Synthesis of Functionalized Benzoxaboroles

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Venkatram R Mereddy

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Abstract

Synthesis of Functionalized Benzoxaboroles

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2-Formylphenylboronic acids upon reaction with activated olefins such as acrylates, methyl vinyl ketone, and acrylonitrile, etc. via Baylis-Hillman reaction to provide functionalized benzoxaboroles. The corresponding homologated benzoxaboroles were synthesized via Barbier allylation reaction of 2-formylphenylboronic acids with α-bromomethylacrylates. Several novel benzoxaborole derivatives were synthesized starting from 2-formylphenylboronic acid utilizing Passerini reaction and aldol reaction protocols as the key step.

An efficient methodology for the preparation of α-hydroxyamides via boric acid mediated addition of isonitriles on to aldehydes has been developed. The reaction of isonitriles with α-boronobenzaldehyde takes place under intramolecular catalysis conditions to provide functionalized benzoxaboroles.

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NBS	N-Bromosuccinimide
Cp	cyclopentyl
p-TsOH	p-Toluene Sulfonic acid
BnOH	Benzyl alcohol
NaH	Sodium hydride
BuLi	Butyl Lithium
$B(iPrO)_3$	Triisopropyl borate
$NaBH_4$	Sodium borohydrate
THF	Tetrahydrofuran
DMF	N, N - Dimethylformamide
Et_3N or TEA	Triethyl amine
TBDMS–Cl	Tertiary- butyldimethylsilyl chloride
DIBAL-H	Diisobutylaluminium hydride
MOM	Methoxymethyl
THP	Tetrahydropyran
DHP	Dihydropyran
PCC	Pyridinium chlorochromate
DCM	Dichloromethane
$Pd(dppf)Cl_2$	(1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
$B(OMe)_3$	Trimethoxy borane

BBr_3	Boron tribromide
NIS	N-iodo succinimide
BH	Baylis-Hillman
EWG	Electron with-drawing group
DABCO	1,4-diazabicyclo[2.2.2] octane
PBu_3	Tributyl phosphine
EtOAc	Ethylacetate
MeOH	Methanol
TLC	Thin layer chromatography
LDA	Lithium diisopropylamide

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Chapter 1: Benzoxaboroles

Introduction

Boron is the fifth element in the periodic table. Boron containing compounds have been highly utilized in several household purposes such as cleaning, insecticide and medicinal uses such as antiseptic, antibacterial, multiple enzyme inhibitors[1,2], etc. Boron containing compound, bortezomib, is a novel chemotherapeutic for multiple myeloma[3]. Apart from these medicinal uses, several boranes had been utilized in boron-neutron capture therapy in cancer treatment[4]. In industry, it is especially utilized in nuclear power plants as a poison to reduce the rate of fission. In material science, boron in the form of borates has been utilized in semiconductors.

Apart from boric acid and some other borates, most of the synthetic boron compounds are air sensitive with a few exceptions such as sodium borohydride. Benzoxaboroles **1** are cyclic hemiesters of phenylboronic acids[5] which are stable compared to the acyclic boronic acids. There are only few scientists working on the synthesis of these hemiesters. Despite benzoxaborole had been known for ~60 years, these compounds are routinely used in cross coupling reactions in organic synthesis[1].

Benzoxaboroles also gained reputation for its medicinal usage[6]. For example, AN2728 **2** is used as *anti*-inflammatory activity against psoriasis, a common skin disease. 5-Fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole,

AN2690 **3**, is a broad-spectrum antifungal drug. 5-chloro-substituted benzoxaborole, AN2718 **4**, is being developed for the topical treatment of *tinea pedis* infection (**Figure 1**).

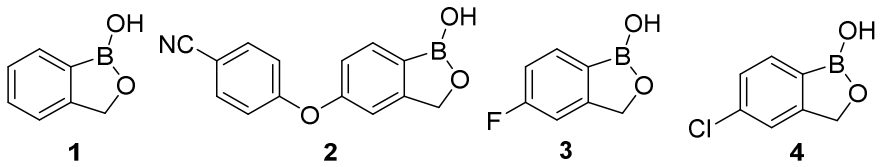
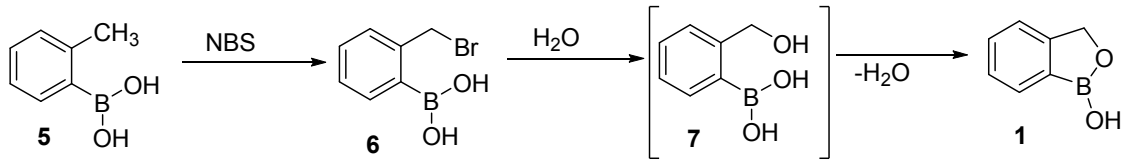


Figure 1 Functionalized Benzoxaboroles

In material science, benzoxaboroles has been used in the construction of molecular receptors, design of self-assembled molecular structures, building blocks in crystal engineering, use as steroid conjugates for molecular imprinting, dyes, biosensors of α-hydroxy-carboxylic acids, and biocides for plastic biodegradation etc.[7] Because of the sugar-like structures, benzoxaboroles have been found to selectively complex with natural oligosaccharides to effect direct glycosidation. They are known for their selective recognition of cell surface glycoconjugates.[8]

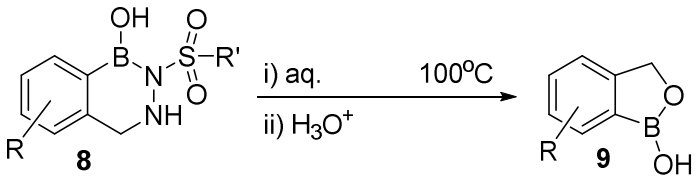
The following are some of the synthetic methods that have been reported for the preparation of benzoxaboroles and their development as medicinal agents.

2-Methylphenylboronic acid **5** was brominated using N-bromosuccinimide, followed by hydrolysis of the bromide **6** to benzyl alcohol intermediate **7**, which upon intramolecular esterification yielded unsubstituted benzoxaborole **1** (**Scheme 1.1**).[9]



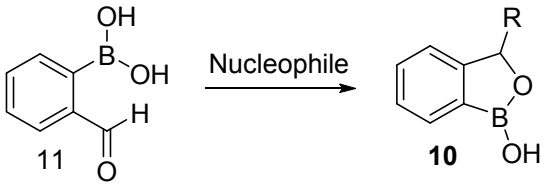
Scheme-1.1 Synthesis of benzoxaborole

Hydrolysis of 1,2-dihydro-1-hydroxy-2,3,1-benzodiazaborines **8** in presence of aqueous sodium hydroxide furnished corresponding benzoxaboroles **9** (**Scheme 1.2**).[10]



Scheme-1.2 Synthesis of substituted benzoxaborole

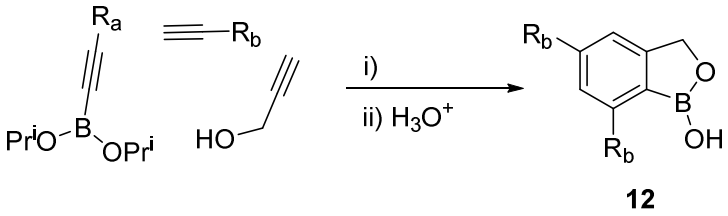
3-substituted benzoxaboroles **10** were obtained upon the treatment of o-formylphenylboronic acid **11** with nucleophiles such as malonic acid, nitromethane, sodium cyanide, etc. (**Scheme 1.3**).[11]



R = CH_2COOH, CH_2NO_2, CN

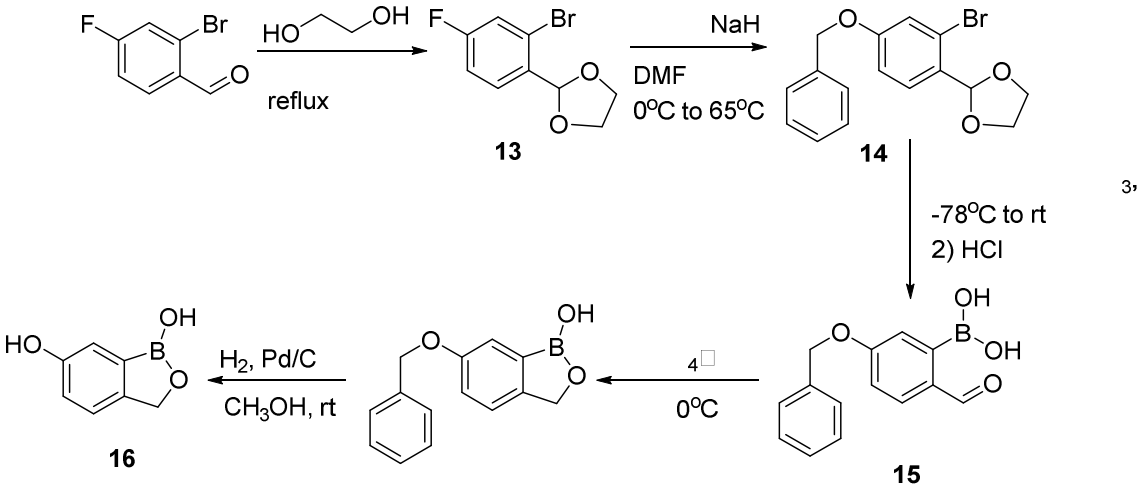
Scheme-1.3 Synthesis of 3-substituted benzoxaborole

Multicomponent coupling of alkynes in presence of a transition metal catalyst resulted in cyclotrimerization of alkynes furnishing substituted benzoxaboroles **12** (**Scheme 1.4**).[12]



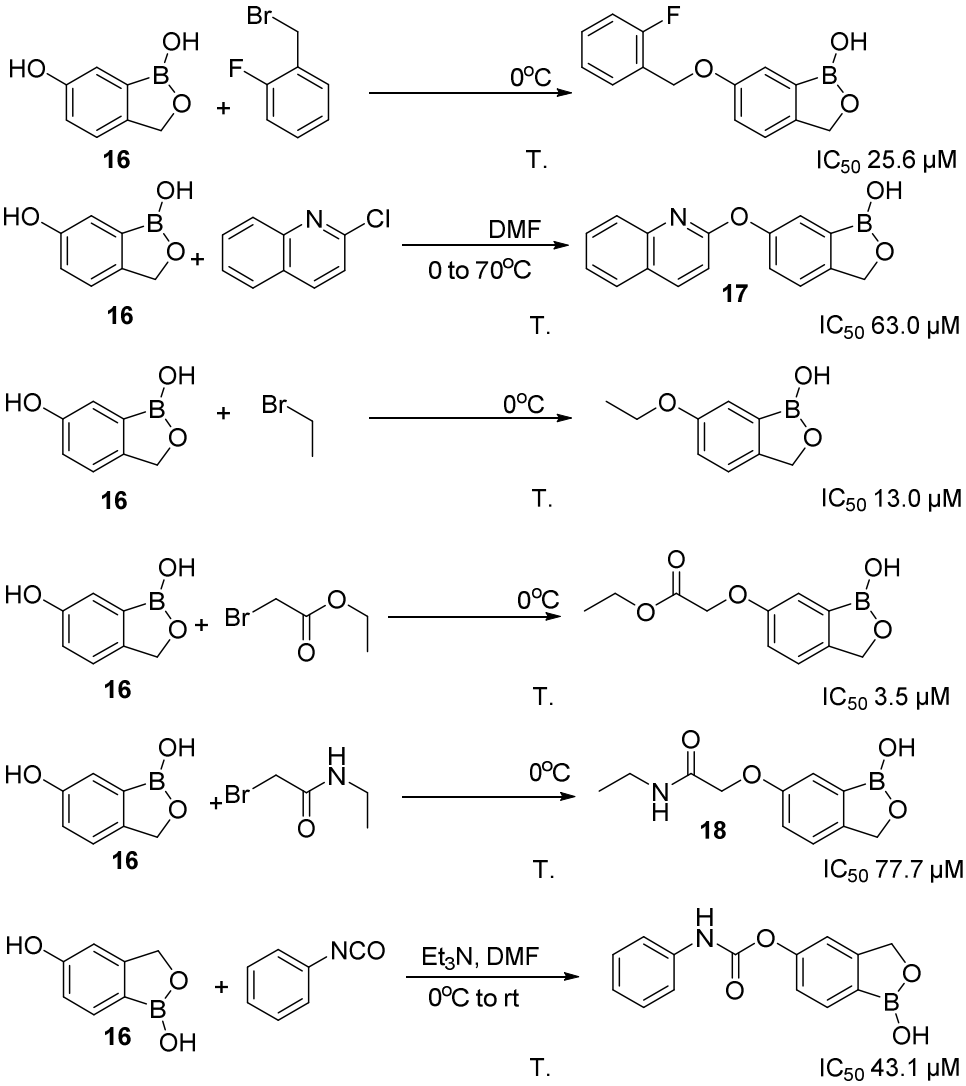
Scheme-1.4 Synthesis of benzoxaborole via multicomponent coupling of alkynes

Hydroxybenzboroxole **16** was synthesized and used as common intermediate in the preperation of various aryl ethers. These ethers have been evaluated as potential anti-Trypsnosomal agents. The formyl group in 2-bromo-4-fluorobenzaldehyde was protected with ethylene glycol as its acetal **13**. Nucleophilic displacement of fluoride with benzyl alcohol furnished 2-(4-(benzyloxy)-2-bromophenyl)-1,3-dioxolane **14.** Reaction of **14** with *n*-butyl lithium followed by triisopropylborate, resulted in the formation of boronic acid, which upon acidification resulted in the deprotection of the acetal-protecting group to furnish the aldehyde **15**. Reduction of **15** with $NaBH_4$ yielded 6-(*O*-benzyl)-benzoxaborole, which was further reduced with Pd/C to obtain 6-hydroxy-benzoxaborole **16** (**Scheme 1.5**).[13]



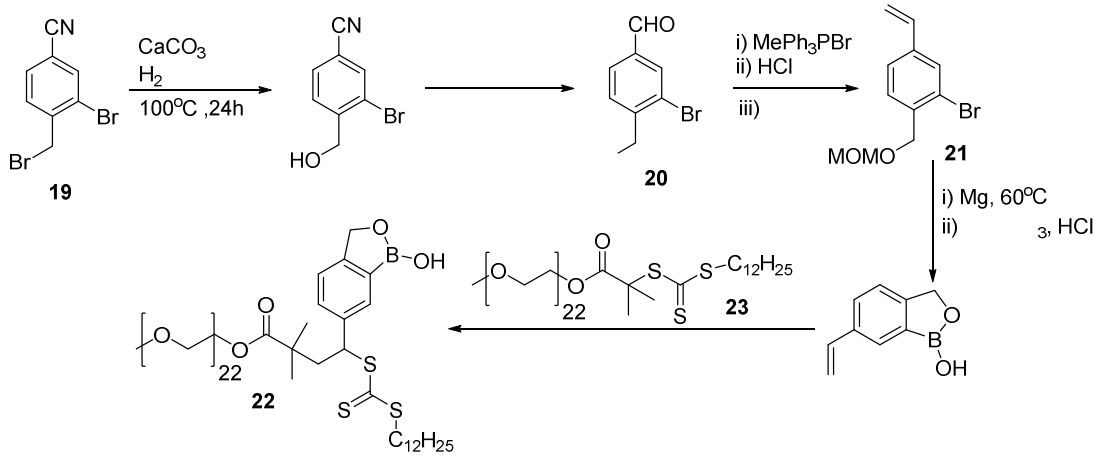
Scheme-1.5: Synthesis of benzoboroxoles as anti-trypanosomal agents

Hydroxybenzoxaborole **16** was coupled to corresponding benzyl bromides, alkyl bromides, or α-bromoacetates in presence of sodium hydride at 0^oC to obtain the benzyl ethers, alkyl ethers and α-alkoxyacetates respectively. Diaryl ethers **17** were prepared from **16** upon reaction with NaH at 70^oC. Treatment of **16** with α-bromoacetamides in the presence of K_2CO_3 with NaI as catalyst yielded α-bromoacetamides **18**. Carbamates were prepared from **16** by coupling with corresponding isocyanates in the presence of Et_3N in DMF at 0^oC (**Scheme 1.6**).[13]



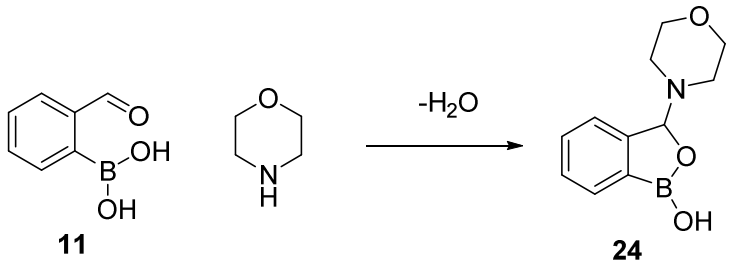
Scheme-1.6: Synthesis of benzoxaboroles as anti-trypanosomal agents

Kim *et. al*. reported the synthesis of polymers of benzoxaboroles as monosaccharide-responsive release of insulin from polymersomes of polyboroxole block copolymers at neutral pH (**Scheme 1.7**). The synthesis was initiated via the treatment of 3-bromo-4-(bromomethyl)benzonitrile **19** with calcium carbonate in presence of water-dioxane at 100^{o}C to obtain 3-bromo-4-(hydroxymethyl) benzonitrile. The hydroxy group was protected by tert-butyldimethylsilyl (TBDMS-Cl) group and the reduction of cyanide with DiBAl-H furnished the aldehyde **20**. Wittig olefination of **20** with methyltriphenylphosphonium bromide followed by the deprotection of TBDMS and re-protection using methoxymethyl (MOM) chloride furnished MOM ether **21**. The aryl bromide was converted into its Grignard by reacting with magnesium at 60^{o}C and subsequently treated with trimethylborate to furnish the benzoxaborole monomer upon acidic work up in the presence of HCl. The monomer was further converted into the polymer by treating **22** with xanthate **23** (**Scheme 1.7**).[14]



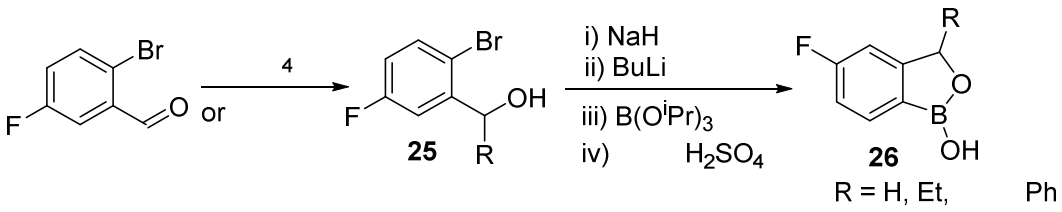
Scheme-1.7: Synthesis of polymeric benzoxaboroles

Morpholinobenzoxaborole **24** was obtained upon the reaction of o-formylphenylboronic acid **11** with morpholine (**Scheme 1.8**).[15]



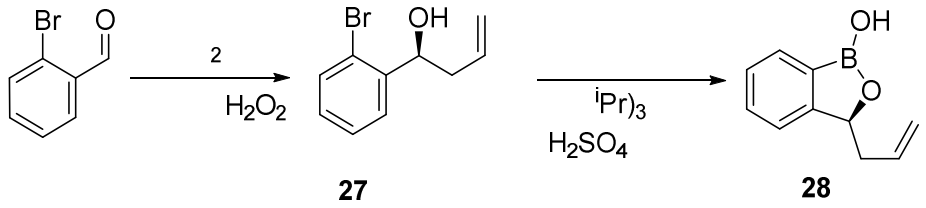
Scheme-1.8: Synthesis of 3-amino-substituted benzoxaboroles

2-Bromo-5-fluorobenzaldehyde was reacted with sodium borohydride or Grignard reagents to obtain substituted alcohols **25**. This was further treated with sodium hydride, followed by *n*-butyl lithium and triisopropylborate and 10% sulfuric acid to furnish corresponding 5-fluoro-3-substituted benzoxaboroles **26** (**Scheme 1.9**).[16]



Scheme-1.9:Practical synthesis of benzoxaboroles

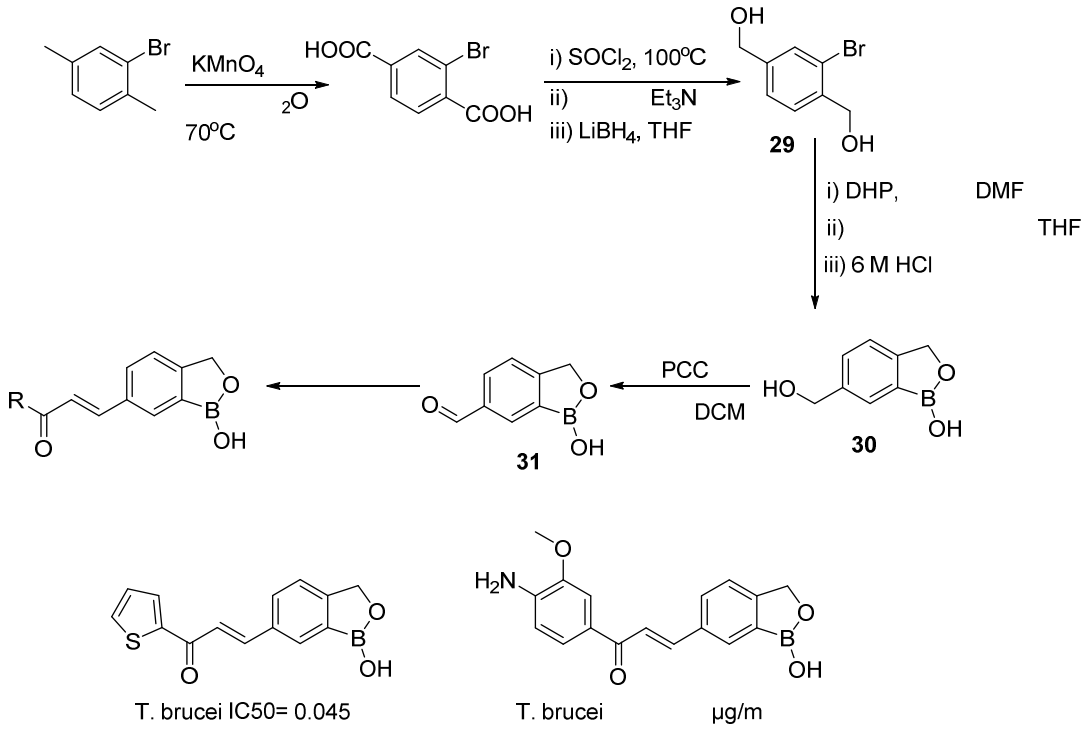
Similarly, chiral benzoxaboroles were prepared by the reaction of aldehydes with asymmetric allylating reagent such as $Ipc_2BAllyl$. 2-bromobenzaldehyde was treated with Ipc_2BAll to obtain (S)-1-(2-bromophenyl)but-3-en-1-ol (**27**), which was cyclized to (S)-3-allylbenzo[c][1,2]oxaborol-1(3H)-ol (**28**) upon reaction with sodium hydride, *n*-butyl lithium, triisopropylborate, and sulfuric acid (**Scheme 1.10**).[16]



Scheme-1.10: Practical synthesis of chiral benzoxaboroles

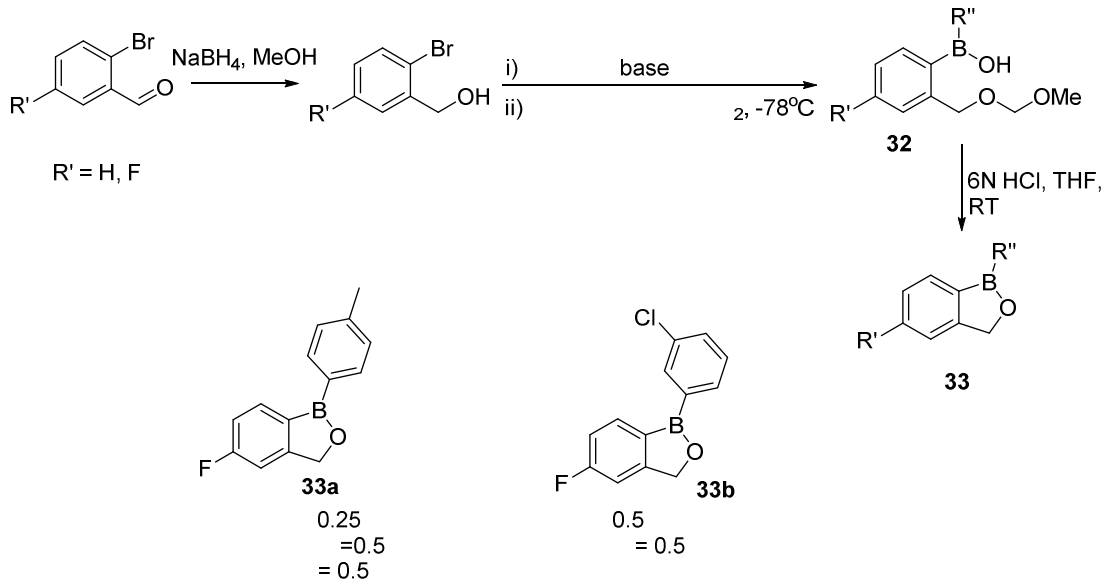
Dimethylbromobenzene was oxidized to dicarboxylic acid using $KMnO_4$ in tertiary butanol and water. Conversion of dicarboxylic acid into the corresponding acid chloride was achieved using thionyl chloride, which upon reaction with methanol in triethylamine resulted in the formation of the dimethyl ester. Reduction of the diester with lithium borohydride furnished the diol **29**. Protection of the alcohol groups as THP acetal followed by the treatment with n-butyl lithium and triisopropylborate, and subsequent deprotection and cyclization in 6 M HCl furnished 5-hydroxymethylbenzoxaborole **30**. This was further oxidized with PCC to obtain 5-formyl benzoxaborole **31**. Chalcone−benzoxaborole hybrid molecules were prepared from this aldehyde **31** by aldol condensation with substituted methylketones in presence of sodium hydroxide in ethanol-water. Some of these

molecules showed excellent anti-trypanosomal activity aganst *T. brucei* with IC_{50} values ranging 0.045 µg/mL (**Scheme 1.11**).[17]



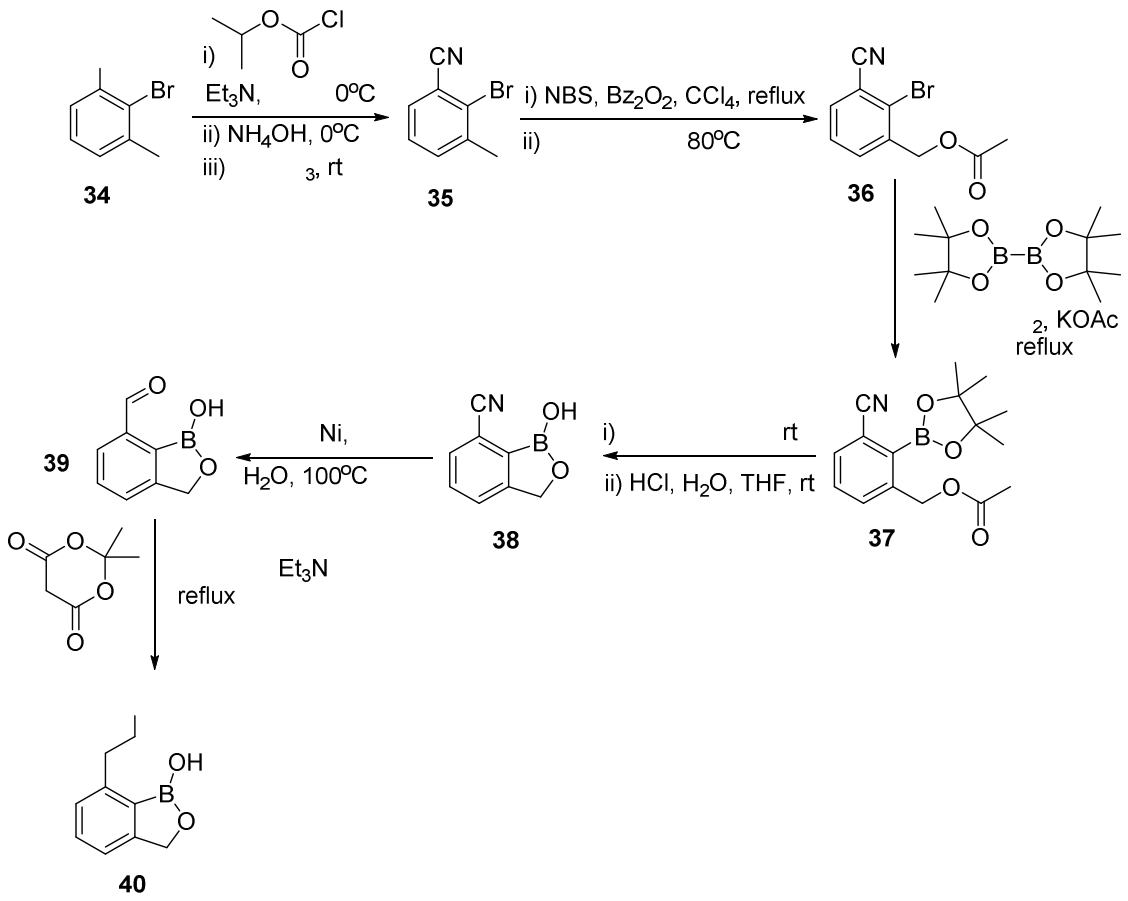
Scheme-1.11:Chalcone−benzoxaborole hybrid molecules as potent anti-trypanosomal agents

2-bromo-5-fluorobenzaldehyde was reduced to alcohol with sodium borohydride in methanol. The hydroxy group was protected as the methoxymethyl ether (MOM) and treated with butyllithium at -78℃, in presence of B-phenylboronic acid ethylene glycol ester to obtain the borinic acid **32**. The protecting group was removed under acidic conditions and the free alcohol spontaneously cyclized to give the target compound **33**.[6c] Some of these derivatives showed antifungal properties on *C. albicans* at a conc of 0.25 µg/mL and *C. neoformans* at 0.5 µg/mL(**Scheme 1.12**).



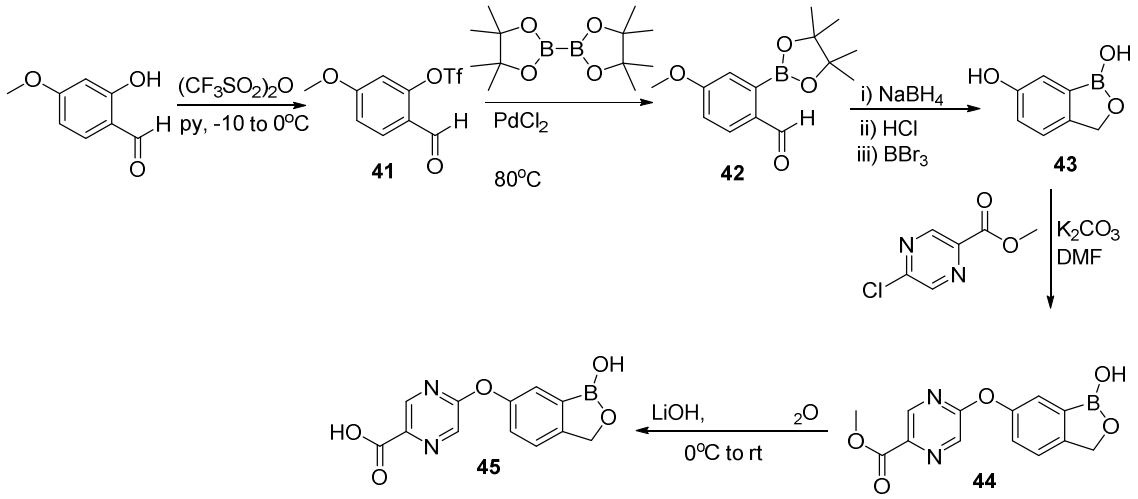
Scheme-1.12: Synthesis of AN2690 and its analogs for the potential treatment of onychomycosis

2-Bromo-3-methylbenzoic acid **34** was converted to cyano compound **35** by amide formation followed by dehydration. Benzylic bromination on the methyl group with NBS followed by nucleophilic substitution with potassium acetate afforded the acetate **36** that upon catalytic borylation with bispinacolatodiboron in the presence of Pd catalyst yielded the arylboronate **37**. Alkaline hydrolysis of the acetate followed by acidification generated the cyano benzoboroxole **38**. Treatment of **38** with Raney nickel in aqueous formic acid gave the aldehyde **39**. The target compound **40** was obtained by reacting the aldehyde with 2,2-dimethyl-1,3-dioxane-4,6-dione in the presence of HCOOH and triethylamine.[18] Some of these compounds were active against malaria parasite Plasmodium falciparum with IC_{50} values in the range of 0.026 µM (**Scheme 1.13**).



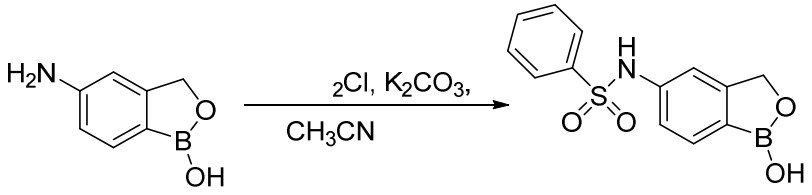
Scheme-1.13: Synthesis and structure–activity relationships of novel benzoxaboroles as a new class of antimalarial agents

2-Hydroxy-4-methoxybenzaldehyde was converted to triflate **41** via treatment with triflic anhydride. Catalytic borylation with bispinacolatodiboron provided compound **42**, which was reduced with $NaBH_4$ in methanol-THF and upon acid-catalyzed cyclization, was converted to 6-methoxy benzoxaborole **43**. Demethylation of **43** with BBr_3 followed by treatment with methyl 5-chloropyrazine-2-carboxylate in potassium carbonate and DMF afforded the ester **44**, which was further hydrolyzed in basic conditions to furnish the corresponding carboxylic acid **45**.[19] Some of these compounds showed activity on *E. cloacae* P99AmpC (MIC = 1–-2 µg/mL) and E. coli SYN2549 CMY-2 (MIC = <0.5 µg/mL) (**Scheme 1.14**).

