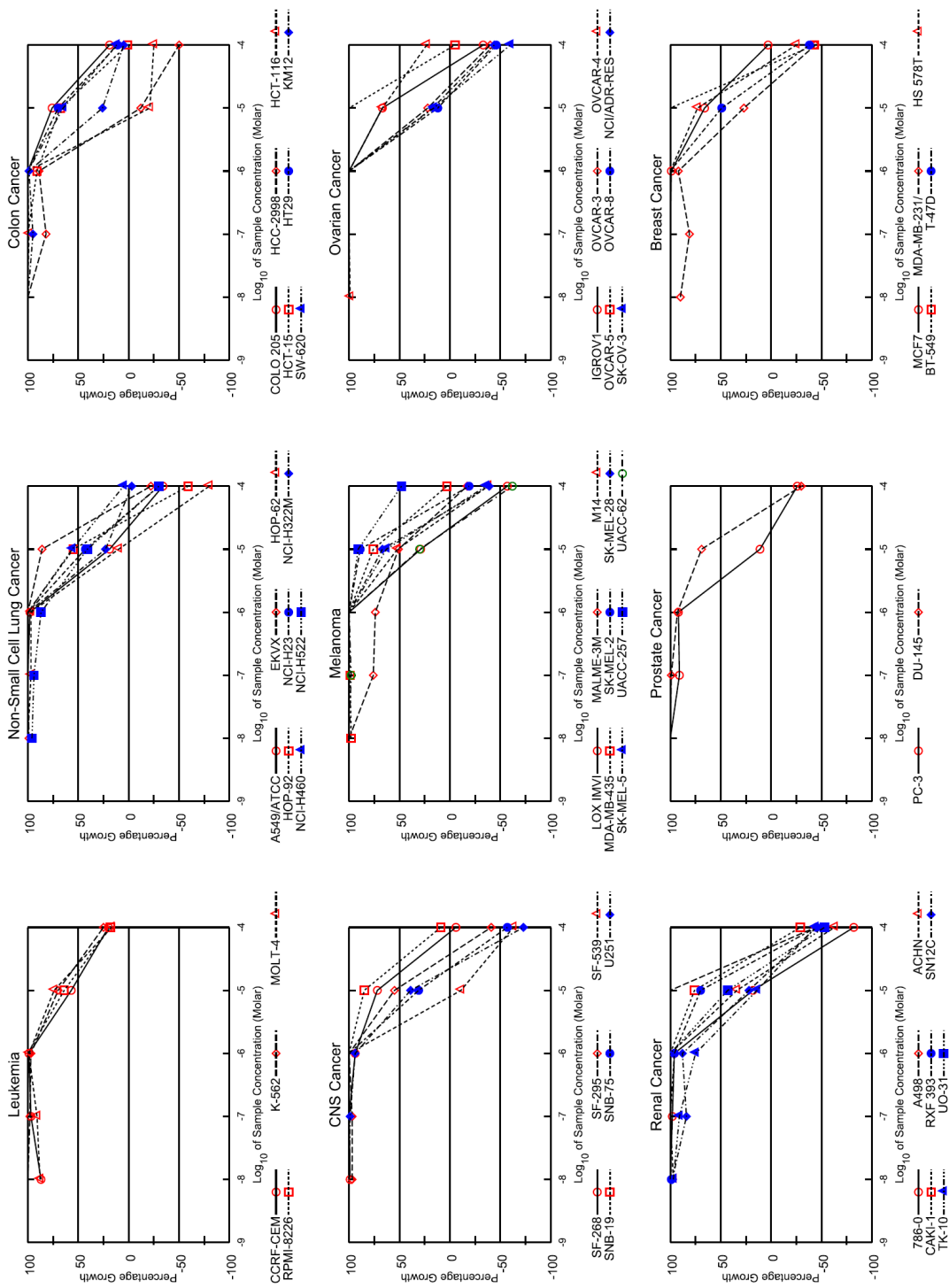
NSC: D - 726978 / 1

Report Date: January 28, 2009

SSPL: 106D

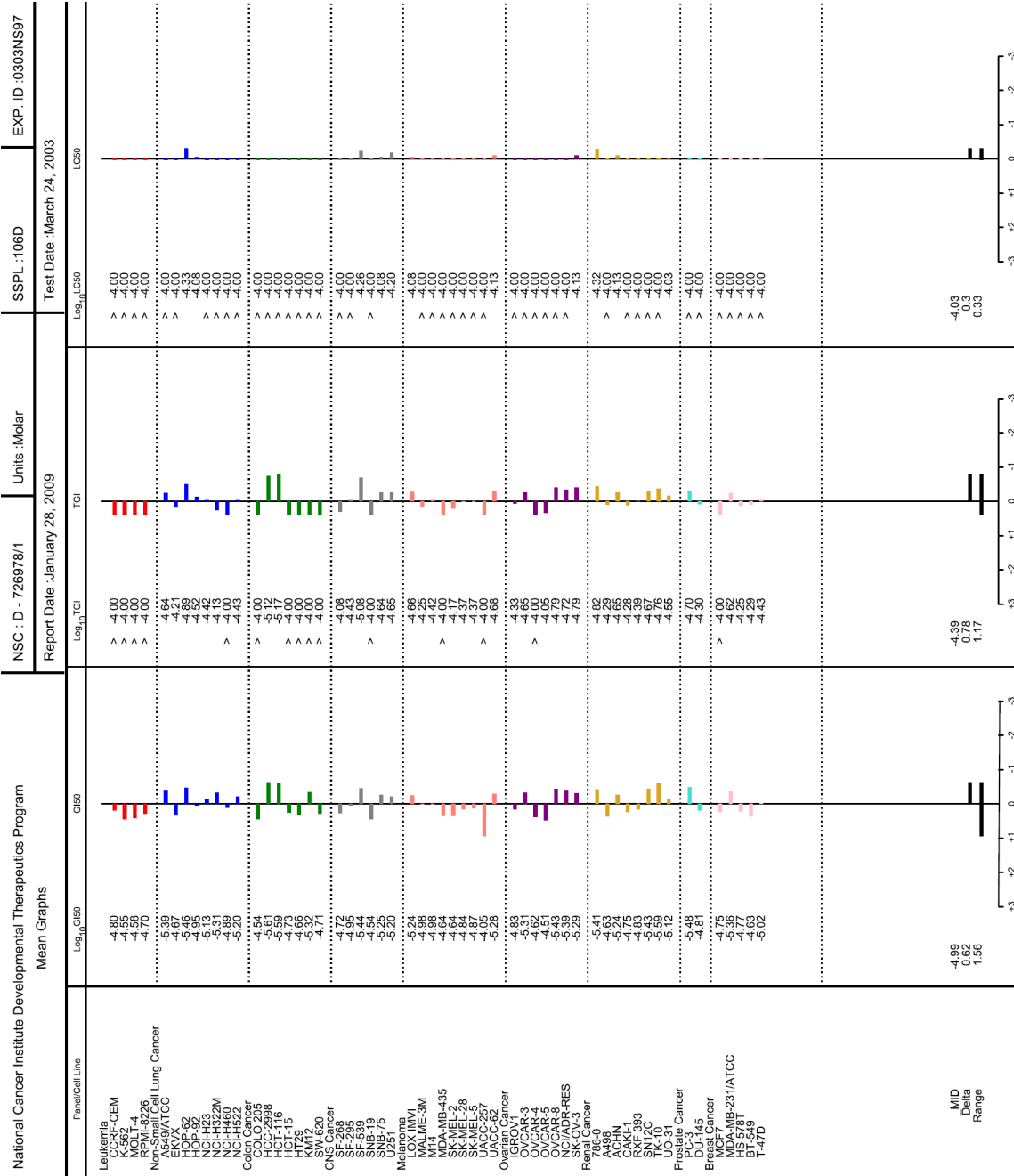
Test Date: March 24, 2003

EXP. ID: 0303NS97

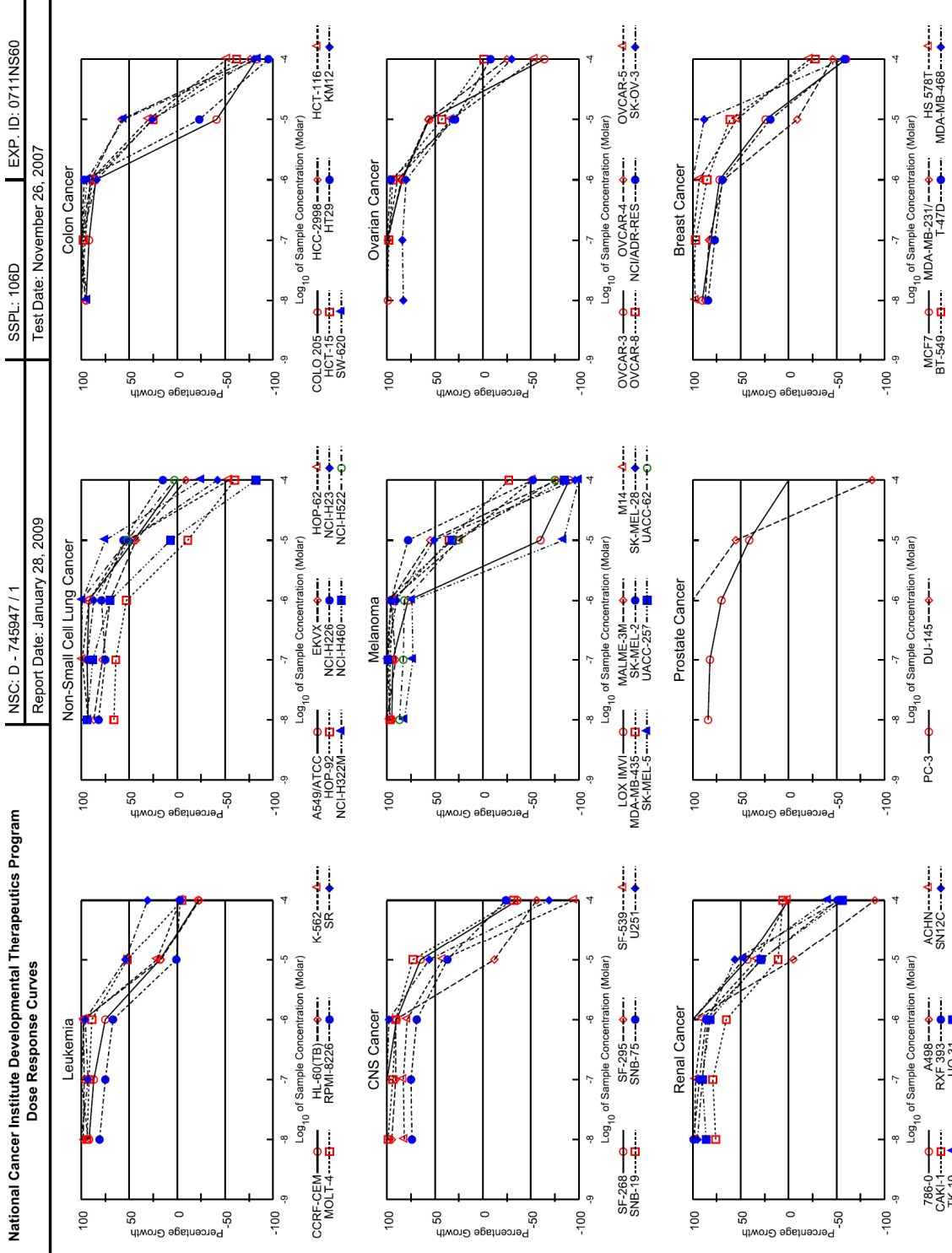


National Cancer Institute Developmental Therapeutics Program In-Vitro Testing Results

NSC : D - 726978 / 1		Experiment ID : 0303NS97				Test Type : 08					Units : Molar				
Report Date : January 28, 2009		Test Date : March 24, 2003				QNS :					MC :				
COMI : 4994 (20525)		Stain Reagent : SRB Dual-Pass Related				SSPL : 106D									
Panel/Cell Line	Time Zero	Ctrl	Mean Optical Densities				Percent Growth				GI50	TGI	LC50		
			-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0				-5.0	-4.0
Leukemia															
CCRFC-CEM	0.141	0.526	0.476	0.516	0.521	0.363	0.219	87	97	99	57	20	1.59E-5	> 1.00E-4	> 1.00E-4
K-562	0.090	0.476	0.539	0.470	0.466	0.361	0.188	116	98	97	70	25	2.82E-5	> 1.00E-4	> 1.00E-4
MOLT-4	0.162	0.786	0.710	0.732	0.778	0.623	0.269	88	91	99	74	17	2.63E-5	> 1.00E-4	> 1.00E-4
RPMI-8226	0.192	0.531	0.580	0.553	0.537	0.408	0.252	114	107	102	64	18	1.98E-5	> 1.00E-4	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.251	1.303	1.342	1.312	1.280	0.455	0.167	104	101	98	19	-34	4.06E-6	2.32E-5	> 1.00E-4
EKVX	0.414	0.865	0.859	0.914	0.982	0.804	0.321	99	111	126	86	-22	2.16E-5	6.22E-5	> 1.00E-4
HOP-62	0.321	0.710	0.729	0.699	0.700	0.359	0.065	105	97	97	10	-80	3.48E-6	1.29E-5	4.64E-5
HOP-92	0.864	1.142	1.175	1.201	1.181	1.018	0.354	112	121	114	55	-59	1.11E-5	3.04E-5	8.34E-5
NCH-H23	0.322	0.800	0.842	0.854	0.800	0.527	0.224	109	111	100	43	-30	7.50E-6	3.84E-5	> 1.00E-4
NCH-H322M	0.507	0.836	0.846	0.849	0.868	0.583	0.490	103	104	110	23	-3	4.90E-6	7.47E-5	> 1.00E-4
NCH-H460	0.330	2.251	2.341	2.257	2.277	1.403	0.424	105	100	101	56	5	1.30E-5	> 1.00E-4	> 1.00E-4
NCH-H522	0.581	1.330	1.303	1.283	1.236	0.886	0.405	96	94	87	41	-30	6.31E-6	3.73E-5	> 1.00E-4
Colon Cancer															
COLO 205	0.342	1.210	1.354	1.255	1.299	1.003	0.506	117	105	110	76	19	2.86E-5	> 1.00E-4	> 1.00E-4
HCC-2998	0.392	0.549	0.620	0.521	0.532	0.345	0.197	145	82	89	-12	-50	2.43E-6	7.61E-6	> 1.00E-4
HCT-116	0.095	0.434	0.471	0.432	0.433	0.075	0.071	111	99	100	-21	-25	2.58E-6	6.69E-6	> 1.00E-4
HCT-15	0.324	1.182	1.179	1.189	1.106	0.907	0.329	100	101	91	68	1	1.85E-5	> 1.00E-4	> 1.00E-4
HT29	0.125	0.859	0.888	0.863	0.895	0.640	0.206	104	101	105	70	11	2.20E-5	> 1.00E-4	> 1.00E-4
KM12	0.268	0.987	1.016	0.949	0.981	0.457	0.307	104	95	99	26	5	4.73E-6	> 1.00E-4	> 1.00E-4
SW-620	0.206	1.238	1.244	1.275	1.281	0.880	0.334	101	104	104	65	12	1.95E-5	> 1.00E-4	> 1.00E-4
CNS Cancer															
SF-268	0.637	1.943	1.926	1.952	1.866	1.582	0.596	99	101	94	72	-6	1.92E-5	8.28E-5	> 1.00E-4
SF-295	0.710	1.801	1.771	1.763	1.932	1.309	0.421	97	97	112	55	-41	1.13E-5	3.75E-5	> 1.00E-4
SF-539	0.323	0.545	0.587	0.549	0.603	0.289	0.118	119	102	126	-11	-63	3.60E-6	8.35E-6	5.56E-5
SNB-19	0.575	1.670	1.805	1.696	1.712	1.508	0.670	112	102	104	85	9	2.88E-5	> 1.00E-4	> 1.00E-4
SNB-75	0.597	1.057	1.081	1.115	1.084	0.742	0.258	105	113	106	31	-57	5.63E-6	2.27E-5	8.36E-5
U251	0.280	1.161	1.165	1.156	1.105	0.622	0.077	100	99	94	39	-73	6.25E-6	2.23E-5	6.26E-5
Melanoma															
LOX IMVI	0.169	0.727	0.790	0.737	0.822	0.333	0.073	111	102	117	29	-57	5.82E-6	2.19E-5	8.28E-5
MALME-3M	0.563	0.989	0.989	0.885	0.877	0.782	0.466	100	76	74	51	-17	1.05E-5	5.61E-5	> 1.00E-4
M14	0.192	0.520	0.549	0.541	0.525	0.363	0.119	109	106	101	52	-38	1.05E-5	3.79E-5	> 1.00E-4
MDA-MB-435	0.561	1.560	1.541	1.550	1.653	1.319	0.592	98	99	109	76	3	2.26E-5	> 1.00E-4	> 1.00E-4
MEL-2	0.643	1.180	1.228	1.395	1.190	1.120	0.523	109	140	102	89	-19	2.30E-5	6.71E-5	> 1.00E-4
SK-MEL-28	0.449	1.274	1.281	1.293	1.287	1.003	0.272	101	102	102	67	-39	1.45E-5	4.26E-5	> 1.00E-4
SK-MEL-5	0.305	0.981	1.080	1.055	0.999	0.728	0.194	115	111	103	63	-36	1.34E-5	4.29E-5	> 1.00E-4
UACC-257	0.230	1.501	1.550	1.508	1.521	1.386	0.835	104	101	102	91	48	8.81E-5	> 1.00E-4	> 1.00E-4
UACC-62	0.552	1.457	1.487	1.440	1.482	0.819	0.208	103	98	103	30	-62	5.26E-6	2.10E-5	7.34E-5
Ovarian Cancer															
IGROV1	0.510	1.230	1.263	1.233	1.245	0.992	0.344	105	100	102	67	-33	1.48E-5	4.71E-5	> 1.00E-4
OVCAR-3	0.441	0.918	0.938	0.971	0.977	0.546	0.263	104	111	112	22	-40	4.89E-6	2.25E-5	> 1.00E-4
OVCAR-4	0.220	0.790	0.783	0.807	0.815	0.601	0.351	99	103	104	67	23	2.42E-5	> 1.00E-4	> 1.00E-4
OVCAR-5	0.436	0.875	0.943	0.968	0.987	0.884	0.413	115	121	126	102	-5	3.06E-5	8.93E-5	> 1.00E-4
OVCAR-8	0.316	1.024	1.093	1.081	1.032	0.403	0.171	110	108	101	12	-46	3.76E-6	1.62E-5	> 1.00E-4
NCI/ADR-RES	0.428	0.963	0.967	0.999	0.970	0.517	0.242	101	107	101	17	-44	4.03E-6	1.88E-5	> 1.00E-4
SK-OV-3	0.761	1.117	1.175	1.163	1.229	0.818	0.308	116	113	132	16	-60	5.08E-6	1.63E-5	7.48E-5
Renal Cancer															
786-0	0.390	1.281	1.313	1.260	1.245	0.551	0.071	104	98	96	18	-82	3.89E-6	1.52E-5	4.80E-5
A498	0.924	1.284	1.331	1.339	1.354	1.305	0.522	113	115	119	106	-44	2.37E-5	5.11E-5	> 1.00E-4
ACHN	0.292	0.793	0.778	0.846	0.794	0.461	0.110	97	111	100	34	-63	5.70E-6	2.24E-5	7.42E-5
CAKI-1	0.612	1.366	1.384	1.428	1.524	1.184	0.434	102	108	121	76	-29	1.76E-5	5.27E-5	> 1.00E-4
RXF 393	0.653	1.522	1.514	1.548	1.491	1.258	0.358	99	103	96	70	-45	1.48E-5	4.04E-5	> 1.00E-4
SN12C	0.333	0.641	0.634	0.592	0.604	0.400	0.184	98	84	88	22	-45	3.73E-6	2.12E-5	> 1.00E-4
TK-10	0.326	0.731	0.718	0.694	0.630	0.381	0.184	97	91	75	14	-44	2.55E-6	1.73E-5	> 1.00E-4
UO-31	0.526	1.562	1.695	1.579	1.583	0.967	0.250	113	102	102	43	-53	7.51E-6	2.80E-5	9.40E-5
Prostate Cancer															
PC-3	0.251	0.654	0.711	0.619	0.621	0.297	0.185	114	91	92	11	-26	3.31E-6	2.00E-5	> 1.00E-4
DU-145	0.190	0.643	0.644	0.638	0.611	0.501	0.133	100	99	93	69	-30	1.55E-5	4.97E-5	> 1.00E-4
Breast Cancer															
MCF7	0.235	1.826	1.822	1.875	1.810	1.278	0.291	100	103	99	66	3	1.78E-5	> 1.00E-4	> 1.00E-4
MDA-MB-231/ATCC	0.402	0.774	0.738	0.703	0.744	0.501	0.224	90	81	92	27	-44	4.38E-6	2.37E-5	> 1.00E-4
HS 578T	0.644	1.203	1.282	1.271	1.258	1.050	0.484	114	112	110	73	-25	1.71E-5	5.56E-5	> 1.00E-4
BT-549	0.519	0.994	1.040	1.056	1.023	1.022	0.295	110	113	106	106	-43	2.37E-5	5.13E-5	> 1.00E-4
T-47D	0.935	1.700	1.732	1.759	1.712	1.311	0.582	104	108	102	49	-38	9.63E-6	3.67E-5	> 1.00E-4



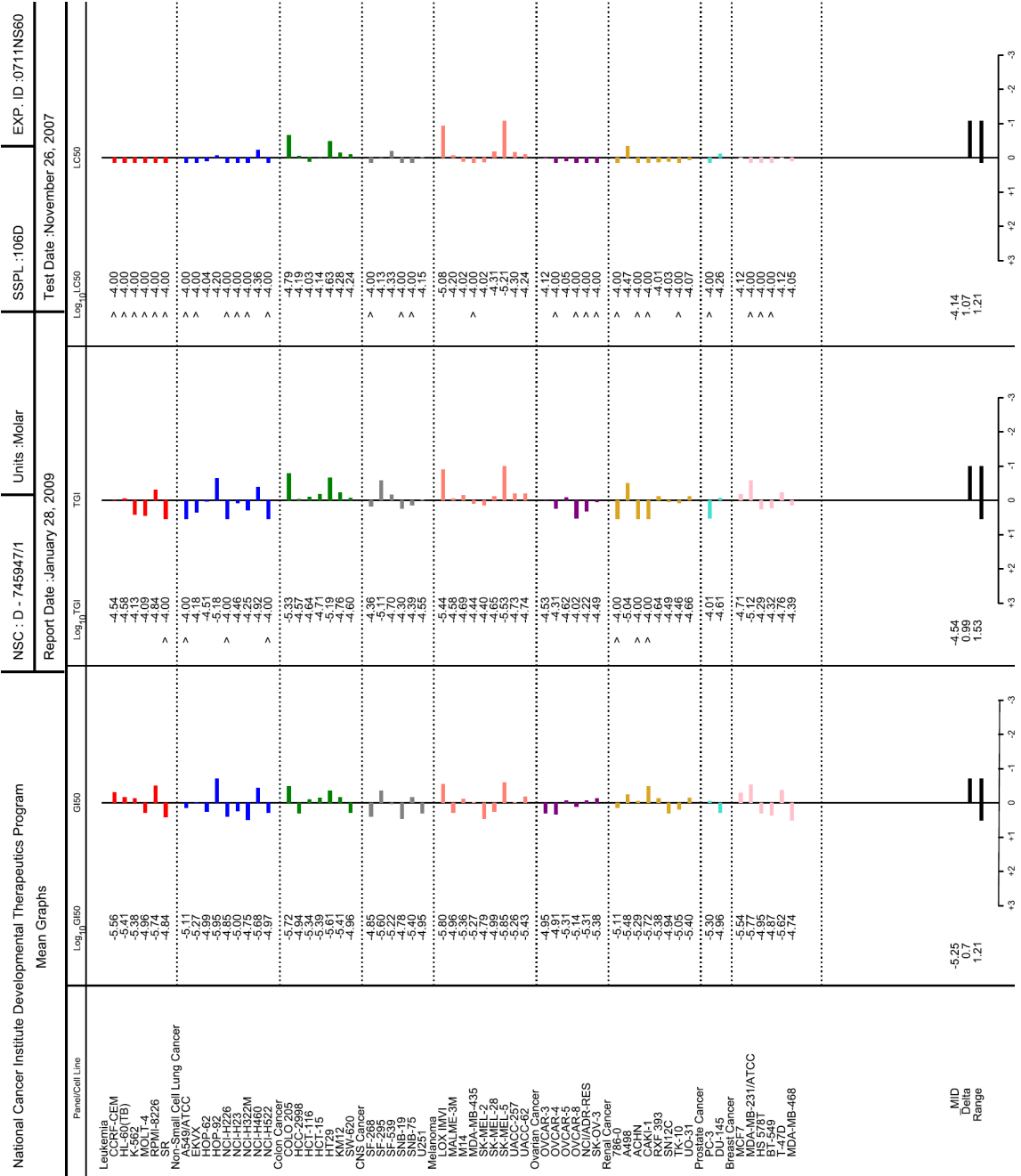
60 Human-Cancer Cell Line 5 Concentration Screen for Compound 174



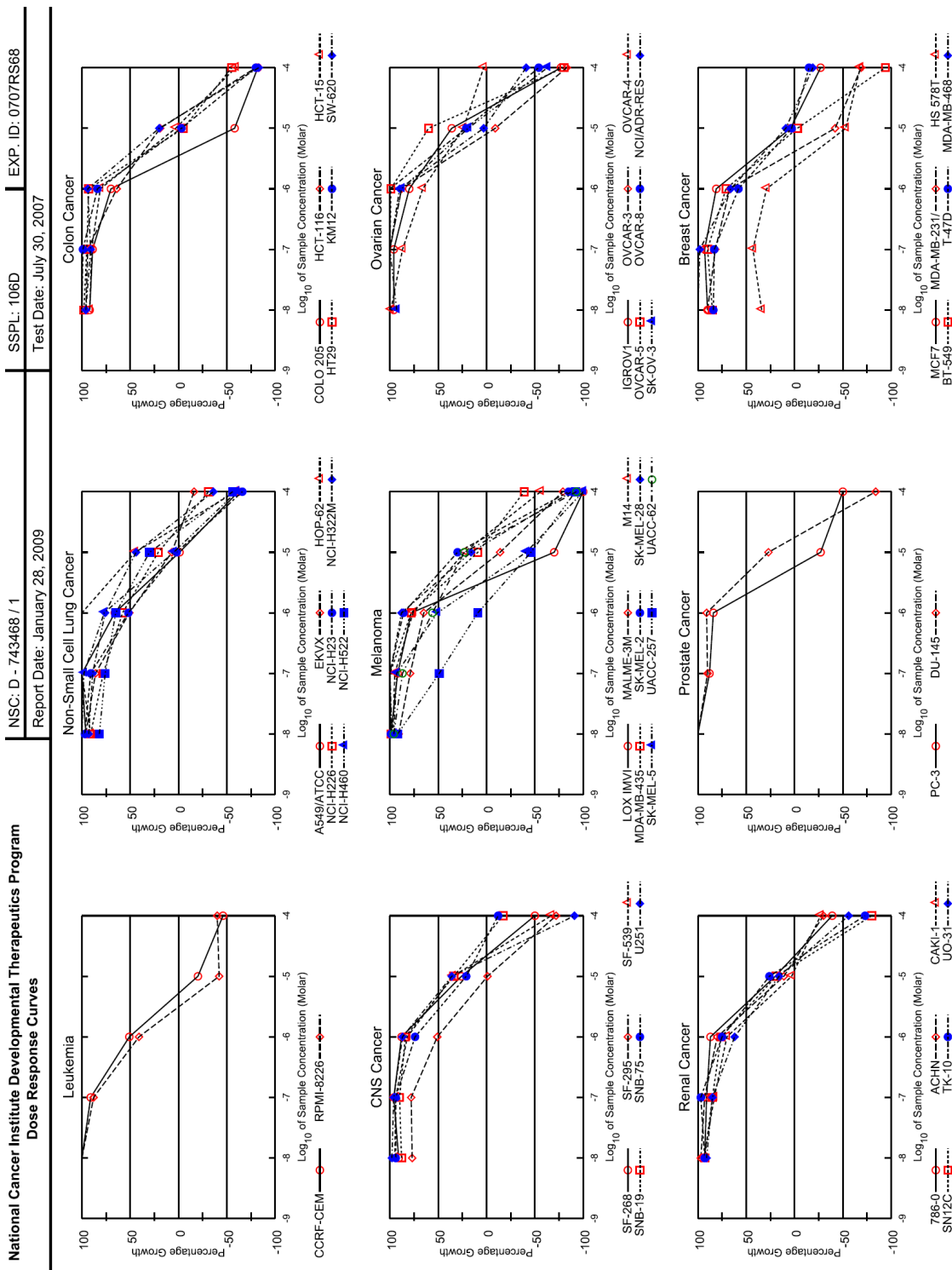
National Cancer Institute Developmental Therapeutics Program In-Vitro Testing Results

NSC : D - 745947 / 1	Experiment ID : 0711NS60	Test Type : 08	Units : Molar
Report Date : January 28, 2009	Test Date : November 26, 2007	QNS :	MC :
COMI : 5836 (56470)	Stain Reagent : SRB Dual-Pass Related	SSPL : 106D	

Panel/Cell Line	Log10 Concentration											GI50	TGI	LC50	
	Time Zero	Ctrl	Mean Optical Densities					Percent Growth							
			-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0				-4.0
Leukemia															
CCRF-CEM	0.445	1.349	1.275	1.232	1.125	0.610	0.349	92	87	75	18	-22	2.77E-6	2.86E-5	> 1.00E-4
HL-60(TB)	0.744	2.037	2.010	1.993	2.013	0.958	0.571	98	97	98	17	-23	3.89E-6	2.60E-5	> 1.00E-4
K-562	0.180	1.263	1.184	1.269	1.227	0.410	0.175	93	101	97	21	-3	4.15E-6	7.48E-5	> 1.00E-4
MOLT-4	0.455	1.508	1.445	1.426	1.389	1.005	0.433	94	92	89	52	-5	1.09E-5	8.19E-5	> 1.00E-4
RPMI-8226	0.654	1.792	1.570	1.510	1.421	0.661	0.633	81	75	67	1	-3	1.82E-6	1.44E-5	> 1.00E-4
SR	0.167	0.639	0.647	0.607	0.619	0.421	0.313	102	93	96	54	31	1.46E-5	> 1.00E-4	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.110	0.665	0.626	0.633	0.621	0.360	0.111	93	94	92	45	.	7.80E-6	> 1.00E-4	> 1.00E-4
EKVX	0.652	2.103	1.918	1.780	1.666	1.271	0.591	87	78	70	43	-9	5.36E-6	6.59E-5	> 1.00E-4
HOP-62	0.342	1.369	1.294	1.356	1.288	0.872	0.157	93	99	92	52	-54	1.03E-5	3.07E-5	> 1.00E-4
HOP-92	0.770	1.133	1.011	1.002	0.963	0.682	0.310	66	64	53	-11	-60	1.11E-6	6.63E-6	6.28E-5
NCI-H226	1.003	1.822	1.671	1.616	1.652	1.462	1.123	82	75	79	56	15	1.40E-5	> 1.00E-4	> 1.00E-4
NCI-H23	0.418	1.276	1.219	1.224	1.161	0.846	0.242	93	94	87	50	-42	9.89E-6	3.48E-5	> 1.00E-4
NCI-H322M	0.347	1.098	1.114	1.141	1.094	0.907	0.261	102	106	99	75	-25	1.77E-5	5.63E-5	> 1.00E-4
NCI-H460	0.245	1.901	1.801	1.696	1.409	0.361	0.044	94	88	70	7	-82	2.09E-6	1.20E-5	4.37E-5
NCI-H522	0.541	1.759	1.757	1.851	1.762	1.171	0.577	100	108	100	52	3	1.08E-5	> 1.00E-4	> 1.00E-4
Colon Cancer															
COLO 205	0.199	1.100	1.059	1.025	0.967	0.117	0.034	95	92	85	-41	-83	1.90E-6	4.72E-6	1.62E-5
HCC-2998	0.268	0.612	0.599	0.652	0.578	0.468	0.065	96	112	90	58	-76	1.15E-5	2.71E-5	6.40E-5
HCT-116	0.138	1.128	1.126	1.084	1.025	0.434	0.066	100	96	90	30	-52	4.60E-6	2.31E-5	9.41E-5
HCT-15	0.285	1.558	1.561	1.535	1.406	0.607	0.109	100	98	88	25	-62	4.03E-6	1.95E-5	7.30E-5
HT29	0.231	1.603	1.629	1.686	1.565	0.179	0.011	102	106	97	-23	-95	2.48E-6	6.46E-6	2.37E-5
KM12	0.217	1.014	1.039	1.045	0.889	0.422	0.044	103	104	84	26	-80	3.85E-6	1.75E-5	5.23E-5
SW-620	0.175	1.087	1.028	1.084	1.032	0.688	0.029	94	100	94	56	-84	1.11E-5	2.52E-5	5.74E-5
CNS Cancer															
SF-268	0.357	1.018	1.057	1.080	0.954	0.784	0.229	106	109	90	65	-36	1.40E-5	4.40E-5	> 1.00E-4
SF-295	0.415	1.672	1.607	1.562	1.565	0.367	0.183	95	91	91	-12	-56	2.52E-6	7.70E-6	7.35E-5
SF-539	0.574	1.594	1.409	1.422	1.376	1.000	0.027	82	83	79	42	-95	5.97E-6	2.02E-5	4.67E-5
SNB-19	0.464	1.515	1.508	1.448	1.416	1.236	0.317	99	94	91	73	-32	1.67E-5	4.99E-5	> 1.00E-4
SNB-75	0.640	1.248	1.088	1.095	1.058	0.868	0.486	74	75	69	37	-24	3.96E-6	4.05E-5	> 1.00E-4
U251	0.220	1.125	1.151	1.156	1.107	0.727	0.069	103	103	98	56	-69	1.12E-5	2.81E-5	7.09E-5
Melanoma															
LOX IMVI	0.363	2.151	2.062	2.049	1.752	0.144	0.037	95	94	78	-60	-90	1.59E-6	3.65E-6	8.40E-6
MALME-3M	0.229	0.494	0.508	0.469	0.484	0.375	0.054	105	91	96	55	-77	1.09E-5	2.62E-5	6.27E-5
M14	0.339	1.479	1.444	1.466	1.432	0.610	0.164	97	99	96	24	-52	4.33E-6	2.06E-5	9.47E-5
MDA-MB-435	0.280	1.382	1.354	1.350	1.303	0.661	0.205	97	97	93	35	-27	5.43E-6	3.66E-5	> 1.00E-4
SK-MEL-2	0.284	0.723	0.743	0.727	0.704	0.626	0.136	104	101	96	78	-52	1.64E-5	3.97E-5	9.63E-5
SK-MEL-28	0.300	0.857	0.876	0.903	0.804	0.586	0.012	103	108	90	51	-96	1.02E-5	2.23E-5	4.87E-5
SK-MEL-5	0.540	2.240	1.942	1.780	1.801	0.087	-0.007	82	73	74	-84	-100	1.42E-6	2.94E-6	6.10E-6
UACC-257	0.493	1.067	1.065	1.063	1.069	0.678	0.072	100	99	100	32	-85	5.48E-6	1.88E-5	4.99E-5
UACC-62	0.431	2.092	1.880	1.802	1.790	0.869	0.110	87	83	82	26	-75	3.75E-6	1.82E-5	5.71E-5
Ovarian Cancer															
OVCA-3	0.305	0.857	0.852	0.859	0.770	0.614	0.110	99	100	84	56	-64	1.12E-5	2.93E-5	7.65E-5
OVCA-4	0.363	0.879	0.882	0.876	0.800	0.659	0.271	101	99	85	57	-25	1.23E-5	4.94E-5	> 1.00E-4
OVCA-5	0.446	0.977	1.002	0.986	0.919	0.619	0.205	105	102	89	33	-54	4.91E-6	2.37E-5	8.96E-5
OVCA-8	0.299	1.271	1.272	1.256	1.210	0.719	0.297	100	98	94	43	-1	7.33E-6	9.65E-5	> 1.00E-4
NCI/ADR-RES	0.436	1.336	1.358	1.388	1.300	0.699	0.400	102	106	96	29	-8	4.88E-6	6.02E-5	> 1.00E-4
SK-OV-3	0.530	1.357	1.214	1.222	1.189	0.793	0.372	83	84	80	32	-30	4.16E-6	3.27E-5	> 1.00E-4
Renal Cancer															
786-0	0.450	1.996	2.190	2.161	2.091	1.114	0.457	113	111	106	43	.	7.73E-6	> 1.00E-4	> 1.00E-4
A498	0.605	1.045	1.151	1.117	1.083	0.578	0.059	124	116	109	-5	-90	3.29E-6	9.12E-6	3.39E-5
ACHN	0.355	1.396	1.375	1.362	1.297	0.703	0.363	98	97	90	33	1	5.12E-6	> 1.00E-4	> 1.00E-4
CAKI-1	0.294	0.915	0.765	0.785	0.697	0.365	0.332	76	79	65	11	6	1.90E-6	> 1.00E-4	> 1.00E-4
RXF 393	0.157	0.447	0.444	0.428	0.406	0.238	0.078	99	93	86	28	-51	4.14E-6	2.27E-5	9.82E-5
SN12C	0.304	1.121	1.080	1.041	0.994	0.763	0.142	95	90	84	56	-53	1.14E-5	3.26E-5	9.33E-5
TK-10	0.362	0.937	0.996	1.038	0.954	0.632	0.215	110	118	103	47	-41	8.83E-6	3.44E-5	> 1.00E-4
UO-31	0.147	0.607	0.541	0.561	0.524	0.281	0.065	86	90	82	29	-56	4.02E-6	2.20E-5	8.55E-5
Prostate Cancer															
PC-3	0.372	1.100	0.986	0.967	0.884	0.674	0.371	84	82	70	41	.	5.07E-6	9.85E-5	> 1.00E-4
DU-145	0.230	0.820	0.844	0.869	0.818	0.555	0.031	104	108	100	55	-87	1.09E-5	2.45E-5	5.51E-5
Breast Cancer															
MCF7	0.282	1.393	1.278	1.180	1.082	0.554	0.112	90	81	72	24	-60	2.90E-6	1.94E-5	7.53E-5
MDA-MB-231/ATCC	0.478	1.311	1.202	1.172	1.043	0.435	0.258	87	83	68	-9	-46	1.70E-6	7.63E-6	> 1.00E-4
HS 578T	0.413	0.856	0.842	0.897	0.824	0.652	0.322	97	109	93	54	-22	1.13E-5	5.13E-5	> 1.00E-4
BT-549	0.254	0.649	0.648	0.639	0.592	0.496	0.182	100	97	85	61	-28	1.34E-5	4.83E-5	> 1.00E-4
T-47D	0.377	0.981	0.886	0.840	0.795	0.491	0.154	84	77	69	19	-59	2.41E-6	1.75E-5	7.63E-5
MDA-MB-468	2.275	3.266	3.331	3.340	3.338	3.148	0.975	107	107	107	88	-57	1.83E-5	4.04E-5	8.93E-5