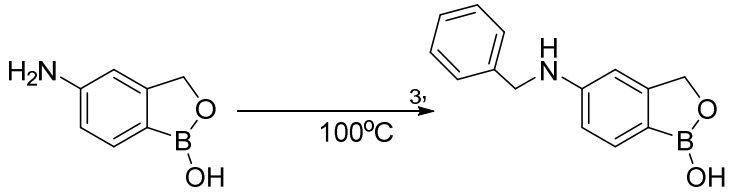


Scheme-1.14: Synthesis and SAR of novel benzoxaboroles as a new class of β-lactamase inhibitors

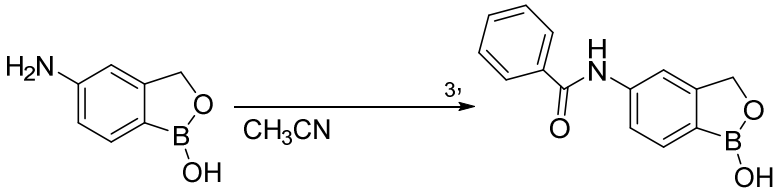
Coupling of 5-amino-benzoxaborole with phenylsulfonylchloride, benzyl bromide and benzoyl chloride provided corresponding sulfonamide, aminomethylene and amide respectively and these compounds showed growth inhibition in T. brucei with IC_{50} values ranging between 0.04-1.2 µg/mL (**Scheme 1.15**).[20]



T. brucei Growth Inhibition IC_{50} = 0.02 µg/mL



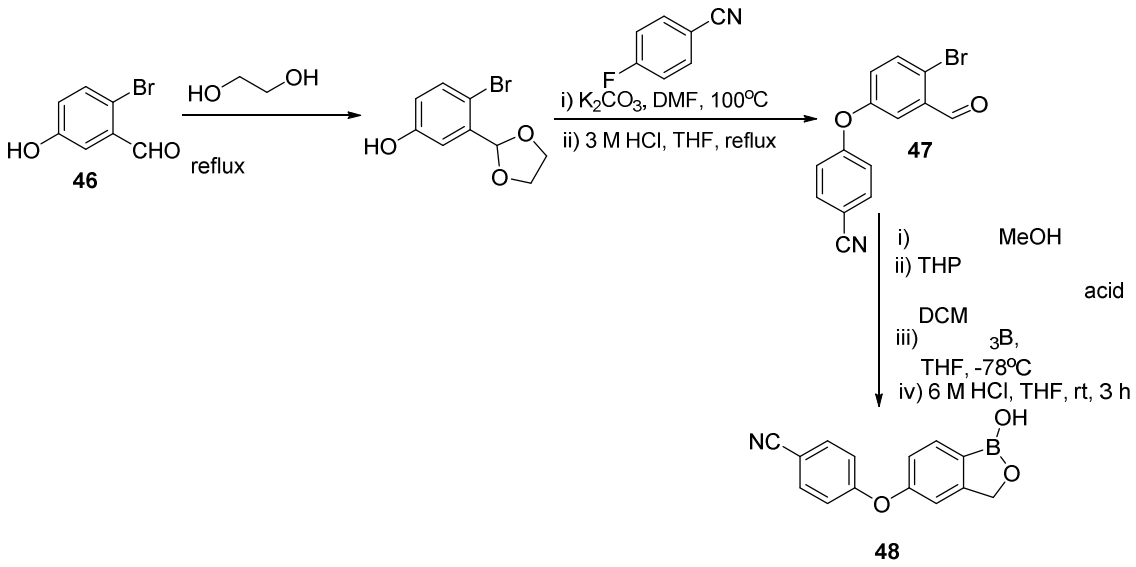
T. brucei Growth Inhibition IC_{50} = 1.21 µg/mL



T. brucei Growth Inhibition IC_{50} = 0.04 µg/mL

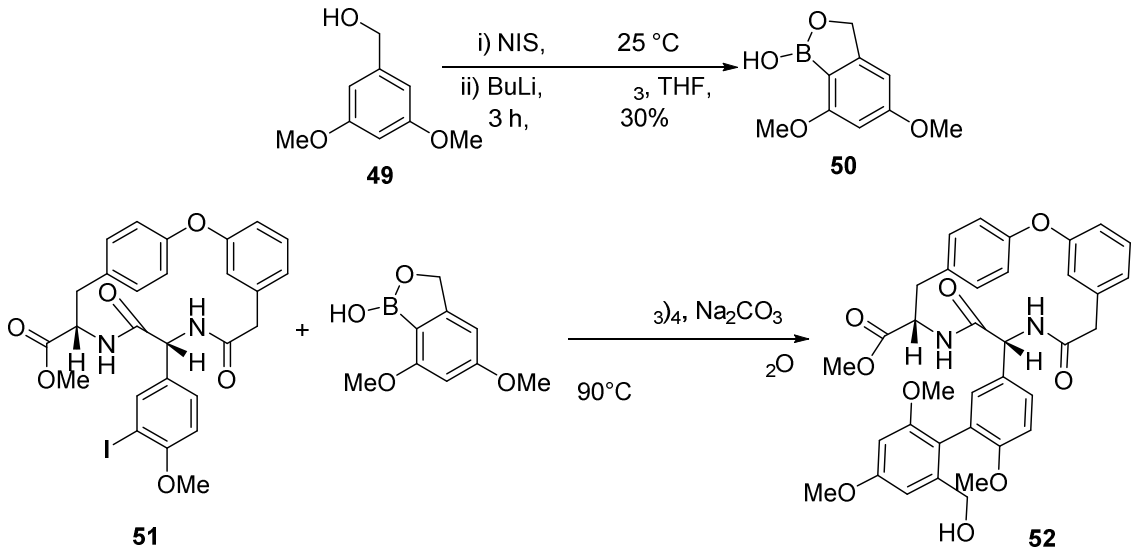
Scheme-1.15: Discovery of Novel Benzoxaborole-Based Potent Antitrypanosomal Agent

The aldehyde group of 2-bromo-5-hydroxybenzaldehyde **46** was protected with ethyleneglycol and treated with 4-fluorobenzonitrile to form 4-(4-bromo-3-formylphenoxy) benzonitrile **47**. Aldehyde **47** was reduced to alcohol using sodium borohydride and protected as a THP ether in presence of 3,4-dihydro-2H-pyran and camphorsulfonic acid. The boron atom was then introduced by halogen–metal exchange with n-butyl lithium using triisopropylborate, which upon reaction with HCl led to the deprotection of the THP acetal and the resultant alcohol spontaneously cyclized to afford 4-((1-hydroxy-1,3-dihydrobenzo [c][1,2]oxaborol-5-yl)oxy)benzonitrile **48** (**Scheme 1.16**).[21] This molecule showed activity against PDE4 (IC_{50} 0.49 µM) and TNF-α (IC_{50} 0.54 µM).



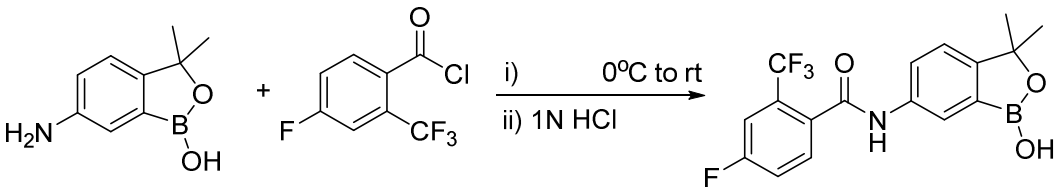
Scheme-1.16: Synthesis of anti-inflammatory agent (AN2728) for the potential topical treatment of psoriasis and atopic dermatitis

3,5-dimethoxybenzyl alcohol **49** was converted to corresponding benzoxaborole **50** by *N*-iodosuccinimide iodination followed by reaction with n-butyllithium and trimethoxyborate. Suzuki coupling of aryl iodide **51** with benzoxaborole **52** was facilitated by $Pd(PPh_3)_4$ catalyst in presence of sodium carbonate in methanol-toluene-water system at 90^oC (**Scheme 1.17**).[22]



Scheme-1.17: Suzuki coupling–macrolactamization approach to the *AB-COD* bicyclic system of vancomycin

6-amino-3,3-dimethyl-3H-benzo[c][1,2]oxaborol-1-ol acetate salt was treated with 2-trifluoromethyl-4-fluorobenzoyl chloride in presence of trimethylamine in DCM at 0^{o}C to afford SCYX-7158 (**53**) (**Scheme 1.18**), which showed activity against Trypanosoma brucei rhodesiense (IC_{50} = 0.294 µg/mL).[23]



Scheme-1.18: Synthesis of amidobenzoxaboroles

Owing to the importance of cyclic boronic acids, we undertook the project involving the development of novel methodologies for the synthesis of benzoxaboroles containing wide array of functional groups. Our results are reported in the succeeding chapters.

Chapter 2: Novel Methodologies for the Synthesis of Functionalized Benzoxaboroles

Introduction

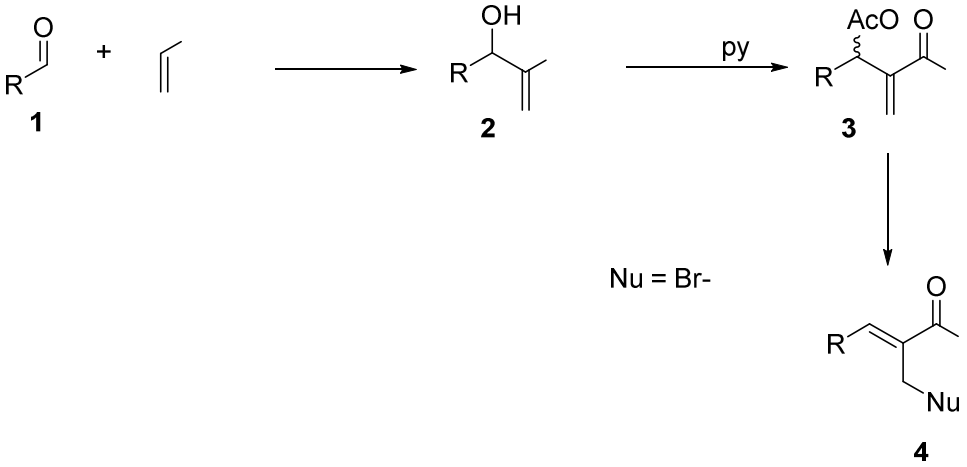
Being a relatively new compound, benzoxaborole has been utilized in synthetic methods and applications, but most of them involve tedious synthesis and in almost all the cases, boron has been introduced in the very last step. Apart from designing novel methods for the synthesis of benzoxaborole, we undertook the project due to its impressive application regime in medicial chemistry[24]. In this chapter, we describe the development of three convenient, flexible and novel protocols for the synthesis of densely functionalized benzoxaboroles based on Baylis-Hillman chemistry, Barbier allylation, and aldol reaction protocols. In all the cases, we used 2-formyl boroaldehyde, a commercial available compound as a synthon.

Results and Discussion

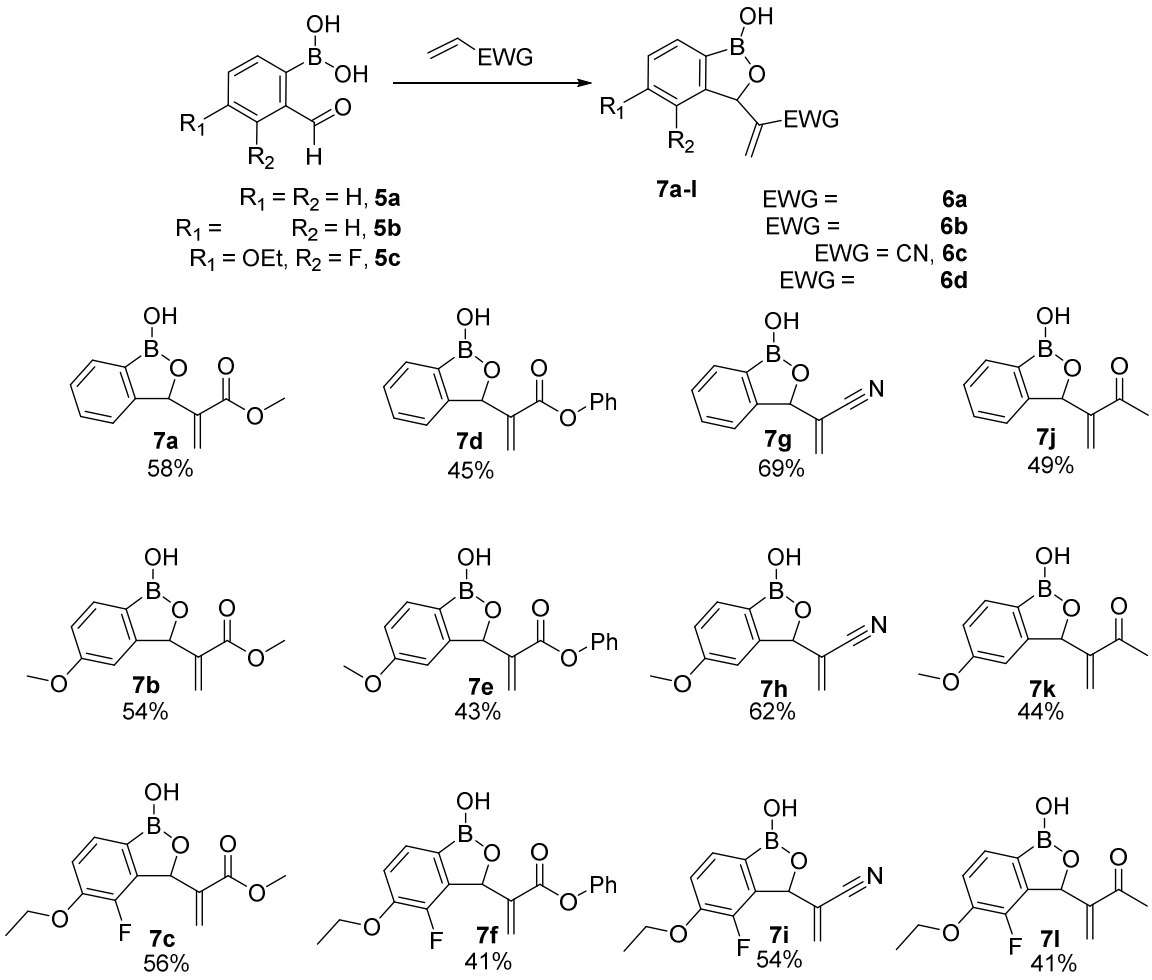
Baylis-Hillman (BH) reaction is one of the best reactions in introducing C-C bond coupling in one step[25]. This reaction is atom efficient and produces activated allyl alcohols which are highly useful in the isomerization upon reaction with several nucleophiles affording valuable synthons. BH reaction usually involves an aldehyde and electron deficient olefin in the presence of hindered tertiary amine like 1,4-diazabicyclo[2.2.2]octane (DABCO). These reactions usually don't require any solvent. In this case, we first utilized formylboronic acids **5a-c** as electrophiles and methyl acrylate **6a**, phenyl acrylate **6b,** acrylonitrile **6c**, methyl vinyl ketone **6d**, and acrolein **8** as electron deficient olefins. Aldehyde **5a** when reacted with 2 parts of methyl acrylate in presence of 10% DABCO resulted in poor yields of the desired product, leaving most of the unreacted starting material. The yield did not improve significantly even when doubling the amount of the catalyst DABCO. But, with stoichiometric amount of DABCO, compound **7a** was obtained with 58% yield after purification via silica gel column chromatography.

The above reaction with simple benzaldehyde usually requires more than a week for the completion. Similar reaction with 4-boronobenzaldehyde resulted in meagre yield even after two weeks. The increased rate of reactivity with 2-boronobenzaldehyde **5a** could be attributed to the activation of carbonyl oxygen via coordination with proximal Lewis acidic boronic acid group.

The other reactions with **5b-c** with methyl acrylate was even slower (5-7 days) because of the alkoxy substituents on the aromatic ring affording the products **7b-c** in 54% and 56% yields respectively. Similar reactions of **5a-c** with phenyl acrylate 6b yielded 41-45% of corresponding benzoxaboroles **7d-f** (**Scheme 2.1**).



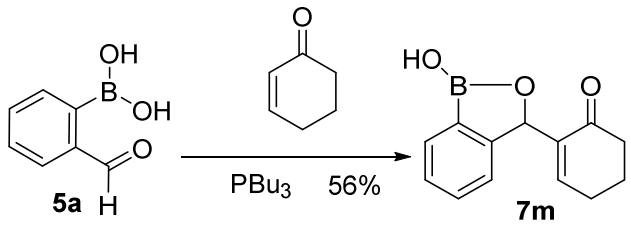
Scheme 2.0: Baylis-Hillman Reaction



Scheme 2.1. Baylis Hillman reaction of β-Boronoaldehydes

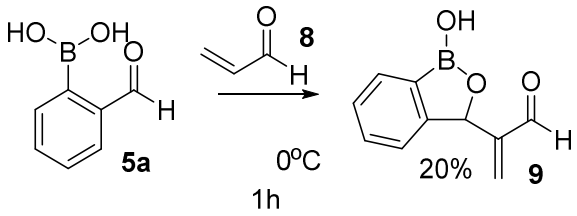
The similar BH reaction with better electron withdrawing group acrylonitrile **6c** was facile with all the boronoaldehydes **5a-c** and the products **7g-i** were obtained in moderate to good yields. Introduction of even stronger electron withdrawing groups resulted in poor yields of **7j-l** (41-49%) due to the higher polymerization rate of methyl vinyl ketone **6d** (**Scheme 2.1**).

We also carried out BH reaction with the aldehyde **5a** and cyclohexenone in presence of tributylphosphene to obtain **7m** in 56% yield (**Scheme 2.2**).



Scheme 2.2: Preparation of α-cyclohexenonyl benzoxaborole

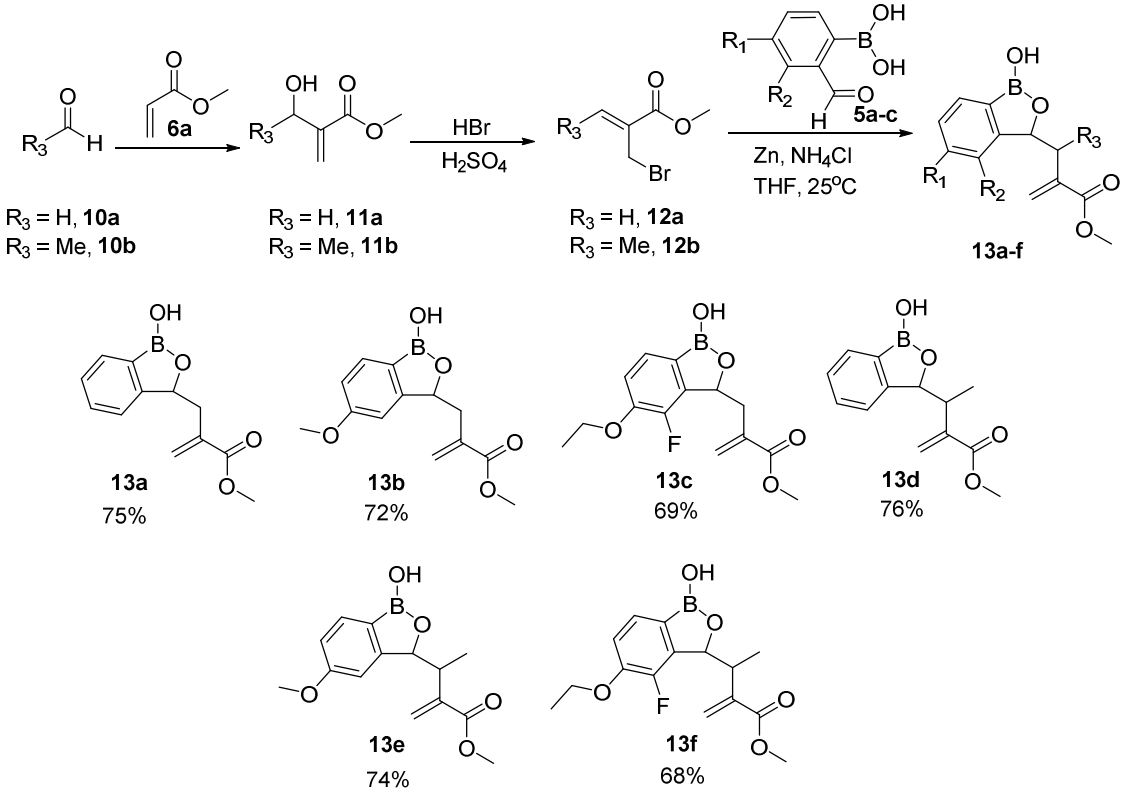
We also utilized acrolein **8**, with boronobenzaldehyde **5a** which resulted in **9** with only 20% yield with 60% of unreacted starting material. The low yield of **9** is due to the fact that acrolein is very sensitive monomer and susceptible for rapid polymerization. Longer reaction time or excessive acrolein resulted in polymerization of the acrolein and did not improve the yields. Hence the reaction was conducted in THF solvent at 0^{o} C to minimize the polymerization. (**Scheme 2.3**).



Scheme 2.3. Reaction of β-Boronoaldehydes with Acrolein

We have utilized Barbier type allylation, another C-C bond forming reaction involving allyl bromides and aldehydes in the presence of metals like

zinc and indium forming a complex with ammonium chloride to synthesize functionalized benzoboroxoles. We synthesized the BH derived bromides **12a-b** by treating the corresponding aldehydes **10a** and **10b** with methyl acrylate **6a** to form allylic alcohols **11a-b**, followed by the reaction with HBr-H_2SO_4. These bromides were then utilized for allylation of boronobenzaldehydes **5a-c** using Barbier allylation conditions to obtain homologated benzoxaboroles **13a-f** in decent yields (**Scheme 2.4**). As expected, products had predominantly *syn* stereochemistry. The relative configuration was confirmed by single crystal X-ray analysis of **13d** (**Figure 2**).



Scheme 2.4. Synthesis of Homologated 0Benzoxaboroles

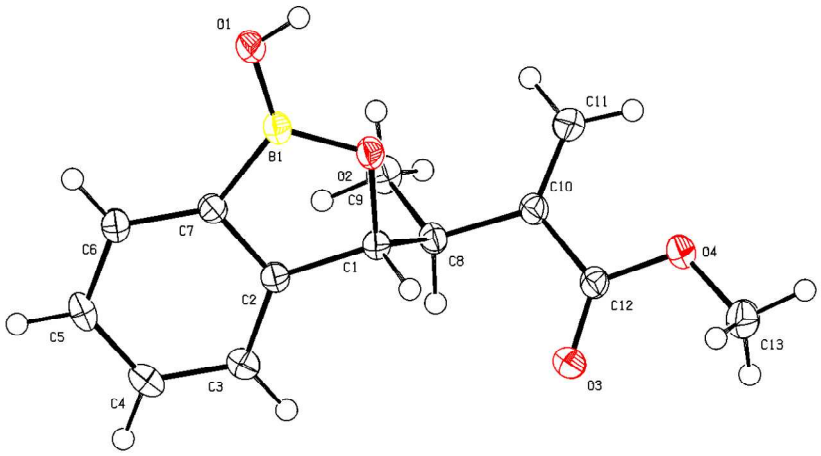
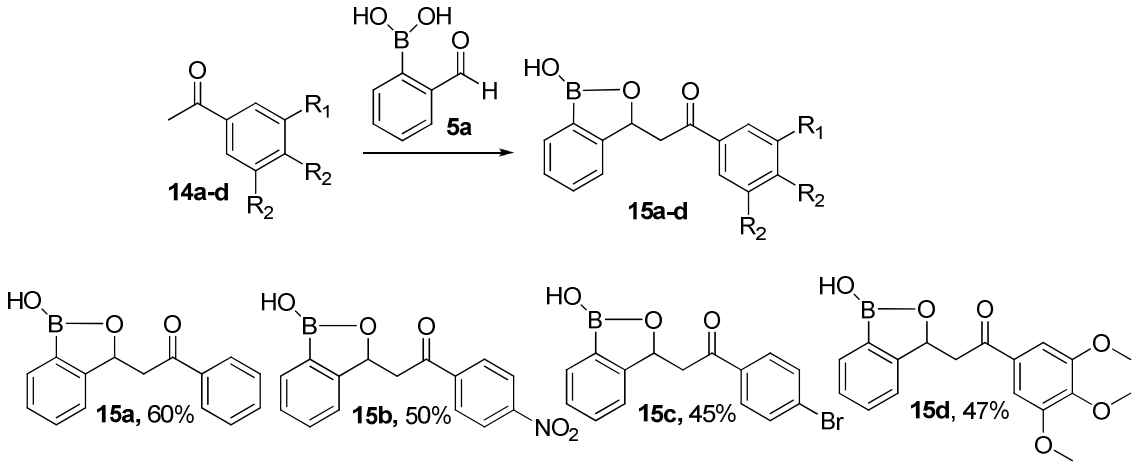


Figure 2. X-ray Crystal Structure of **13d**

We have also utilized aldol reaction with boronobenzaldehyde **5a** and methyl ketones **14a-d** to obtain β-ketobenzoxaboroles **15a-d**. With bases such as sodium hydride, sodium hydroxide, etc., the reaction did not go to completion and the product was impure. When LDA is used at -78^{o} C to generate enolate, the reaction resulted in aldol product **15a** in 60% yield (brsm) (**Scheme 2.5**). Other substituted acetophenones such as *p*-nitroacetophenone, *p*-bromoacetophenone, and 3,4,5-trimethoxyacetophenone upon reaction with 2-boronobenzaldehyde resulted in corresponding products **15b-d**. Irrespective of the amount of base used, the reaction was still incomplete with ~30-50% of starting material left. Benzoxaboroles **15e-g** were obtained upon similar reaction using acetone, dimethyl and diethyl malonates with boronobenzaldehyde **6a** which resulted in 40-62% yields (**Figure 3**).



Scheme 2.5: Synthesis of β-ketobenzoxaboroles

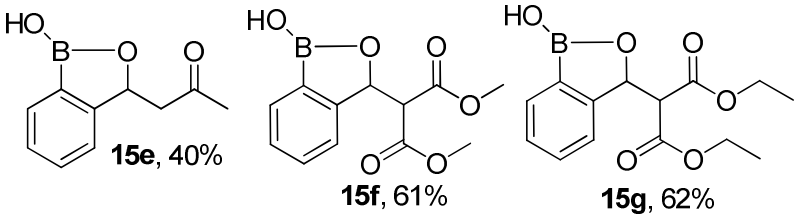


Figure 3: β-Ketobenzoxaboroles via aldol reaction

All the synthesized compounds were tested for their antimicrobial efficacy as well as general cytotoxicity. None of the compounds exhibited any biological activity. This concludes that the substitution of carbon on the benzylic carbon of benzoxaborole lead to the loss of activity.

Experimental Procedures

1. Representative procedure for the preparation of benzoxaboroles via Baylis-Hillman reaction 7a-l: To a stirred suspension of 2-boronobenzaldehyde **5a** (0.3 g, 2.0 mmol) and methyl acrylate **6a** (0.7 mL, 8.0 mmol) was added DABCO (224 mg, 2.0 mmol) and stirred for 2 days at room temperature. Upon completion (TLC), the reaction mixture was quenched with dilute HCl and worked up with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified via silica gel column chromatography (hexane:acetone, 3:1) to obtain 0.25 g (58%) of benzoboroxole **7a** as a white powder. *mp*: 91-93^oC, (Found: C, 60.62%; H, 5.25%; $C_{12}H_{13}BO_4$ requires: C, 60.60%; H, 5.09%); ^1H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.70-7.72 (m, 1H), 7.40-7.44 (m, 1H), 7.25-7.35 (m, 2H), 6.16 (s, 1H), 5.93 (s, 1H), 5.79-5.80 (m, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 155.5, 140.6, 131.5, 131.2, 128.1, 126.6, 122.3, 79.3, 52.5; ESI-MS: 217 [$(M-H)^+$, 100%].

2. Representative procedure for the preparation of benzoxaboroles via Barbier reaction 13a-f: To a stirred solution of 2-boronobenzaldehyde **5a** (0.3 g, 2.0 mmol) and zinc (0.19 g, 3.0 mmol), in THF (5.0 mL) was added methyl α-bromomethylacrylate **12a** (0.72 g, 4.0 mmol), and saturated NH_4Cl (1 mL) and stirred overnight at room temperature. Upon completion (TLC), the reaction mixture was filtered over celite, and worked up with water and ethyl acetate (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in*

vacuo, and purified via silica gel column chromatography (hexane:acetone, 3:1) to obtain 0.35 g (75%) of benzoboroxole **13a** as a viscous liquid. (Found: C, 62.01%; H, 5.52%; $C_{12}H_{13}BO_4$ requires: C, 62.11%; H, 5.65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.41-7.45 (m, 1H), 7.29-7.36 (m, 2H), 6.12 (d, *J* = 1.2 Hz, 1H), 5.69 (d, *J* = 1.2 Hz, 1H), 5.26 (dd, *J* = 4.0, 8.4 Hz, 1H), 3.64 (s, 3H), 2.89 (dd, *J* = 8.4, 14.4 Hz, 1H), 2.39 (dd, *J* = 8.4, 14.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 156.8, 136.9, 131.2, 131.1, 128.2, 127.9, 122.2, 79.1, 52.5, 39.2; ESI-MS: 231 $(M-H)^+$, 189 (100%).

3. Representative procedure for the preparation of benzoxaboroles via aldol reaction 15a: To a stirred solution of acetophenone **14a** (10 mmol) in 20 mL THF was added LDA (12 mmol) at -78^{o}C and stirred for 1 h. A solution of 2-boronobenzaldehyde **5a** (9 mmol) in 5 mL THF was added to the reaction at -78^{o}C, and stirred overnight at room temperature. Upon completion (TLC), the reaction was quenched with NH_4Cl and worked up with ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified by silica gel column chromatography to obtain the pure benzoxaborole **15a** in 60% yield. ^{1}H NMR (500 MHz, DMSO-d6): δ 9.21 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.65-7.68 (m, 1H), 7.48-7.57 (m, 4H), 7.37-7.40 (m, 1H), 5.71 (dd, *J* = 4.0, 8.8 Hz, 1H), 3.58 (dd, *J* = 3.5 Hz, 17.5 Hz, 1H), 3.34 (dd, *J* = 8.5 Hz, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 198.6, 157.5, 137.7, 134.3, 131.6, 131.4, 129.7, 129.2, 128.2, 122.5, 77.7, 46.3; ESI-MS: 251 [$(M-H)^+$, 100%].

Antimicrobial Assay

Due to their importance as antimicrobial agents, the synthesized molecules have been evaluated for their activity as antibacterial and antifungal agents. For initial testing, *Pseudomonas aeruginosa* and *Streptococcus thermophiles* have been selected as gram negative and gram positive bacterial strains respectively. For antifungal activity, we chose *Candida albicans* and *Aspergillus niger*. Standard Kirby-Bauer disk susceptibility method was used for all the species. Mueller Hinton agar plates were used to grow the colonies of microbes. The microbial suspension was inoculated onto the agar plates and the sterile disc saturated with 20 µL test compound was placed on the plate. The final concentration of the compound was maintained at 5 and 1 µg/disc. These plated were incubated at 37^{o} C for 24-48 hours. The diameter of the zone of inhibition was measured in millimeters using calipers to determine the antimicrobial activity. None of the synthesized compounds showed any antimicrobial activity compared to compound **1**, which exhibited moderate activity.

Cytotoxicity Assay

These compounds were also tested for their toxicity on MCF-7 breast cancer cell line using sulforhodamine-B assay. Briefly, 5×10^4 cells/mL were plated in a 48-well plate and incubated for 18-24 hours. The test compounds were dissolved in DMSO and added to the wells and incubated for 3 more days. The growth media

was removed on the third day and the wells were washed with 1% phosphate buffered saline solution. The wells were dried and the SRB in 1% acetic acid was added. The plate was incubated for ~45 minutes and the wells were dried and dissolve in tris base (10mM, pH 10.2). The absorbance was recorded at 540nm, which gives the % survival of the cells. The assay was carried out in triplicates. All the compounds were tested at 100 and 50 µM. None of the synthesized compounds were toxic even at 100 µM concentration. This concludes that these molecules are generally non-toxic in nature.

Conclusions

In conclusion, we have successfully devised three methodologies using boronobenzaldehyde to synthesize functionalized benzoboroxoles via Baylis-Hillman, Barbier-type allylation and Aldol chemistry. These protocols can be applied in the synthesis of various benzoboroxoles in large scale. The synthesized molecules were evaluated for their antimicrobial efficacy. These methodologies can be used to develop synthons for various synthetic products.

Chapter 3: Boric Acid Mediated Synthesis of α-Hydroxyamides and Synthesis of Benzoxaboroles via Passerini Reaction

Introduction

Boric acid, usually available in nature in the form of borax and boracite. It is used for industrial as well as household purposes due to its non-toxic nature and it is very inexpensive. Hence, it is usually considered as a green material[26]. Various borates and organoboranes can be synthesized starting from boric acid. Due to the vacant orbital, it can be used as a mild Lewis acid catalyst in several organic reactions[27].

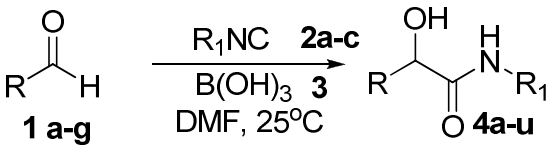
Passerini and Ugi reactions are well-studied multicomponent coupling reactions involving aldehyde/imine, acid and isonitrile[28]. α-Hydroxyamides can be easily oxidized to prepare keto acids/amides which are biologically relevant since pyruvic acid is one of the important metabolites in glycolysis. Hence, α-Hydroxyamides are important synthons for the synthesis of various agents in medicinal chemistry[29]. In this chapter, we have developed a novel methodology for the synthesis of several α-hydroxyamides using boric acid as a catalyst for the addition of isonitriles on to carbonyl compounds[30].

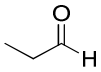
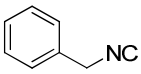
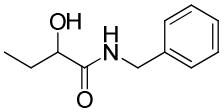
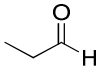
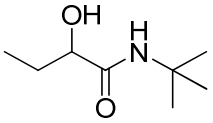
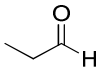
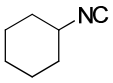
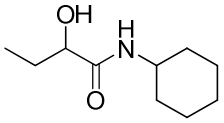
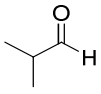
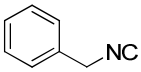
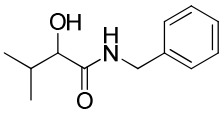
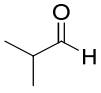
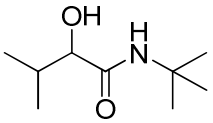
Results and Discussion

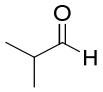
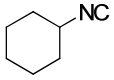
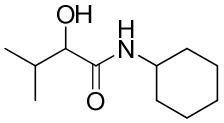
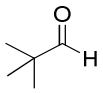
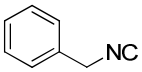
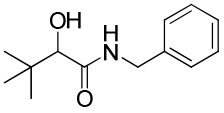
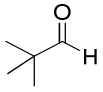
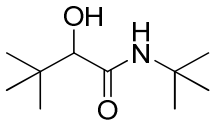
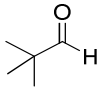
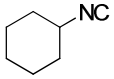
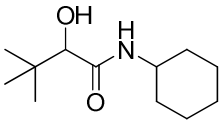
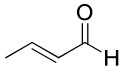
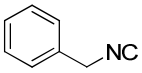
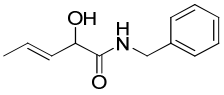
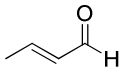
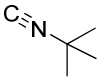
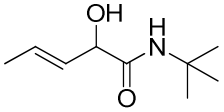
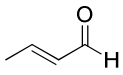
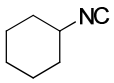
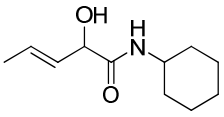
We envisioned the usage of boric acid to couple isonitriles and aldehydes to synthesize α-hydroxyamides. For this purpose, benzyl, cyclohexyl and tert-butyl isonitriles **2a-c** were taken as representative examples for isonitriles. Aldehydes **1a-g** containing aliphatic, aromatic and heterocycles were utilized. For initial purposes, propionaldehyde and benzyl isonitrile were utilized for the optimization. Solvent study was conducted to figure out the suitable solvent for the reaction with maximum yield. Different solvents such as THF, CH_2Cl_2, EtOAc, DMF, DMSO, Dioxane, MeOH and water were used. The amount of boric acid was varied in each reaction to obtain decent yield. DMF and 1 equivalent of boric acid were found to provide α-hydroxyamides with good yields. The reaction with aliphatic aldehydes and aliphatic isonitriles was found to be fast with the generation of small amount of heat whereas the reactions with aromatic systems tended to be relatively slow.

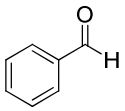
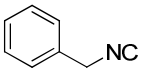
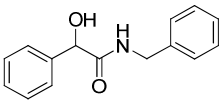
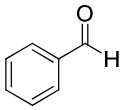
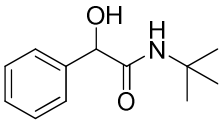
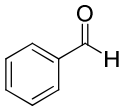
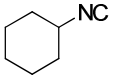
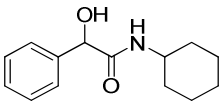
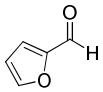
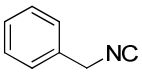
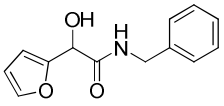
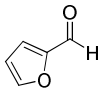
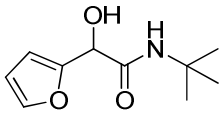
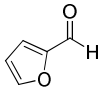
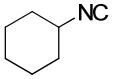
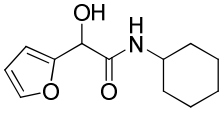
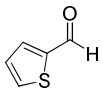
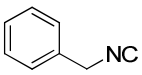
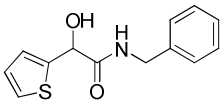
Similar reactions were performed replacing the aldehyde with ketones such as 3-pentanone and acetophenone. In this case, the reactions did not produce the product in acceptable yields even when the boric acid is increased to two equivalents at 80^o C.

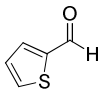
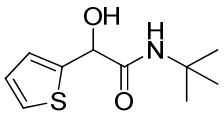
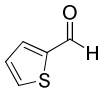
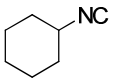
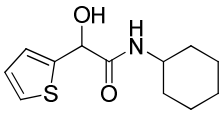
Table 1. Boric acid mediated addition of isonitriles and aldehydes for the synthesis of α-hydroxyamides.



Entry	Aldehyde	Isonitrile	Product	Yield
1				78%
2				74%
3				75%
4				70%
5				71%

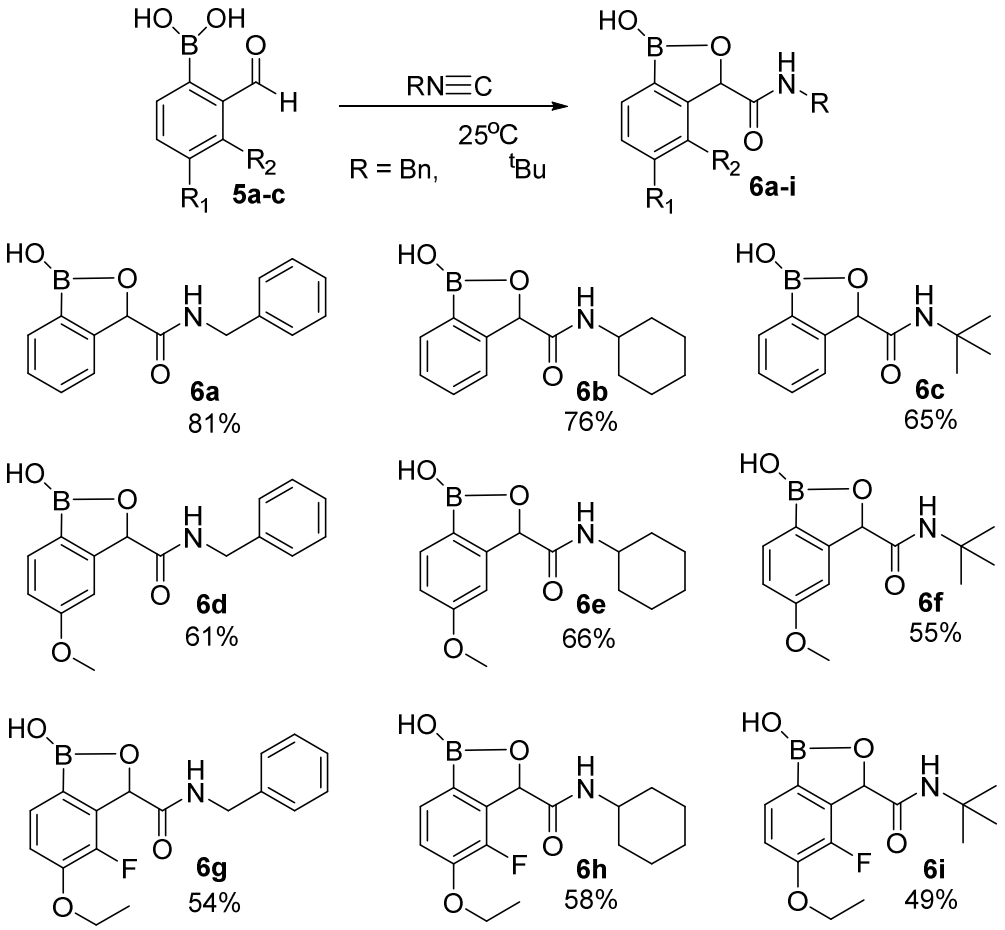
6				74%
7				61%
8				64%
9				72%
10				78%
11				74%
12				72%

13				82%
14				76%
15				80%
16				65%
17				68%
18				67%
19				75%

20				72%
21				78%

We then explored this method by replacing simple aldehydes with 2-formyl phenylboronic acid **5**. Due to the presence of borinic acid group ortho to aldehyde, we expected that **5** could self-catalyze the reaction with isonitrile. To our surprise, the reaction progressed and benzoxoborole was formed in 84% yield by dehydration. This was evident by the characteristic peak of B-OH at ~9ppm in ^{1}H-NMR.

In a similar way, benzoboroxoles **6b** and **6c** were obtained upon reaction of **5** with isonitriles **2b** and **2c** respectively (**Scheme 3.1**). Also, products **6a-l** were synthesized by the reaction of aldehydes **5a-c** with isonitriles **2a-c** (**Scheme 3.1**).[31]



Scheme 3.1: Synthesis of functionalized benzoxaboroles.

The above synthesized structural entities can be utilized in the applications of material chemistry as well as synthetic chemistry as these compounds act as intermediates for Suzuki cross coupling reactions.[32]

Experimental Procedures

1. Representative procedure for the preparation of hydroxyamide 4a: To a stirred solution of propion-aldehyde **1a** (0.14 mL, 2.0 mmol) in 2mL DMF was added benzyl isonitrile **2a** (0.24 mL, 2.0 mmol), and boric acid (0.12 g, 2.0 mmol) and stirred overnight at room temperature. Upon completion (TLC), the reaction mixture was worked up with water and diethyl ether (3 x 25 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (silica gel, hexane:acetone, 4:1) to obtain 0.30 g (78%) of hydroxy amide **4a**. ^{1}H NMR (500 MHz, $CDCl_3$): 7.22-7.32 (m, 5H), 7.18 (bs, 1H), 4.47 (t, *J* = 4.5 Hz, 1H), 4.42 (dd, *J* = 4.0, 15.0 Hz, 1H), 4.36 (dd, *J* = 4.0, 15.0 Hz, 1H),4.05-4.08 (m, 1H), 1.78-1.90 (m, 1H), 1,62-1.72 (m, 1H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 174.5, 138.2, 128.9, 127.9, 127.7, 73.2, 43.3, 28.1, 9.4; ESI-MS: 216 [$(M+Na)^+$, 100%], 194 $(M+H)^+$.

2. Represenative procedure for the preparation of benzoxaborole 6c: To a stirred solution of boronoaldehyde **5** (0.3 g, 2.0 mmol) in 2mL DMF was added *tert*-butyl isonitrile (0.23 mL, 2.0 mmol), and stirred overnight at room temperature. Upon completion (TLC), the reaction mixture was worked up with water and ethyl acetate (3 x 25 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified by column chromatography (silica gel, hexane:ethyl acetate, 3:1) to obtain 0.30 g (65%) of benzoxaborole **6c**. (Found: C, 61.53; H, 8.10; N, 6.02 %; $C_{12}H_{16}BNO_3$ requires: C, 61.84; H, 6.92; N, 6.01%); ^{1}H NMR (500 MHz, DMSO-d6): 9.33 (bs, 1H), 7.67 (d, *J* = 7.2 Hz, 1H),

7.62 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 6.52 (s, 1H), 5.27 (s, 1H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 169.4, 152.3, 131.3, 130.8, 128.1, 122.9, 80.2, 51.1, 28.9; ESI-MS: 232 [$(M-H)^+$, 100%].

Conclusions

In conclusion, we have introduced a novel methodology for the synthesis of α-hydroxyamides using boric acid as catalyst upon the α-addition of isonitriles to aldehydes. We have also extended this protocol for the synthesis of functionalized benzoxaboroles via intramolecular cyclization utilized Passerini type multicomponent coupling reaction. These synthesized compounds act as excellent synthons and intermediates for the applications in organic and medicinal chemistry.

Overall conclusion

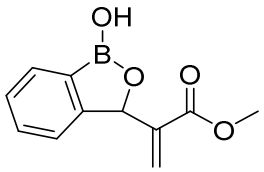
As these compounds did not exhibit any antimicrobial efficacy or cytotoxicity, they can be used for boron neutron capture therapy (BNCT) since this these compounds mimic glycolytic metabolites such as fructose.

Boron neutron capture therapy is a binary therapy in which, the tumor cells are loaded with high concentration of ^{10}B and later activated by applying a radiation field of low energy neutrons. ^{10}B is non-radioactive and is present in 20% of natural boron. Neutron capture results in the formation of excited ^{11}B nuclei, which then undergo fission to produce high linear energy transfer (LET) particles such as α- ($^{4}He_2$), $^{7}Li_3$ and γ-particles. Cell death is triggered by the release of these heavily charged particles (He and Li) that create ionization tracks along their trajectories.

$$^{10}B_5 + {}^{1}n_0 \text{ ----------> } {}^{4}He_2 + {}^{7}Li_3 + 2.3 \text{ MeV}$$

Binding studies and boron accumulation studies have to be carried out to determine the potency of these compound for their use in BNCT.

Spectral Characterization

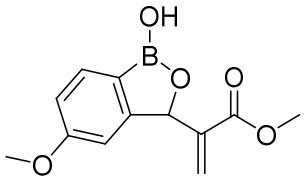


7a

Methyl 2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)acrylate 7a: yield = 58%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 6.20 (s, 1H), 5.98 (s, 1H), 5.84 (s, 1H), 3.72 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 166.2, 155.6, 140.8, 131.5, 131.3, 128.1, 126.6, 122.3, 79.3, 52.6

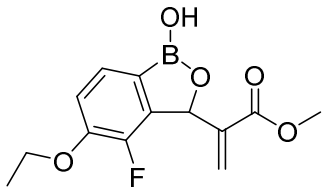


7b

Methyl 2-(1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)acrylate 7b: yield = 54%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.63 (d, *J* = 8 Hz, 1H), 6.94 (d, *J* = 8 Hz, 1H), 6.80 (s, 1H), 6.19 (s, 1H), 5.89 (s, 1H), 5.81 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 166.3, 162.5, 157.9, 140.8, 132.6, 126.6, 115.1, 107.2, 78.8, 55.8, 52.6

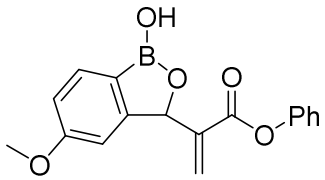


7c

Methyl 2-(5-ethoxy-4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylate 7c: yield = 56%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.52 (d, *J* = 7 Hz, 1H), 7.19 (t, *J* = 5 Hz, 1H), 6.22 (s, 1H), 6.04 (s, 1H), 5.89 (s, 1H), 4.17 (q, *J* = 6 Hz, 2H), 3.70 (s, 3H), 1.38 (t, *J* = 6 Hz, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 165.8, 144.3, 142.8, 140.6, 139.3, 128.6, 127.7, 115.9, 76.8, 65.3, 52.6, 15.3

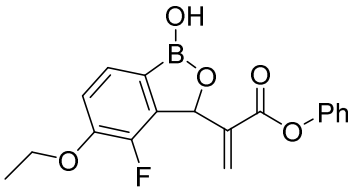


7e

Phenyl 2-(1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylate 7e: yield = 48%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.44 (t, *J* = 8 Hz, 2H), 7.29 (t, *J* = 7 Hz, 1H), 7.12 (d, *J* = 9 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.88 (s, 1H), 6.49 (s, 1H), 6.08 (s, 1H), 6.00 (s, 1H), 3.78 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 164.5, 162.6, 157.9, 150.9, 140.2, 132.6, 130.3, 129.2, 126.8, 122.3, 115.3, 107.1, 79.1, 55.9



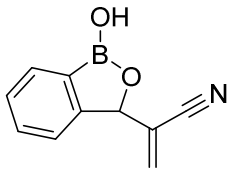
7f

Phenyl 2-(5-ethoxy-4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) acrylate 7f: yield = 41%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.40 (s, 1H), 7.50 (d, *J* = 8 Hz, 3H), 7.44 (t, *J* = 8 Hz, 2H), 7.30 (t, *J* = 8 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 2H),

6.55 (s, 1H), 6.18 (s, 1H), 6.08 (s, 1H), 4.187(q, *J* = 7 Hz, 2H), 1.37 (t, *J* = 7 Hz, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 164.1, 150.8, 138.9, 130.9, 130.3, 126.8, 122.3, 116.0, 77.0, 65.4, 15.3

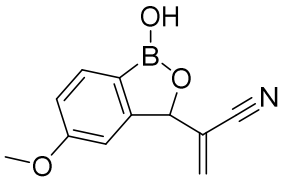


7g

2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)acrylonitrile 7g: yield = 69%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.63 (s, 1H), 7.80 (d, *J* = 7 Hz, 1H), 7.56 (t, *J* = 7 Hz, 1H), 7.46 (t, *J* = 7 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 6.49 (s, 1H), 6.32 (s, 1H), 5.87 (s, 1H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 153.0, 134.3, 131.8, 131.2, 128.8, 124.0, 122.4, 116.5, 80.2

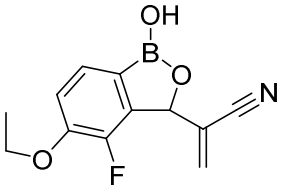


7h

2-(1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)acrylonitrile 7h: yield = 62%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 6.47 (s, 1H), 6.32 (s, 1H), 5.78 (s, 1H), 3.80 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 162.9, 155.8, 134.6, 132.8, 124.2, 116.8, 116.3, 107.1, 80.1, 56.0

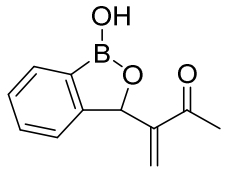


7i

2-(5-ethoxy-4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)acrylonitrile 7i: yield = 54%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.65 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.50 (s, 1H), 6.39 (s, 1H), 6.01 (s, 1H), 4.18 (q, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7 Hz, 1H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 149.5, 149.2, 148.0, 145.0, 139.3, 139.2, 135.6, 128.2, 128.1, 122.9, 117.0, 116.5, 79.9, 77.6, 65.5, 15.2

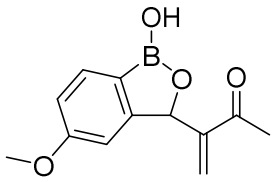


7j

3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)but-3-en-2-one 7j: yield = 49%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.38 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 3H), 7.35 (t, *J* = 7 Hz, 1H), 7.20 (d, *J* = 7 Hz , 1H), 6.28 (s, 1H), 6.05 (s, 1H), 5.90 (s, 1H), 2.39 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 199.9, 156.4, 148.4, 131.5, 131.3, 128.0, 126.8, 122.5, 78.1, 27.3

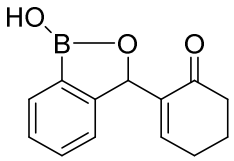


7k

3-(1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)but-3-en-2-one 7k: yield = 44%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.63 (d, *J* = 8 Hz, 1H), 6.92 (d, *J* = 8 Hz, 1H), 6.72 (s, 1H), 6.28 (s, 1H), 6.98 (s, 1H), 5.89 (s, 1H), 3.74 (s, 1H), 2.40 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 200.0, 162.5, 158.8, 148.5, 132.6, 126.8, 115.0, 107.4, 77.7, 55.8, 27.3



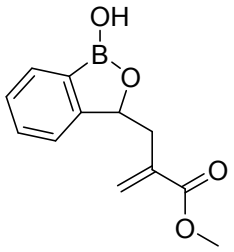
7m

2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)cyclohex-2-en-1-one

7m: yield = 56%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.71 (d, *J* = 7 Hz, 1H), 7.42 (t, *J* = 7 Hz, 1H), 7.33 (t, *J* = 7 Hz, 1H), 7.22 (d, *J* = 7 Hz, 1H), 6.82 (t, *J* = 4 Hz, 1H), 5.98 (s, 1H), 2.42 (t, *J* = 7 Hz, 2H), 2.34 (m, 2H), 1.89 (m, 2H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 198.7, 157.0, 147.1, 139.0, 131.5, 131.1, 127.8, 122.5, 77.4, 25.8, 22.9

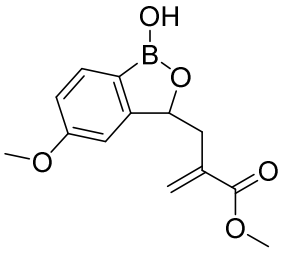


13a

Methyl 2-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl)acrylate 13a: yield = 75%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.17 (s, 1H), 7.71 (d, *J* = 7 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.17 (s, 1H), 5.76 (s, 1H), 5.31 (dd, *J* = 7 Hz, 1H), 3.98 (s, 3H), 2.94 (d, *J* = 14.5, 1H), 2.43 (dd, *J* = 8.5 Hz, 1H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 157.4, 156.8, 137.1, 131.2, 128.2, 127.9, 122.2, 79.2, 52.5,

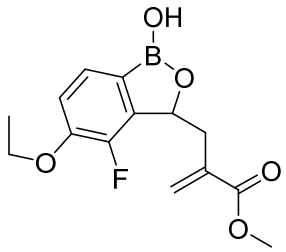


13b

methyl 2-((1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl) acrylate 13b: yield = 72%

^{1}H NMR (500MHz, DMSO-d_6) δ 8.96 (s, 1H), 7.58 (d, *J* = 8 Hz, 1H), 6.94 (s, 1H), 6.91 (d, *J* = 8 Hz, 1H), 6.16 (s, 1H), 5.76 (s, 1H), 5.22 (dd, *J* = 4 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 2.94 (dd, *J* = 6 Hz, 1H), 2.40 (dd, *J* =, 1H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 167.6, 162.4, 159.4, 137.2, 132.4, 128.1, 115.3, 106.8, 78.8, 55.9, 52.5

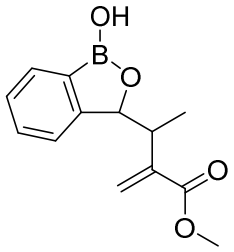


13c

Methyl 2-((5-ethoxy-4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl) methyl)acrylate 13c: yield = 69%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.43 (d, *J* = 8 Hz, 1H), 7.17 (t, *J* = 7 Hz, 1H), 6.14 (s, 1H), 5.71 (s, 1H), 5.44 (dd, *J* = 2.5, 8, 1H), 4.15 (q, *J* = 6.5 Hz, 2H), 3.66 (s, 3H), 3.03 (d, *J* = 12 Hz, 1H), 2.47 (dd, *J* = 8.5 Hz, 14.5, 1H), 1.36 (t, *J* = 6 Hz, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 167.4, 149.1, 147.7, 145.8, 142.6, 142.5, 136.6, 128.6, 127.7, 115.9, 76.5, 65.3, 52.5, 15.3

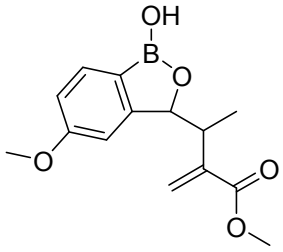


13d

Methyl 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)-2-methylene butanoate 13d: yield = 76%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.24(s, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.48 (t, *J* = 6 Hz, 1H), 7.36 (t, *J* = 7 Hz, 2H), 6.30 (s, 1H), 5.84 (s, 1H), 5.28 (s, 1H), 3.75 (s, 3H), 3.16(q, *J* = 3.5, 1H), 0.67 (d, *J* = 7 Hz, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 156.0, 143.0, 131.5, 131.1, 127.4, 126.4, 121.9, 81.9, 52.7, 39.7, 39.3, 12.4

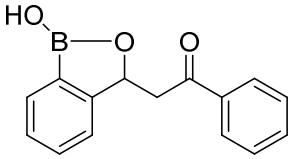


13e

Methyl 3-(1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)-2-methylenebutanoate 13e: yield = 74%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.61 (d, *J* = 8 Hz, 1H), 6.93 (dd, *J* = 2, 8 Hz, 1H), 6.89 (s, 1H), 6.29 (s, 1H), 5.85 (s, 1H), 5.21 (d, *J* = 3 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.17-3.3.13 (m, 1H), 0.68 (d, *J* = 7 Hz, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 162.6, 158.6, 143.1, 132.4, 126.3, 115.2, 106.5, 81.6, 55.9, 52.7, 39.2, 31.4, 12.3



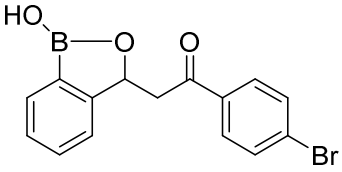
15a

2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)-1-phenylethan-1-one

15a: yield = 60%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.03 (dd, *J* = 1, 7.5, 2H), 7.74 (d, *J* = 7.5, 1H), 7.68-7.65 (m, 1H), 7.56-7.48 (m, 4H), 7.40-7.37 (m, 1H), 5.71 (dd, *J* = 3.75, 8.75, 1H), 3.63-3.55 (m, 1H), 3.38-3.33 (m 1H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 198.1, 157.0, 137.2, 133.8, 131.2, 130.9, 130.8, 129.2, 128.7, 127.7, 122.0, 77.3, 70.6, 45.8

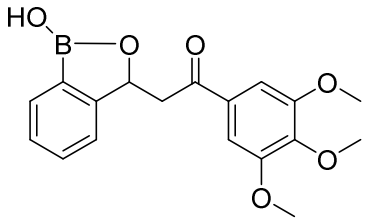


15c

1-(4-bromophenyl)-2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)ethan-1-one 15c: yield = 45%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.2 (s, 1H), 7.95 (d, *J* = 8, 2H), 7.76-7.72 (m, 3H), 7.51-7.38 (m, 3H), 5.68 (dd, *J* = 3.5, 5, 1H), 3.58 (dd, *J* = 3.5, 17, 1H), 3.33 (dd, *J* = 9, 17, 1H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 197.0, 157.1, 153.6, 142.4, 132.6, 131.1, 130.9, 127.7, 122.1, 106.3, 77.3, 60.6, 56.5, 45.6

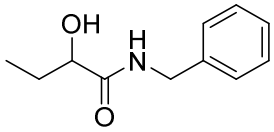


15d

2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)-1-(3,4,5-trimethoxyphenyl)ethan-1-one 15d: yield = 47%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.2 (s, 1H), 7.74 (d, *J* = 7, 1H), 7.52 (t, *J* = 7.75, 2H), 7.38 (t, *J* = 7, 1H), 7.31 (s, 2H), 5.71 (dd, *J* = 4, 8.5, 1H), 3.86 (s, 3H), 3.76 (s, 6H), 3.47 (m, 2H)

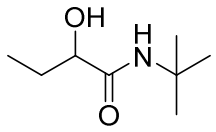
^{13}C NMR (125 MHz, DMSO-d_6) δ 197.0, 157.1, 153.3, 142.4, 132.6, 131.1, 130.9, 127.7, 122.1, 106.3, 77.3, 60.6, 56.5, 45.6



1

***N*-benzyl-2-hydroxybutanamide 1:** yield = 78%

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 138.2, 129.0, 127.9, 127.8, 73.2, 43.3, 28.0, 9.4

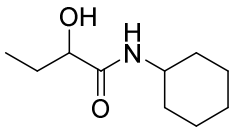


2

***N*-(tert-butyl)-2-hydroxybutanamide 2:** yield = 74%

^{1}H NMR (500MHz, $CDCl_3$) δ 6.67 (br, s, 1H), 4.53 (d, *J* = 5 Hz, 1H), 3.90 (m, 1H), 1.78 (m, 1H), 1.64 (m, 1H), 1.32 (s, 9H), 0.91(t *J* = 8 Hz)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 73.0, 51.0, 28.8, 27.9, 9.1

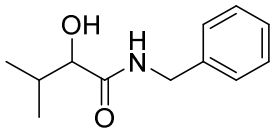


3

***N*-cyclohexyl-2-hydroxybutanamide 3:** yield = 75%

^{1}H NMR (500MHz, $CDCl_3$) δ 6.59 (br, d, 1H), 4.03 (t, *J* = 3.5, 1H), 3.72 (m, 2H), 1.86 (m, 4H), 1.65 (m, 4H), 1.18 (m, 3H), 0.96 (t, *J* = 7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 73.0, 48.1, 33.3, 28.1, 25.7, 25.0, 9.2

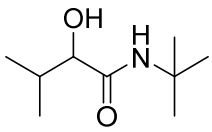


4

***N*-benzyl-2-hydroxy-3-methylbutanamide 4:** yield = 70%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 7.00 (br, s 1H), 4.46 (dd, *J* = 6 Hz, 2H), 4.02 (s, 1H), 2.20 (m, 1H), 1.03 (d, *J* = 7 Hz, 3H), 0.87 (d, *J* = 7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 138.3, 129.0, 128.0, 127.8, 76.6, 43.4, 32.1, 19.4, 15.8

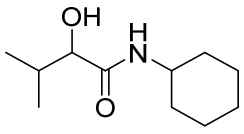


5

***N*-(tert-butyl)-2-hydroxy-3-methylbutanamide 5:** yield = 71%

^{1}H NMR (500MHz, $CDCl_3$) δ 6.53(br, s, 1H), 3.92(d, *J* = 5.5 Hz, 1H), 3.80(m, 1H), 2.10(m, 1H), 1.35(s, 9H), 0.99(d, *J* = 6.5 Hz, 3H), 0.84(d, *J* =7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 76.3, 51.1, 32.0, 29.0, 19.5, 15.6

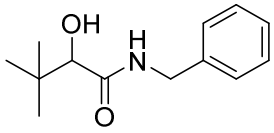


6

***N*-cyclohexyl-2-hydroxy-3-methylbutanamide 6**: yield = 74%

^{1}H NMR (500MHz, $CDCl_3$) δ 6.57 (br, d, *J* = 7.5 Hz, 1H), 3.90 (d, *J* = 8 Hz, 1H), 3.76 (m, 1H), 3.59 (d, *J* = 5 Hz, 1H), 2.14 (m, 1H), 1.89 (m, 2H), 1.71 (m, 2H), 1.61 (m, 1H), 1.36 (m, 2H), 1.16 (m, 3H), 1.01 (d, *J* = 7 Hz, 3H), 0.84 (d, *J* = 6.5, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 76.2, 48.0, 33.4, 33.2, 32.1, 25.7, 25.0, 19.4, 15.6

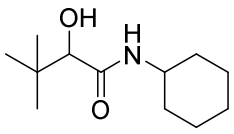


7

***N*-benzyl-2-hydroxy-3,3-dimethylbutanamide 7:** yield = 61%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 6.81 (br, s, 1H), 4.44 (dd, *J* = 5.5 Hz, 2H), 3.74 (d, *J* = 5 Hz, 1H), 3.51 (d, *J* = 5.5 Hz, 1H), 0.90 (s, 9H)

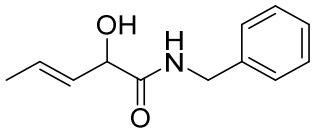
^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 138.3, 128.9, 128.0, 127.7, 79.8, 43.4, 35.4, 26.3



9

***N*-cyclohexyl-2-hydroxy-3,3-dimethylbutanamide 9:** yield = 72%

^{1}H NMR (500MHz, $CDCl_3$) δ 6.08 (br, s, 1H), 3.80 (br, 1H), 3.65 (d, *J* = 6 Hz, 1H), 3.18 (d, *J* = 5.5 Hz, 1H), 1.90 (m, 2H), 1.73-1.61 (m, 2H), 1.42-1.16 (m, 6H), 0.99 (s, 9H)

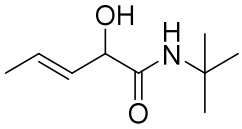


10

(*E*)-*N*-benzyl-2-hydroxypent-3-enamide 10: yield = 78%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 6.82 (br, s, 1H), 5.88 (dd, *J* = 6.5 Hz, 1H), 5.60 (dd, *J* = 7 Hz, 1H), 4.53 (d, *J* = 7 Hz, 1H), 4.45 (d, *J* = 6 Hz, 2H), 3.71 (br, s, 1H), 1.74 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 138.0, 131.0, 129.1, 129.0, 127.9, 127.8, 73.18, 43.6, 18.0

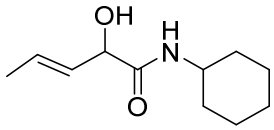


11

(***E*)-*N*-(tert-butyl)-2-hydroxypent-3-enamide 11:** yield = 74%

^{1}H NMR (500MHz, $CDCl_3$) δ 5.99(br, s, 1H), 5.88(m, 1H), 5.54(dd, *J* = 7.5 Hz, 1H), 4.35(d, *J* =11 Hz, 3.39(d, *J* =3.5 Hz, 1H), 1.77(d, 7.5 Hz, 3H), 1.37(s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 131.3, 129.6, 73.3, 51.6, 29.0, 18.0

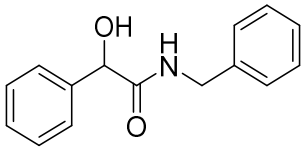


12

(*E*)-*N*-cyclohexyl-2-hydroxypent-3-enamide 12: yield = 72%

^{1}H NMR (500MHz, $CDCl_3$) δ 5.88 (br, s, 1H) 5.81 (dd,*J* = 6.5 Hz, 1H), 5.47 (dd, *J* = 7.5 Hz,1H), 4.36 (d,*J* = 7.5 Hz, 1H), 3.70(m, 1H), 1.84 (d, *J* =12.5, 3H), 1.69 (d, *J* =6.5, 3H), 1.67-0.76 (m, 8H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 131.3, 129.4, 73.1, 48.6, 33.3, 25.7, 25.0, 18.0

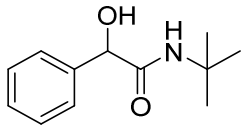


13

***N*-benzyl-2-hydroxy-2-phenylacetamide 13:** yield = 80%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.34-7.12(m, 10H), 4.95(s, 1H), 4.65(br, s, 1H), 4.31(s, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 139.9, 138.0, 128.9, 128.6, 128.0, 127.8, 127.7, 127.0, 74.4, 43.5

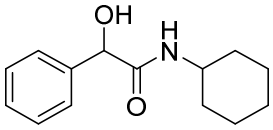


14

***N*-(tert-butyl)-2-hydroxy-2-phenylacetamide 14:** yield = 76%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 6.21 (br, s, 1H), 4.84 (s, 1H), 4.22 (br, s, 1H), 1.31 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 140.1, 129.1, 128.8, 127.1, 74.5, 51.7, 28.8

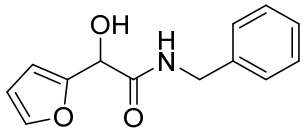


15

***N*-cyclohexyl-2-hydroxy-2-phenylacetamide 15:** yield = 80%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.31 (s, 1H), 4.81 (s, 1H), 4.22 (s, 1H), 3.61 (m, 1H), 1.73-0.71 (m, 10H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 128.8, 128.4, 127.0, 74.2, 48.4, 33.0, 32.9, 25.7, 25.0

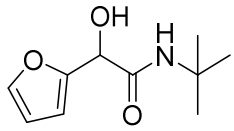


16

***N*-benzyl-2-(furan-2-yl)-2-hydroxyacetamide 16:** yield = 65%

^{1}H NMR (500MHz, $CDCl_3$) δ7.32 (d, *J* = 2 HZ 1H), 7.27-7.12 (m, 5H), 6.54 (br s, 1H), 6.30 (d, *J* =20, 2H), 5.08(s, 1H), 4.43 (m, 2H), 3.63(br, 1H),

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 152.0, 143.2, 137.8, 129.0, 127.9, 127.8, 110.8, 108.9, 68.1, 43.7