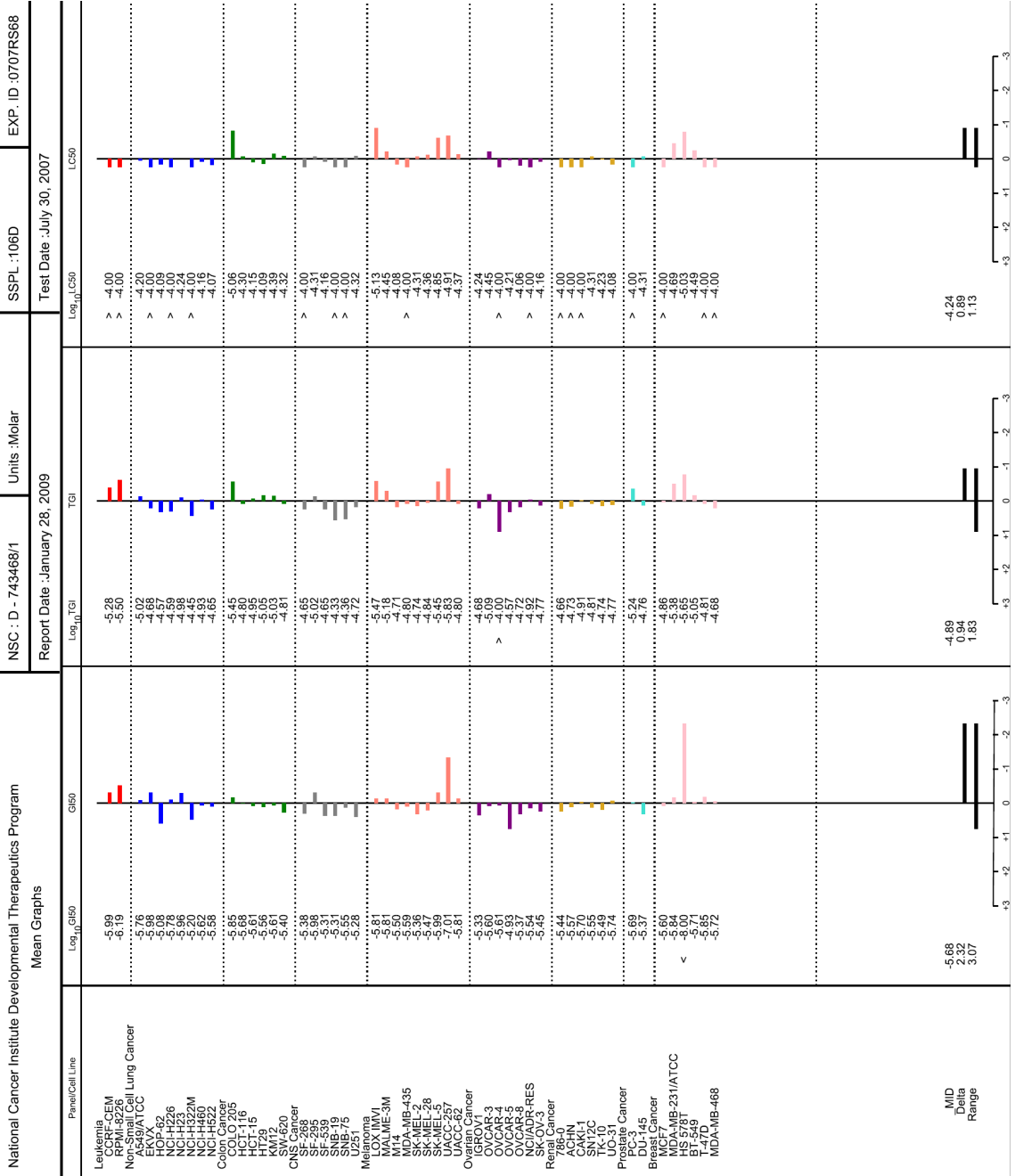
60 Human-Cancer Cell Line 5 Concentration Screen for Compound 177



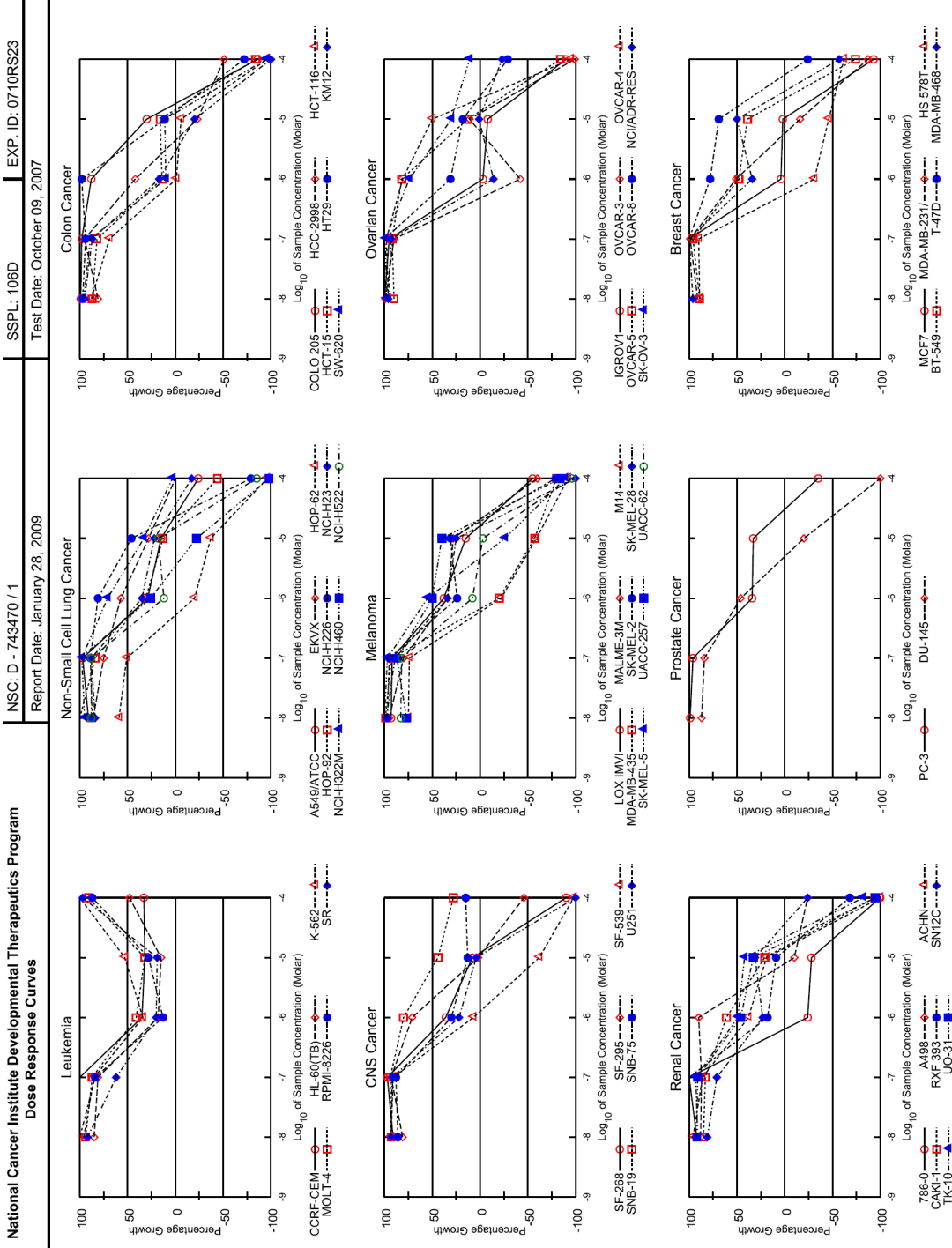
National Cancer Institute Developmental Therapeutics Program In-Vitro Testing Results

NSC : D - 743468 / 1	Experiment ID : 0707RS68	Test Type : 08	Units : Molar
Report Date : January 28, 2009	Test Date : July 30, 2007	QNS :	MC :
COMI : 5826 (55525)	Stain Reagent : SRB Dual-Pass Related	SSPL : 106D	

Panel/Cell Line	Log10 Concentration																		
	Mean Optical Densities							Percent Growth					GI50	TGI	LC50				
	Time Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0							
Leukemia																			
CCRF-CEM	0.565	2.019	2.048	1.886	1.306	0.454	0.304	102	91	51	-20	-46	1.03E-6	5.27E-6	> 1.00E-4				
RPMI-8226	0.464	1.296	1.330	1.199	0.806	0.271	0.281	104	88	41	-42	-40	6.48E-7	3.14E-6	> 1.00E-4				
Non-Small Cell Lung Cancer																			
A549/ATCC	0.241	0.857	0.832	0.966	0.647	0.238	0.092	96	118	66	-1	-62	1.72E-6	9.52E-6	6.33E-5				
EKVX	0.713	1.821	1.781	1.665	1.276	0.796	0.599	96	86	51	7	-16	1.04E-6	2.08E-5	> 1.00E-4				
HOP-62	0.648	1.654	1.568	1.699	1.734	1.102	0.264	91	104	108	45	-59	8.35E-6	2.70E-5	8.14E-5				
NCI-H226	0.769	1.780	1.694	1.563	1.358	0.984	0.534	91	78	58	21	-31	1.67E-6	2.57E-5	> 1.00E-4				
NCI-H23	0.633	1.638	1.605	1.552	1.157	0.649	0.213	97	91	52	2	-66	1.10E-6	1.06E-5	5.73E-5				
NCI-H322M	0.680	1.666	1.597	1.557	1.426	1.111	0.436	93	89	76	44	-36	6.36E-6	3.54E-5	> 1.00E-4				
NCI-H460	0.251	2.189	2.192	2.153	1.753	0.345	0.100	100	98	77	5	-60	2.39E-6	1.19E-5	6.94E-5				
NCI-H522	0.800	1.861	1.666	1.608	1.487	1.114	0.355	82	76	65	30	-56	2.62E-6	2.22E-5	8.59E-5				
Colon Cancer																			
COLO 205	1.287	2.130	2.059	2.038	1.875	0.540	0.227	92	89	70	-58	-82	1.43E-6	3.51E-6	8.65E-6				
HCT-116	0.156	1.499	1.444	1.419	1.019	0.417	0.032	96	94	64	19	-80	2.08E-6	1.57E-5	5.01E-5				
HCT-15	0.325	1.666	1.556	1.538	1.405	0.368	0.133	92	90	81	3	-59	2.48E-6	1.12E-5	7.15E-5				
HT29	0.173	1.294	1.276	1.236	1.218	0.164	0.079	98	95	93	-5	-85	2.75E-6	8.85E-6	8.06E-5				
KM12	0.284	0.990	1.005	0.982	0.878	0.276	0.056	102	99	84	-3	-80	2.46E-6	9.24E-6	4.06E-5				
SW-620	0.203	0.937	0.911	0.872	0.893	0.350	0.035	96	91	94	20	-83	3.94E-6	1.57E-5	4.80E-5				
CNS Cancer																			
SF-268	0.352	0.923	0.874	0.900	0.857	0.502	0.177	91	96	88	26	-50	4.15E-6	2.22E-5	> 1.00E-4				
SF-295	0.714	2.220	1.878	1.883	1.486	0.707	0.202	77	78	51	-1	-72	1.06E-6	9.55E-6	4.92E-5				
SF-539	0.500	1.671	1.616	1.602	1.466	0.912	0.167	95	94	82	35	-67	4.86E-6	2.21E-5	6.86E-5				
SNB-19	0.639	1.478	1.377	1.398	1.346	0.926	0.533	88	90	84	34	-17	4.84E-6	4.72E-5	> 1.00E-4				
SNB-75	0.504	0.953	0.927	0.929	0.837	0.598	0.446	94	94	74	21	-12	2.83E-6	4.40E-5	> 1.00E-4				
U251	0.240	1.010	0.993	0.980	0.908	0.515	0.022	98	96	87	36	-91	5.24E-6	1.92E-5	4.76E-5				
Melanoma																			
LOX IMVI	0.348	1.871	1.860	1.743	1.539	0.106	0.002	99	92	78	-70	-100	1.55E-6	3.38E-6	7.37E-6				
MALME-3M	0.747	1.493	1.424	1.338	1.233	0.642	0.154	91	79	65	-14	-79	1.55E-6	6.64E-6	3.55E-5				
M14	0.502	1.844	1.801	1.774	1.526	0.817	0.220	97	95	76	23	-56	3.14E-6	1.97E-5	8.36E-5				
MDA-MB-435	0.549	1.961	1.943	1.963	1.654	0.681	0.338	99	100	78	9	-39	2.57E-6	1.57E-5	> 1.00E-4				
SK-MEL-2	0.610	1.114	1.111	1.149	1.042	0.763	0.090	99	107	86	30	-85	4.41E-6	1.83E-5	4.95E-5				
SK-MEL-28	0.351	0.619	0.614	0.625	0.586	0.395	0.043	98	102	88	16	-88	3.38E-6	1.44E-5	4.34E-5				
SK-MEL-5	0.714	2.821	2.739	2.673	1.787	0.419	0.003	96	93	51	-41	-100	1.02E-6	3.57E-6	1.41E-5				
UACC-257	0.565	0.693	0.683	0.628	0.577	0.305	0.048	92	49	9	-46	-92	9.69E-8	1.48E-6	1.22E-5				
UACC-62	0.737	2.405	2.345	2.190	1.676	1.115	0.050	96	87	56	23	-93	1.54E-6	1.57E-5	4.24E-5				
Ovarian Cancer																			
IGROV1	0.477	1.449	1.412	1.413	1.251	0.824	0.111	96	96	80	36	-77	4.73E-6	2.08E-5	5.78E-5				
OVCAR-3	0.404	0.860	0.866	0.878	0.807	0.370	0.068	101	104	88	-9	-83	2.49E-6	8.16E-6	3.59E-5				
OVCAR-4	0.410	1.130	1.122	1.037	0.888	0.586	0.435	99	87	66	24	3	2.45E-6	> 1.00E-4	> 1.00E-4				
OVCAR-5	0.320	0.779	0.793	0.794	0.773	0.596	0.064	103	103	99	60	-80	1.18E-5	2.68E-5	6.11E-5				
OVCAR-8	0.236	0.683	0.721	0.699	0.682	0.331	0.108	108	104	100	21	-54	4.31E-6	1.91E-5	8.73E-5				
NCI/ADR-RES	0.236	0.580	0.581	0.584	0.545	0.248	0.140	100	101	90	3	-41	2.90E-6	1.20E-5	> 1.00E-4				
SK-OV-3	1.086	1.726	1.679	1.747	1.652	1.209	0.404	93	103	88	19	-63	3.59E-6	1.71E-5	6.98E-5				
Renal Cancer																			
786-0	0.562	2.198	2.089	2.051	1.991	0.893	0.343	93	91	87	20	-39	3.60E-6	2.19E-5	> 1.00E-4				
ACHN	0.357	1.247	1.225	1.183	1.065	0.455	0.251	97	93	80	11	-30	2.70E-6	1.86E-5	> 1.00E-4				
CAKI-1	0.470	1.263	1.217	1.128	1.024	0.492	0.344	94	83	70	3	-27	1.98E-6	1.24E-5	> 1.00E-4				
SN12C	0.446	1.484	1.415	1.330	1.231	0.640	0.088	93	85	76	19	-80	2.82E-6	1.54E-5	4.94E-5				
TK-10	0.550	1.129	1.089	1.113	0.987	0.699	0.150	93	97	75	26	-73	3.25E-6	1.82E-5	5.87E-5				
UO-31	0.757	1.513	1.444	1.400	1.222	0.881	0.335	91	85	62	16	-56	1.80E-6	1.69E-5	8.31E-5				
Prostate Cancer																			
PC-3	0.498	1.006	1.016	0.944	0.924	0.364	0.250	102	88	84	-27	-50	2.02E-6	5.71E-6	> 1.00E-4				
DU-145	0.223	0.697	0.728	0.648	0.652	0.350	0.035	107	90	91	27	-84	4.31E-6	1.74E-5	4.91E-5				
Breast Cancer																			
MCF7	0.242	1.282	1.175	1.211	1.081	0.286	0.177	90	93	81	4	-27	2.52E-6	1.37E-5	> 1.00E-4				
MDA-MB-231/ATCC	0.539	1.082	1.026	0.982	0.905	0.315	0.169	90	82	67	-42	-69	1.44E-6	4.15E-6	2.05E-5				
HS 578T	0.626	0.815	0.690	0.708	0.680	0.296	0.203	34	43	29	-53	-68	< 1.00E-8	2.25E-6	9.24E-6				
BT-549	1.028	1.684	1.584	1.619	1.496	0.993	0.059	85	90	71	-3	-94	1.93E-6	9.00E-6	3.26E-5				
T-47D	0.513	1.086	0.995	0.986	0.846	0.533	0.437	84	83	58	3	-15	1.40E-6	1.54E-5	> 1.00E-4				
MDA-MB-468	0.393	1.102	1.106	1.084	0.862	0.454	0.320	101	98	66	9	-19	1.91E-6	2.07E-5	> 1.00E-4				