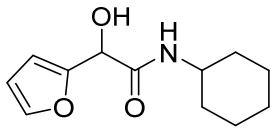


17

***N*-(tert-butyl)-2-(furan-2-yl)-2-hydroxyacetamide 17:** yield = 68%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.412(t, *J* = 1 Hz, 1H), 6.37(d, *J* = 3 Hz, 2H), 6.10(br, s, 1H), 5.00(s, 1H), 3.96(br, s, 1H), 1.37(s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ169.0, 152.5, 143.1, 110.8, 108.5, 68.0, 51.9, 28.9

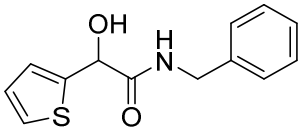


18

***N*-cyclohexyl-2-(furan-2-yl)-2-hydroxyacetamide 18:** yield = 67%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.41 (d, *J* = 1.5 Hz, 1H), 6.40-6.37 (m, 2H), 6.2 (d, *J* = 3.5 Hz, 1H), 3.92(br, s, 1H), 3.84-3.78 (m, 1H), 1.95-187 (m, 2H), 1.77-1.60 (m, 4H), 1.42-1.33 (m, 2H), 1.27-1.14 (m,3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 152.2, 143.1, 110.9, 108.6, 67.9, 48.9, 33.1 25.7, 24.9

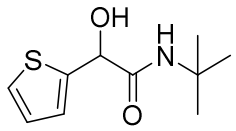


19

***N*-benzyl-2-hydroxy-2-(thiophen-2-yl)acetamide 19:** yield = 75%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.28 (m, 6H), 7.07 (d, *J* = 3.5, 1H), 7.04 (br, s, 1H), 6.95 (t, *J* = 5 Hz, 1H), 5.30 (s, 1H), 4.65 (br, s, 1H), 4.41 (t, *J* = 5.5 Hz, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 161.7, 142.9, 137.8, 129.0, 128.0, 127.9, 127.1, 126.1, 70.4, 43.7

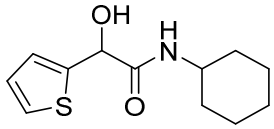


20

***N*-(tert-butyl)-2-hydroxy-2-(thiophen-2-yl)acetamide 20:** yield = 72%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.28(d, *J* = 5.5 Hz, 1H), 7.06(d, *J* = 4.5 Hz, 1H), 6.98(t, *J* = 4.5 Hz, 1H), 6.34(br,s, 1H), 5.13(s,1H), 4.48(br, s, 1H),1.35(s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 143.3, 127.0, 126.1, 126.0, 70.4, 51.7, 28.8

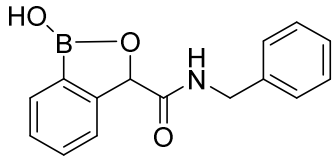


21

***N*-cyclohexyl-2-hydroxy-2-(thiophen-2-yl)acetamide 21:** yield = 78%

^{1}H NMR (500MHz, $CDCl_3$) δ 7.31 (d, *J* = 4 Hz, 1H), 7.11 (d, *J* = 3.5, 1H), 7.00(t, *J* = 3 Hz,1H), 6.25 (br, d, *J* =6.5, 1H), 4.09 (d, *J* = 4 Hz, 1H), 3.80 (m, 1H), 1.91-1.90 (m, 2H), 1.73-1.60 (m,3H), 1.41-1.32(m,2H), 1.21-1.16(m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 143.0,127.1, 126.3, 126.2, 70.2, 48.8, 33.0, 25.7, 24.9

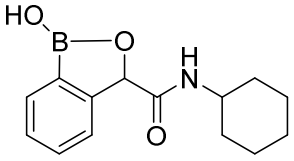


6a

***N*-benzyl-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-3-carboxamide 6a:** yield = 81%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.57 (t, *J* = 8 Hz, 1H), 7.76 (d, *J* = 7 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.30-7.19 (m, 3H), 5.56 (s, 1H), 4.31 (dd, *J* = 6.5 Hz, 1H), 4.22 (dd, *J* = 6 Hz, 1H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 170.2, 153.1, 140.0, 131.6, 131.2, 128.9, 128.5, 127.9, 127.5, 122.6, 80.4, 42.6

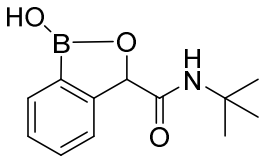


6b

***N*-cyclohexyl-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-3-carboxamide 6b:** yield = 76%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.42 (br, s, 1H), 7.82 (d, *J* = 8 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.51-7.38 (m, 3H), 5.42 (s, 1H), 3.56 (m, 1H), 1.79-0.85 (m, 10H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 153.3, 131.5, 131.1, 128.3, 122.3, 80.2, 79.9, 48.3, 32.9, 32.8, 25.8, 25.4, 25.3



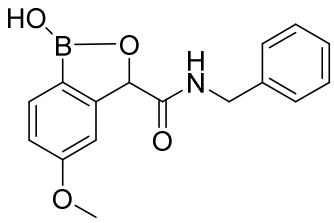
6c

***N*-(tert-butyl)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-3-carboxamide**

6c: yield = 65%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.42 (br, s, 1H), 7.71 (d, *J* = 7 Hz, 1H), 7.56-7.45 (m, 3H), 7.40-7.38 (m, 1H), 5.42 (s, 1H), 1.24 (s, 9H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 169.1, 153.4, 131.4, 131.0, 128.3, 122.3, 80.3, 79.9, 51.0, 29.1

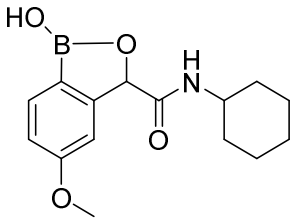


6d

***N*-benzyl-1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborole-3-carboxamide 6d:** yield = 61%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.36(s, 1H), 8.56 (t, *J* = 6 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.25 (m, 5H), 7.06 (d, *J* = 2.5, 1H), 6.97 (dd, *J* = 2.5, 8.5, 1H), 5.49 (s, 1H), 4.36 (dd, *J* = 6.5 Hz, 15, 1H), 4.19 (dd, *J* = 6 Hz, 15, 1H), 3.78 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 162.5, 155.5, 140.1, 132.5, 128.9, 128.0, 127.5, 115.8, 107.0, 80.1, 55.9, 42.6

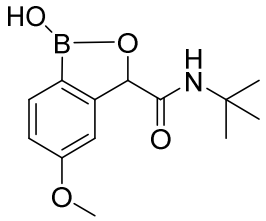


6e

***N*-cyclohexyl-1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborole-3-carboxamide 6e:** yield = 55%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.63 (d, *J* = 8 Hz, 1H), 7.03 (s, 1H), 6.95 (d, *J* = 8 Hz, 1H), 6.40 (s, 1H), 3.78 (s, 3H), 3.55 (br, s, 1H), 1.71-1.53 (m, 5H), 1.27-1.09 (m, 6H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 162.4, 155.7, 132.4, 115.5, 107.0, 79.9, 55.9, 48.2, 32.9, 32.8, 25.8, 25.4

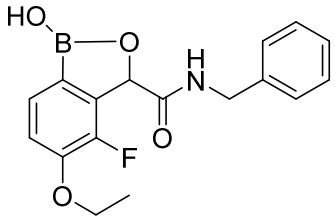


6f

***N*-(tert-butyl)-1-hydroxy-5-methoxy-1,3-dihydrobenzo[c][1,2]oxaborole-3-carboxamide 6f:** yield = 54%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.63 (d, *J* = 8 Hz, 1H), 7.4 (s, 1H), 7.03 (s, 1H), 6.96 (dd, *J* = 2 HZ 8, 1H), 5.34 (s, 1H), 3.79 (s, 3H), 1.28 (s, 9H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 169.1, 162.4, 155.7, 132.4, 115.3, 107.1, 79.9, 55.9, 51.0, 29.1

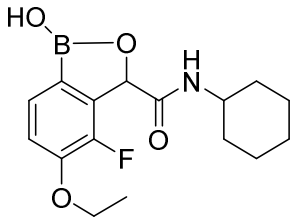


6g

***N*-benzyl-5-ethoxy-4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-3-carboxamide 6g:** yield = 54%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.86 (t, *J* = 6 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H), 7.33-7.25 (m, 6H), 5.68 (s, 1H), 4.39-4.07 (m, 4H), 1.36 4.19 (t, *J* = 6.7, 3H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 168.7, 139.7, 129.0, 127.9, 127.6, 127.6, 116.2, 78.1, 65.4, 42.9, 15.3

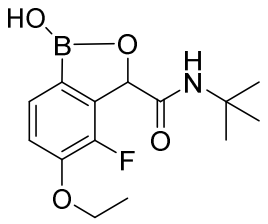


6h

***N*-cyclohexyl-5-ethoxy-4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2] oxaborole-3-carboxamide 6h:** yield = 58%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.31 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 5.60 (s, 1H), 4.13 (q, *J* =7, 2H), 3.53 (br, d, *J* = 7.5 Hz, 1H), 1.72-1.13 (m, 13H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 167.4, 149.2, 149.1, 147.7, 145.7, 139.7, 127.5, 115.9, 77.8, 65.3, 48.3, 32.9, 31.4, 25.9, 25.2, 15.3



6i

***N*-(tert-butyl)-5-ethoxy-4-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2] oxaborole-3-carboxamide 6i:** yield = 49%

^{1}H NMR (500MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.09 (s, 1H), 7.45 (d, *J* = 8 Hz, 1H), 7.2 (t, *J* = 8, 1H), 5.62 (s, 1H), 4.13 (q, *J* = 7 Hz, 1H),1.36 (t, *J* = 7 Hz, 3H), 1.28 (s, 9H)

^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 149.2, 149.0, 139.8, 127.5, 115.9, 78.0, 65.3, 51.1, 29.0, 15.3

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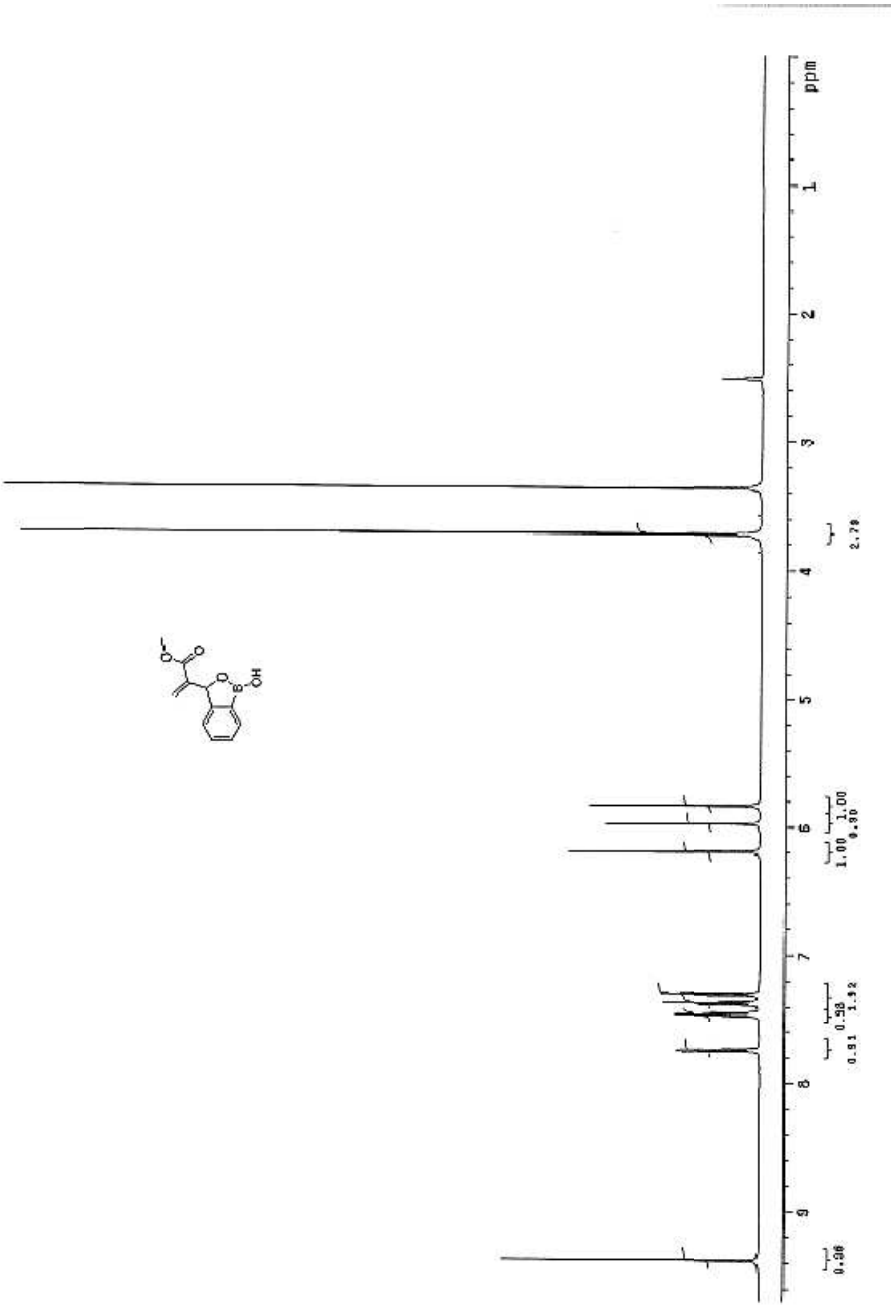
APPENDIX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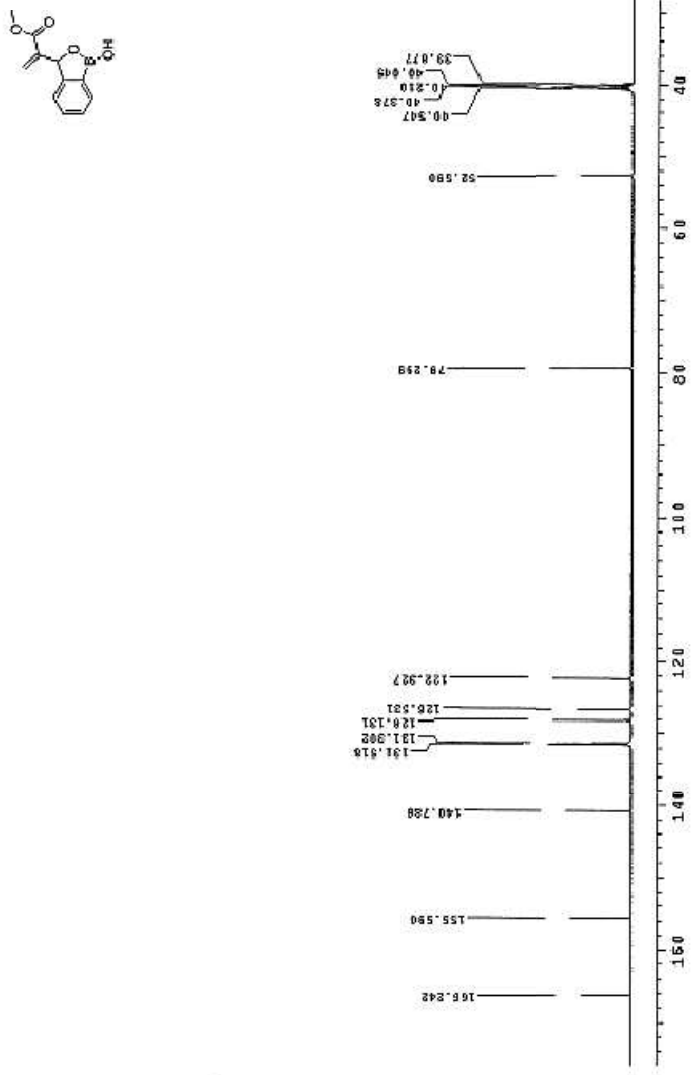
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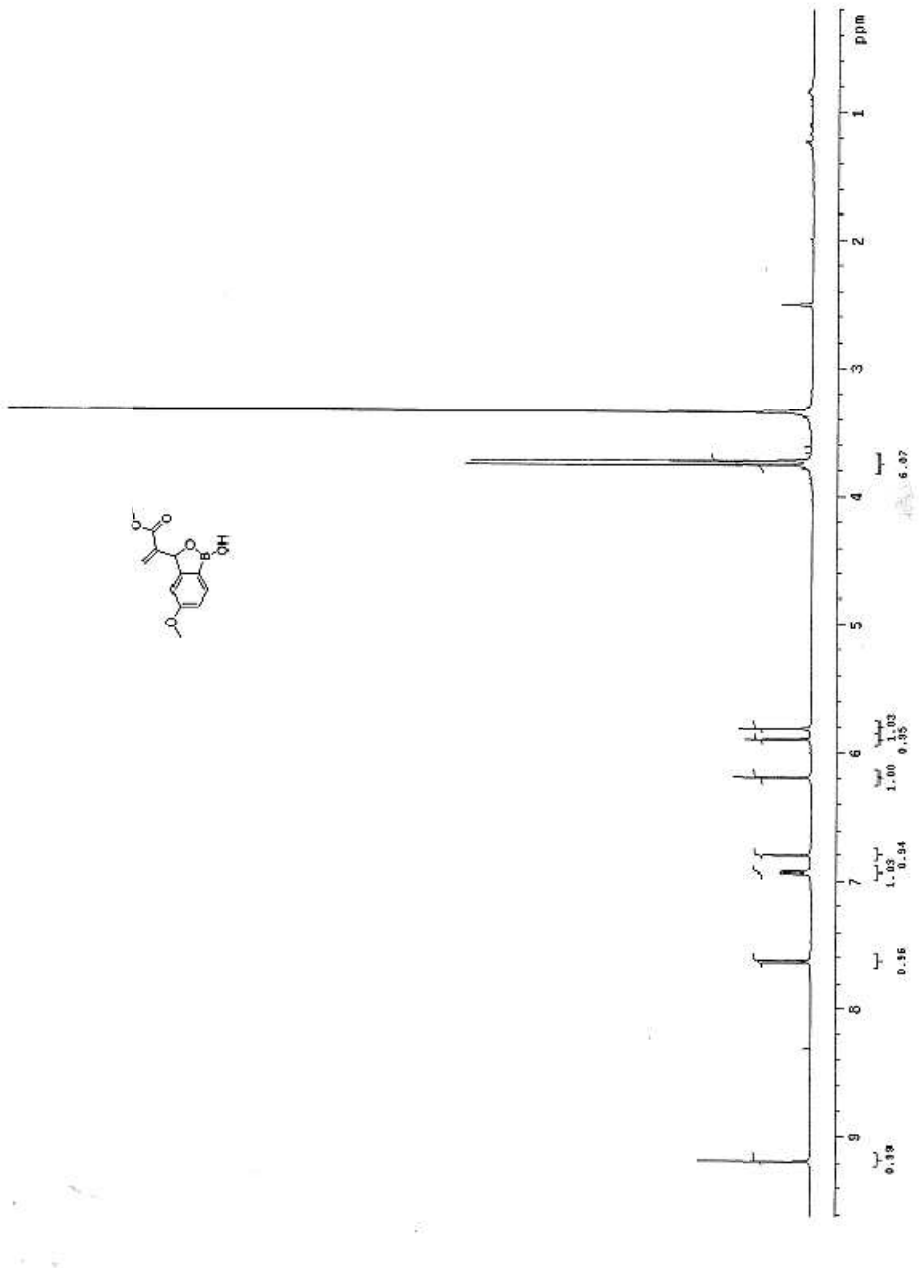
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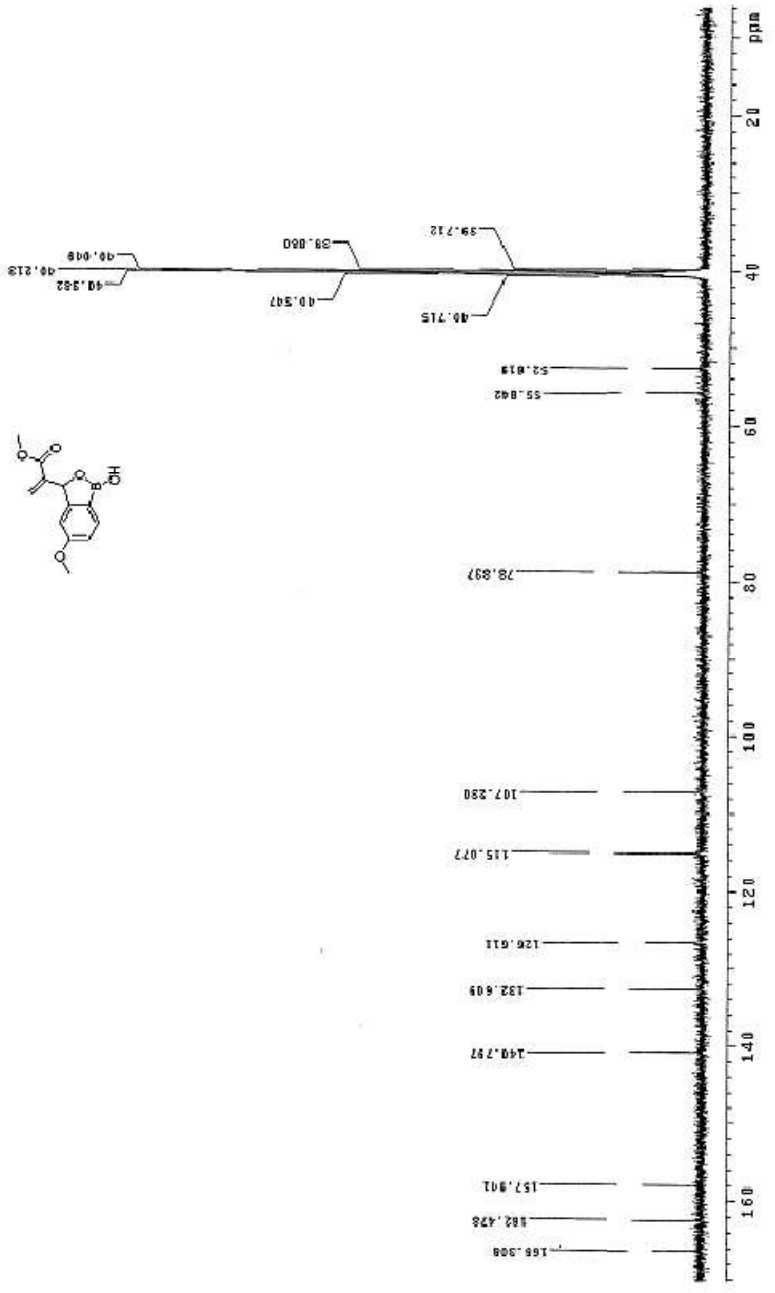
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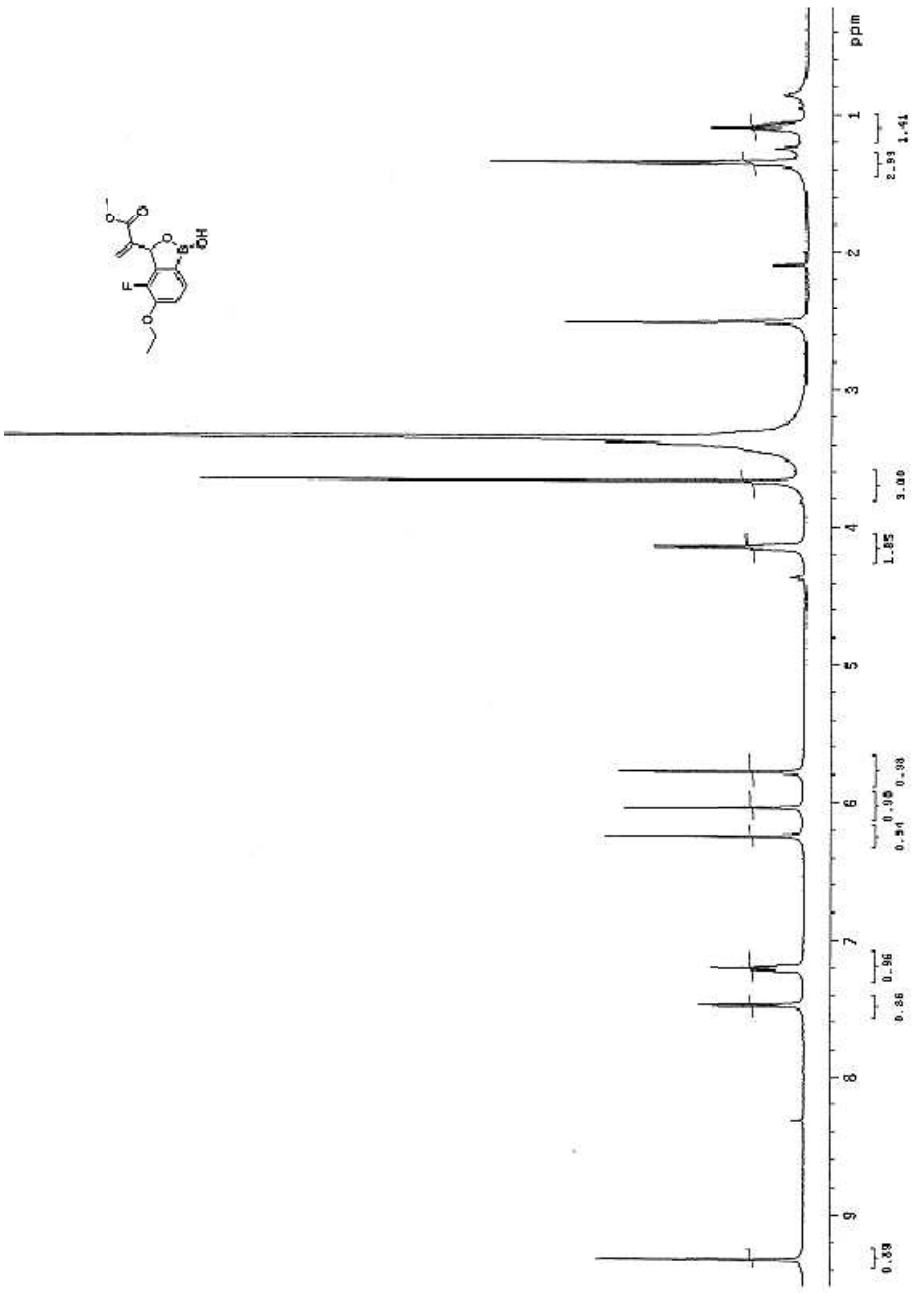
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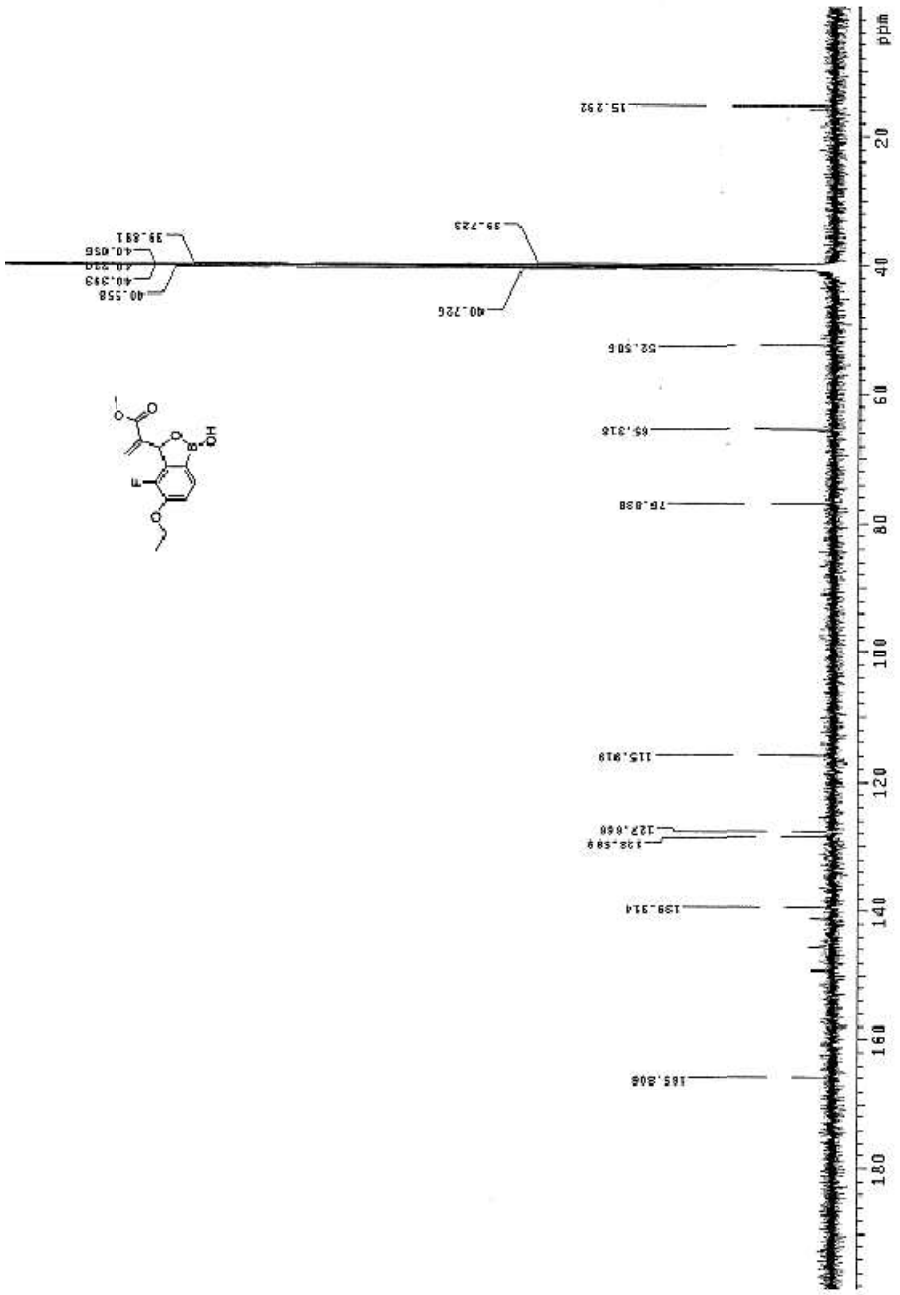
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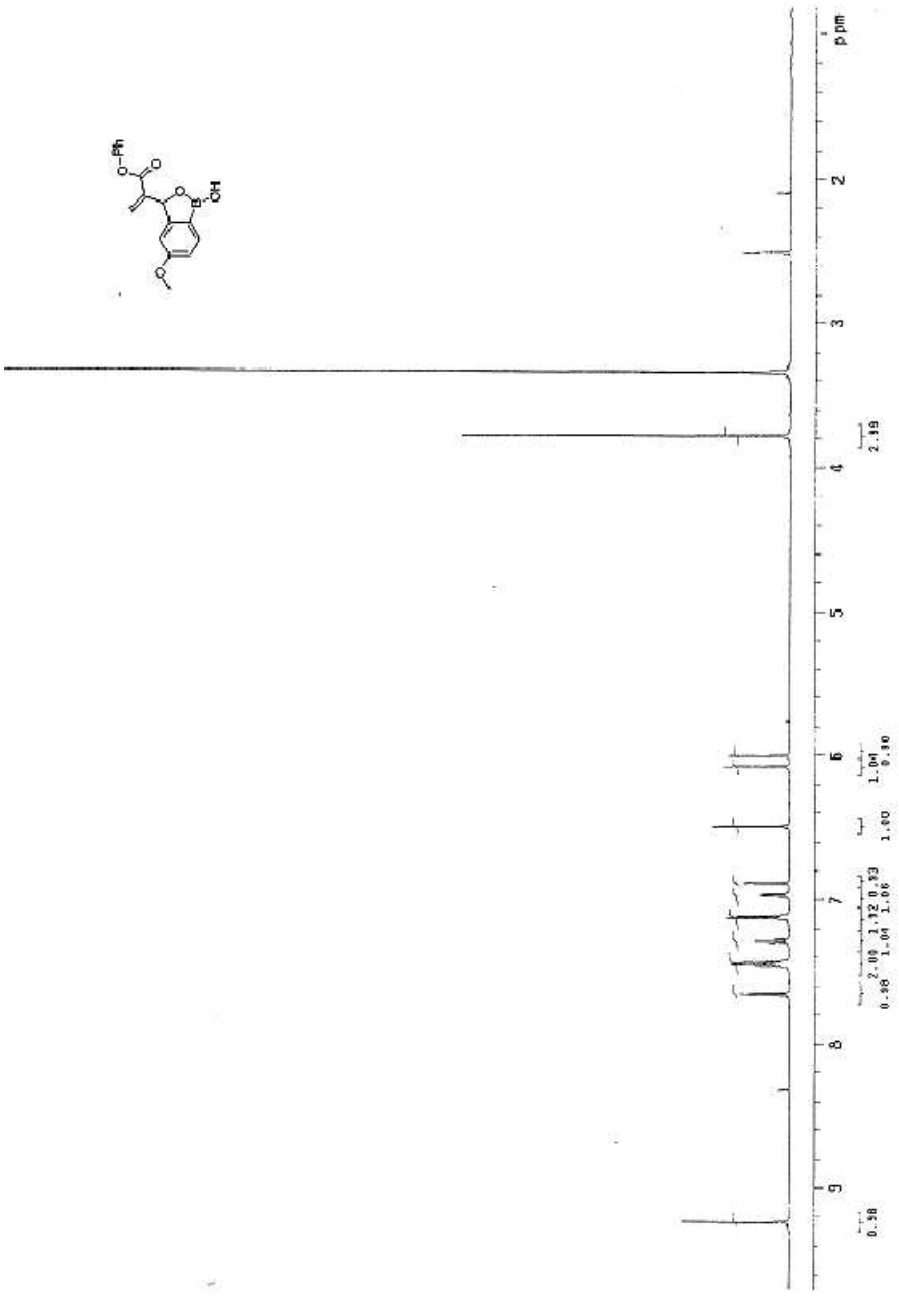
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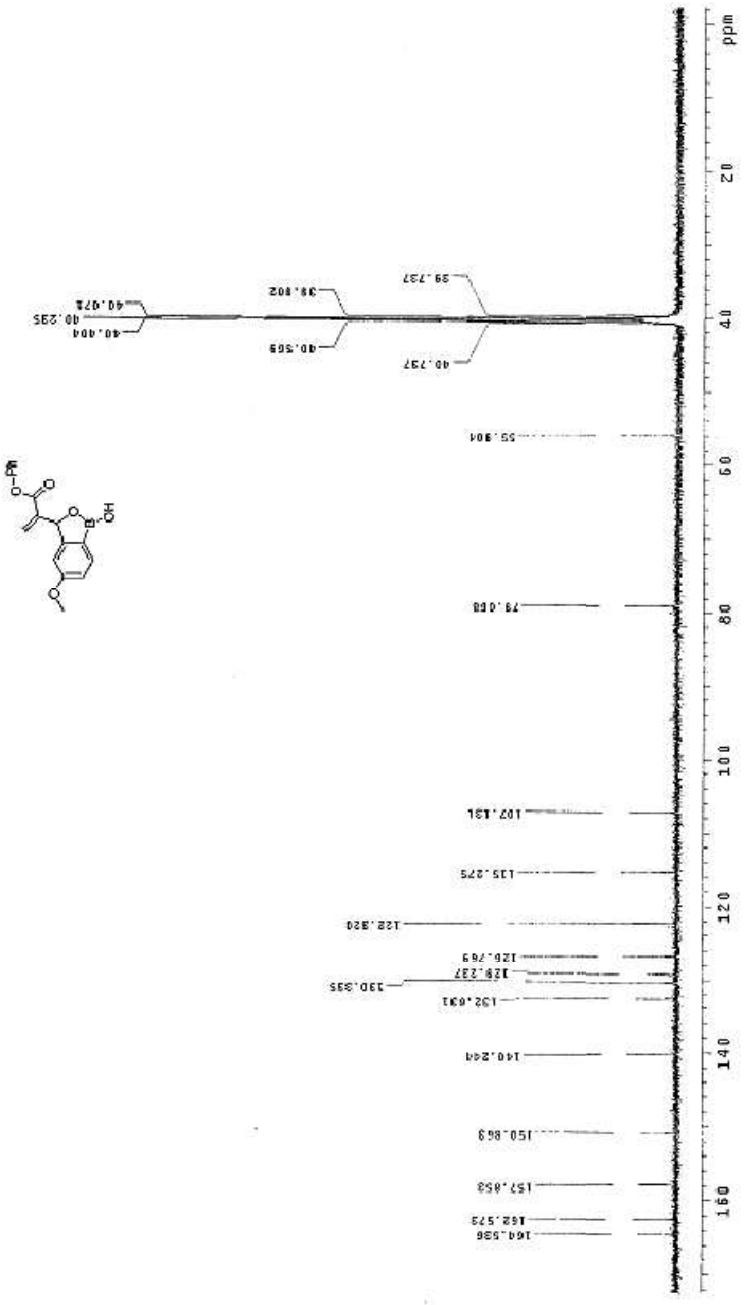
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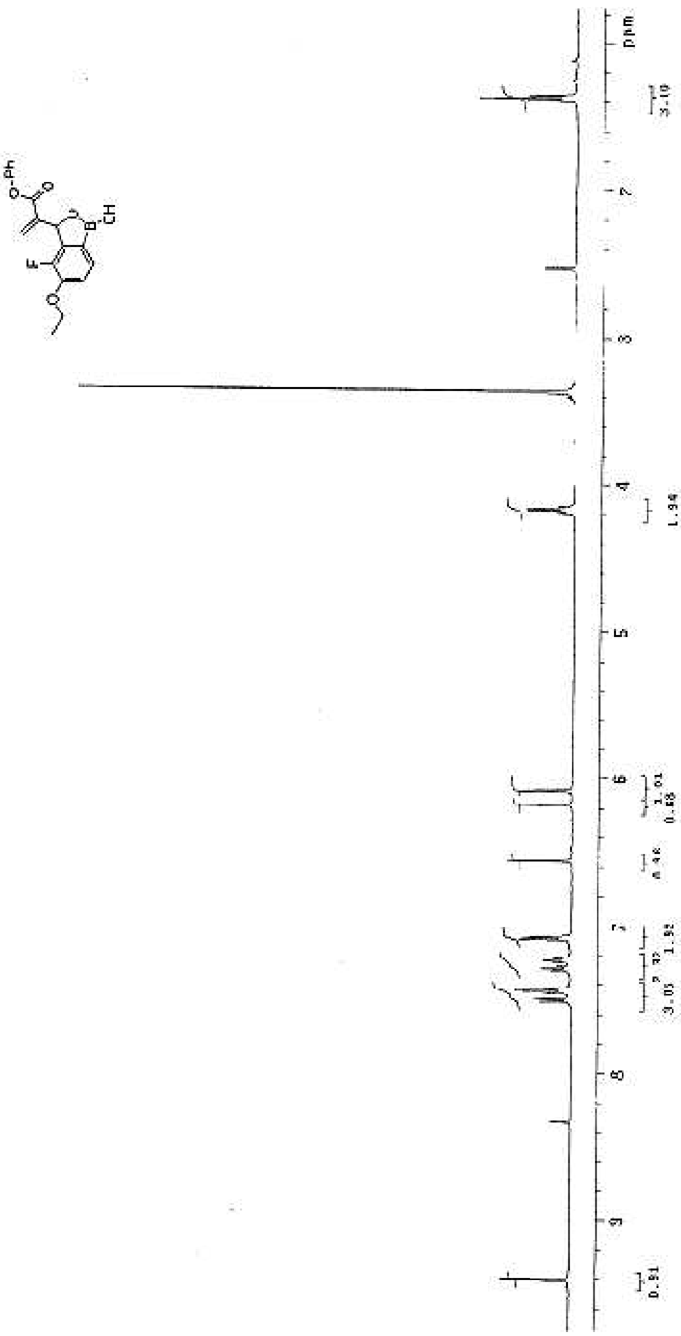