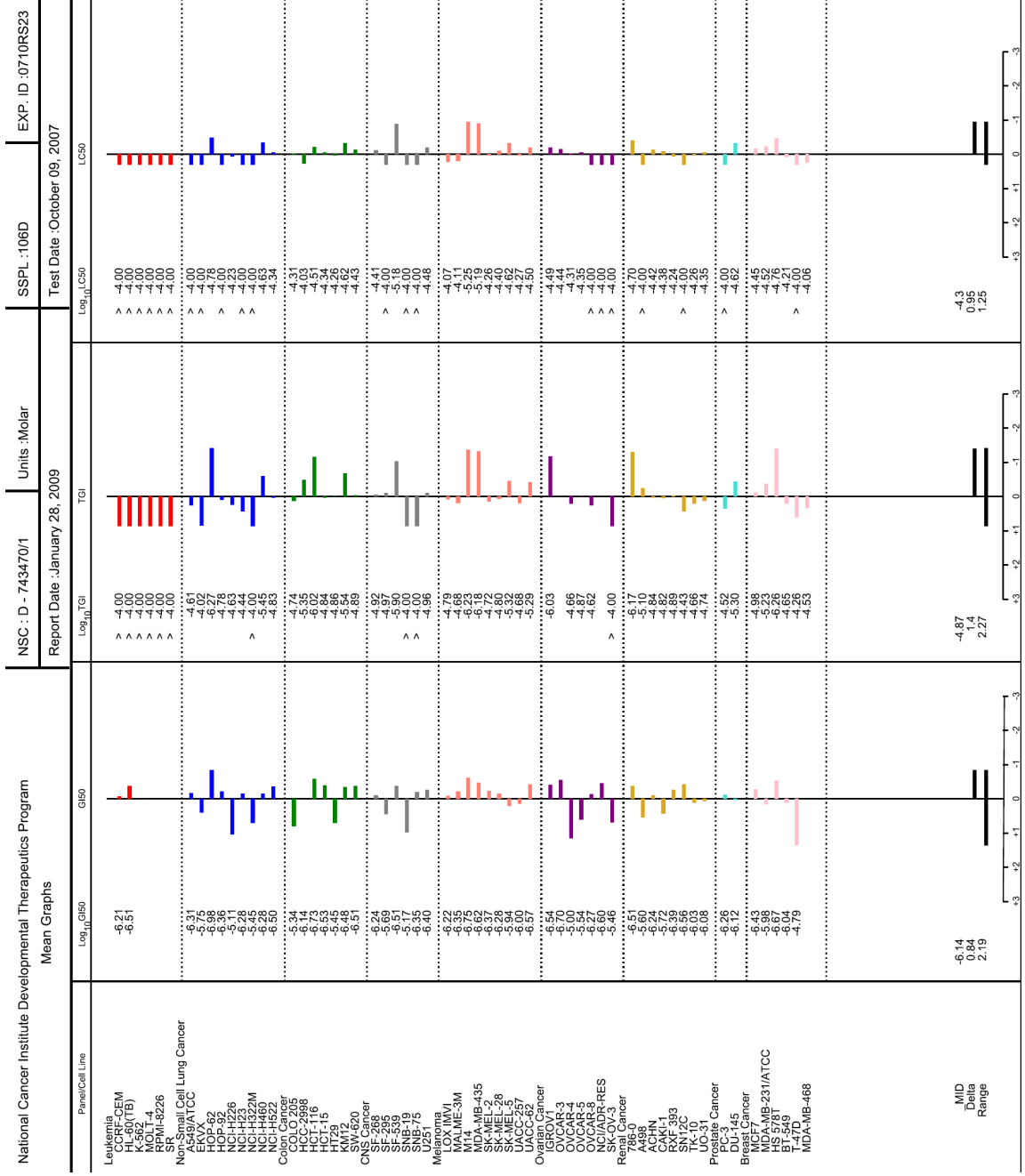
60 Human-Cancer Cell Line 5 Concentration Screen for Compound 214



National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NCS : D - 743470 / 1	Experiment ID : 0710RS23	Test Type : 08	Units : Molar
Report Date : January 28, 2009	Test Date : October 09, 2007	QNS :	MC :
COMI : 5828 (55527)	Stain Reagent : SRB Dual-Pass Related	SSPL : 106D	

Panel/Cell Line	Time	Log10 Concentration						Percent Growth					GI50	TGI	LC50
		Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0			
Leukemia															
CCR5-CEM	0.167	0.725	0.813	0.761	0.363	0.348	0.351	116	106	35	32	33	6.17E-7	> 1.00E-4	> 1.00E-4
HL-60(TB)	0.232	1.475	1.291	1.241	0.453	0.419	0.831	85	81	18	15	48	3.10E-7	> 1.00E-4	> 1.00E-4
K-562	0.087	0.756	0.727	0.655	0.317	0.443	0.933	96	85	34	53	126	.	> 1.00E-4	> 1.00E-4
MOLT-4	0.186	1.019	0.969	0.914	0.525	0.451	0.945	94	87	41	32	91	.	> 1.00E-4	> 1.00E-4
RPMI-8226	0.178	0.510	0.515	0.458	0.220	0.272	0.467	102	84	13	28	87	.	> 1.00E-4	> 1.00E-4
SR	0.191	0.824	0.774	0.586	0.320	0.313	0.807	92	82	20	19	97	.	> 1.00E-4	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.131	0.577	0.536	0.564	0.258	0.200	0.100	91	97	29	15	-24	4.87E-7	2.46E-5	> 1.00E-4
EKVX	0.930	2.565	2.341	2.163	1.870	1.386	0.926	86	75	57	28	.	1.79E-6	9.61E-5	> 1.00E-4
HOP-62	0.241	0.428	0.351	0.337	0.194	0.151	0.010	59	51	-20	-37	-96	1.05E-7	5.31E-7	1.65E-5
HOP-92	0.416	0.744	0.747	0.692	0.517	0.457	0.232	101	84	31	13	-44	4.36E-7	1.66E-5	> 1.00E-4
NCI-H226	0.552	1.273	1.180	1.193	1.134	0.884	0.115	87	89	81	46	-79	7.71E-6	2.33E-5	5.85E-5
NCI-H23	0.331	1.016	0.910	0.936	0.569	0.480	0.274	84	88	35	22	-17	5.19E-7	3.60E-5	> 1.00E-4
NCI-H322M	0.531	1.625	1.569	1.604	1.310	0.890	0.563	95	98	71	33	3	3.56E-6	> 1.00E-4	> 1.00E-4
NCI-H460	0.183	1.072	1.140	1.156	0.418	0.143	0.004	108	109	26	-22	-98	5.20E-7	3.53E-6	2.35E-5
NCI-H522	0.780	1.978	1.840	1.837	0.921	0.991	0.116	88	88	12	18	-85	3.16E-7	1.48E-5	4.55E-5
Colon Cancer															
COLO 205	0.246	1.095	1.088	1.080	0.993	0.503	0.036	99	98	88	30	-86	4.55E-6	1.83E-5	4.93E-5
HCC-2998	0.165	0.612	0.526	0.591	0.355	0.127	0.081	81	95	42	-23	-51	7.19E-7	4.45E-6	9.28E-5
HCT-116	0.110	0.506	0.458	0.385	0.109	0.103	0.005	88	69	-1	-6	-96	1.88E-7	9.57E-7	3.07E-5
HCT-15	0.311	1.571	1.404	1.348	0.486	0.509	0.050	87	82	14	16	-84	2.96E-7	1.44E-5	4.56E-5
HT29	0.137	0.928	0.908	0.884	0.911	0.228	0.039	97	94	98	11	-72	3.57E-6	1.37E-5	5.50E-5
KM12	0.261	0.926	0.890	0.838	0.372	0.210	-0.003	95	87	17	-20	-100	3.35E-7	2.89E-6	2.39E-5
SW-620	0.187	0.973	0.941	0.885	0.265	0.276	0.009	96	89	10	11	-95	3.11E-7	1.28E-5	3.75E-5
CNS Cancer															
SF-268	0.369	1.060	1.000	1.037	0.615	0.424	0.036	91	97	36	8	-90	5.80E-7	1.20E-5	3.88E-5
SF-295	0.846	2.737	2.371	2.604	2.195	0.878	0.454	81	93	71	2	-46	2.03E-6	1.08E-5	> 1.00E-4
SF-539	0.523	1.480	1.408	1.397	0.588	0.197	0.013	93	91	7	-62	-98	3.08E-7	1.25E-6	6.63E-6
SNB-19	0.601	1.417	1.359	1.368	1.257	0.958	0.833	93	94	80	44	28	6.73E-6	> 1.00E-4	> 1.00E-4
SNB-75	0.825	1.345	1.274	1.283	0.981	0.891	0.905	86	88	30	13	15	4.52E-7	> 1.00E-4	> 1.00E-4
U251	0.236	1.078	1.019	1.013	0.422	0.267	-0.016	93	92	22	4	-100	4.00E-7	1.09E-5	3.29E-5
Melanoma															
LOX IMVI	0.315	1.799	1.695	1.675	0.883	0.534	0.142	93	92	38	15	-55	6.03E-7	1.63E-5	8.50E-5
MALME-3M	0.677	1.354	1.318	1.216	0.909	0.865	0.274	95	80	34	28	-60	4.49E-7	2.08E-5	7.76E-5
M14	0.245	0.512	0.444	0.442	0.191	0.100	0.019	75	74	-22	-59	-92	1.77E-7	5.89E-7	5.66E-6
MDA-MB-435	0.428	1.744	1.730	1.656	0.343	0.184	0.084	99	93	-20	-57	-80	2.41E-7	6.66E-7	6.43E-6
SK-MEL-2	0.476	1.228	1.209	1.189	0.654	0.711	0.100	97	95	24	31	-79	4.26E-7	1.92E-5	5.45E-5
SK-MEL-28	0.275	0.749	0.739	0.699	0.438	0.395	-0.008	98	89	34	25	-100	5.19E-7	1.59E-5	3.99E-5
SK-MEL-5	0.552	1.977	1.987	1.937	1.335	0.408	0.058	101	97	55	-26	-89	1.15E-6	4.76E-6	2.38E-5
UACC-257	0.744	1.346	1.207	1.266	1.045	0.986	0.119	77	87	50	40	-84	1.00E-6	2.11E-5	5.32E-5
UACC-62	0.660	1.915	1.695	1.684	0.762	0.638	0.025	83	82	8	-3	-96	2.69E-7	5.11E-6	3.18E-5
Ovarian Cancer															
IGROV1	0.260	0.501	0.523	0.489	0.252	0.240	0.026	109	95	-3	-8	-90	2.88E-7	9.30E-7	3.26E-5
OVCAR-3	0.332	0.882	0.878	0.825	0.194	0.394	0.004	99	90	-42	11	-99	2.00E-7	.	3.59E-5
OVCAR-4	0.474	1.279	1.250	1.260	1.123	0.876	0.025	96	98	81	50	-95	9.94E-6	2.21E-5	4.90E-5
OVCAR-5	0.294	0.705	0.664	0.671	0.630	0.346	0.047	90	92	82	13	-84	2.87E-6	1.35E-5	4.44E-5
OVCAR-8	0.279	0.854	0.898	0.863	0.456	0.382	0.198	108	101	31	18	-29	5.34E-7	2.41E-5	> 1.00E-4
NCI/ADR-RES	0.348	0.987	0.964	0.941	0.298	0.354	0.268	96	93	-14	1	-23	2.51E-7	.	> 1.00E-4
SK-OV-3	0.638	1.589	1.571	1.576	1.343	0.921	0.742	98	99	74	30	11	3.49E-6	> 1.00E-4	> 1.00E-4
Renal Cancer															
786-0	0.393	0.728	0.700	0.801	0.297	0.283	-0.001	92	122	-24	-28	-100	3.09E-7	6.80E-7	2.02E-5
A498	0.754	1.396	1.319	1.315	1.331	0.677	0.570	88	87	90	-10	-24	2.50E-6	7.89E-6	> 1.00E-4
ACHN	0.340	0.995	0.967	0.905	0.592	0.466	-0.024	96	86	38	19	-100	5.73E-7	1.45E-5	3.81E-5
CAKI-1	0.809	2.257	2.040	2.005	1.697	1.115	0.045	85	83	61	21	-94	1.91E-6	1.52E-5	4.12E-5
RXF 393	0.365	0.830	0.864	0.828	0.447	0.405	0.115	107	100	18	9	-68	4.03E-7	1.29E-5	5.76E-5
SN12C	0.463	1.276	1.118	1.042	0.647	0.716	0.354	81	71	23	31	-24	2.72E-7	3.71E-5	> 1.00E-4
TK-10	0.519	1.339	1.268	1.279	0.917	0.866	0.093	91	93	49	42	-82	9.27E-7	2.19E-5	5.51E-5
UO-31	0.476	1.257	1.198	1.188	0.838	0.731	0.026	92	91	46	33	-95	8.30E-7	1.80E-5	4.46E-5
Prostate Cancer															
PC-3	0.192	0.759	0.753	0.736	0.383	0.378	0.125	99	96	34	33	-35	5.45E-7	3.05E-5	> 1.00E-4
DU-145	0.221	0.669	0.611	0.596	0.425	0.177	-0.006	87	84	46	-20	-100	7.63E-7	4.96E-6	2.38E-5
Breast Cancer															
MCF7	0.329	1.039	1.095	1.129	0.354	0.343	0.024	108	113	-4	2	-93	3.75E-7	1.05E-5	3.54E-5
MDA-MB-231/ATCC	0.539	1.138	1.087	1.131	0.846	0.455	0.073	91	99	51	-16	-87	1.04E-6	5.84E-6	3.05E-5
HS 578T	0.360	0.593	0.568	0.569	0.249	0.194	0.137	89	90	-31	-46	-62	2.14E-7	5.55E-7	1.73E-5
BT-549	0.711	1.589	1.491	1.551	1.135	1.053	0.186	89	96	48	39	-74	9.22E-7	2.22E-5	6.15E-5
T-47D	0.427	0.935	0.951	0.962	0.823	0.780	0.325	103	105	78	69	-24	1.62E-5	5.55E-5	> 1.00E-4
MDA-MB-468	0.236	0.463	0.455	0.463	0.314	0.351	0.103	96	100	34	50	-57	.	2.96E-5	8.68E-5



In Vivo Toxicity Tests for Compound 214

Nontumored Animal Toxicity Assay for S743470

Report generated on 28-Jan-2009

EXPERIMENT: AAZ-176 / 0 / 8B	TUMOR: NO CELLS	HOST: Athymic Nudes	IMPLANT DATE: 06-MAR-2008
MEMO NO:	SOURCE/LINE: 0	SOURCE: APA	STAGING DATE: 06-MAR-2008
BOOK NO:	IMPLANT SITE: 0	SEX: F	EVALUATION DATE: 21-MAR-2008

TREATMENT

Grp	NSC	Dose/Units	Rt.	Schedule	Death Days	Surv/Total Day 15
4	D-S743470	400.00 mg/kg/dose	IP	QD X 1, Day 0	2	0/1
5	D-S743470	200.00 mg/kg/dose	IP	QD X 1, Day 0	3	0/1
6	D-S743470	100.00 mg/kg/dose	IP	QD X 1, Day 0	--	1/1

VEHICLES

Grp 4 →	NSC # S743470 / 2 (Dose = 400.00)	: in 100% DMSO	(Soluble - no visible particles)	Inj. Vol.: 5 ul/gm body wt
Grp 5 →	NSC # S743470 / 2 (Dose = 200.00)	: in 100% DMSO	(Soluble - no visible particles)	Inj. Vol.: 2.5 ul/gm body wt
Grp 6 →	NSC # S743470 / 2 (Dose = 100.00)	: in 100% DMSO	(Soluble - no visible particles)	Inj. Vol.: 1.25 ul/gm body wt

NOTE: All treatment was administered according to exact body weight.

Hollow Fiber Test for Compound 214

Hollow Fiber Data NSC: 743470

It was tested against the following disease types and cell lines:

Experiment ID: HF1502

Panel Name	Cell Name	Schedule	High Dose
Breast Cancer	MDA-MB-231	QD X 4, Day 3	37.5 mg/kg/dose
Non-Small Cell Lung Cancer	NCI-H23	QD X 4, Day 3	37.5 mg/kg/dose
Colon Cancer	SW-620	QD X 4, Day 3	37.5 mg/kg/dose

Experiment ID: HF1503

Panel Name	Cell Name	Schedule	High Dose
Colon Cancer	COLO 205	QD X 4, Day 3	37.5 mg/kg/dose
Melanoma	LOX IMVI	QD X 4, Day 3	37.5 mg/kg/dose
Ovarian Cancer	OVCAR-3	QD X 4, Day 3	37.5 mg/kg/dose

Experiment ID: HF1504

Panel Name	Cell Name	Schedule	High Dose
Non-Small Cell Lung Cancer	NCI-H522	QD X 4, Day 3	37.5 mg/kg/dose
CNS Cancer	U251	QD X 4, Day 3	37.5 mg/kg/dose
Melanoma	UACC-62	QD X 4, Day 3	37.5 mg/kg/dose

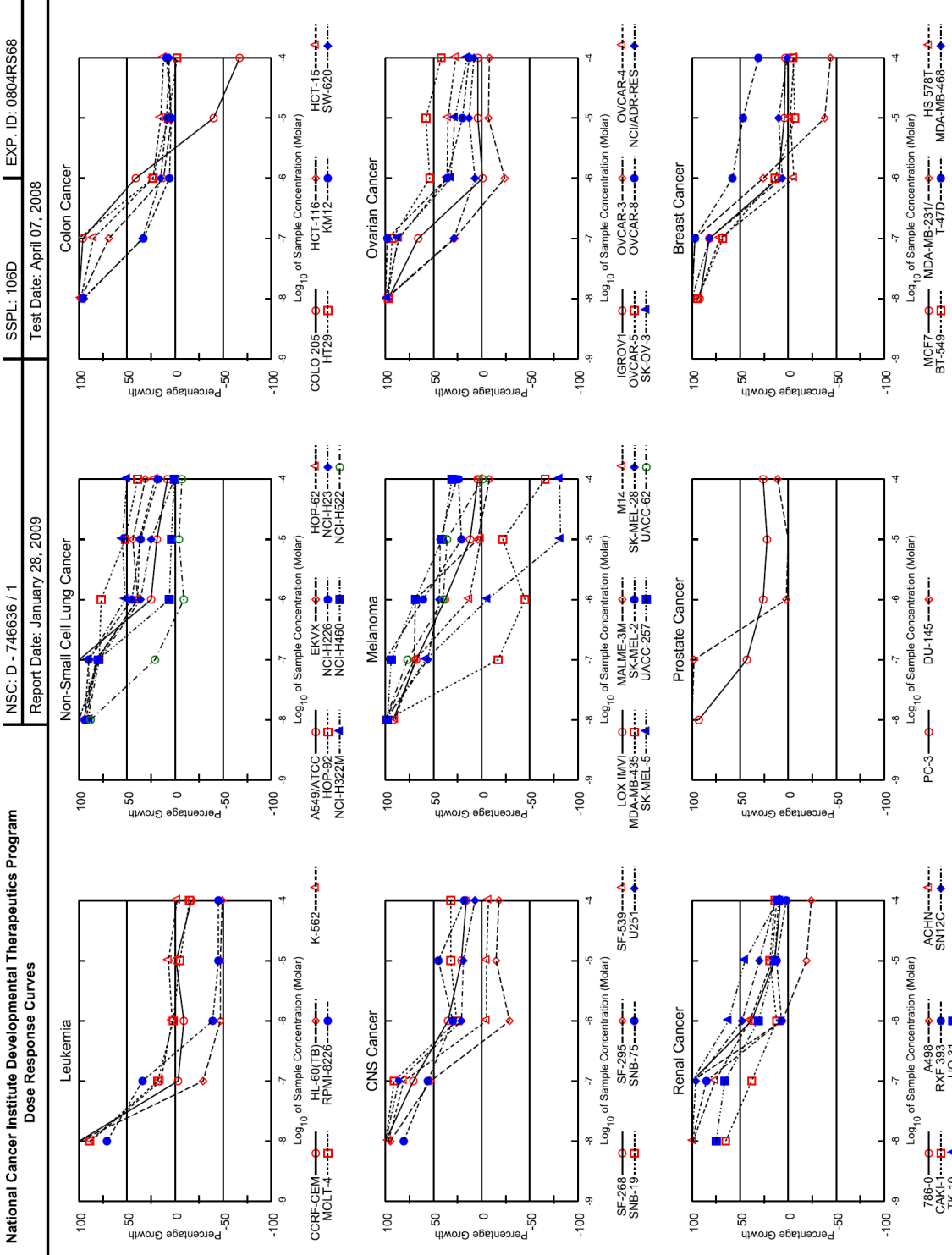
Experiment ID: HF1505

Panel Name	Cell Name	Schedule	High Dose
Melanoma	MDA-MB-435	QD X 4, Day 3	37.5 mg/kg/dose
Ovarian Cancer	OVCAR-5	QD X 4, Day 3	37.5 mg/kg/dose
CNS Cancer	SF-295	QD X 4, Day 3	37.5 mg/kg/dose

Your compound was scored as follows:

IP Score	4 out of 48
SC Score	0 out of 48
Total	4 out of 96
Cell Kill	N

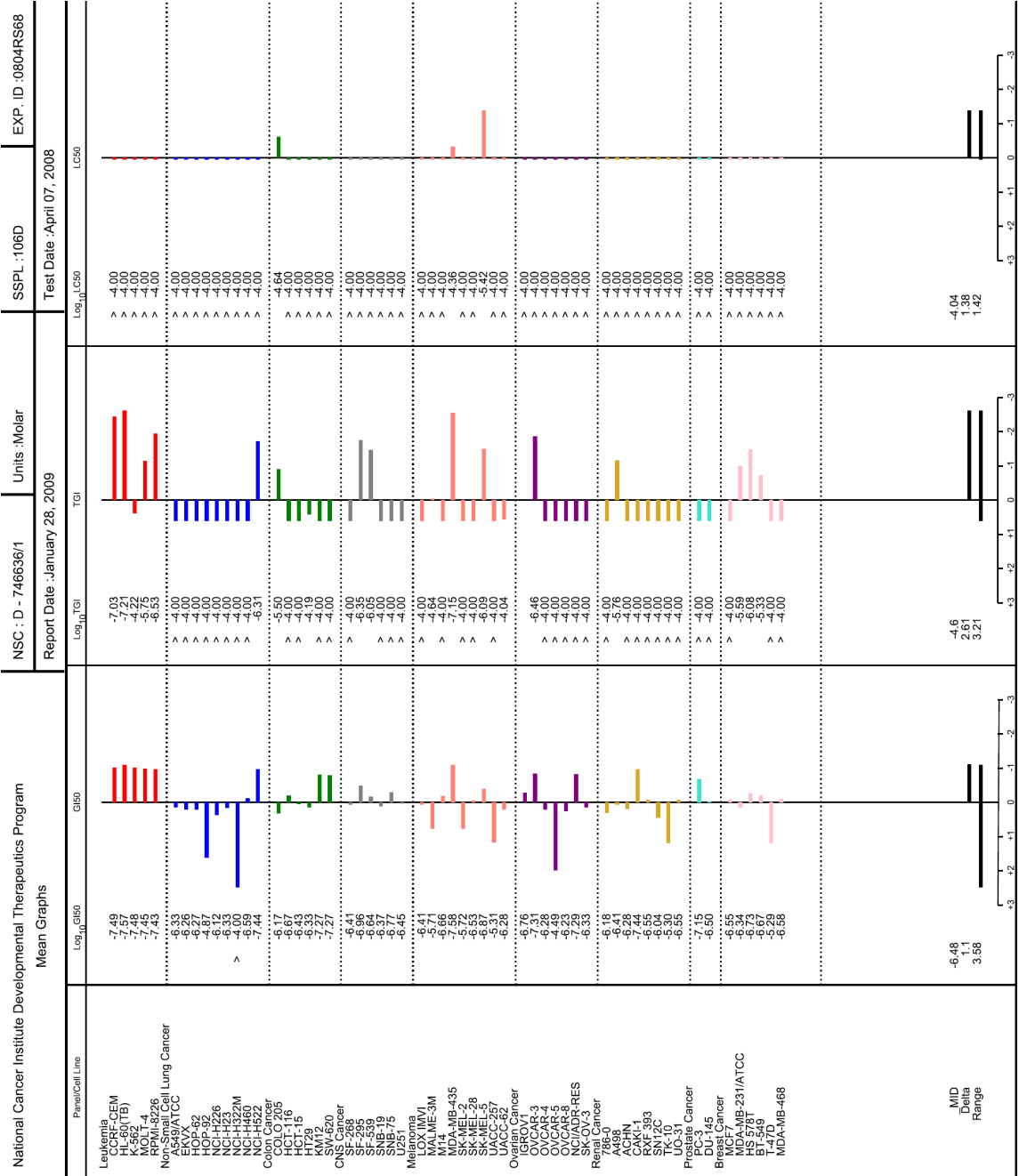
60 Human-Cancer Cell Line 5 Concentration Screen for Compound 215



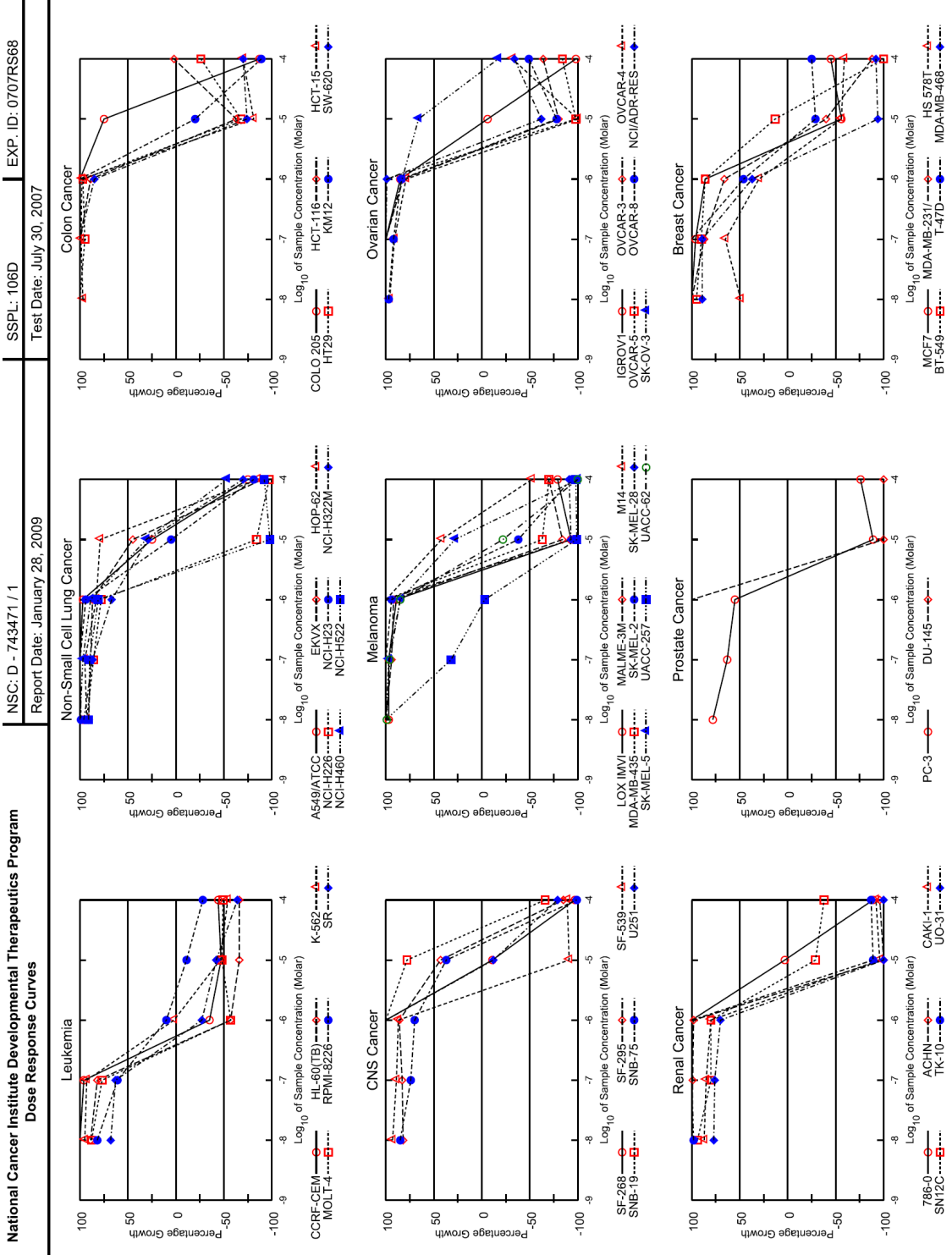
**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

NSC : D - 746636 / 1	Experiment ID : 0804RS68	Test Type : 08	Units : Molar
Report Date : January 28, 2009	Test Date : April 07, 2008	QNS :	MC :
COMI : 5837 (56471)	Stain Reagent : SRB Dual-Pass Related	SSPL : 106D	