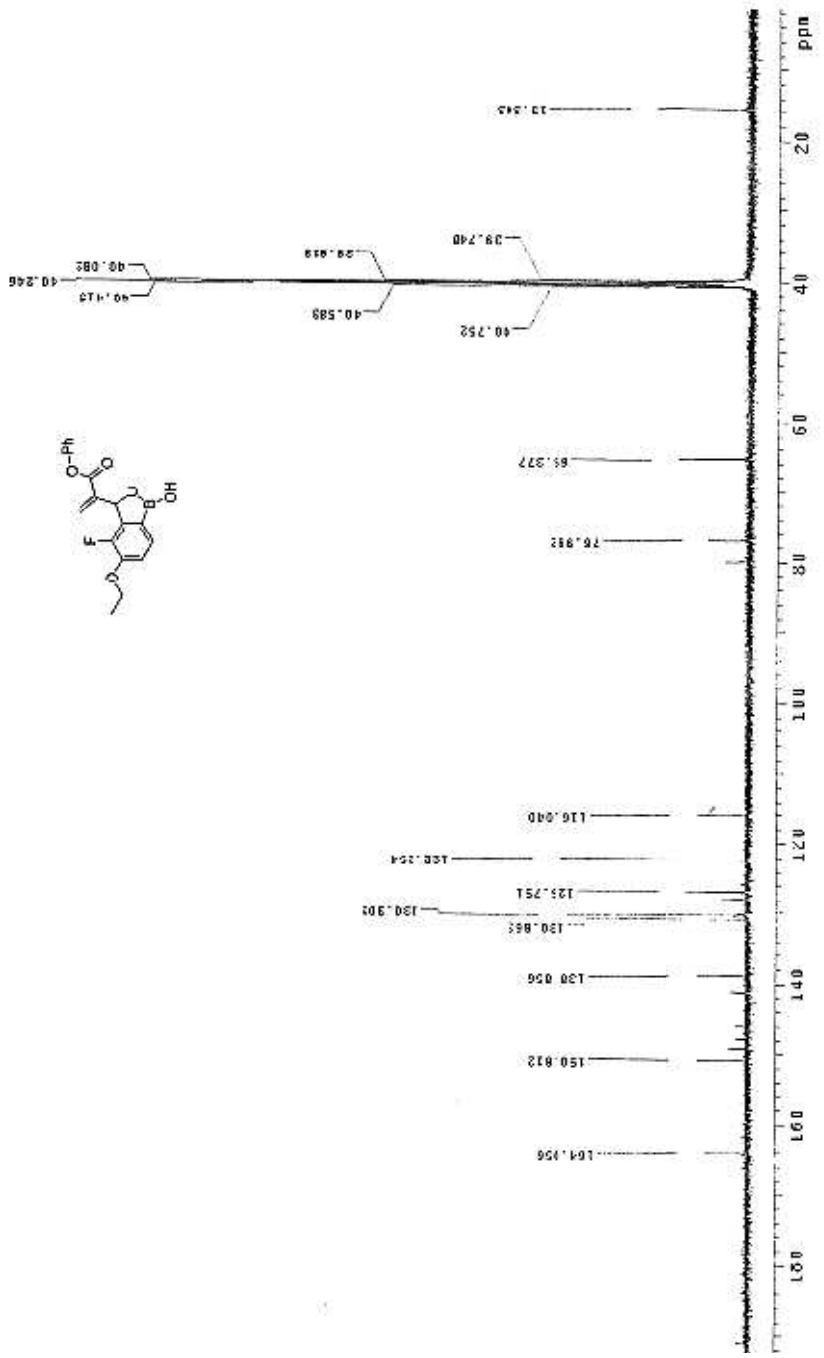
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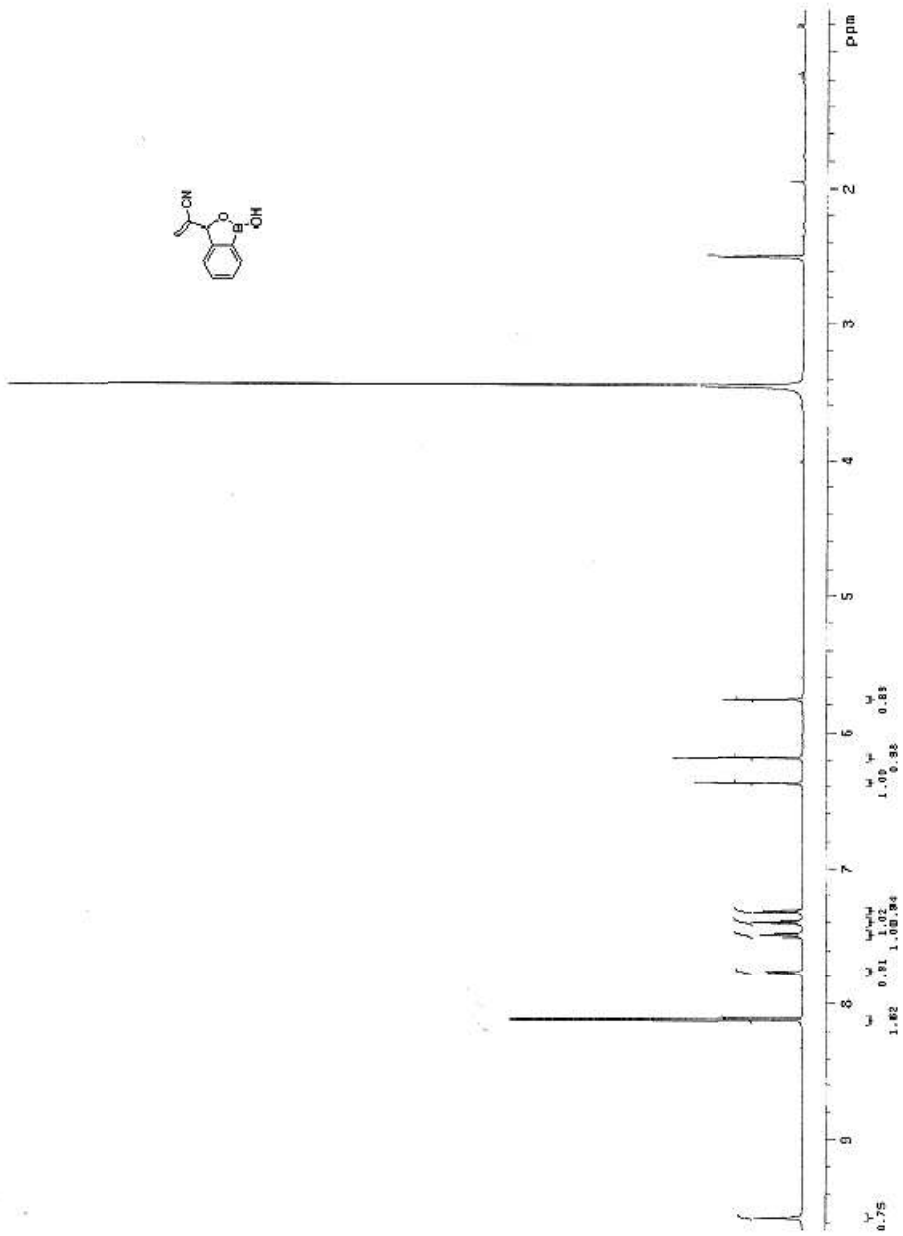
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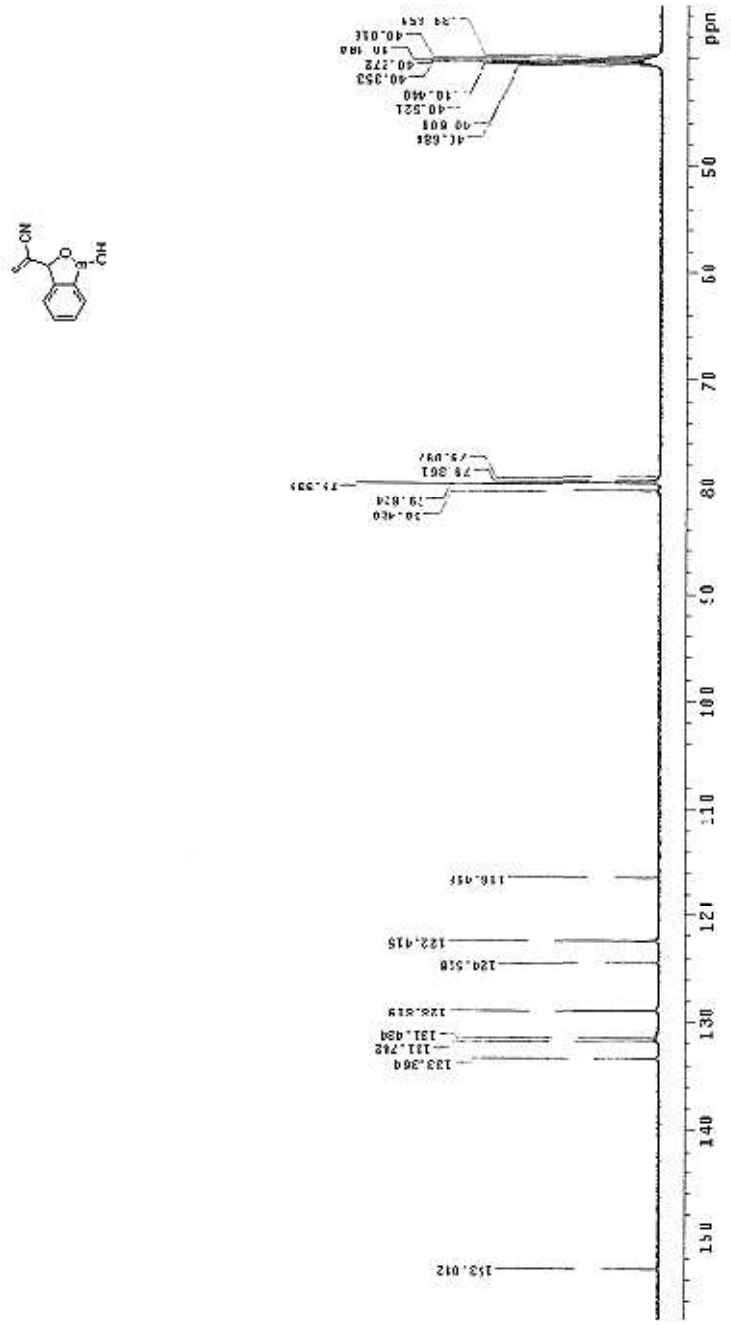

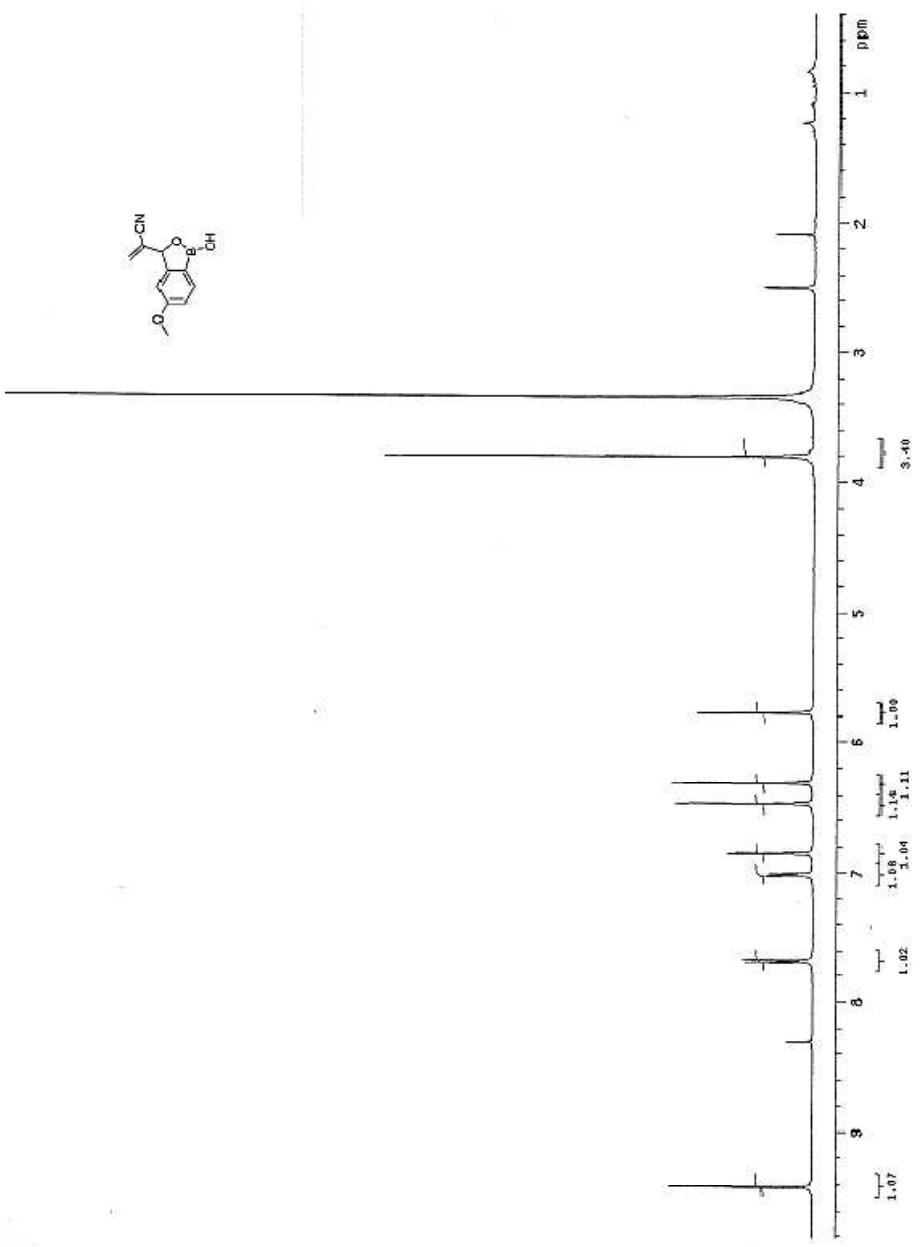
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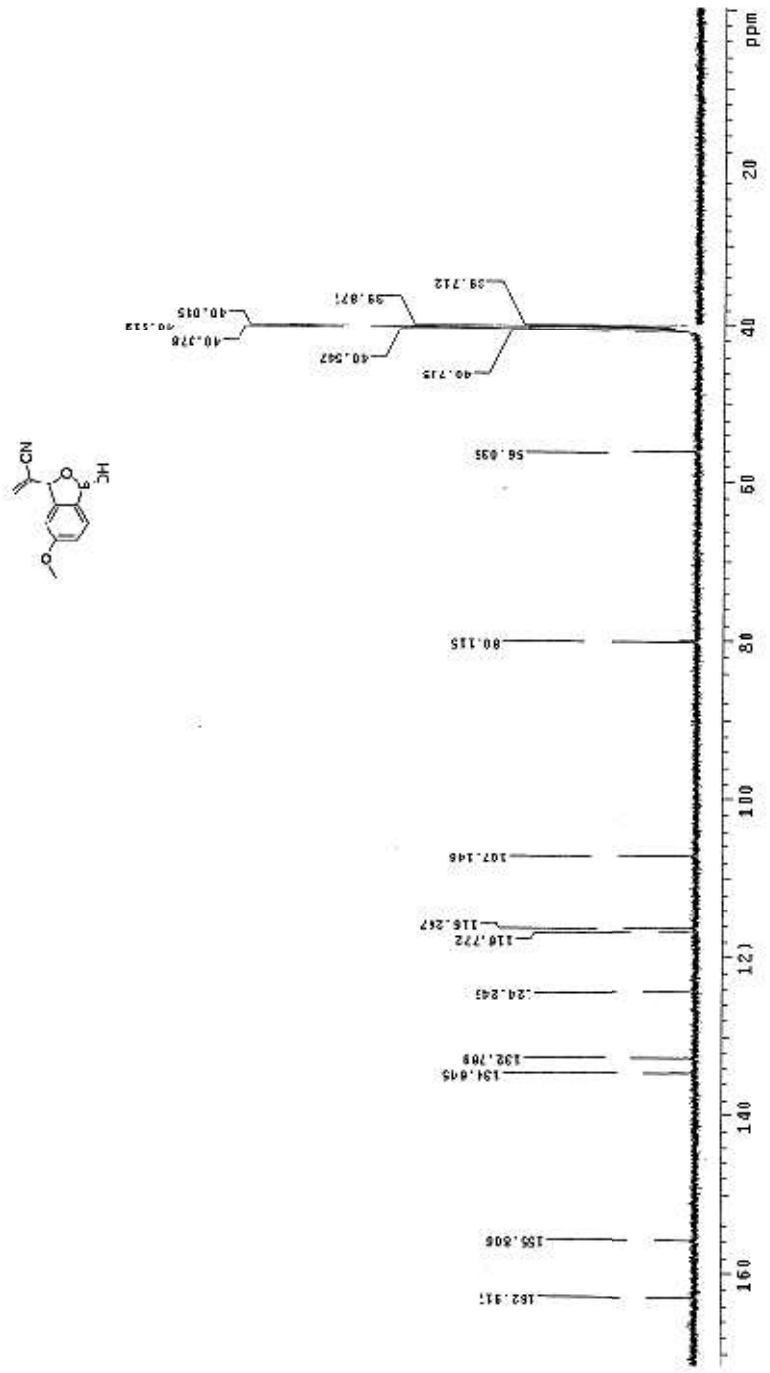
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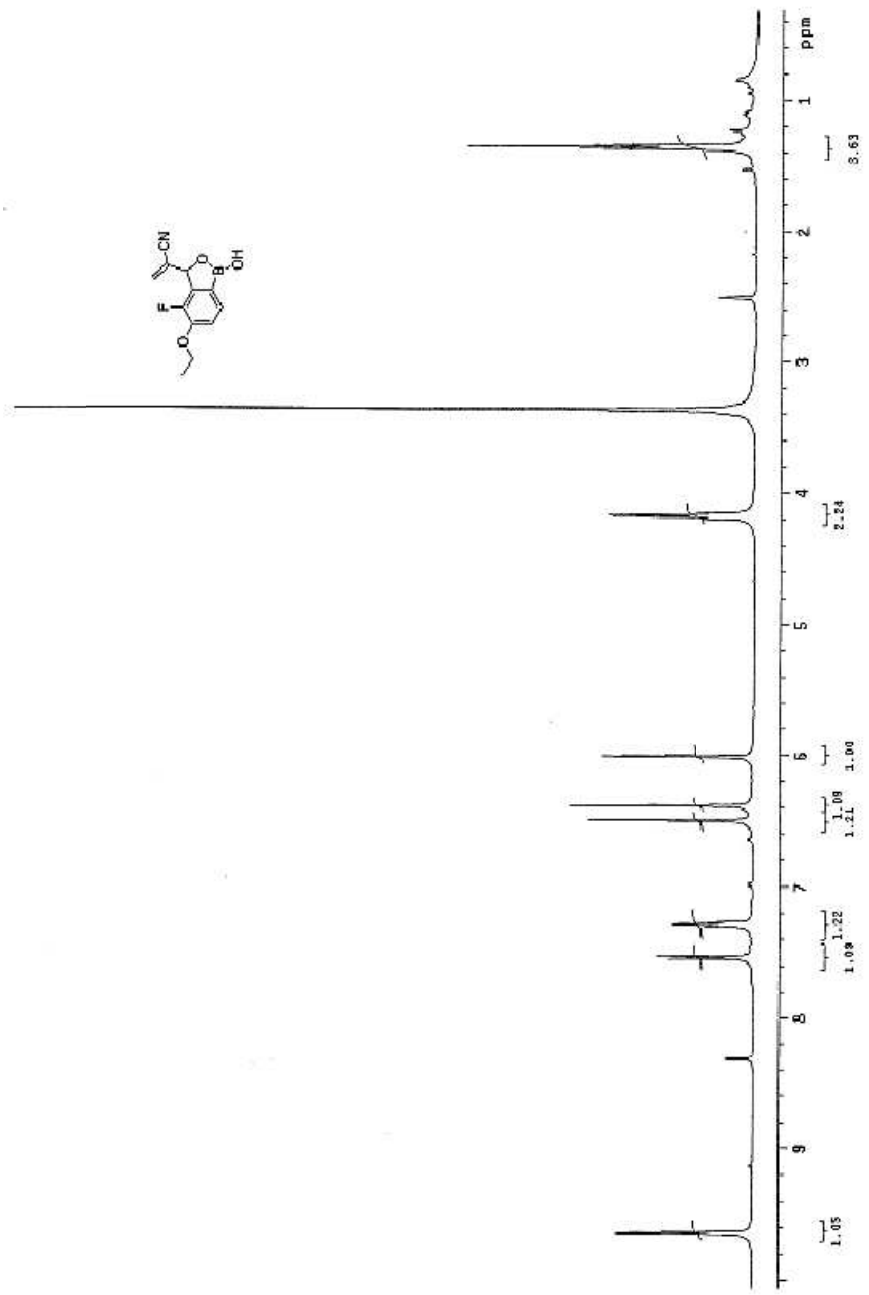
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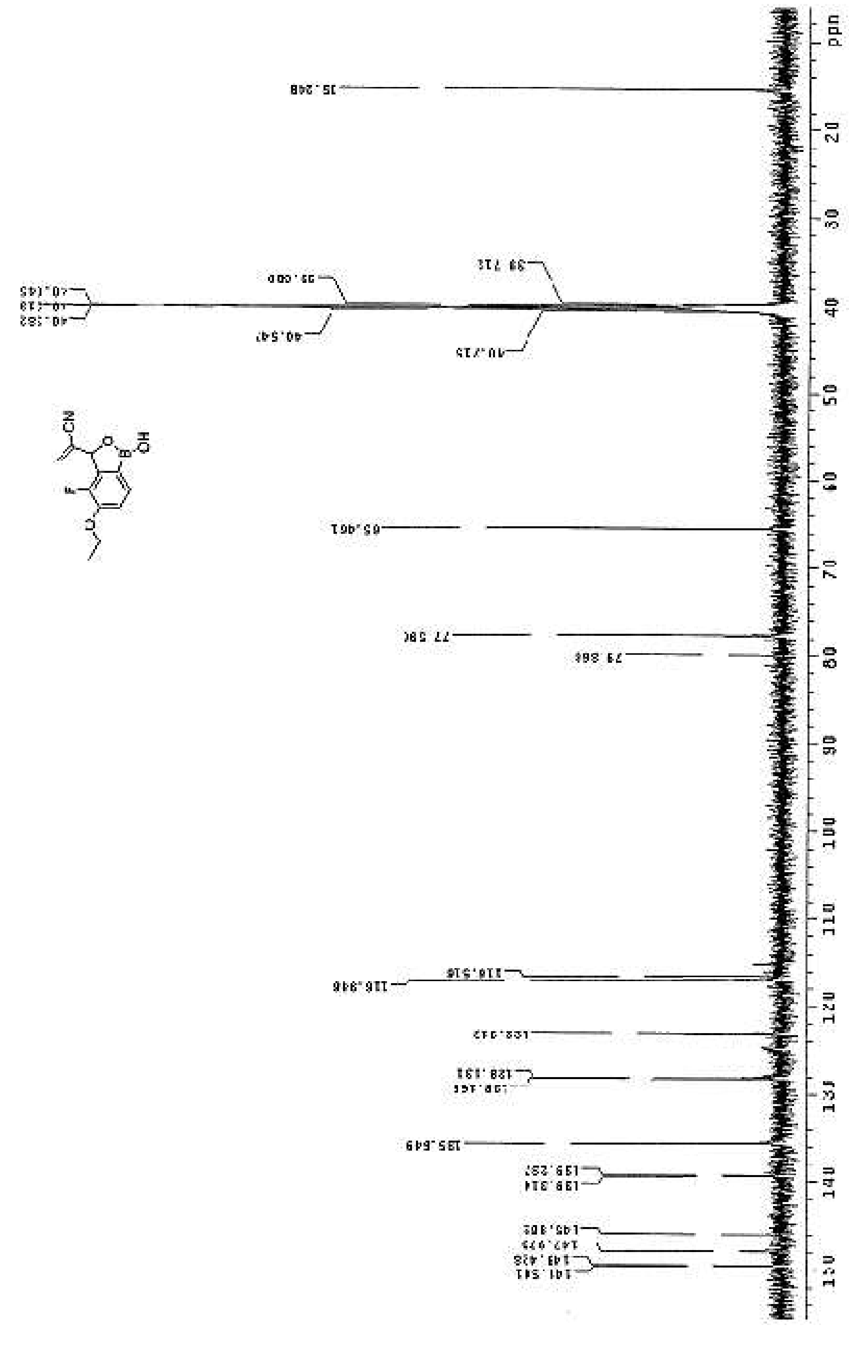

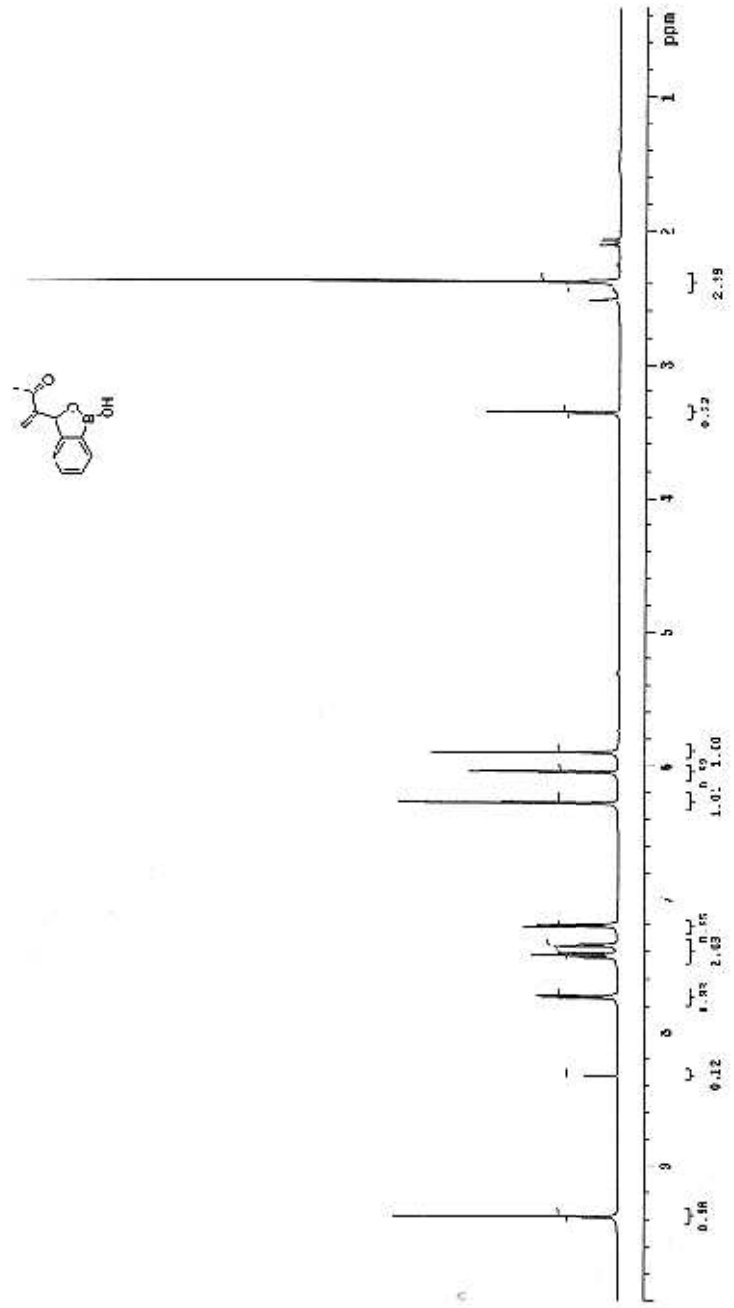
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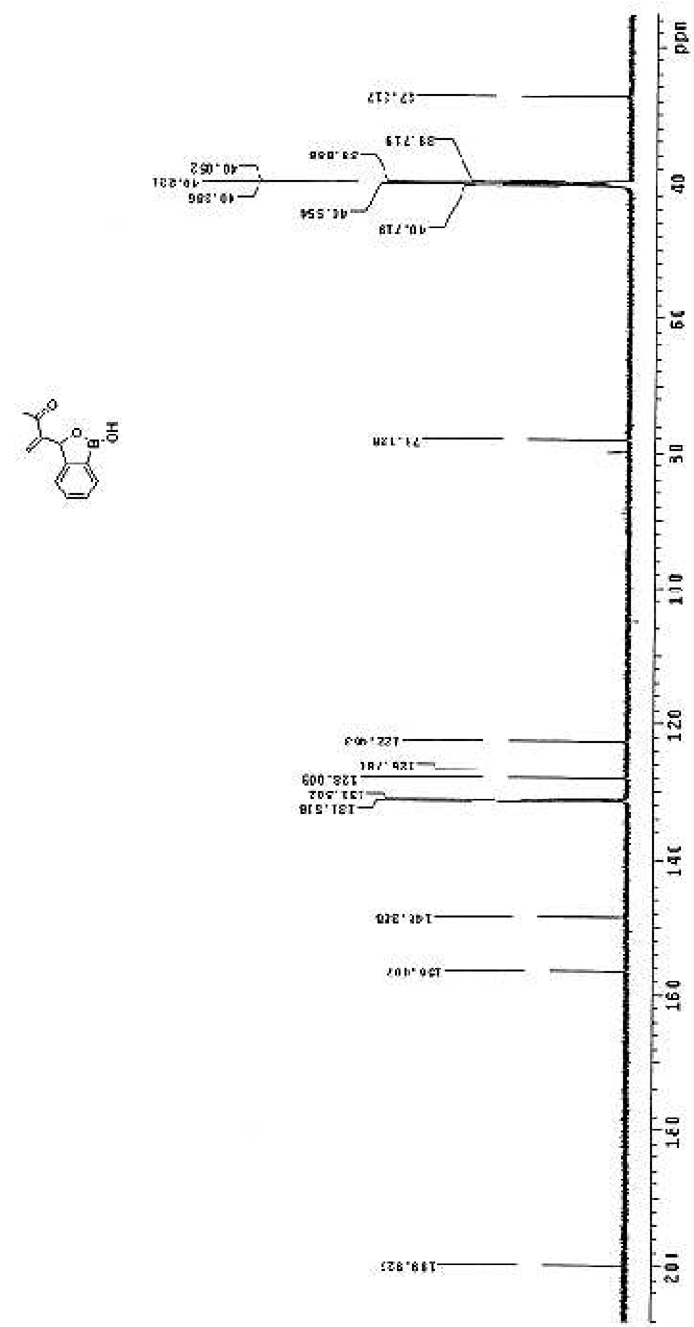