Panel/Cell Line	Time Zero	Ctrl	Log10 Concentration					Percent Growth					GI50	TGI	LC50
			Mean Optical Densities												
			-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0			
Leukemia															
CCR5-CEM	0.162	0.586	0.607	0.157	0.148	0.160	0.134	105	-3	-9	-1	-17	3.22E-8	9.30E-8	> 1.00E-4
HL-60(TB)	0.282	0.952	1.008	0.201	0.149	0.150	0.144	108	-29	-47	-47	-49	2.66E-8	6.17E-8	> 1.00E-4
K-562	0.076	0.691	0.618	0.166	0.098	0.118	0.075	88	15	3	7	-2	3.30E-8	5.97E-5	> 1.00E-4
MOLT-4	0.182	0.743	0.680	0.284	0.193	0.172	0.156	89	18	2	-5	-15	3.54E-8	1.80E-6	> 1.00E-4
RPMI-8226	0.257	0.586	0.490	0.370	0.157	0.142	0.142	71	34	-39	-45	-45	3.68E-8	2.93E-7	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.305	1.350	1.400	1.352	0.568	0.504	0.393	105	100	25	19	8	4.66E-7	> 1.00E-4	> 1.00E-4
EKVX	0.809	1.786	1.739	1.606	1.187	1.243	1.108	95	82	39	44	31	5.43E-7	> 1.00E-4	> 1.00E-4
HOP-62	0.572	1.556	1.490	1.364	0.954	0.934	0.774	93	81	39	37	21	5.38E-7	> 1.00E-4	> 1.00E-4
HOP-92	0.478	0.928	0.955	0.833	0.825	0.711	0.654	106	79	77	52	39	1.38E-5	> 1.00E-4	> 1.00E-4
NCI-H226	0.776	2.278	2.188	2.125	1.446	1.318	1.048	94	90	45	36	18	7.59E-7	> 1.00E-4	> 1.00E-4
NCI-H23	0.577	1.668	1.574	1.440	0.970	0.855	0.588	91	79	36	25	1	4.72E-7	> 1.00E-4	> 1.00E-4
NCI-H322M	0.591	1.512	1.410	1.424	1.066	1.098	1.052	89	90	52	55	50	> 1.00E-4	> 1.00E-4	> 1.00E-4
NCI-H460	0.183	1.468	1.504	1.214	0.263	0.240	0.193	103	80	6	4	1	2.56E-7	> 1.00E-4	> 1.00E-4
NCI-H522	0.515	1.186	1.103	0.654	0.467	0.493	0.477	88	21	-9	-4	-7	3.64E-8	4.88E-7	> 1.00E-4
Colon Cancer															
COLO 205	0.162	0.667	0.669	0.648	0.367	0.097	0.053	100	96	41	-40	-67	6.79E-7	3.17E-6	2.27E-5
HCT-116	0.188	1.514	1.484	1.101	0.343	0.235	0.281	98	69	12	4	7	2.14E-7	> 1.00E-4	> 1.00E-4
HCT-15	0.294	1.654	1.633	1.453	0.609	0.497	0.460	98	85	23	15	12	3.69E-7	> 1.00E-4	> 1.00E-4
HT29	0.168	1.032	1.083	1.063	0.369	0.233	0.165	106	104	23	7	-2	4.65E-7	6.41E-5	> 1.00E-4
KM12	0.254	1.156	1.123	0.548	0.309	0.291	0.333	96	33	6	4	9	5.34E-8	> 1.00E-4	> 1.00E-4
SW-620	0.190	1.052	1.006	0.480	0.318	0.265	0.242	95	34	15	9	6	5.39E-8	> 1.00E-4	> 1.00E-4
CNS Cancer															
SF-268	0.439	1.248	1.283	1.012	0.726	0.605	0.567	104	71	35	21	16	3.87E-7	> 1.00E-4	> 1.00E-4
SF-295	0.568	1.583	1.530	1.111	0.405	0.481	0.466	95	53	-29	-15	-18	1.10E-7	4.48E-7	> 1.00E-4
SF-539	0.583	1.874	1.832	1.624	0.557	0.555	0.542	97	81	-5	-5	-7	2.29E-7	8.84E-7	> 1.00E-4
SNB-19	0.261	0.845	0.857	0.792	0.413	0.446	0.450	102	91	26	32	32	4.26E-7	> 1.00E-4	> 1.00E-4
SNB-75	0.541	1.024	0.932	0.811	0.688	0.758	0.628	81	56	30	45	18	1.69E-7	> 1.00E-4	> 1.00E-4
U251	0.207	1.036	1.063	0.917	0.378	0.361	0.265	103	86	21	19	7	3.53E-7	> 1.00E-4	> 1.00E-4
Melanoma															
LOX IMVI	0.382	2.111	1.966	1.550	1.033	0.594	0.449	92	68	38	12	4	3.86E-7	> 1.00E-4	> 1.00E-4
MALME-3M	0.465	0.706	0.713	0.635	0.630	0.476	0.430	103	70	69	4	-8	1.95E-6	2.31E-5	> 1.00E-4
M14	0.382	1.393	1.291	1.083	0.510	0.395	0.406	90	69	13	1	2	2.19E-7	> 1.00E-4	> 1.00E-4
MDA-MB-435	0.515	1.773	1.766	0.428	0.282	0.404	0.176	99	-17	-45	-22	-66	2.68E-8	> 1.00E-4	> 1.00E-4
SK-MEL-2	0.694	1.428	1.447	1.459	1.145	0.848	0.867	103	104	61	21	24	1.92E-6	> 1.00E-4	> 1.00E-4
SK-MEL-28	0.355	0.936	0.999	0.679	0.608	0.604	0.509	111	56	44	43	26	2.93E-7	> 1.00E-4	> 1.00E-4
SK-MEL-5	0.551	1.811	1.833	1.288	0.521	0.102	0.105	102	58	-6	-82	-81	1.36E-7	8.19E-7	3.84E-6
UACC-257	1.012	1.939	1.925	1.885	1.653	1.396	1.304	98	94	69	41	31	4.89E-6	> 1.00E-4	> 1.00E-4
UACC-62	0.691	2.146	2.166	1.810	1.267	1.213	0.681	101	77	40	36	-1	5.25E-7	9.15E-5	> 1.00E-4
Ovarian Cancer															
IGROV1	0.457	1.183	1.162	0.937	0.453	0.489	0.490	97	66	-1	4	4	1.74E-7	.	> 1.00E-4
OVCAR-3	0.298	0.786	0.781	0.436	0.227	0.278	0.275	99	28	-24	-7	-8	4.92E-8	3.48E-7	> 1.00E-4
OVCAR-4	0.518	1.375	1.386	1.258	0.826	0.821	0.753	101	86	36	35	27	5.26E-7	> 1.00E-4	> 1.00E-4
OVCAR-5	0.501	1.190	1.170	1.143	0.873	0.901	0.792	97	93	54	58	42	3.21E-5	> 1.00E-4	> 1.00E-4
OVCAR-8	0.613	1.896	1.893	1.875	1.072	0.874	0.784	100	98	36	20	13	5.92E-7	> 1.00E-4	> 1.00E-4
NCI/ADR-RES	0.512	1.573	1.586	0.819	0.587	0.650	0.598	101	29	7	13	8	5.10E-8	> 1.00E-4	> 1.00E-4
SK-OV-3	0.552	1.241	1.230	1.151	0.773	0.744	0.655	98	87	32	28	15	4.69E-7	> 1.00E-4	> 1.00E-4
Renal Cancer															
786-0	0.668	2.239	2.312	2.308	1.262	0.882	0.800	105	104	38	14	8	6.56E-7	> 1.00E-4	> 1.00E-4
A498	0.531	0.955	1.027	1.011	0.557	0.432	0.403	117	113	6	-19	-24	3.88E-7	1.75E-6	> 1.00E-4
ACHN	0.437	1.812	1.791	1.486	0.981	0.669	0.604	99	76	40	17	12	5.20E-7	> 1.00E-4	> 1.00E-4
CAKI-1	0.409	0.602	0.534	0.483	0.433	0.446	0.436	65	38	12	19	14	3.60E-8	> 1.00E-4	> 1.00E-4
RXF 393	0.558	0.980	1.023	0.919	0.587	0.609	0.567	110	85	7	12	2	2.83E-7	> 1.00E-4	> 1.00E-4
SN12C	0.427	1.521	1.517	1.478	0.953	0.761	0.568	100	96	48	30	13	9.11E-7	> 1.00E-4	> 1.00E-4
TK-10	0.576	1.226	1.279	1.250	0.978	0.869	0.650	108	104	62	45	11	5.06E-6	> 1.00E-4	> 1.00E-4
UO-31	0.300	1.039	0.851	0.786	0.528	0.406	0.372	75	66	31	14	10	2.82E-7	> 1.00E-4	> 1.00E-4
Prostate Cancer															
PC-3	0.168	0.509	0.487	0.313	0.256	0.244	0.258	93	43	26	22	26	7.13E-8	> 1.00E-4	> 1.00E-4
DU-145	0.190	0.702	0.760	0.691	0.200	0.192	0.248	111	98	2	.	11	3.15E-7	> 1.00E-4	> 1.00E-4
Breast Cancer															
MCF7	0.277	1.359	1.268	1.163	0.390	0.318	0.307	92	82	10	4	3	2.79E-7	> 1.00E-4	> 1.00E-4
MDA-MB-231/ATCC	0.489	1.130	1.146	1.110	0.656	0.305	0.275	103	97	26	-38	-44	4.59E-7	2.56E-6	> 1.00E-4
HS 578T	0.432	0.872	0.847	0.744	0.405	0.425	0.404	94	71	-6	-2	-6	1.86E-7	8.30E-7	> 1.00E-4
BT-549	1.053	2.121	2.053	1.781	1.203	0.981	1.004	94	68	14	-7	-5	2.16E-7	4.68E-6	> 1.00E-4
T-47D	0.462	1.101	1.140	1.085	0.836	0.760	0.660	106	97	58	47	31	5.13E-6	> 1.00E-4	> 1.00E-4
MDA-MB-468	0.330	0.754	0.762	0.679	0.356	0.372	0.336	102	82	6	10	1	2.65E-7	> 1.00E-4	> 1.00E-4



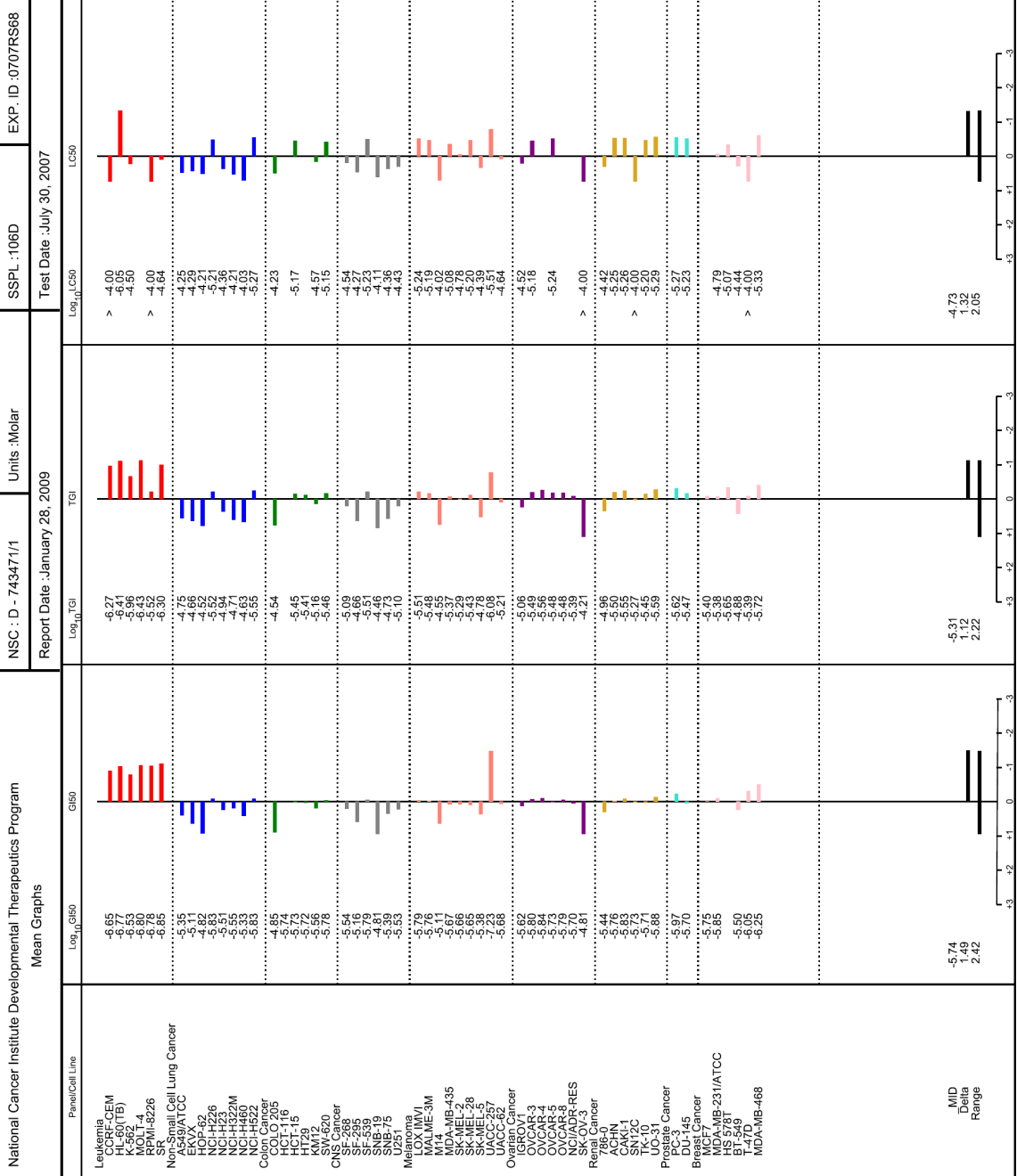
60 Human-Cancer Cell Line 5 Concentration Screen for Compound 226



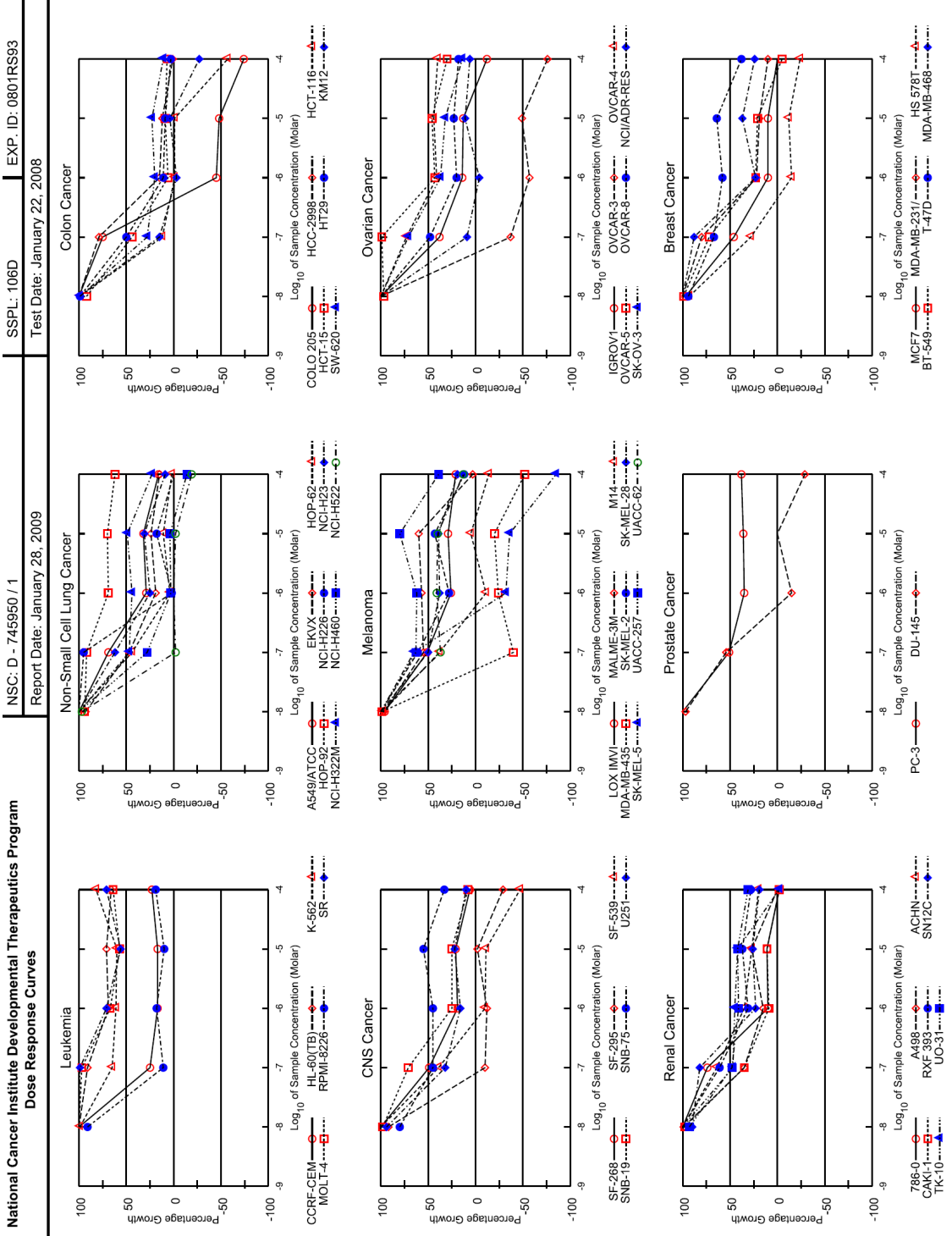
**National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results**

NSC : D - 743471 / 1	Experiment ID : 0707RS68	Test Type : 08	Units : Molar
Report Date : January 28, 2009	Test Date : July 30, 2007	QNS :	MC :
COMI : 5829 (55528)	Stain Reagent : SRB Dual-Pass Related	SSPL : 106D	

Panel/Cell Line	Time Zero	Log10 Concentration													GI50	TGI	LC50
		Ctrl	Mean Optical Densities						Percent Growth								
			-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0					
Leukemia																	
CCRF-CEM	0.565	2.038	2.043	1.980	0.368	0.297	0.316	100	96	-35	-47	-44	2.25E-7	5.42E-7	> 1.00E-4		
HL-60(TB)	0.686	1.308	1.239	1.198	0.296	0.236	0.234	89	82	-57	-66	-66	1.71E-7	3.90E-7	8.92E-7		
K-562	0.243	1.338	1.279	1.266	0.265	0.131	0.113	95	93	2	-46	-54	2.98E-7	1.10E-6	3.16E-5		
MOLT-4	0.396	1.366	1.245	1.142	0.170	0.208	0.200	88	77	-57	-48	-49	1.59E-7	3.75E-7	.		
RPMI-8226	0.464	1.392	1.228	1.030	0.560	0.413	0.336	82	61	10	-11	-28	1.65E-7	3.05E-6	> 1.00E-4		
SR	0.500	0.953	0.810	0.787	0.365	0.289	0.182	68	63	-27	-42	-64	1.41E-7	5.03E-7	2.31E-5		
Non-Small Cell Lung Cancer																	
A549/ATCC	0.241	0.893	0.941	0.959	0.872	0.406	0.060	107	110	97	25	-75	4.51E-6	1.79E-5	5.62E-5		
EKVX	0.713	1.977	1.861	1.842	1.819	1.285	0.074	91	89	87	45	-90	7.71E-6	2.16E-5	5.08E-5		
HOP-62	0.648	1.512	1.448	1.466	1.362	1.331	0.100	93	95	83	79	-85	1.50E-5	3.04E-5	6.15E-5		
NCI-H226	0.769	1.735	1.667	1.601	1.525	1.121	0.021	93	86	78	-84	-97	1.49E-6	3.03E-6	6.15E-6		
NCI-H23	0.633	1.673	1.664	1.690	1.608	0.684	0.122	99	102	94	5	-81	3.11E-6	1.14E-5	4.38E-5		
NCI-H322M	0.680	1.853	1.802	1.700	1.466	1.020	0.202	96	87	67	29	-70	2.80E-6	1.96E-5	6.24E-5		
NCI-H460	0.251	2.153	2.191	2.100	1.938	0.841	0.119	102	97	89	31	-53	4.69E-6	2.35E-5	9.31E-5		
NCI-H522	0.800	2.093	1.979	1.965	1.852	0.015	0.064	91	90	81	-98	-92	1.49E-6	2.84E-6	5.39E-6		
Colon Cancer																	
COLO 205	1.287	2.972	3.013	3.078	3.017	2.551	0.172	102	106	103	75	-87	1.43E-5	2.91E-5	5.93E-5		
HCT-116	0.156	1.290	1.333	1.369	1.162	0.059	0.181	104	107	89	-63	2	1.80E-6	.	.		
HCT-15	0.325	1.763	1.718	1.745	1.738	0.061	0.097	97	99	98	-81	-70	1.86E-6	3.53E-6	6.70E-6		
HT29	0.173	1.284	1.299	1.230	1.247	0.055	0.128	101	95	97	-68	-26	1.92E-6	3.85E-6	.		
KM12	0.284	1.012	1.093	1.090	1.051	0.226	0.032	111	111	105	-20	-89	2.76E-6	6.88E-6	2.71E-5		
SW-620	0.203	0.864	0.886	0.898	0.765	0.054	0.062	103	105	85	-74	-70	1.66E-6	3.43E-6	7.10E-6		
CNS Cancer																	
SF-268	0.352	0.964	0.982	0.984	0.971	0.315	0.012	103	103	101	-11	-97	2.87E-6	8.05E-6	2.88E-5		
SF-295	0.714	2.407	2.097	2.114	2.179	1.442	0.109	82	83	86	43	-85	6.89E-6	2.17E-5	5.35E-5		
SF-539	0.500	1.552	1.475	1.438	1.420	0.047	0.056	93	89	87	-91	-89	1.62E-6	3.10E-6	5.91E-6		
SNB-19	0.639	1.487	1.500	1.511	1.488	1.302	0.216	101	103	100	78	-66	1.57E-5	3.48E-5	7.71E-5		
SNB-75	0.504	0.941	0.876	0.827	0.808	0.668	0.007	85	74	70	37	-99	4.05E-6	1.88E-5	4.39E-5		
U251	0.240	1.055	1.102	1.096	1.103	0.212	0.051	106	105	106	-12	-79	2.98E-6	7.93E-6	3.70E-5		
Melanoma																	
LOX IMVI	0.348	1.986	1.941	1.937	1.808	0.023	0.073	97	97	89	-93	-79	1.64E-6	3.08E-6	5.79E-6		
MALME-3M	0.747	1.472	1.490	1.430	1.412	0.123	0.225	102	94	92	-84	-70	1.73E-6	3.34E-6	6.44E-6		
M14	0.502	1.738	1.816	1.869	1.891	1.027	0.240	106	111	112	42	-52	7.79E-6	2.81E-5	9.48E-5		
MDA-MB-435	0.549	2.075	2.180	2.095	2.161	0.202	0.165	107	101	106	-63	-70	2.14E-6	4.22E-6	8.35E-6		
SK-MEL-2	0.610	1.207	1.234	1.225	1.173	0.380	0.041	105	103	94	-38	-93	2.17E-6	5.18E-6	1.66E-5		
SK-MEL-28	0.351	0.574	0.609	0.629	0.630	0.025	0.032	116	125	125	-93	-91	2.22E-6	3.75E-6	6.36E-6		
SK-MEL-5	0.714	2.675	2.683	2.618	2.382	1.269	-0.003	100	97	85	28	-100	4.15E-6	1.66E-5	4.08E-5		
UACC-257	0.565	0.701	0.714	0.609	0.549	0.006	0.011	110	32	-3	-99	-98	5.94E-8	8.31E-7	3.10E-6		
UACC-62	0.737	2.484	2.464	2.408	2.214	0.575	-0.004	99	96	85	-22	-100	2.11E-6	6.21E-6	2.28E-5		
Ovarian Cancer																	
IGROV1	0.477	1.646	1.729	1.650	1.466	0.451	0.008	107	100	85	-6	-98	2.42E-6	8.68E-6	3.01E-5		
OVCA3	0.404	0.885	0.906	0.904	0.798	0.082	0.147	104	104	82	-80	-64	1.57E-6	3.21E-6	6.55E-6		
OVCA4	0.410	1.138	1.110	1.072	0.985	0.001	0.279	96	91	79	-100	-32	1.45E-6	2.77E-6	.		
OVCA5	0.320	0.780	0.800	0.810	0.806	0.007	0.052	104	106	106	-98	-84	1.88E-6	3.30E-6	5.81E-6		
OVCA8	0.236	0.743	0.729	0.705	0.660	0.052	0.121	97	92	84	-78	-49	1.61E-6	3.29E-6	.		
NCI/ADR-RES	0.236	0.567	0.579	0.601	0.563	0.090	0.156	104	110	99	-62	-34	2.01E-6	4.11E-6	.		
SK-OV-3	1.086	1.698	1.782	1.764	1.596	1.488	0.901	114	111	83	66	-17	1.55E-5	6.22E-5	> 1.00E-4		
Renal Cancer																	
786-0	0.562	2.066	2.160	2.228	2.210	0.613	0.063	106	111	110	3	-89	3.64E-6	1.09E-5	3.79E-5		
ACHN	0.357	1.342	1.407	1.336	1.324	-0.002	0.015	107	99	98	-100	-96	1.75E-6	3.13E-6	5.59E-6		
CAKI-1	0.470	1.362	1.243	1.227	1.180	0.017	0.040	87	85	80	-96	-92	1.47E-6	2.83E-6	5.45E-6		
SN12C	0.446	1.546	1.479	1.331	1.326	0.315	0.279	94	80	80	-29	-38	1.88E-6	5.38E-6	> 1.00E-4		
TK-10	0.550	1.225	1.211	1.242	1.274	0.061	0.074	98	103	107	-89	-87	1.96E-6	3.52E-6	6.33E-6		
UC-31	0.757	1.607	1.410	1.403	1.354	-0.009	-0.001	77	76	70	-100	-100	1.31E-6	2.59E-6	5.08E-6		
Prostate Cancer																	
PC-3	0.498	0.980	0.873	0.802	0.762	0.053	0.118	78	63	55	-89	-76	1.08E-6	2.40E-6	5.33E-6		
DU-145	0.223	0.703	0.734	0.792	0.775	-0.003	-0.010	106	119	115	-100	-100	2.00E-6	3.42E-6	5.85E-6		
Breast Cancer																	
MCF7	0.242	1.256	1.306	1.214	1.110	0.107	0.134	105	96	86	-56	-45	1.78E-6	4.02E-6	.		
MDA-MB-231/ATCC	0.539	1.052	1.059	0.988	0.877	0.324	0.066	101	87	66	-40	-88	1.41E-6	4.20E-6	1.62E-5		
HS 578T	0.626	0.756	0.689	0.710	0.665	0.276	0.254	49	65	30	-56	-59	.	2.24E-6	8.52E-6		
BT-549	1.028	1.790	1.756	1.711	1.687	1.129	0.005	95	90	86	13	-100	3.15E-6	1.31E-5	3.64E-5		
T-47D	0.513	1.077	1.146	1.166	0.774	0.365	0.385	112	116	46	-29	-25	8.82E-7	4.12E-6	> 1.00E-4		
MDA-MB-468	0.393	1.020	0.953	0.952	0.626	0.025	0.033	89	89	37	-94	-92	5.67E-7	1.92E-6	4.63E-6		

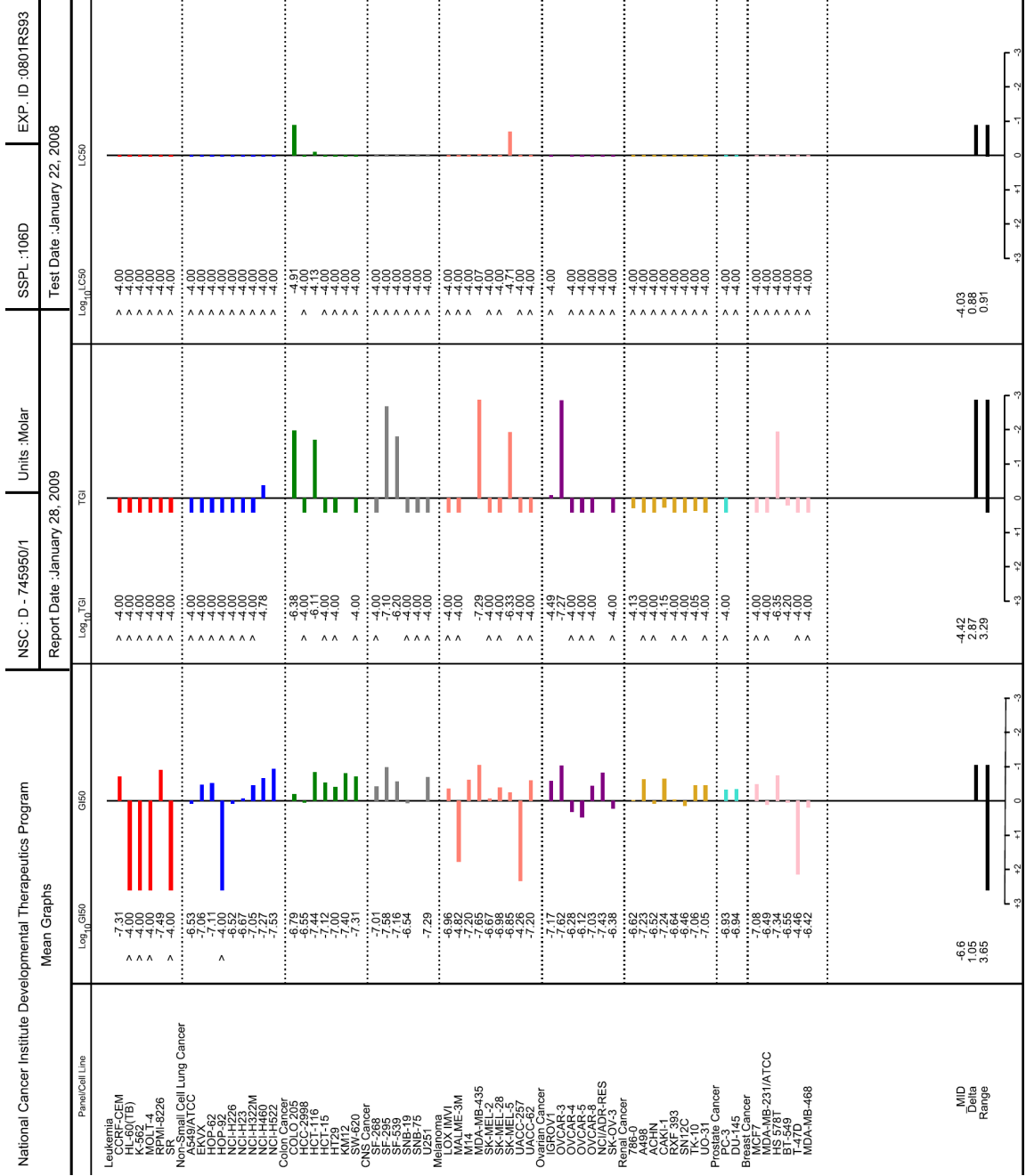


60 Human-Cancer Cell Line 5 Concentration Screen for Compound 227



National Cancer Institute Developmental Therapeutics Program In-Vitro Testing Results