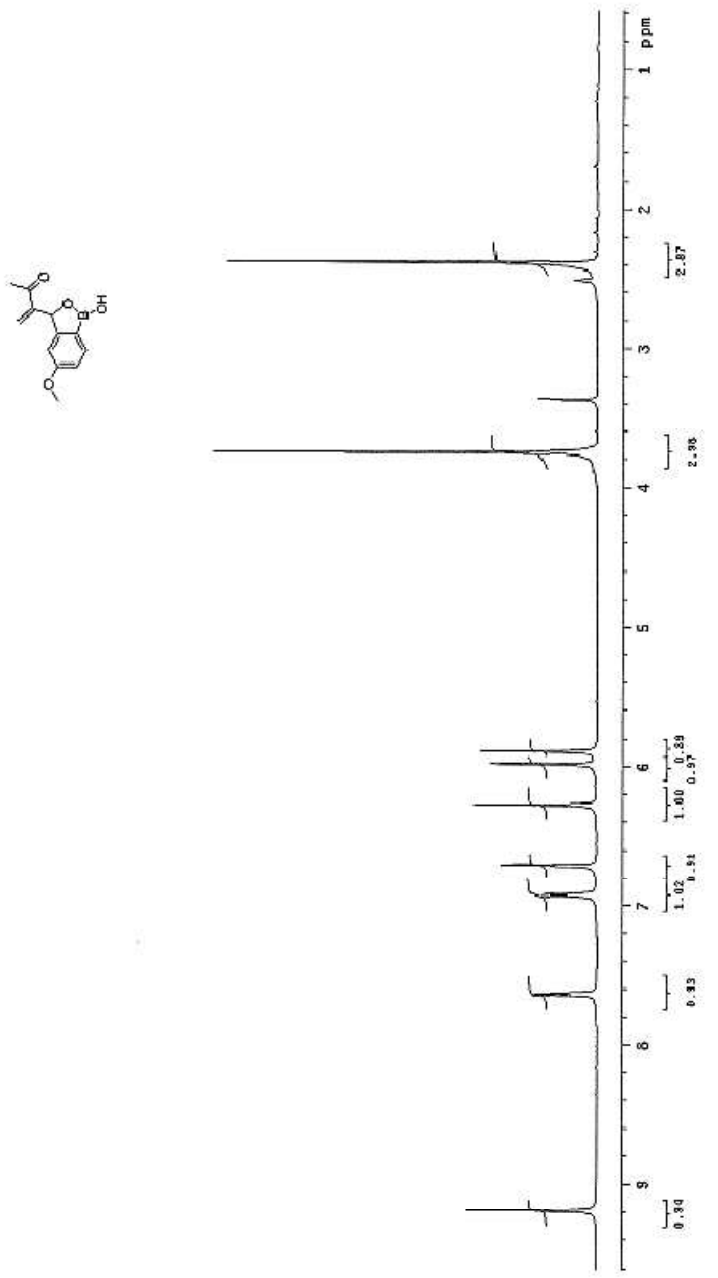

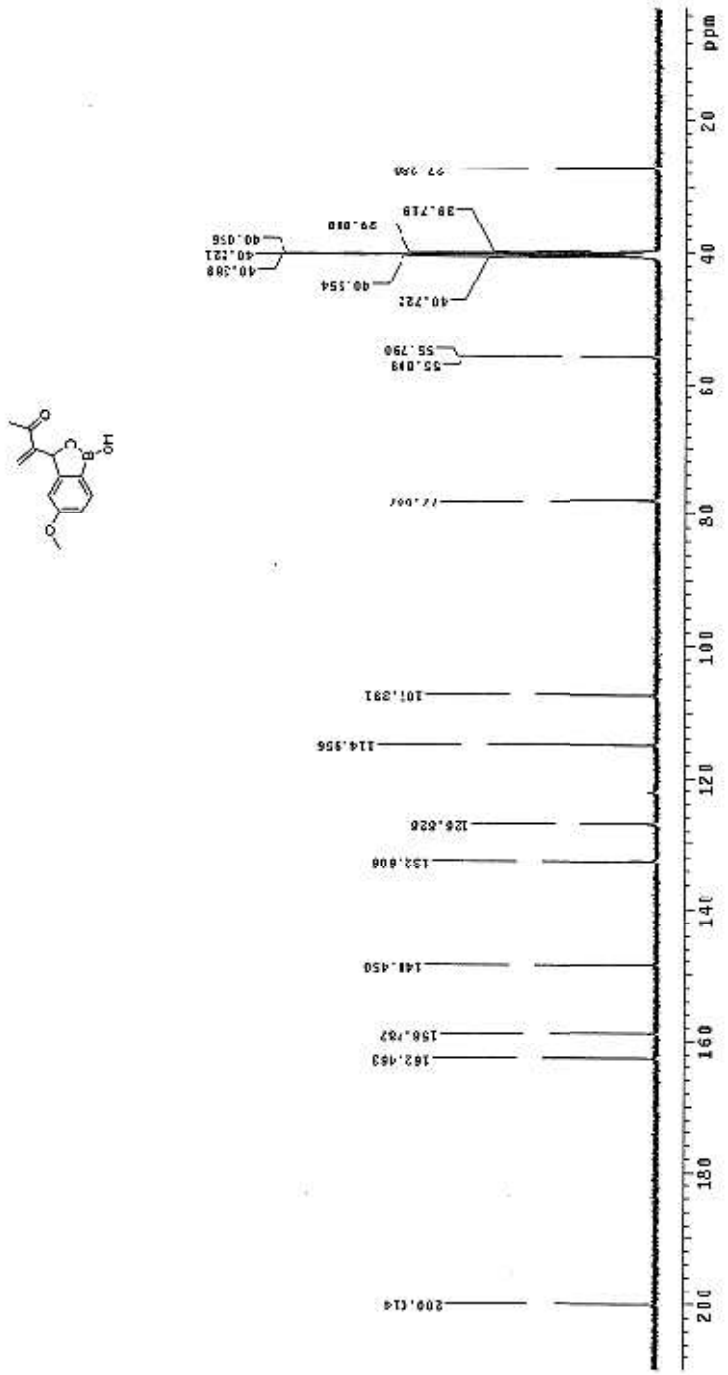
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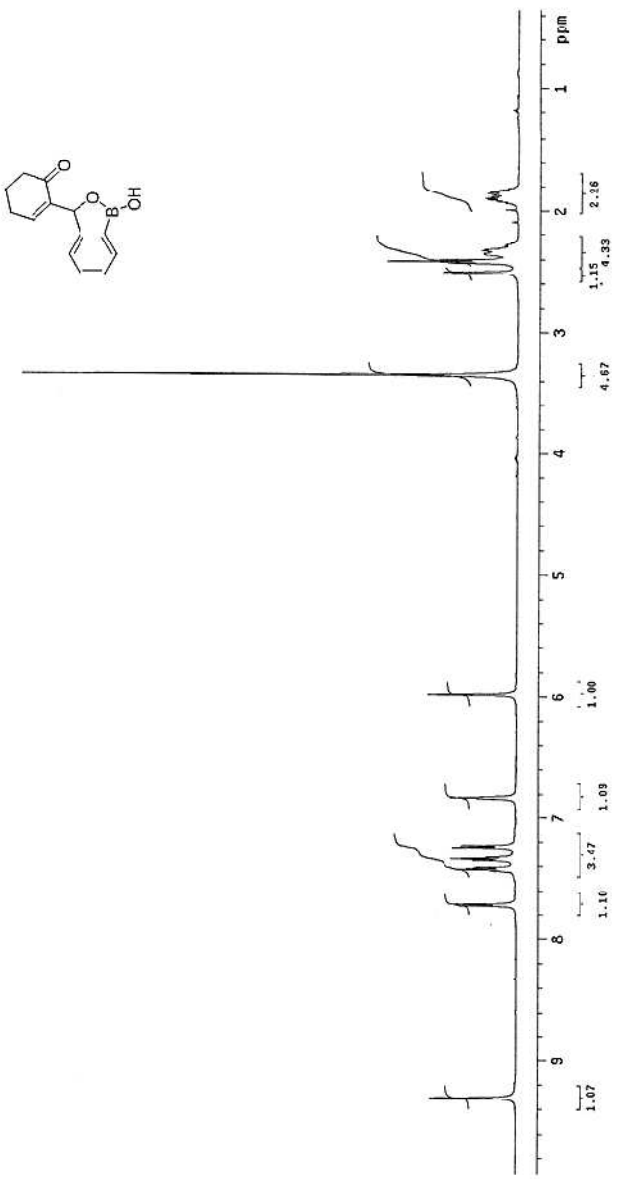
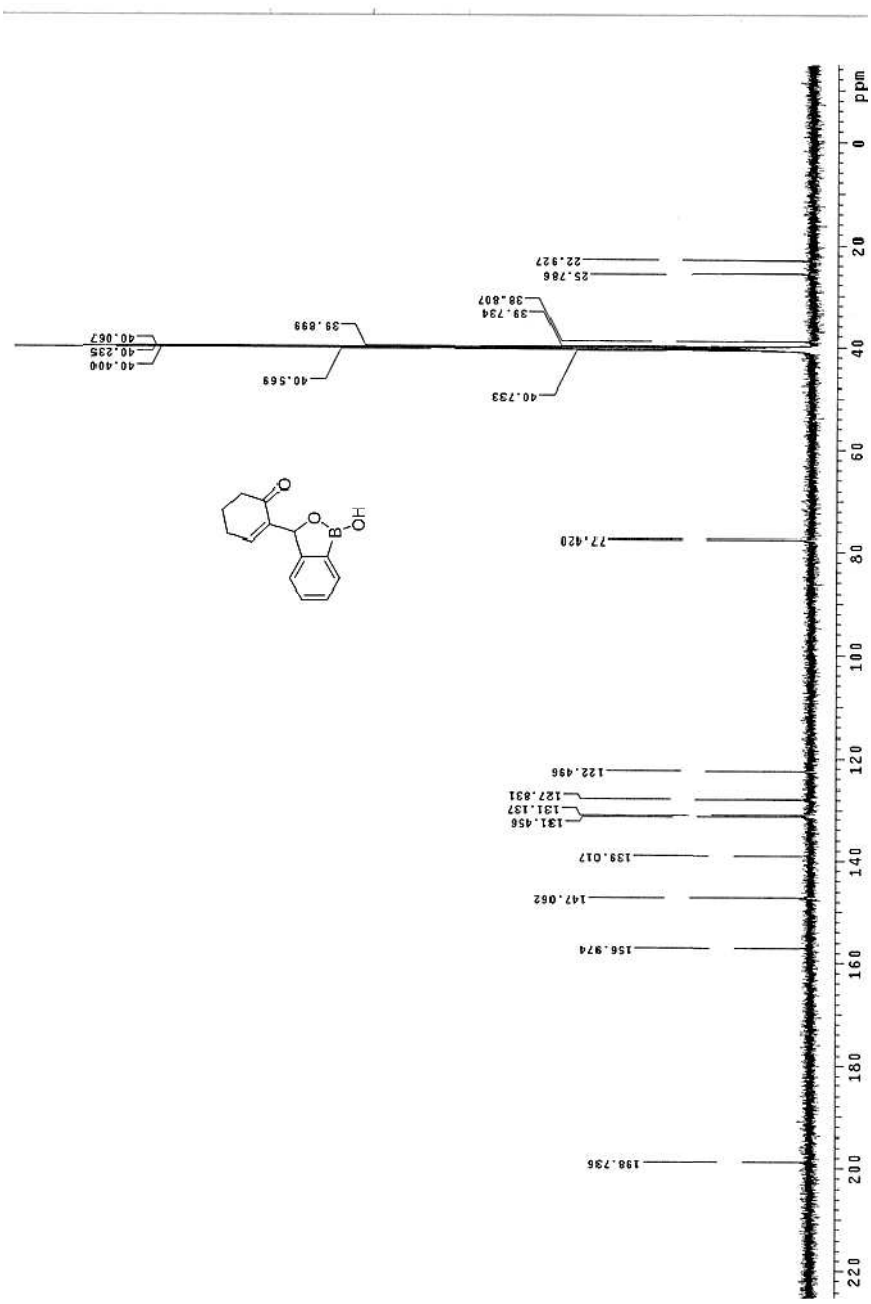
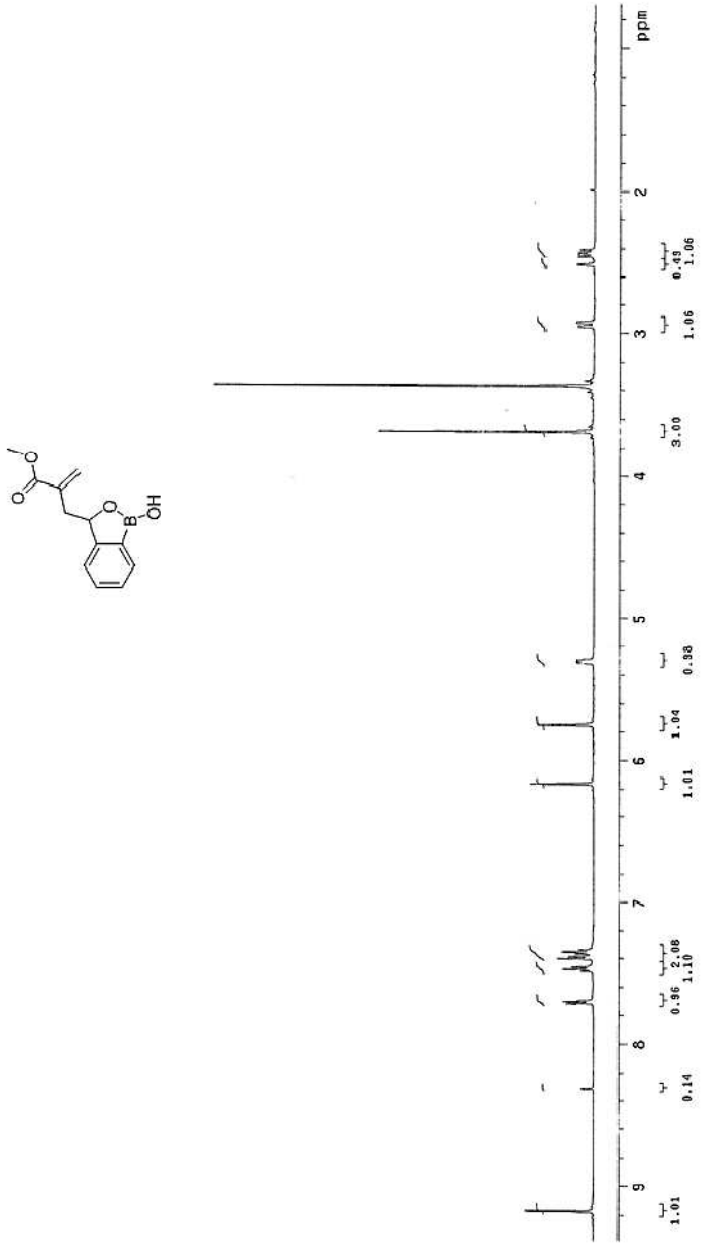
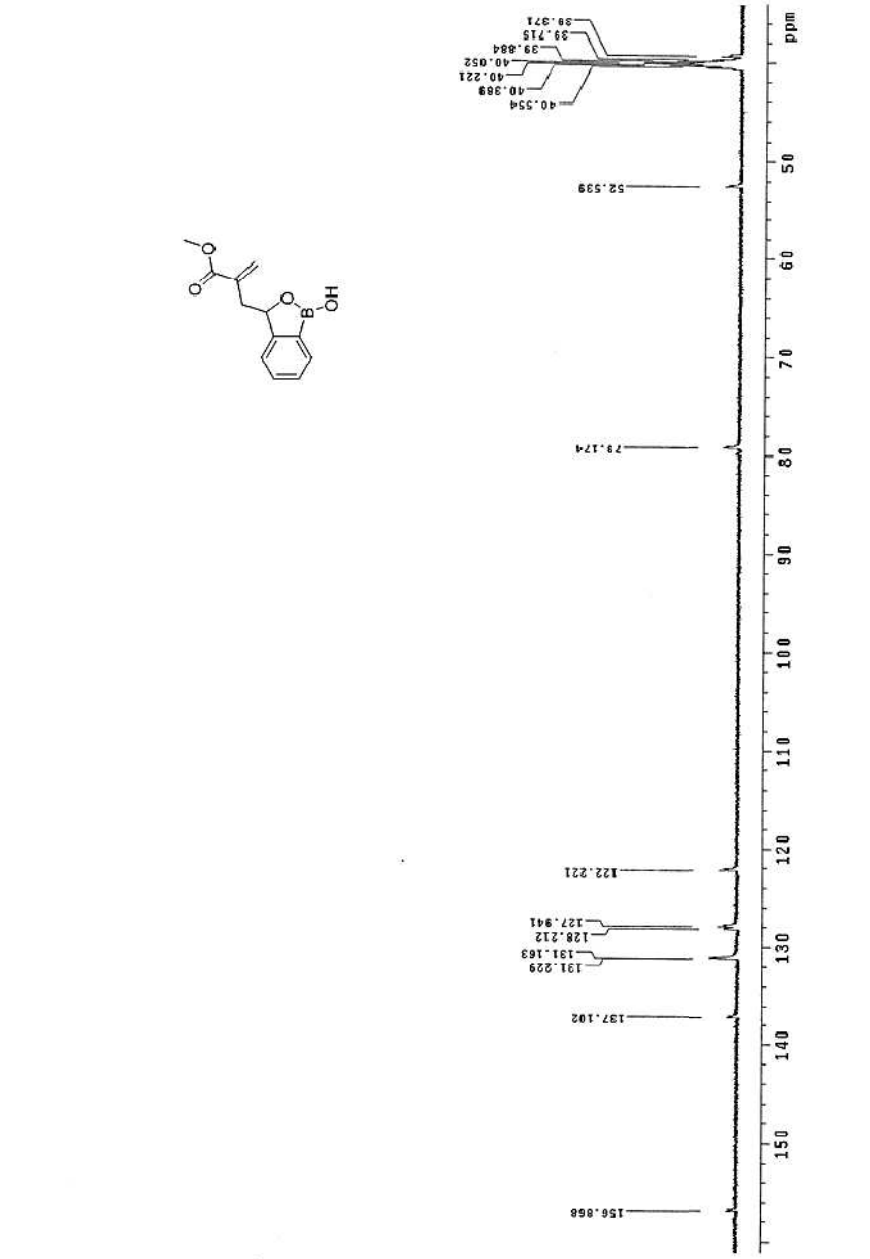
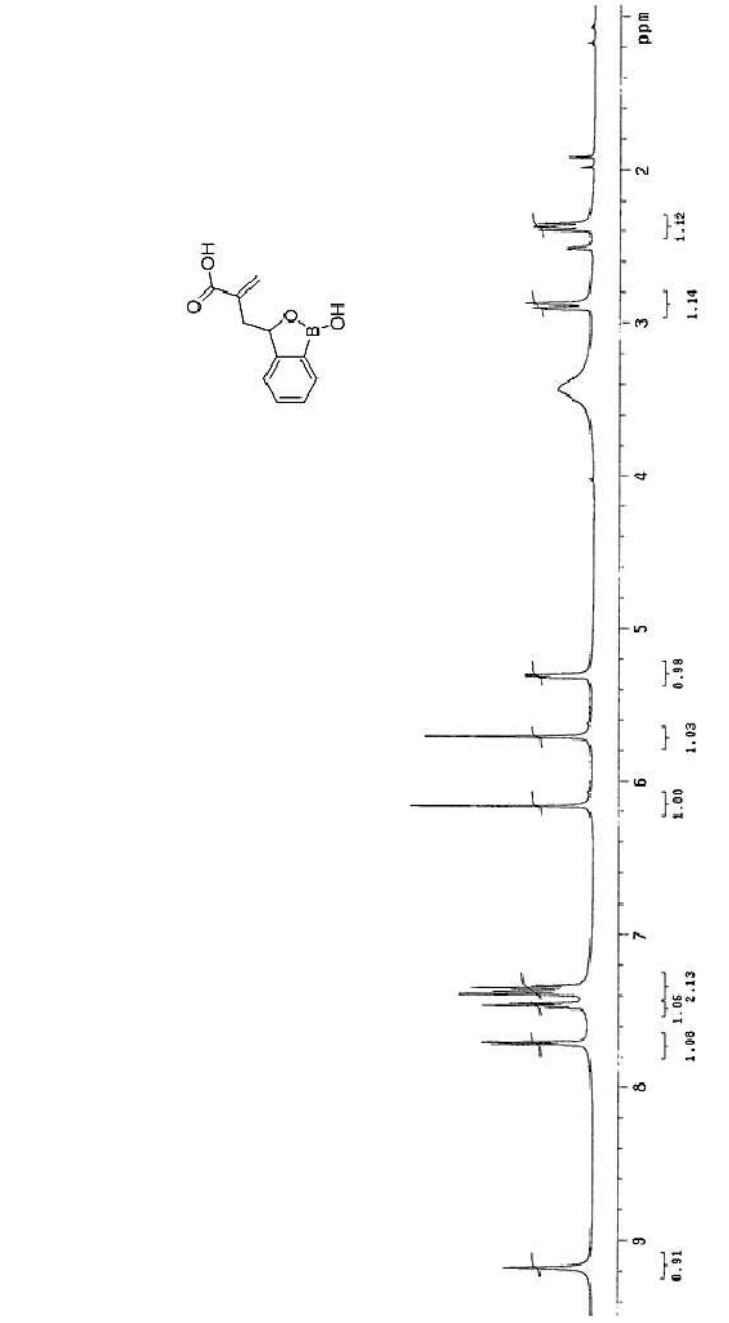
37.384

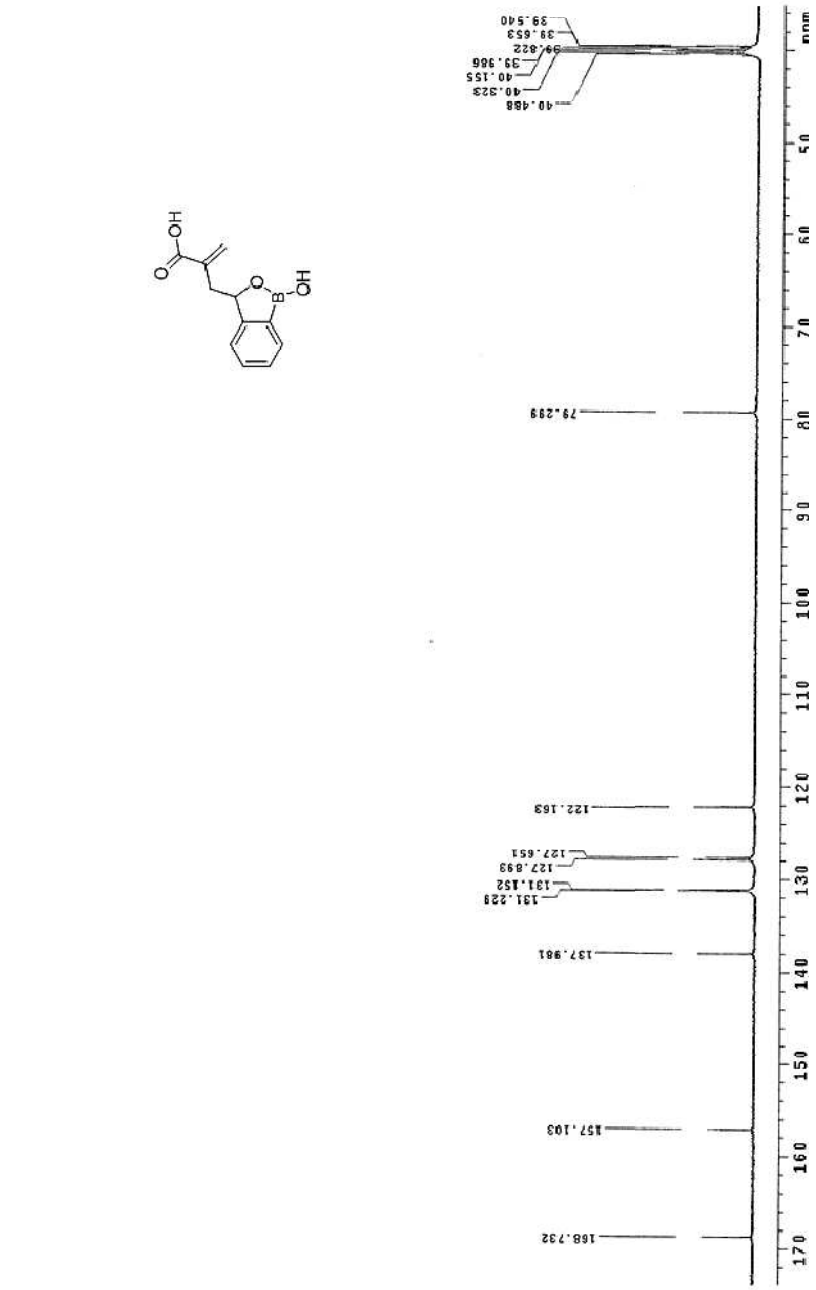

O
O
B
OH
ppm
1
2
3
4
5
6
7
8
9
1.07
1.10
3.47
1.09
1.00
4.67
1.15
4.33
2.26

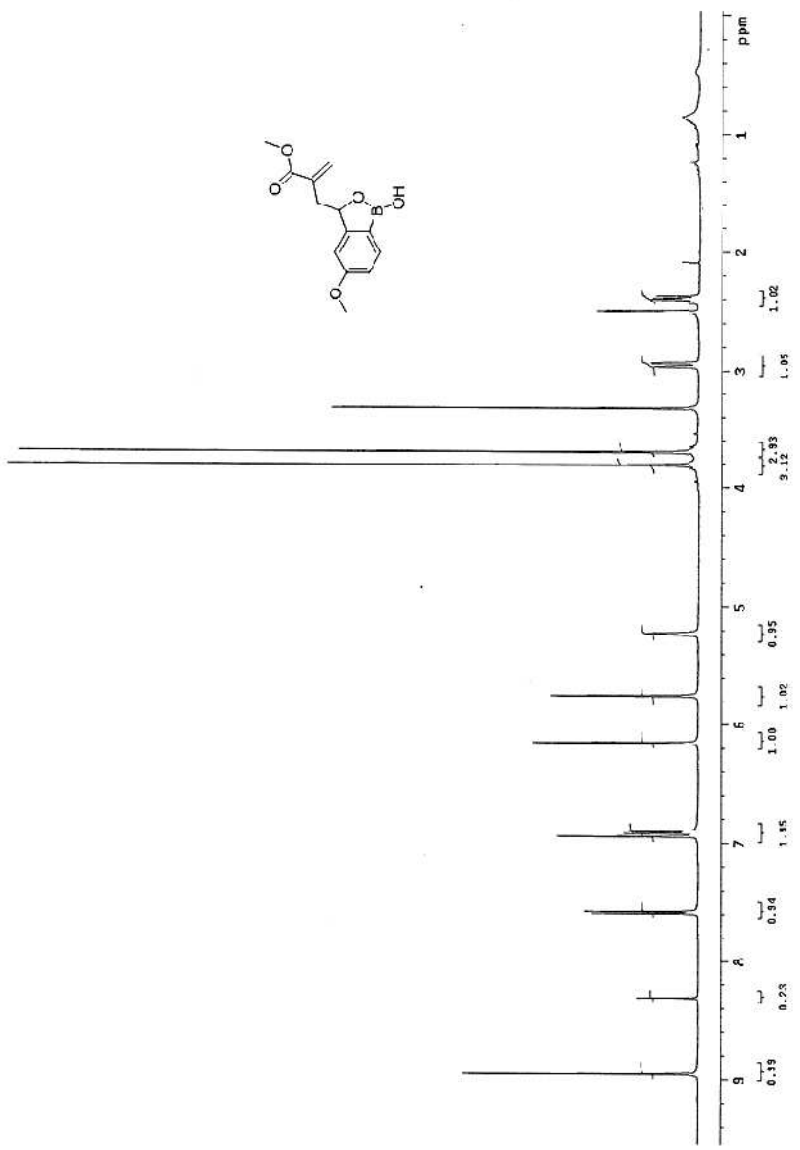

ppm
0
20
40
60
80
100
120
140
160
180
200
220
198.736
156.974
147.062
139.017
131.456
131.137
127.831
122.496
77.420
40.733
40.569
39.899
38.807
39.734
25.786
22.927
40.067
40.235
40.400
O
O
B
OH

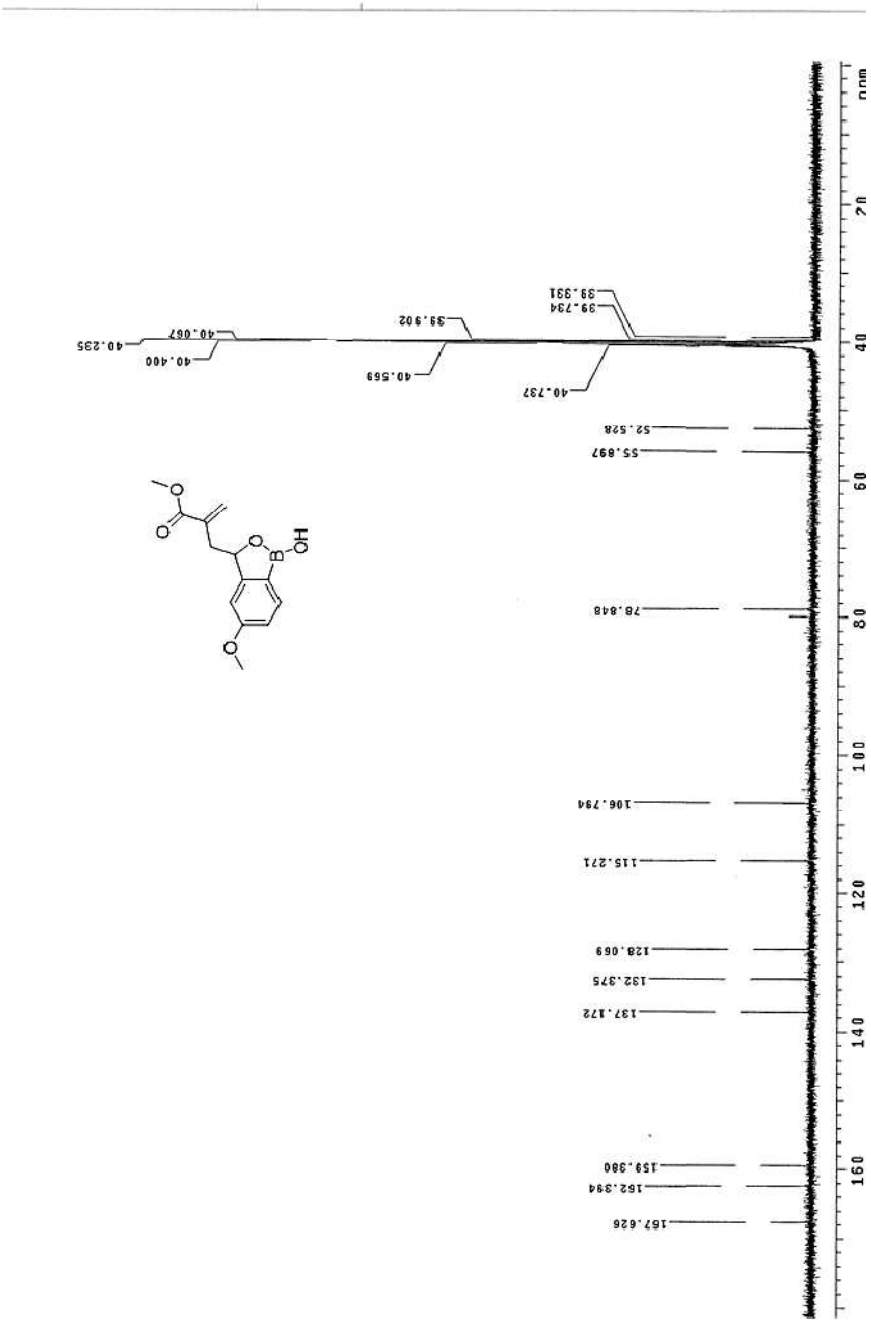

O
O
O
B
OH
ppm
1
2
3
4
5
6
7
8
9
3.00
1.06
0.49
1.06
0.98
1.04
1.01
2.08
1.10
0.96
0.14
1.01