NSC : D - 745950 / 1		Experiment ID : 0801RS93					Test Type : 08					Units : Molar				
Report Date : January 28, 2009		Test Date : January 22, 2008					QNS :					MC :				
COMI : 5840 (56474)		Stain Reagent : SRB Dual-Pass Related					SSPL : 106D									
Log10 Concentration																
Panel/Cell Line	Time Zero	Ctrl	Mean Optical Densities					Percent Growth					GI50	TGI	LC50	
			-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0				
Leukemia																
CCR-F-CEM	0.230	1.245	1.308	0.483	0.398	0.405	0.461	106	25	17	17	23	4.91E-8	> 1.00E-4	> 1.00E-4	
HL-60(TB)	0.336	1.753	1.771	1.630	1.313	1.349	1.271	101	91	69	71	66	> 1.00E-4	> 1.00E-4	> 1.00E-4	
K-562	0.086	1.750	1.733	1.160	1.101	1.080	1.451	99	65	61	60	82	> 1.00E-4	> 1.00E-4	> 1.00E-4	
MOLT-4	0.273	1.895	1.988	1.843	1.368	1.205	1.311	106	97	67	57	64	> 1.00E-4	> 1.00E-4	> 1.00E-4	
RPMI-8226	0.429	1.527	1.427	0.546	0.626	0.538	0.641	91	11	18	10	19	3.23E-8	> 1.00E-4	> 1.00E-4	
SR	0.135	1.429	1.476	1.418	1.058	0.864	1.060	104	99	71	56	71	> 1.00E-4	> 1.00E-4	> 1.00E-4	
Non-Small Cell Lung Cancer																
A549/ATCC	0.551	1.938	1.942	1.503	0.954	0.998	0.778	100	69	29	32	16	2.96E-7	> 1.00E-4	> 1.00E-4	
EKVX	0.439	1.229	1.177	0.813	0.593	0.631	0.556	93	47	19	24	15	8.72E-8	> 1.00E-4	> 1.00E-4	
HOP-62	0.233	0.874	0.885	0.514	0.261	0.304	0.243	102	44	4	11	2	7.80E-8	> 1.00E-4	> 1.00E-4	
HOP-92	0.785	1.491	1.446	1.433	1.270	1.276	1.222	94	92	69	70	62	> 1.00E-4	> 1.00E-4	> 1.00E-4	
NCI-H226	0.780	1.764	1.787	1.714	0.802	0.955	0.781	102	95	2	18	.	3.05E-7	> 1.00E-4	> 1.00E-4	
NCI-H23	0.452	1.305	1.307	0.984	0.670	0.720	0.530	100	62	25	31	9	2.16E-7	> 1.00E-4	> 1.00E-4	
NCI-H322M	0.310	0.681	0.698	0.486	0.473	0.492	0.395	105	47	44	49	23	8.99E-8	> 1.00E-4	> 1.00E-4	
NCI-H460	0.229	1.866	2.054	0.681	0.276	0.293	0.198	112	28	3	4	-14	5.41E-8	1.66E-5	> 1.00E-4	
NCI-H522	0.336	1.149	1.122	0.330	0.339	0.330	0.271	97	-2	.	-2	-19	2.98E-8	.	> 1.00E-4	
Colon Cancer																
COLO 205	0.211	0.813	0.872	0.665	0.115	0.111	0.056	110	75	-45	-48	-74	1.62E-7	4.20E-7	1.23E-5	
HCC-2998	0.326	1.122	1.126	0.957	0.443	0.418	0.336	101	79	15	12	1	2.84E-7	> 1.00E-4	> 1.00E-4	
HCT-116	0.142	1.103	1.091	0.256	0.140	0.141	0.061	99	12	-1	-1	-57	3.64E-8	7.83E-7	7.39E-5	
HCT-15	0.274	1.809	1.692	0.949	0.364	0.405	0.377	92	44	6	9	7	7.51E-8	> 1.00E-4	> 1.00E-4	
HT29	0.174	1.222	1.212	0.699	0.291	0.274	0.204	99	50	11	9	3	1.01E-7	> 1.00E-4	> 1.00E-4	
KM12	0.224	0.885	0.897	0.325	0.217	0.253	0.163	102	15	-3	4	-27	3.97E-8	.	> 1.00E-4	
SW-620	0.159	0.979	0.968	0.389	0.319	0.351	0.253	99	28	20	23	11	4.89E-8	> 1.00E-4	> 1.00E-4	
CNS Cancer																
SF-268	0.347	1.065	1.089	0.702	0.482	0.496	0.391	103	49	19	21	6	9.74E-8	> 1.00E-4	> 1.00E-4	
SF-298	0.598	1.466	1.400	0.540	0.529	0.586	0.426	92	-10	-12	-2	-29	2.60E-8	8.04E-8	> 1.00E-4	
SF-539	0.657	1.930	1.987	1.158	0.592	0.584	0.350	104	39	-10	-11	-47	6.86E-8	6.28E-7	> 1.00E-4	
SNB-19	0.279	1.032	1.020	0.814	0.467	0.467	0.340	98	71	25	25	8	2.86E-7	> 1.00E-4	> 1.00E-4	
SNB-75	0.649	1.558	1.379	1.059	1.063	1.148	0.954	80	45	45	55	33	.	> 1.00E-4	> 1.00E-4	
U251	0.231	1.304	1.238	0.573	0.406	0.463	0.341	94	32	16	22	10	5.09E-8	> 1.00E-4	> 1.00E-4	
Melanoma																
LOX IMVI	0.311	2.301	2.213	1.325	0.820	0.889	0.727	96	51	26	29	21	1.09E-7	> 1.00E-4	> 1.00E-4	
MALME-3M	0.403	0.684	0.676	0.559	0.563	0.573	0.411	97	55	57	60	3	1.52E-5	> 1.00E-4	> 1.00E-4	
M14	0.352	1.169	1.151	0.661	0.314	0.390	0.303	98	38	-11	5	-14	6.26E-8	.	> 1.00E-4	
MDA-MB-435	0.426	1.485	1.478	0.256	0.325	0.342	0.204	99	-40	-24	-20	-52	2.26E-8	5.16E-8	8.60E-5	
SK-MEL-2	0.212	0.537	0.541	0.410	0.302	0.352	0.250	101	61	28	43	12	2.13E-7	> 1.00E-4	> 1.00E-4	
SK-MEL-28	0.363	1.017	1.032	0.691	0.610	0.619	0.485	102	50	38	39	19	1.04E-7	> 1.00E-4	> 1.00E-4	
SK-MEL-5	0.644	2.444	2.485	1.813	0.435	0.413	0.095	102	65	-32	-36	-85	1.42E-7	4.64E-7	1.93E-5	
UACC-257	0.466	1.102	1.109	0.867	0.862	0.973	0.717	101	63	62	80	39	5.44E-5	> 1.00E-4	> 1.00E-4	
UACC-62	0.828	2.312	2.313	1.384	1.443	1.423	1.027	100	37	41	40	13	6.30E-8	> 1.00E-4	> 1.00E-4	
Ovarian Cancer																
IGROV1	0.313	1.149	1.214	0.631	0.427	0.420	0.274	108	38	14	13	-12	6.74E-8	3.20E-5	> 1.00E-4	
OVCAR-3	0.237	0.717	0.729	0.149	0.102	0.122	0.058	103	-37	-57	-49	-76	2.38E-8	5.41E-8	.	
OVCAR-4	0.449	1.349	1.400	1.102	0.820	0.849	0.806	106	73	41	44	40	5.24E-7	> 1.00E-4	> 1.00E-4	
OVCAR-5	0.372	1.107	1.084	1.097	0.692	0.710	0.590	97	99	43	46	30	7.62E-7	> 1.00E-4	> 1.00E-4	
OVCAR-8	0.271	1.159	1.219	0.702	0.451	0.479	0.434	107	48	20	23	18	9.41E-8	> 1.00E-4	> 1.00E-4	
NCI/ADR-RES	0.476	1.631	1.696	0.577	0.457	0.608	0.543	106	9	-4	11	6	3.75E-8	.	> 1.00E-4	
SK-OV-3	0.521	1.442	1.505	1.178	0.860	0.815	0.646	107	71	37	32	14	4.13E-7	> 1.00E-4	> 1.00E-4	
Renal Cancer																
786-0	0.611	2.007	2.034	1.644	0.755	0.759	0.601	102	74	10	11	-2	2.38E-7	7.34E-5	> 1.00E-4	
A498	0.575	1.182	1.174	0.790	0.667	0.738	0.575	99	35	15	27	.	5.86E-8	> 1.00E-4	> 1.00E-4	
ACHN	0.370	1.616	1.616	1.170	0.804	0.708	0.615	100	64	35	27	20	3.04E-7	> 1.00E-4	> 1.00E-4	
CAKI-1	0.369	1.509	1.491	0.768	0.474	0.498	0.362	98	35	9	11	-2	5.80E-8	7.04E-5	> 1.00E-4	
RXF 393	0.826	2.198	2.279	1.660	1.253	1.341	1.205	106	61	31	37	28	2.31E-7	> 1.00E-4	> 1.00E-4	
SN12C	0.518	1.587	1.478	1.394	0.761	0.794	0.722	90	82	23	26	19	3.46E-7	> 1.00E-4	> 1.00E-4	
TK-10	0.190	0.467	0.486	0.319	0.315	0.306	0.186	107	47	45	42	-2	8.80E-8	8.96E-5	> 1.00E-4	
UO-31	0.483	1.371	1.311	0.909	0.848	0.854	0.759	93	48	41	42	31	9.01E-8	> 1.00E-4	> 1.00E-4	
Prostate Cancer																
PC-3	0.138	0.579	0.584	0.364	0.295	0.297	0.304	101	51	35	36	38	1.18E-7	> 1.00E-4	> 1.00E-4	
DU-145	0.200	0.720	0.707	0.481	0.171	0.202	0.142	97	54	-15	.	-29	1.14E-7	.	> 1.00E-4	
Breast Cancer																
MCF7	0.451	2.056	2.004	1.187	0.616	0.605	0.456	97	46	10	10	.	8.28E-8	> 1.00E-4	> 1.00E-4	
MDA-MB-231/ATCC	0.444	1.060	1.073	0.935	0.578	0.563	0.505	102	80	22	19	10	3.25E-7	> 1.00E-4	> 1.00E-4	
HS 578T	0.415	0.863	0.833	0.539	0.354	0.367	0.317	93	28	-15	-12	-24	4.56E-8	4.48E-7	> 1.00E-4	
BT-549	0.571	1.078	1.073	0.936	0.689	0.677	0.541	99	72	23	21	-5	2.83E-7	6.30E-5	> 1.00E-4	
T-47D	0.393	1.044	1.003	0.833	0.768	0.810	0.640	94	67	58	64	38	3.44E-5	> 1.00E-4	> 1.00E-4	
MDA-MB-468	0.211	0.521	0.526	0.484	0.281	0.326	0.285	102	88	23	37	24	3.82E-7	> 1.00E-4	> 1.00E-4	



(Retrieved from <http://dtp.nci.nih.gov/screening.html> on 1/29/2009)

DTP Human Tumor Cell Line Screen

Process

The In Vitro Cell Line Screening Project (IVCLSP) is a dedicated service providing direct support to the DTP anticancer drug discovery program. The in vitro cell line screen was implemented in fully operational form in April of 1990. It required approximately five years (1985 - 1990) to develop, and persistence in the effort reflected dissatisfaction with the performance of prior in vivo primary screens. This project is designed to screen up to 3,000 compounds per year for potential anticancer activity. The operation of this screen utilizes 60 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. The aim is to prioritize for further evaluation, synthetic compounds or natural product samples showing selective growth inhibition or cell killing of particular tumor cell lines. This screen is unique in that the complexity of a 60 cell line dose response produced by a given compound results in a biological response pattern which can be utilized in pattern recognition algorithms (COMPARE program. See: <http://dtp.nci.nih.gov/docs/compare/compare.html>). Using these algorithms, it is possible to assign a putative mechanism of action to a test compound, or to determine that the response pattern is unique and not similar to that of any of the

standard prototype compounds included in the NCI database (see DTP Overview tab). In addition, following characterization of various cellular molecular targets in the 60 cell lines, it may be possible to select compounds most likely to interact with a specific molecular target.

The screening is a two-stage process, beginning with the evaluation of all compounds against the 60 cell lines at a single dose of 10 μ M. The output from the single dose screen is reported as a mean graph and is available for analysis by the COMPARE program. Compounds which exhibit significant growth inhibition are evaluated against the 60 cell panel at five concentration levels.

Methodology Of The In Vitro Cancer Screen

The human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100 μ L at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37° C, 5 % CO₂, 95 % air and 100 % relative humidity for 24 h prior to addition of experimental drugs.

After 24 h, two plates of each cell line are fixed in situ with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs are solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug

addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 µg/ml gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 µl of these different drug dilutions are added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final drug concentrations.

Following drug addition, the plates are incubated for an additional 48 h at 37°C, 5 % CO₂, 95 % air, and 100 % relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed in situ by the gentle addition of 50 µl of cold 50 % (w/v) TCA (final concentration, 10 % TCA) and incubated for 60 minutes at 4°C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4 % (w/v) in 1 % acetic acid is added to each well, and plates are incubated for 10 minutes at room temperature. After staining, unbound dye is removed by washing five times with 1 % acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 µl of 80 % TCA (final concentration, 16 % TCA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

$[(Ti-Tz)/(C-Tz)] \times 100$ for concentrations for which $Ti \geq Tz$

$[(Ti-Tz)/Tz] \times 100$ for concentrations for which $Ti < Tz$.

Three dose response parameters are calculated for each experimental agent. Growth inhibition of 50 % (GI50) is calculated from $[(Ti-Tz)/(C-Tz)] \times 100 = 50$, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from $Ti = Tz$. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from $[(Ti-Tz)/Tz] \times 100 = -50$. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested.

Publications

Alley, M.C., Scudiero, D.A., Monks, P.A., Hursey, M. L., Czerwinski, M.J., Fine, D.L., Abbott, B.J., Mayo, J.G., Shoemaker, R.H., and Boyd, M.R. Feasibility of Drug Screening with Panels of Human Tumor Cell Lines Using a Microculture Tetrazolium Assay. *Cancer Research* 48: 589-601, 1988.

Grever, M.R., Schepartz, S.A., and Chabner, B.A. The National Cancer Institute: Cancer Drug Discovery and Development Program. *Seminars in Oncology*, Vol. 19, No. 6, pp 622-638, 1992.

Boyd, M.R., and Paull, K.D. Some Practical Considerations and Applications of the National Cancer Institute In Vitro Anticancer Drug Discovery Screen. *Drug Development Research* 34: 91-109, 1995.

Review: Shoemaker, R. H. The NCI60 Human Tumour Cell line Anticancer Drug Screen. *Nature Reviews*, 6: 813-823, 2006.

Acute Toxicity Determination

Generally, the determination of maximum tolerated dose (MTD) is performed in a way that conserves compound and minimizes the number of animals sacrificed. Thus, a single mouse is given a single injection (IP, IV, SC, IM or PO) of 400 mg/kg (or lower if the compound is anticipated to be extremely potent, e.g. natural products); a second mouse receives a dose of 200 mg/kg and a third mouse receives a single dose of 100 mg/kg. The mice are observed for a period of 2 weeks. They are sacrificed if they lose more than 20% of their body weight or if there are other signs of significant toxicity. If all 3 mice must be sacrificed, the next 3 dose levels (50, 35 and 12.5 mg/kg) are tested in a similar manner. This process is repeated until a tolerated dose is found. This dose

is then designated the MTD and is used to calculate the amount of material administered to mice during anti-tumor testing. The mice are allowed ad libitum feed and water. Injections are most commonly administered IP, but SC, PO and IV dosing may be required on occasion. Dose volumes are generally 0.1 mL/10 grams body weight but may be up to 0.2 mL/10 grams of body weight for IP, IV, SC and PO routes.

For the standard hollow fiber assay (HFA), the high and low dose levels are determined using the MTD as determined above using the formula below.

High dose = $[\text{MTD} \times 1.5]/4$

Low dose = $0.67 \times \text{high dose}$

The standard vehicle used for both acute toxicity testing and HFA is 10% DMSO in saline/0.05% Tween 80.

Primary Anti-cancer Drug Screening Activities

Hollow Fiber Assay

Process

Advancement of potential anticancer agents from identification in the in vitro screen to preclinical development is enhanced with demonstration of in vivo efficacy in one or more animal models of neoplastic disease. Most such models require considerable

materials in terms of laboratory animals and test compound as well as substantial amounts of time and cost to determine whether a given experimental agent or series of agents have even minimal anti-tumor activity. The hollow fiber assay described below has demonstrated the ability to provide quantitative indices of drug efficacy with minimum expenditures of time and materials and is currently being utilized as the initial in vivo experience for agents found to have reproducible activity in the in vitro anticancer drug screen.

Methodology of the Hollow Fiber Assay

A standard panel of 12 tumor cell lines are used for the routine hollow fiber screening of the in vitro actives. These include NCI-H23, NCI-H522, MDA-MB-231, MDA-MB-435, SW-620, COLO 205, LOX, UACC-62, OVCAR-3, OVCAR-5, U251 and SF-295. In addition, alternate lines can be used for specialized testing of compounds on a nonroutine basis. The cell lines are cultivated in RPMI-1640 containing 10% FBS and 2 mM glutamine. On the day preceding hollow fiber preparation, the cells are given a supplementation of fresh medium to maintain log phase growth. For fiber preparation, the cells are harvested by standard trypsinization technique and resuspended at the desired cell density (($2-10 \times 10^6$ cells/ml). The cell suspension is flushed into 1 mm (internal diameter) polyvinylidene fluoride hollow fibers with a molecular weight exclusion of 500,000 Da. The hollow fibers are heat-sealed at 2 cm intervals and the samples generated from these seals are placed into tissue culture medium and incubated at 37°C in 5% CO₂ for 24 to 48 hours prior to implantation. A total of 3 different tumor lines are prepared for each experiment so that each mouse receives 3 intraperitoneal

implants (1 of each tumor line) and 3 subcutaneous implants (1 of each tumor line). On the day of implantation, samples of each tumor cell line preparation are quantitated for viable cell mass by a stable endpoint MTT assay so that the time zero cell mass is known. Mice are treated with experimental agents starting on day 3 or 4 following fiber implantation and continuing daily for 4 days. Each agent is administered by intraperitoneal injection at 2 dose levels. The doses are based on the maximum tolerated dose (MTD) determined during prior acute toxicity testing. The fibers are collected from the mice on the day following the fourth compound treatment and subjected to the stable endpoint MTT assay. The optical density of each sample is determined spectrophotometrically at 540 nm and the mean of each treatment group is calculated. The percent net growth for each cell line in each treatment group is calculated and compared to the percent net growth in the vehicle treated controls. A 50% or greater reduction in percent net growth in the treated samples compared to the vehicle control samples is considered a positive result. Each positive result is given a score of 2 and all of the scores are totaled for a given compound. The maximum possible score for an agent is 96 (12 cell lines X 2 sites X 2 dose levels X 2 [score]). A compound is considered for xenograft testing if it has a combined ip + sc score of 20 or greater, a sc score of 8 or greater, or produces cell kill of any cell line at either dose level evaluated. This scoring system has been validated by DCTDC statisticians in CTEP to represent a level of detection expected to score current "standard" agents as active.

Appendix 3. X-Ray Crystallographic Data for Compound 119 in Part II.

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'x+1/2, -y+1/2, z-1/2'

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Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2 , conventional R-factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F , and R-factors based on ALL data will be even larger.

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C7A C8A H8AB 109.5 . . ?
H8AA C8A H8AB 109.5 . . ?
C7A C8A H8AC 109.5 . . ?
H8AA C8A H8AC 109.5 . . ?
H8AB C8A H8AC 109.5 . . ?
C7B C8B H8BA 109.5 . . ?
C7B C8B H8BB 109.5 . . ?
H8BA C8B H8BB 109.5 . . ?
C7B C8B H8BC 109.5 . . ?
H8BA C8B H8BC 109.5 . . ?
H8BB C8B H8BC 109.5 . . ?

loop_

_geom_torsion_atom_site_label_1
_geom_torsion_atom_site_label_2
_geom_torsion_atom_site_label_3
_geom_torsion_atom_site_label_4
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_geom_torsion_site_symmetry_2
_geom_torsion_site_symmetry_3
_geom_torsion_site_symmetry_4
_geom_torsion_publ_flag
C3A C1A C2A N1A -0.3(2) ?
C4A N1A C2A C1A 0.3(2) ?
C3B C1B C2B N1B 0.4(2) ?
C4B N1B C2B C1B -0.2(2) ?
C2A C1A C3A C4A 0.3(2) ?
C2B C1B C3B C4B -0.5(2) ?
C1A C3A C4A N1A -0.2(2) ?
C1A C3A C4A C5A 176.35(18) ?

C2A N1A C4A C3A -0.1(2) ?
C2A N1A C4A C5A -176.91(16) ?
C1B C3B C4B N1B 0.3(2) ?
C1B C3B C4B C5B -177.61(18) ?
C2B N1B C4B C3B -0.1(2) ?
C2B N1B C4B C5B 178.08(16) ?
C7A O1A C5A C4A -74.3(2) ?
C7A O1A C5A C6A 161.40(16) ?
C3A C4A C5A O1A 116.2(2) ?
N1A C4A C5A O1A -67.8(2) ?
C3A C4A C5A C6A -123.7(2) ?
N1A C4A C5A C6A 52.3(2) ?
C7B O1B C5B C4B 70.91(19) ?
C7B O1B C5B C6B -164.68(15) ?
C3B C4B C5B O1B -110.9(2) ?
N1B C4B C5B O1B 71.4(2) ?
C3B C4B C5B C6B 128.9(2) ?
N1B C4B C5B C6B -48.8(2) ?
C5A O1A C7A C8A -174.81(16) ?
C5B O1B C7B C8B -175.36(17) ?

_diffn_measured_fraction_theta_max 1.000
_diffn_reflns_theta_full 25.08
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_refine_diff_density_max 0.156
_refine_diff_density_min -0.285
_refine_diff_density_rms 0.037
_diffn_ambient_pressure 101.325

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