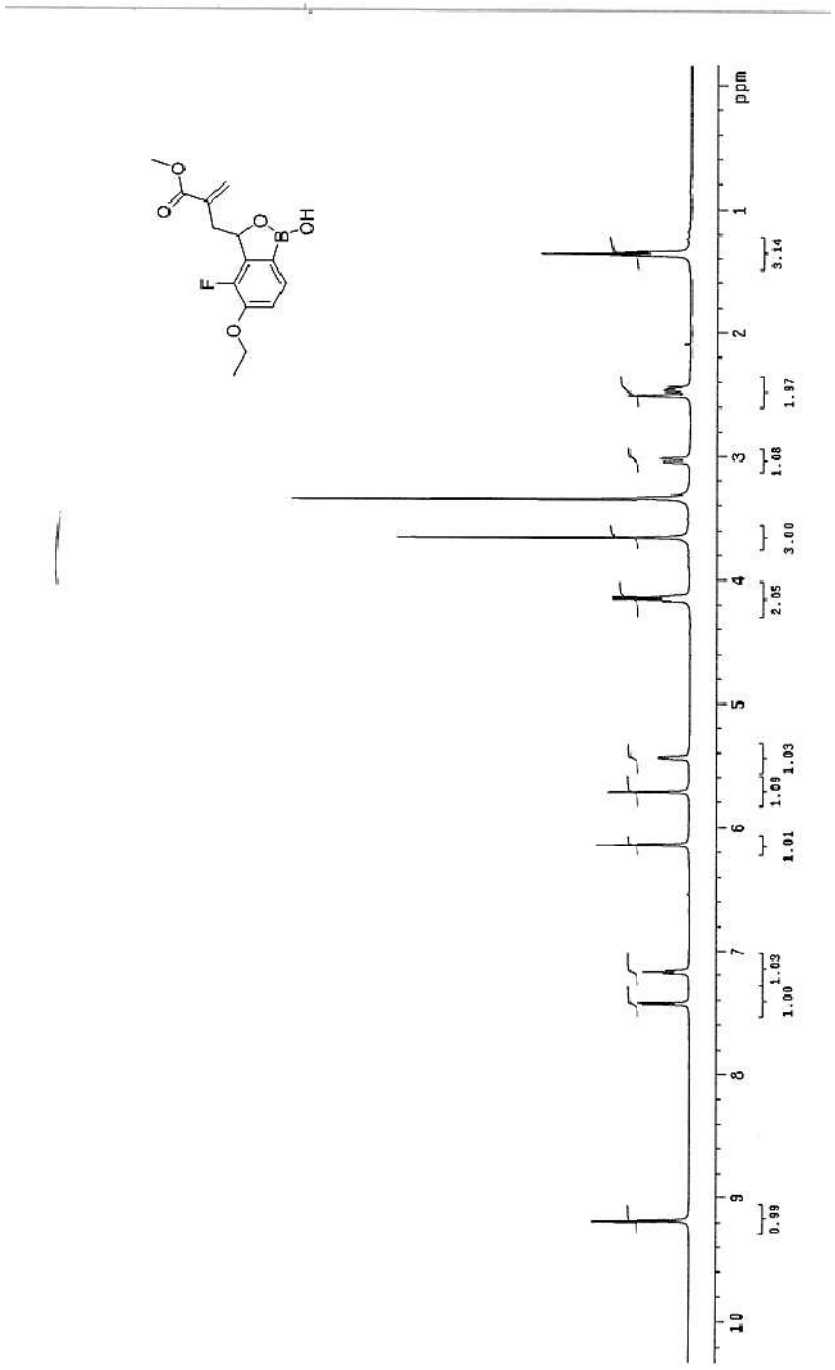

ppm
50
60
70
80
90
100
110
120
130
140
150
39.371
39.715
39.884
40.052
40.221
40.389
40.554
52.599
79.174
122.221
127.941
128.212
131.163
131.229
137.102
156.868
B
O
HO

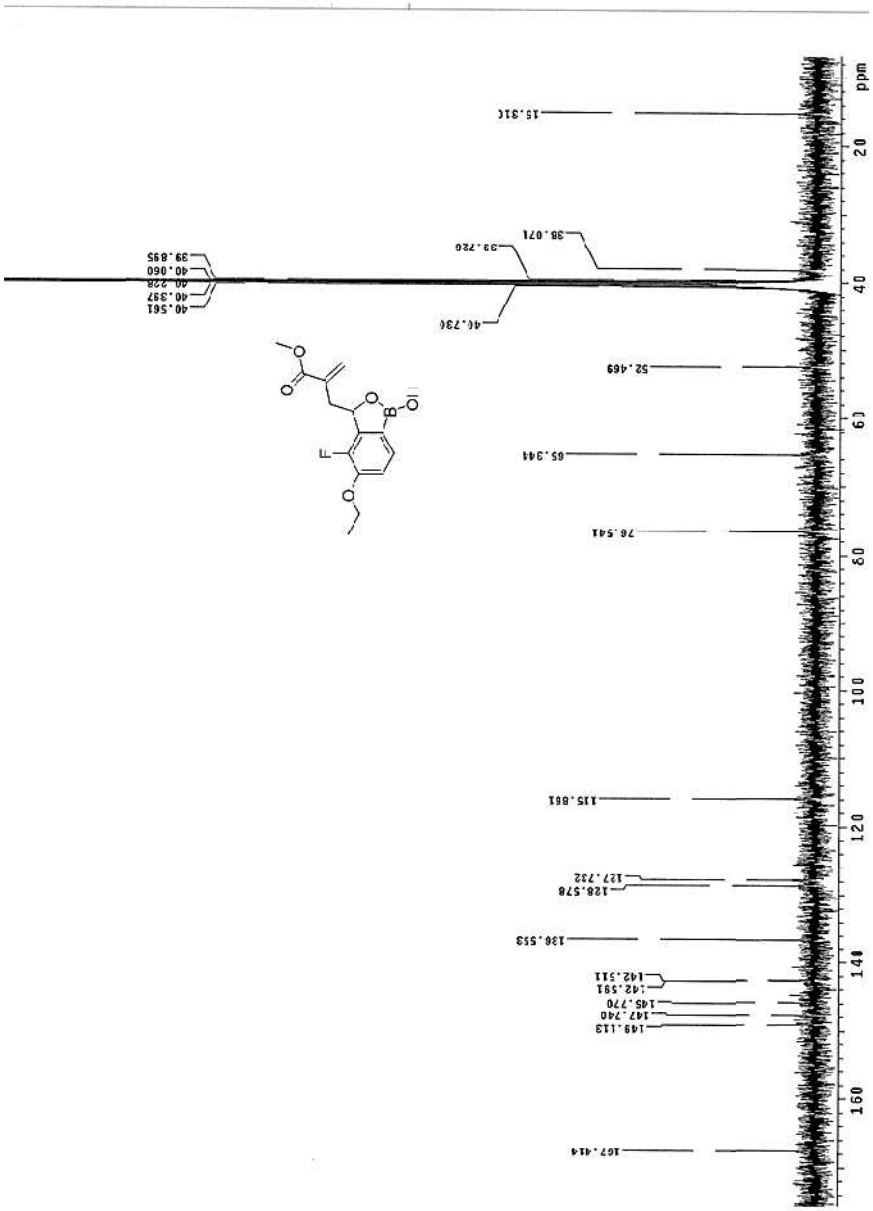

OH
O
O
B
OH
ppm
9
8
7
6
5
4
3
2
0.91
1.08
1.06
2.13
1.00
1.03
0.98
1.14
1.12

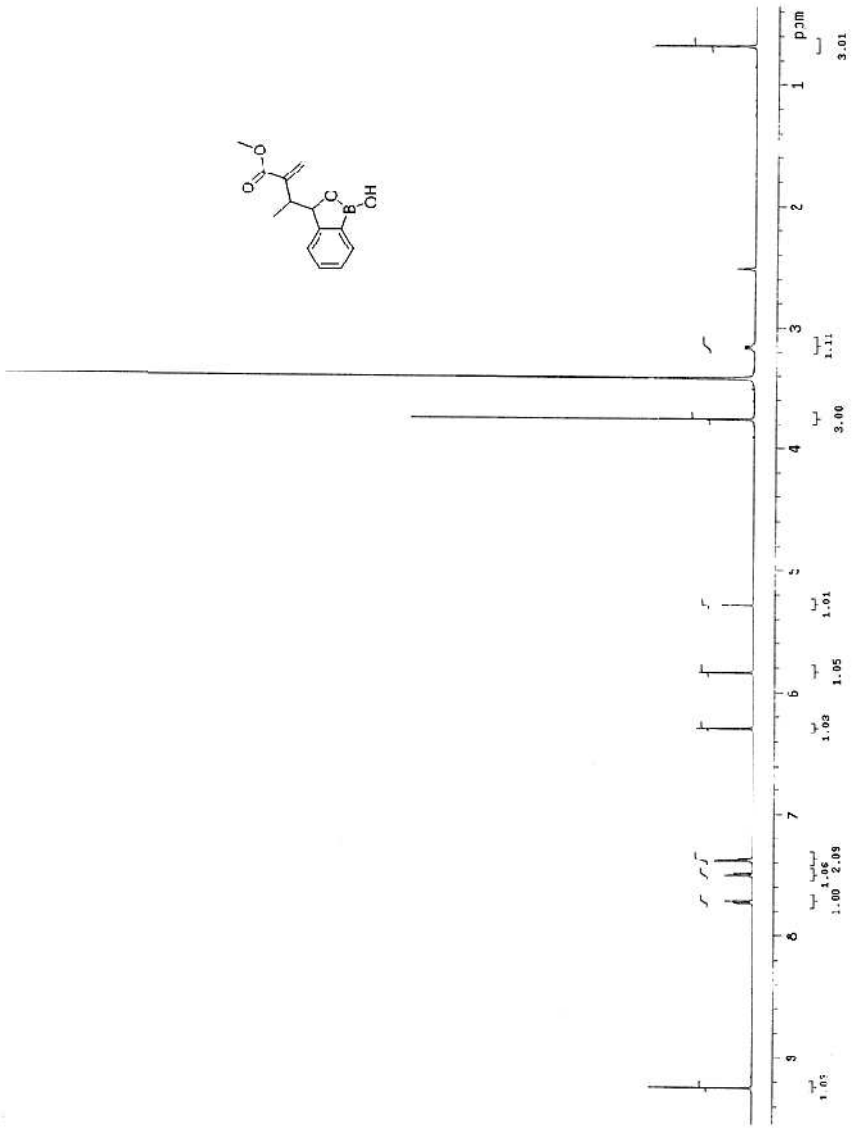

39.540
39.653
39.822
39.966
40.155
40.323
40.488
79.289
122.163
127.651
127.893
131.152
131.229
137.961
157.103
168.732
ppm

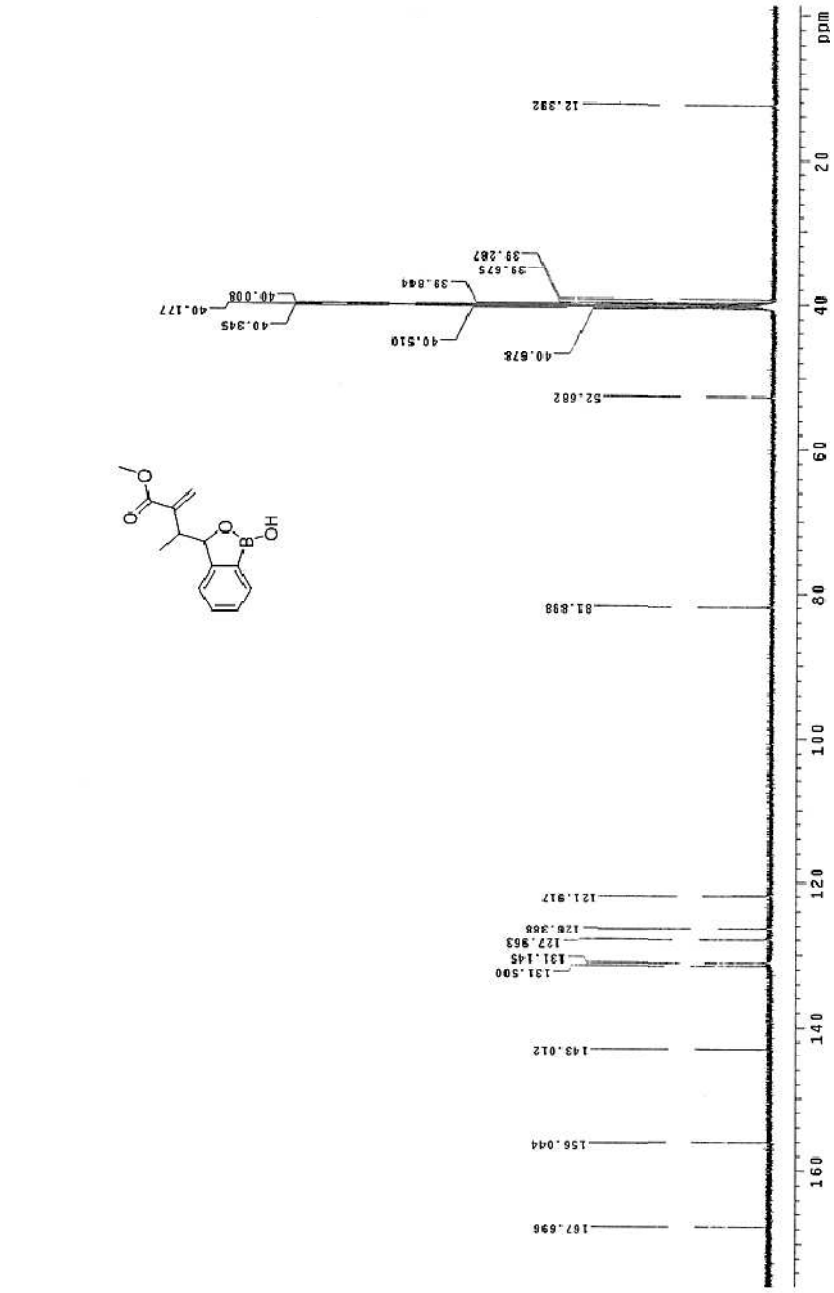

ppm

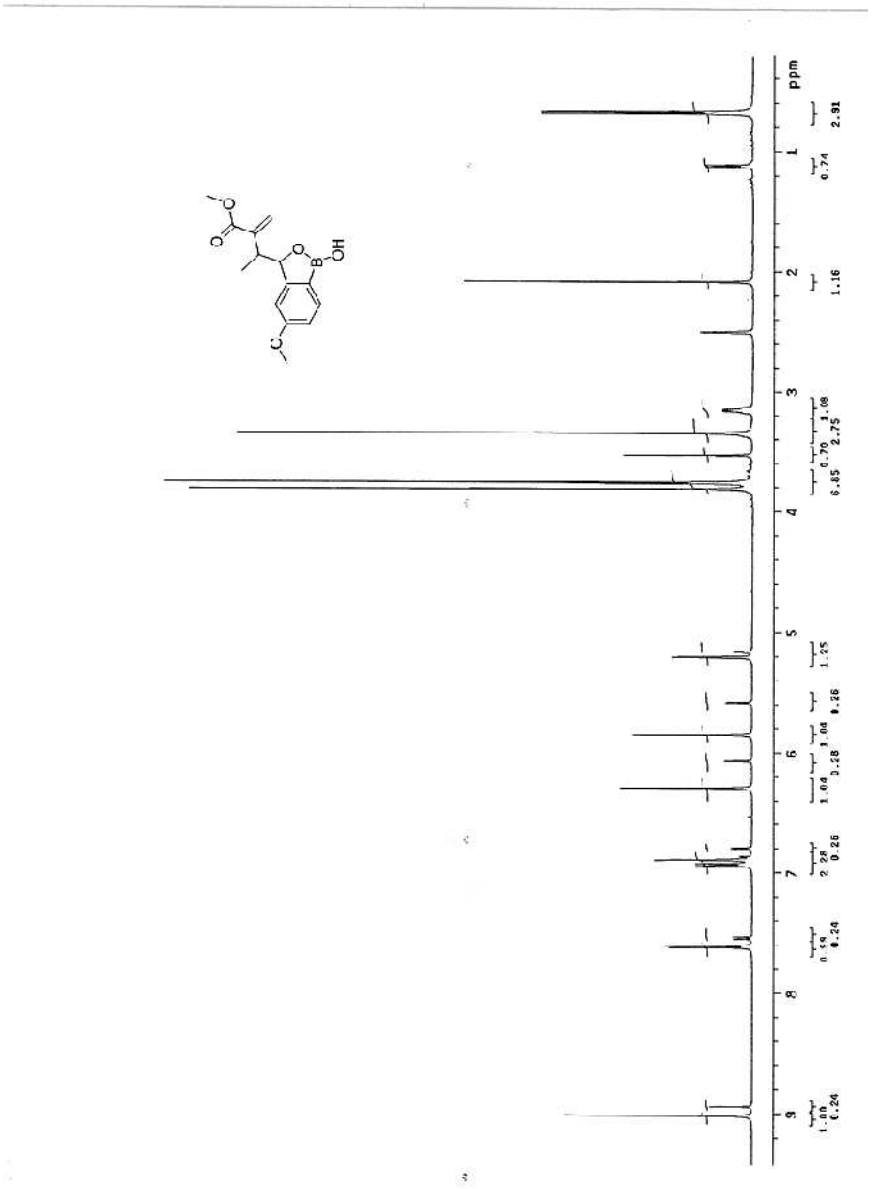

39.331
39.734
39.902
40.067
40.235
40.400
40.569
40.737
52.528
55.897
78.048
106.794
115.271
128.069
132.375
137.172
159.380
162.394
167.626
ppm

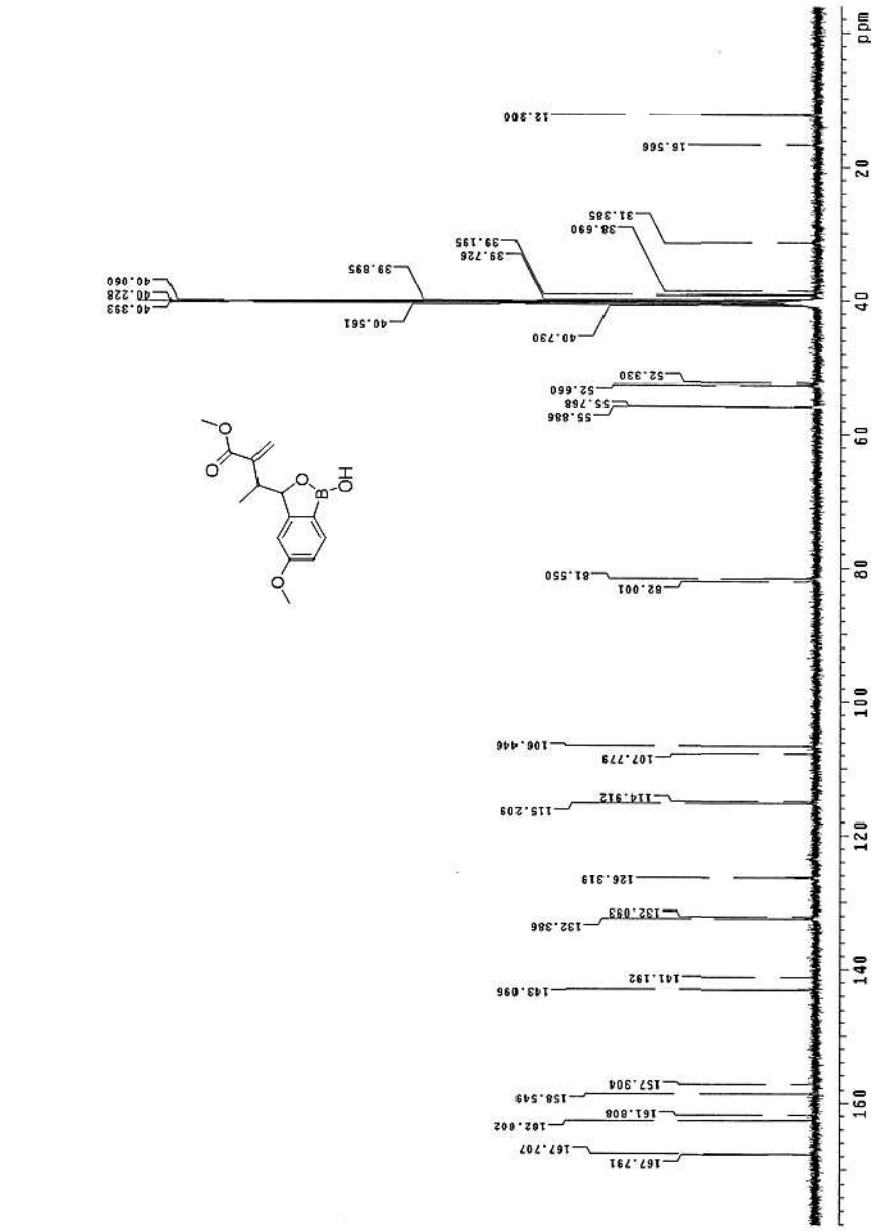

F
B
OH
O
ppm
0.99
1.00
1.03
1.01
1.09
1.03
2.05
3.00
1.08
1.97
3.14

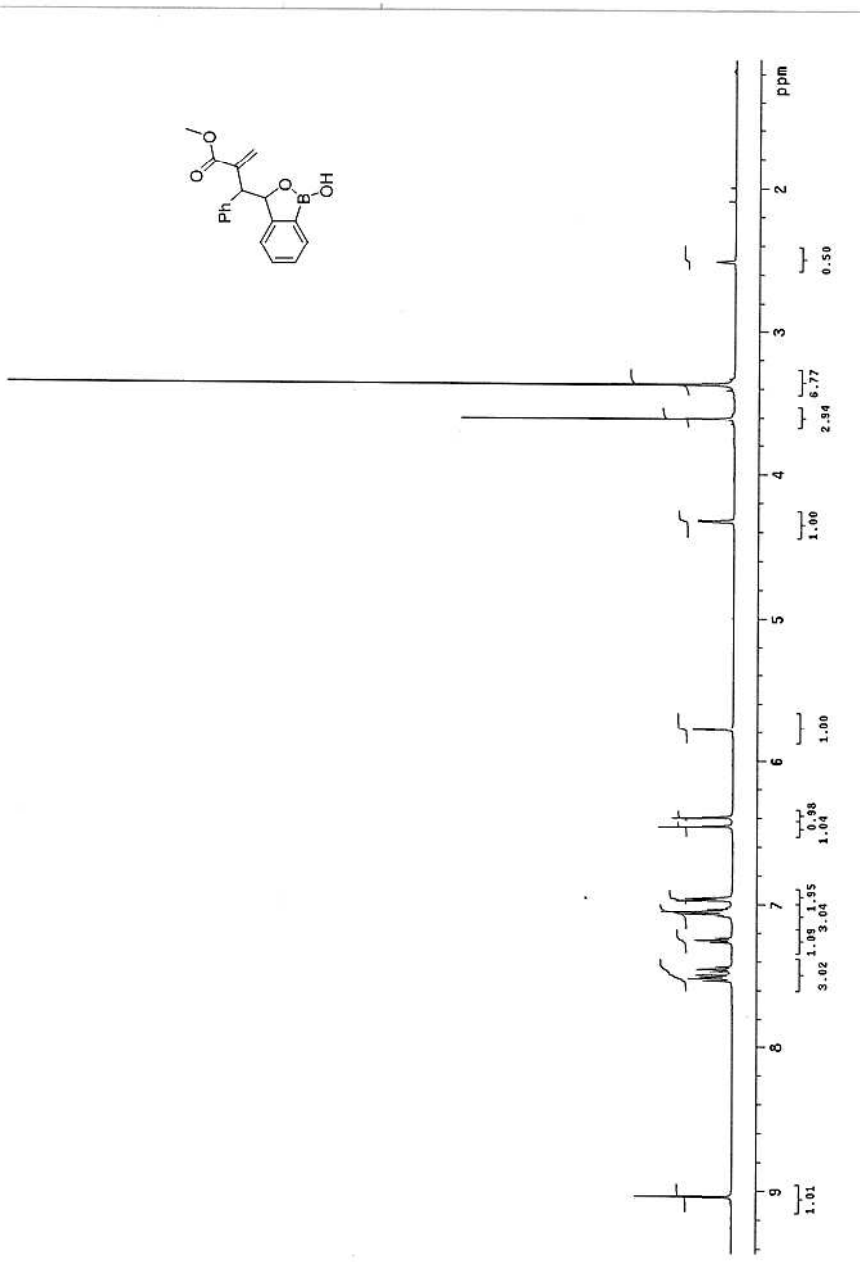

15.316
38.071
39.260
39.895
40.060
40.228
40.397
40.561
40.736
52.469
65.944
76.541
135.861
127.732
128.578
136.553
142.511
142.591
145.770
147.740
149.113
167.444
ppm
20
40
60
80
100
120
140
160
F
O
B
O

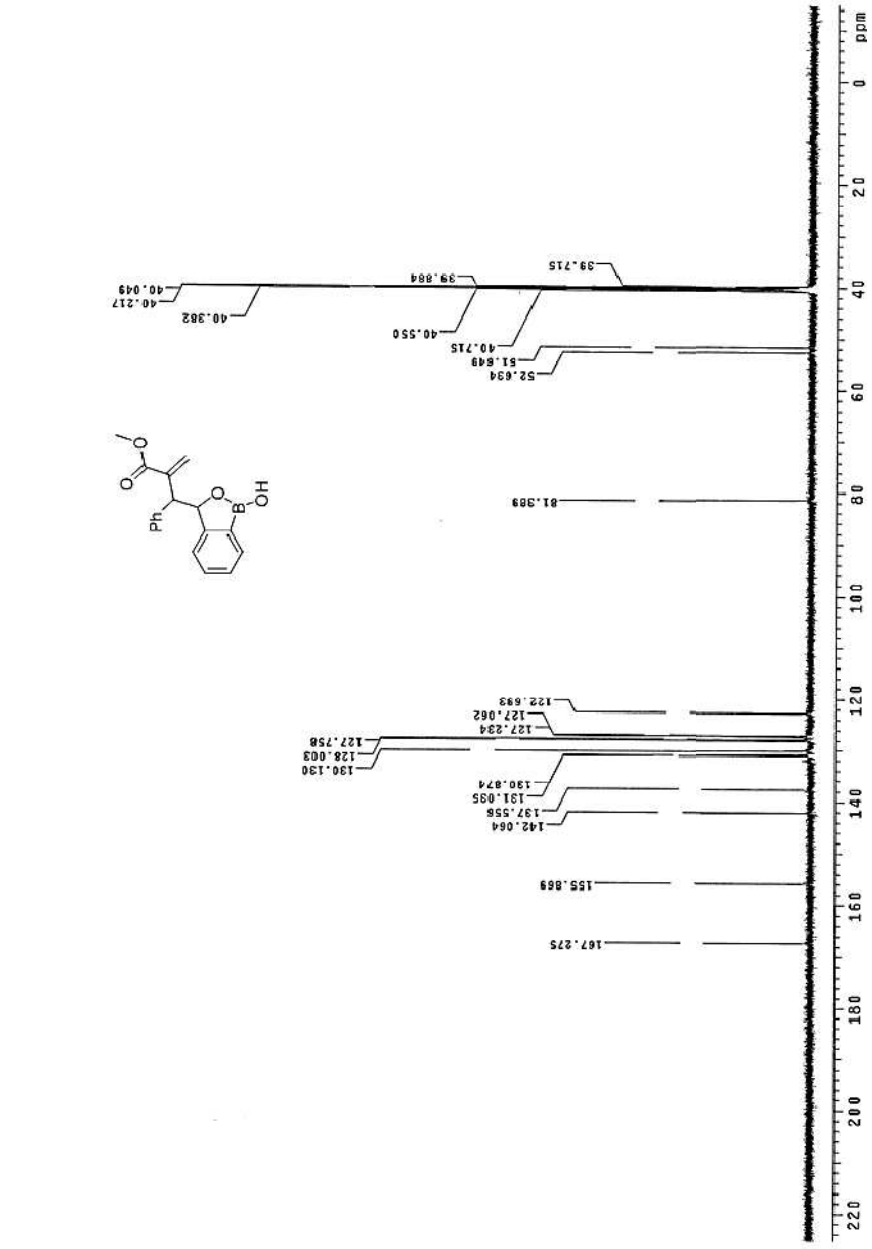


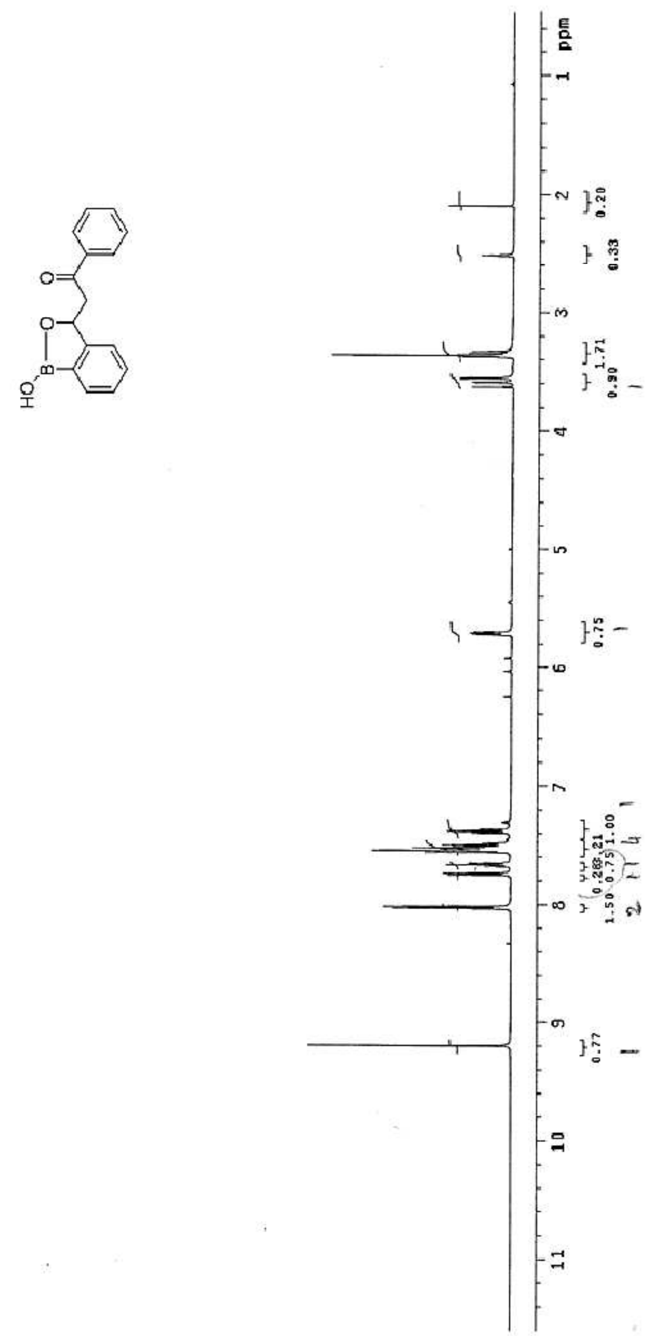

ppm
20
40
60
80
100
120
140
160
12.382
39.287
39.675
39.844
40.008
40.177
40.345
40.510
40.678
52.682
81.898
121.917
128.368
127.963
131.145
131.500
143.012
156.044
167.696
O
O
B
OH

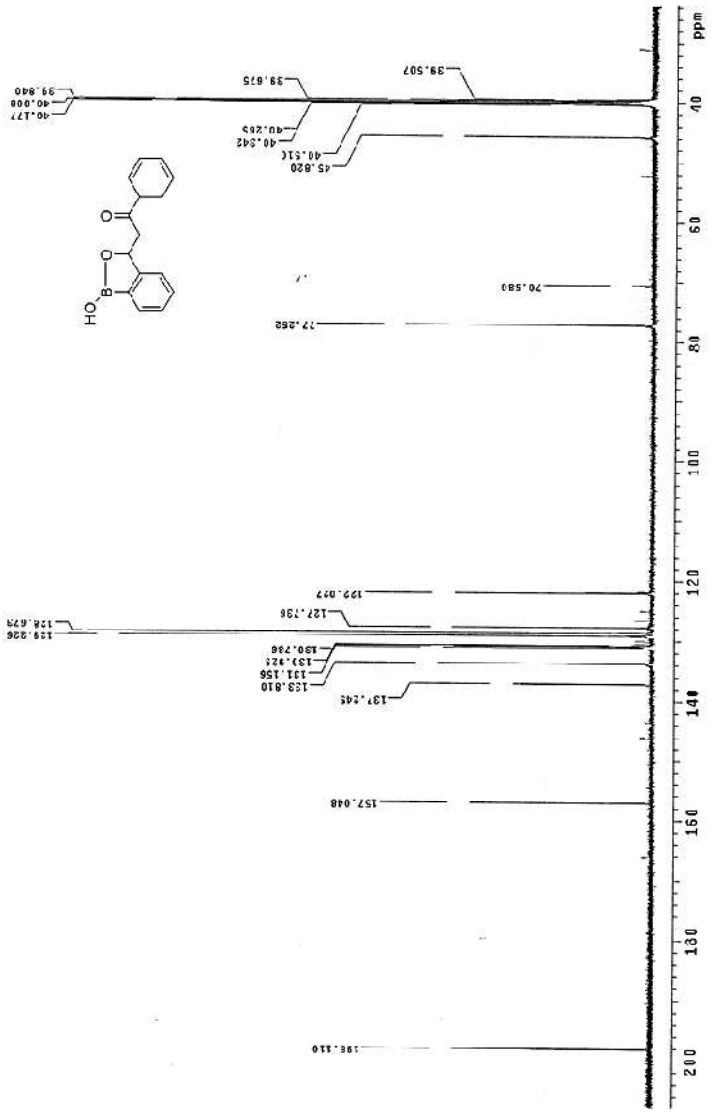

OH
ppm

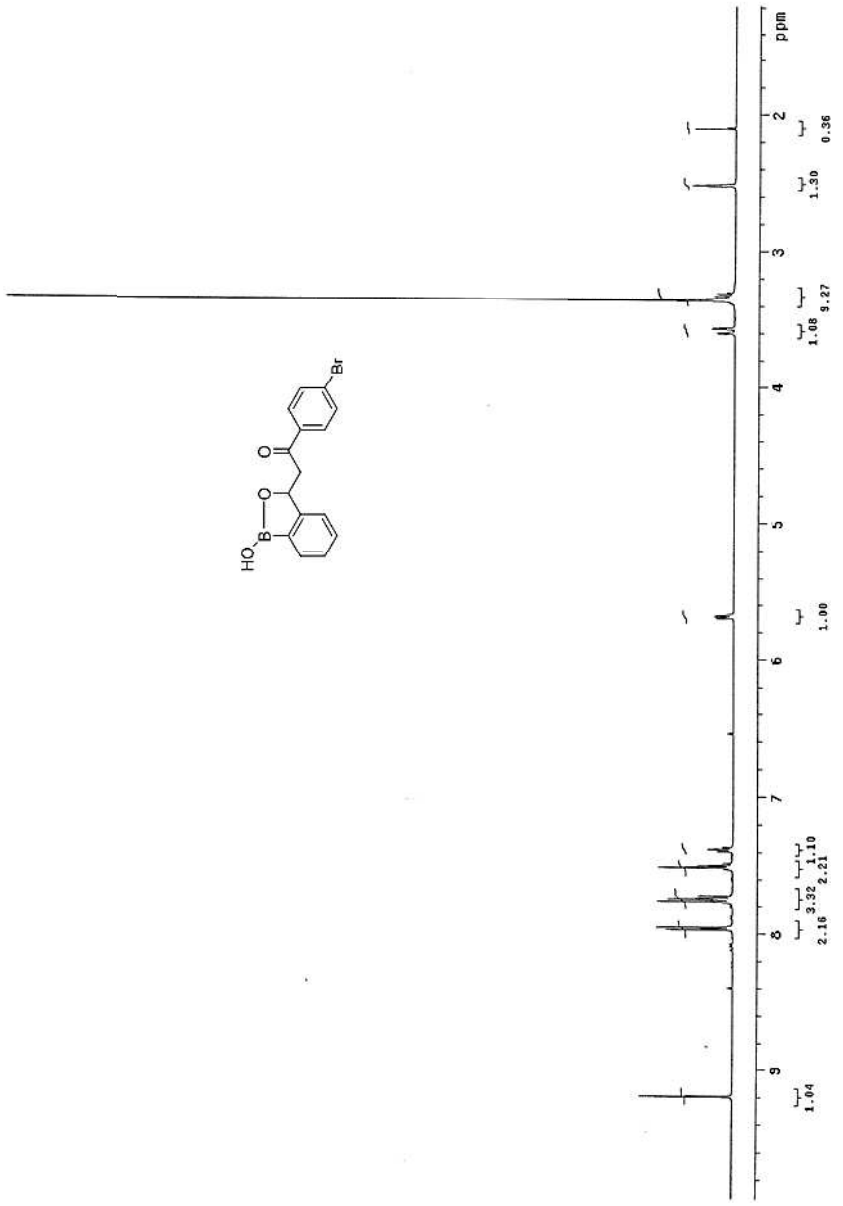

12.300
18.566
31.385
38.690
39.135
39.728
39.895
40.060
40.228
40.393
40.561
40.730
52.330
52.660
55.768
55.886
61.550
82.001
106.446
107.779
114.912
115.209
126.319
132.083
132.386
141.192
143.096
157.304
158.549
161.808
162.602
167.707
167.791
ppm
20
40
60
80
100
120
140
160
O
O
O
B
OH
O

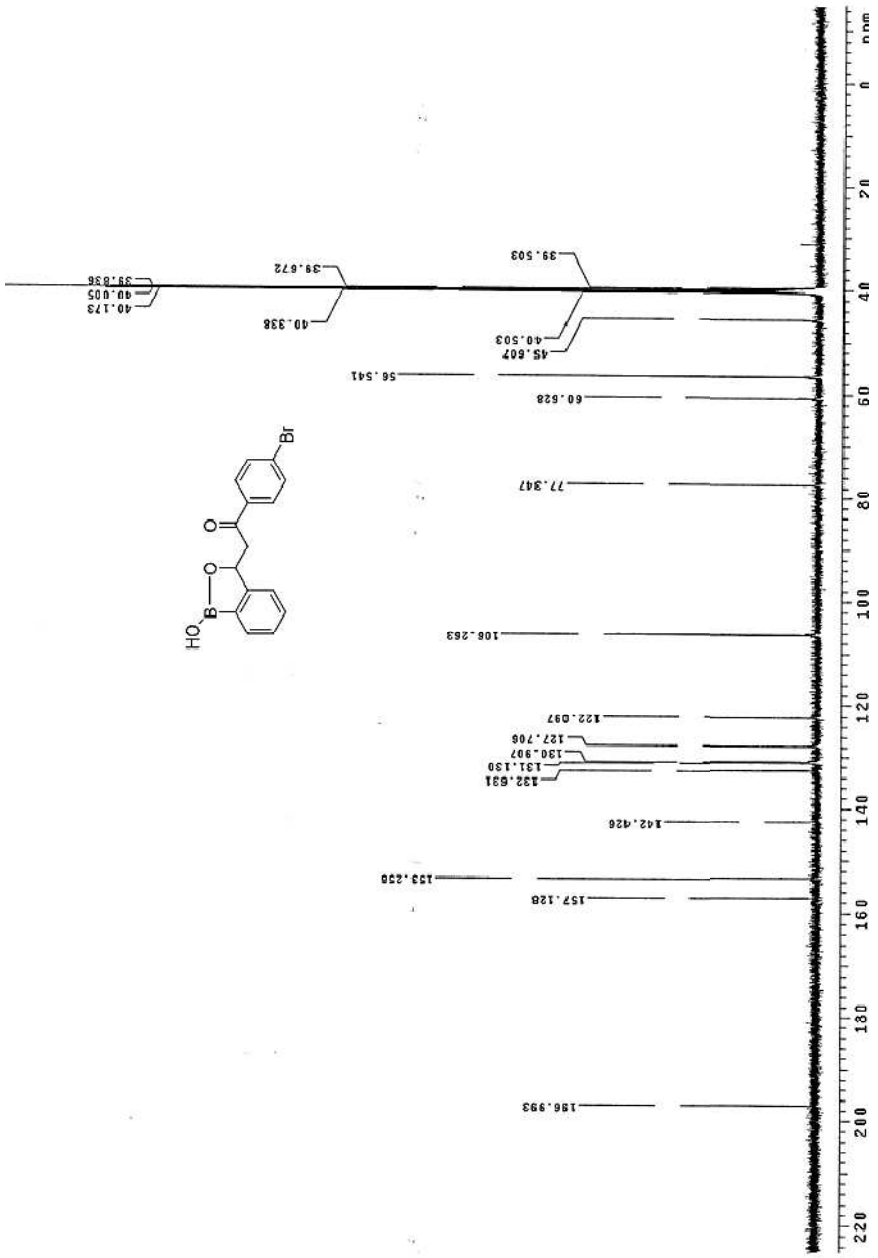

Ph
O
B
OH
ppm
1.01
3.02
1.09
1.55
3.04
0.98
1.04
1.00
1.00
6.77
2.94
0.50

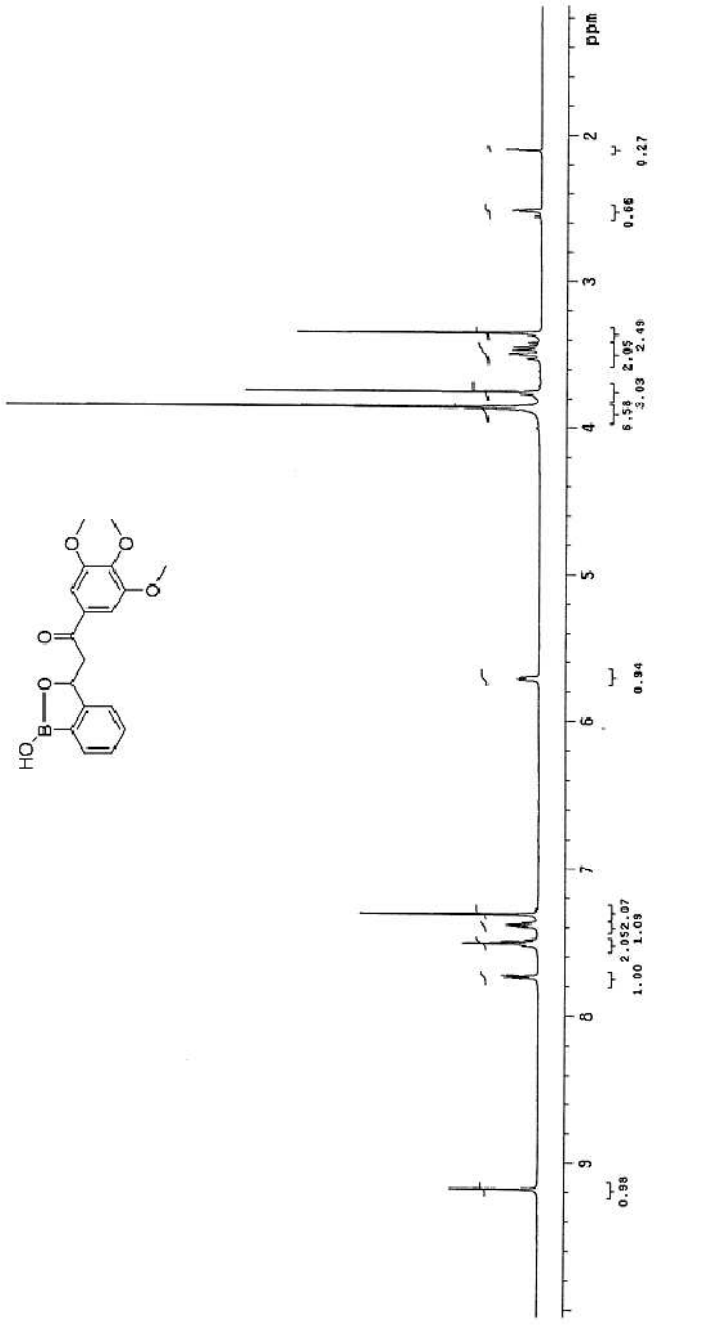

39.715
39.884
40.049
40.217
40.382
40.550
40.715
51.849
52.694
81.389
122.693
127.062
127.234
127.758
128.003
130.130
130.874
131.085
137.558
142.064
155.869
167.275
ppm
0
20
40
60
80
100
120
140
160
180
200
220
O
O
Ph
O
B
OH

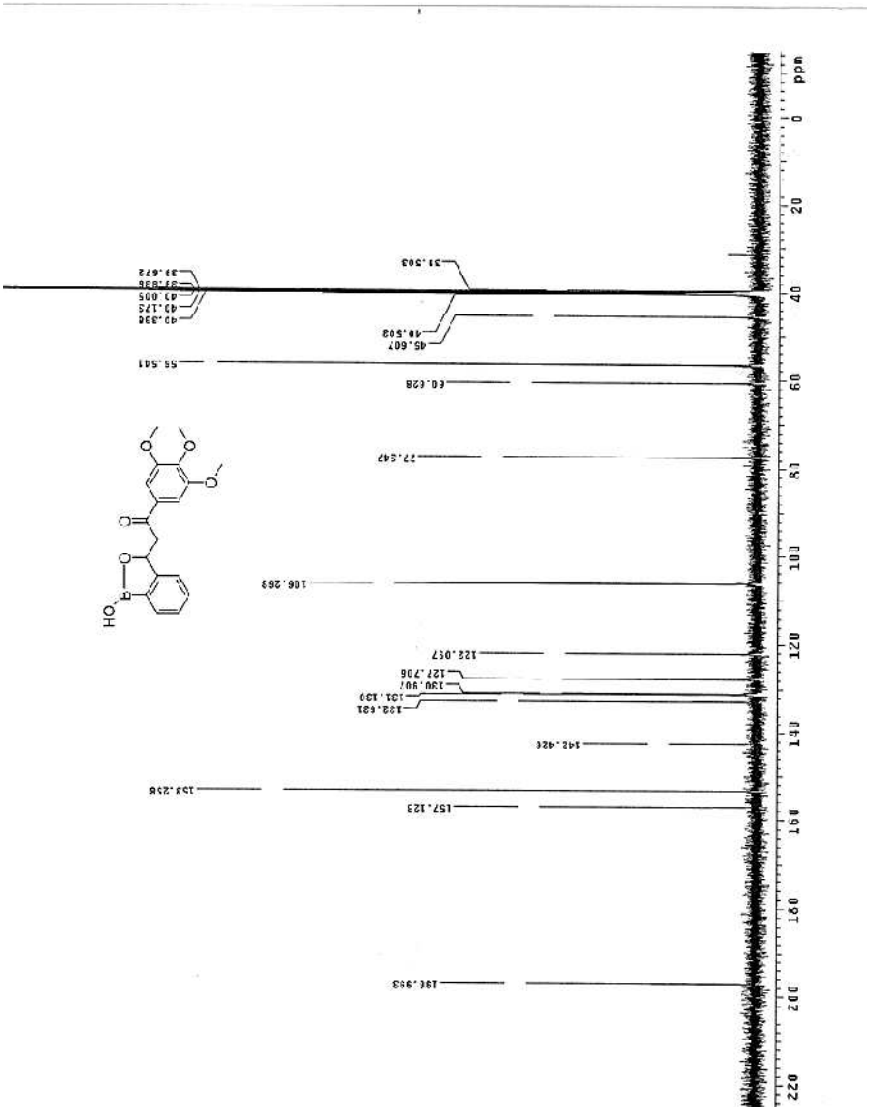


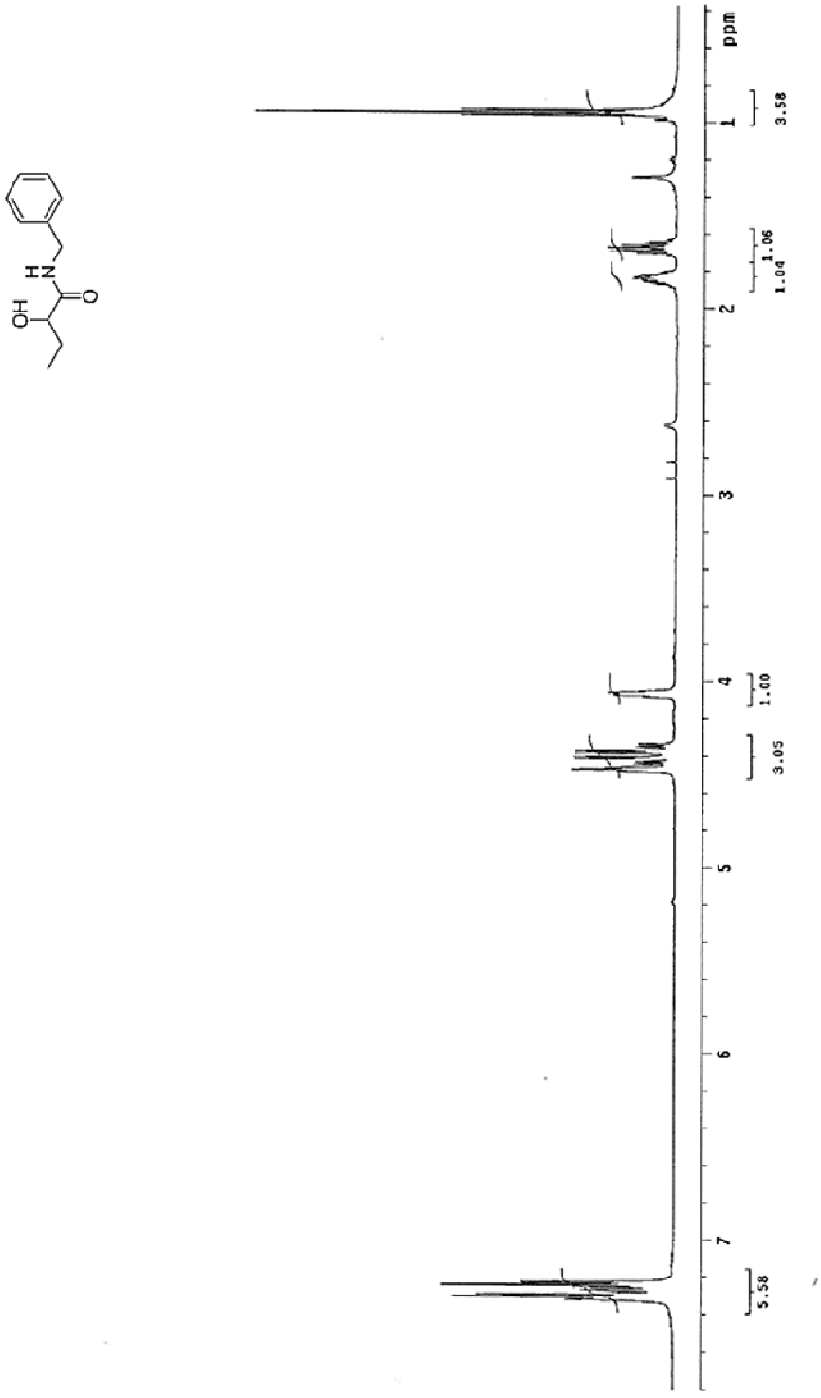

ppm
39.507
39.675
39.840
40.008
40.177
40.342
40.510
40.679
40.847
45.820
70.580
77.262
127.136
128.473
129.026
130.736
131.156
133.925
133.810
137.245
157.048
196.110

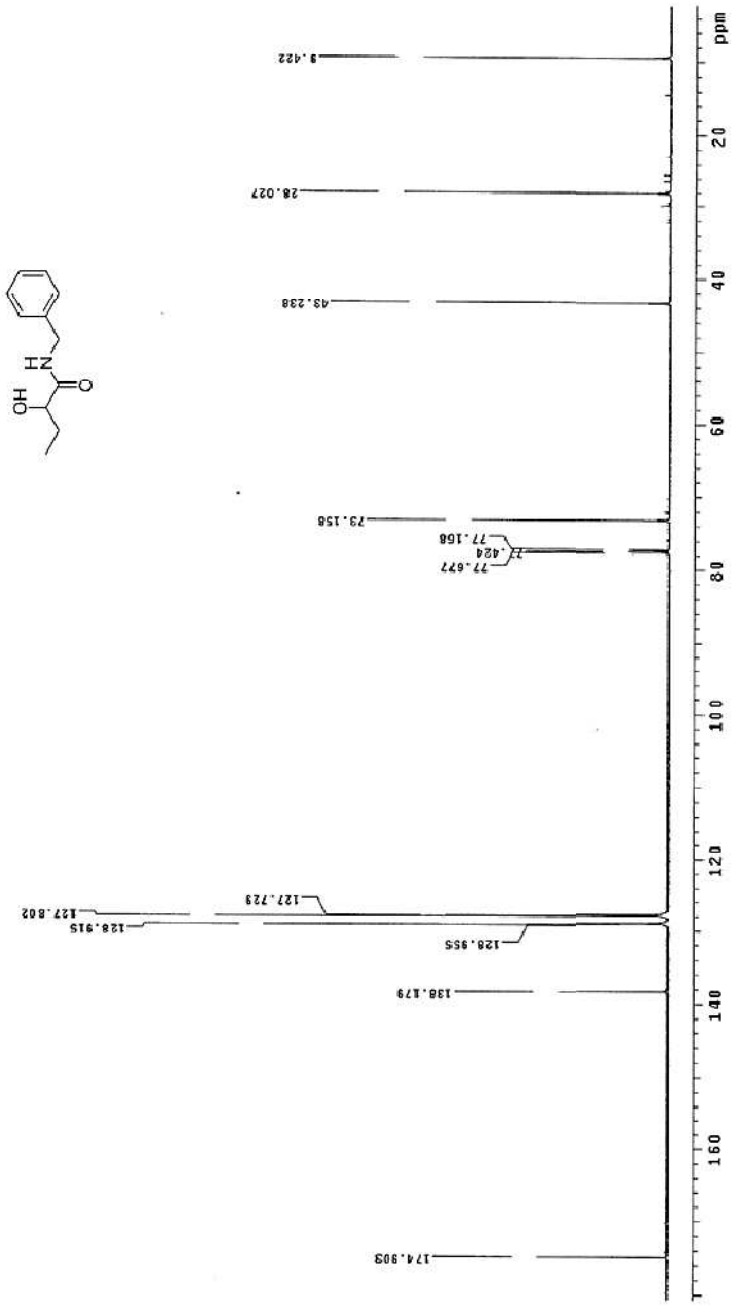

Br
O
O
B
HO
ppm
1.04
2.16
3.32
1.10
2.21
1.00
1.08
9.27
1.30
0.36

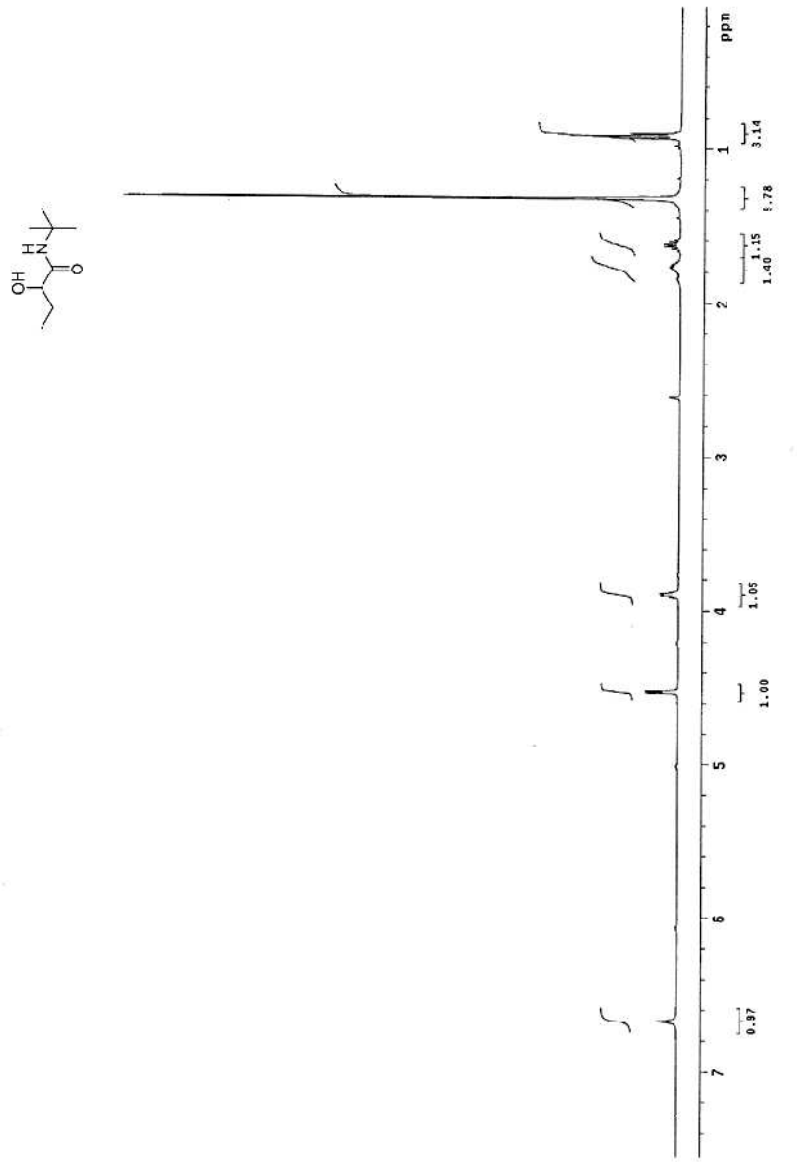

39.503
39.672
39.836
40.005
40.173
40.338
40.503
45.607
56.541
60.628
77.347
106.263
122.097
127.706
130.907
131.130
132.631
142.426
153.238
157.128
186.993
Br
O
O
B
HO

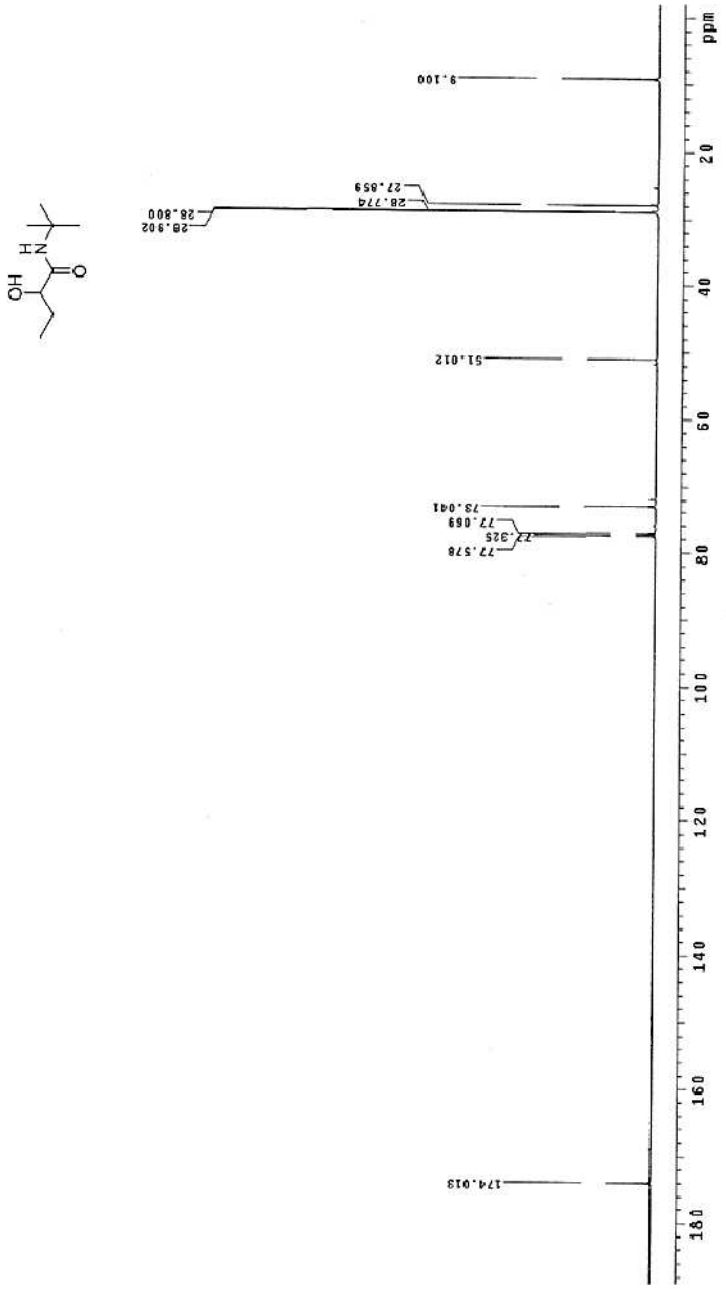

ppm
1
2
3
4
5
6
7
8
9
0.98
1.00
2.05
2.07
1.09
6.58
3.03
2.05
2.49
0.66
0.27
0.94
HO
B
O
O
O
O
O

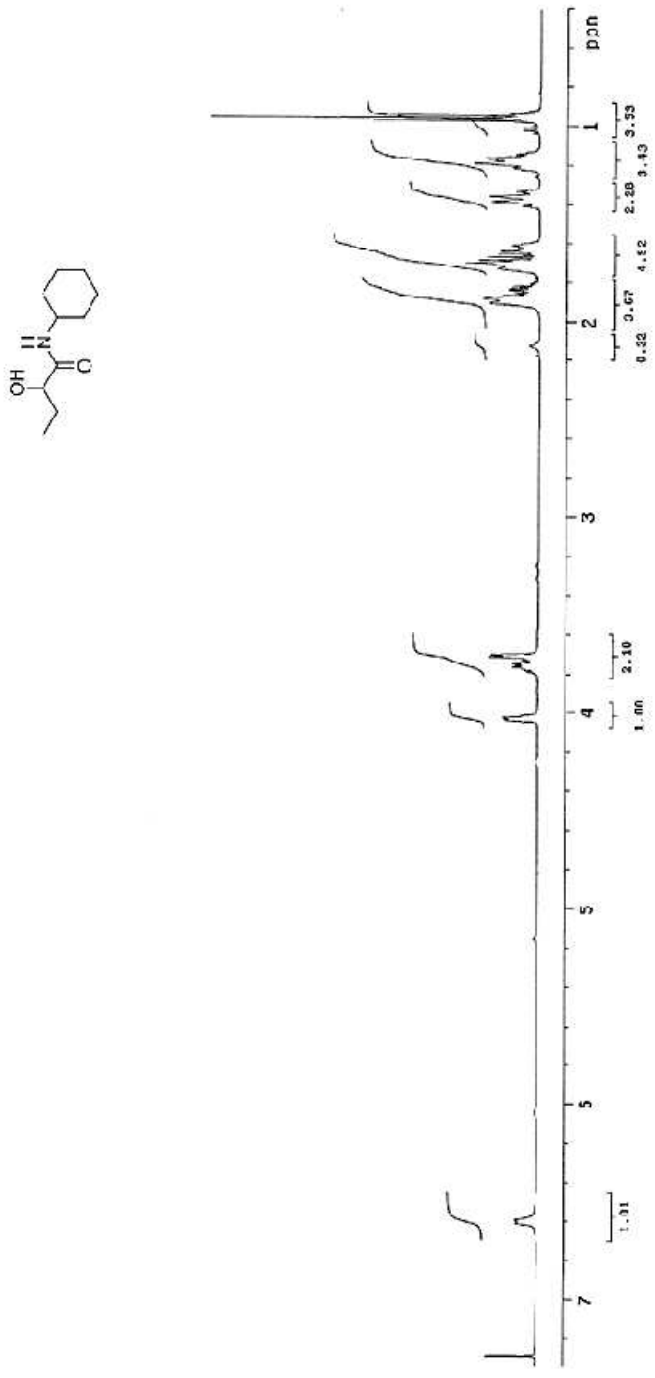

ppm
0
20
40
60
80
100
120
140
160
180
200
220
31.503
45.607
49.503
55.501
60.628
77.342
106.269
122.057
127.706
130.997
131.130
132.631
142.426
153.256
157.123
196.953
HO

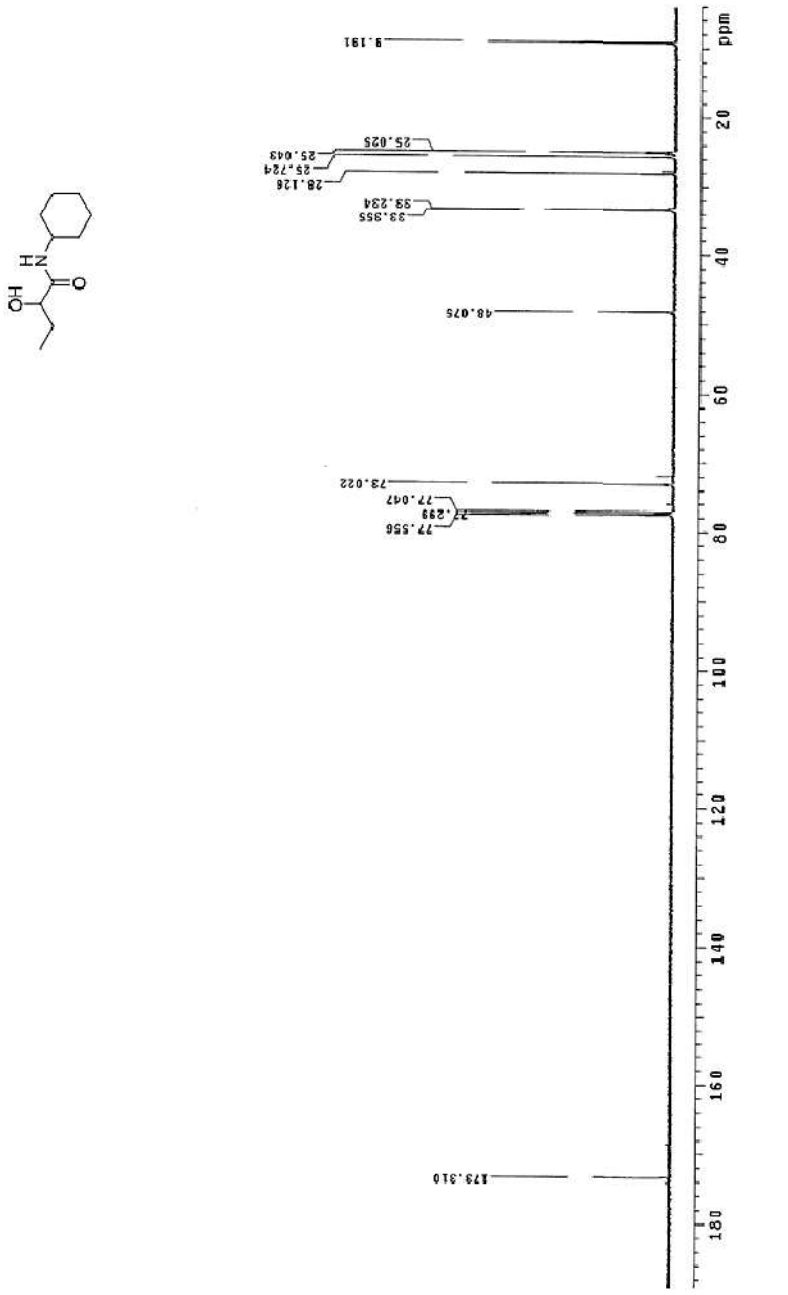

H
N
O
OH
ppm
1
2
3
4
5
6
7
3.58
1.06
1.04
1.00
3.05
5.58

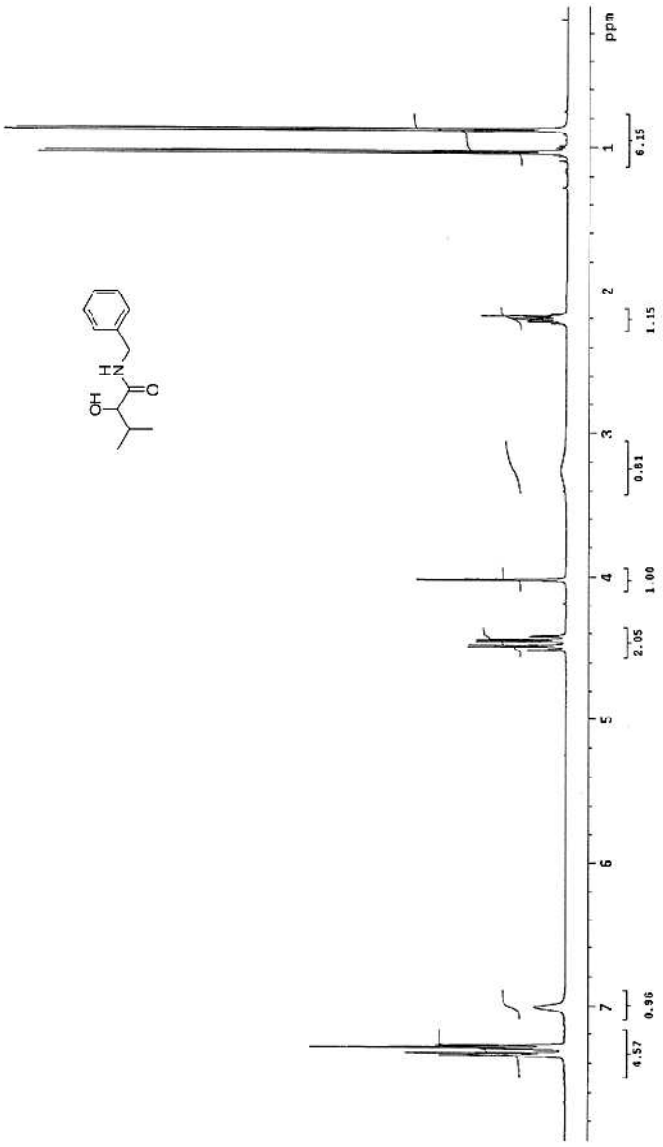

174.903
138.479
128.955
128.915
127.802
127.729
77.677
77.424
77.168
73.158
43.238
28.027
9.422
ppm

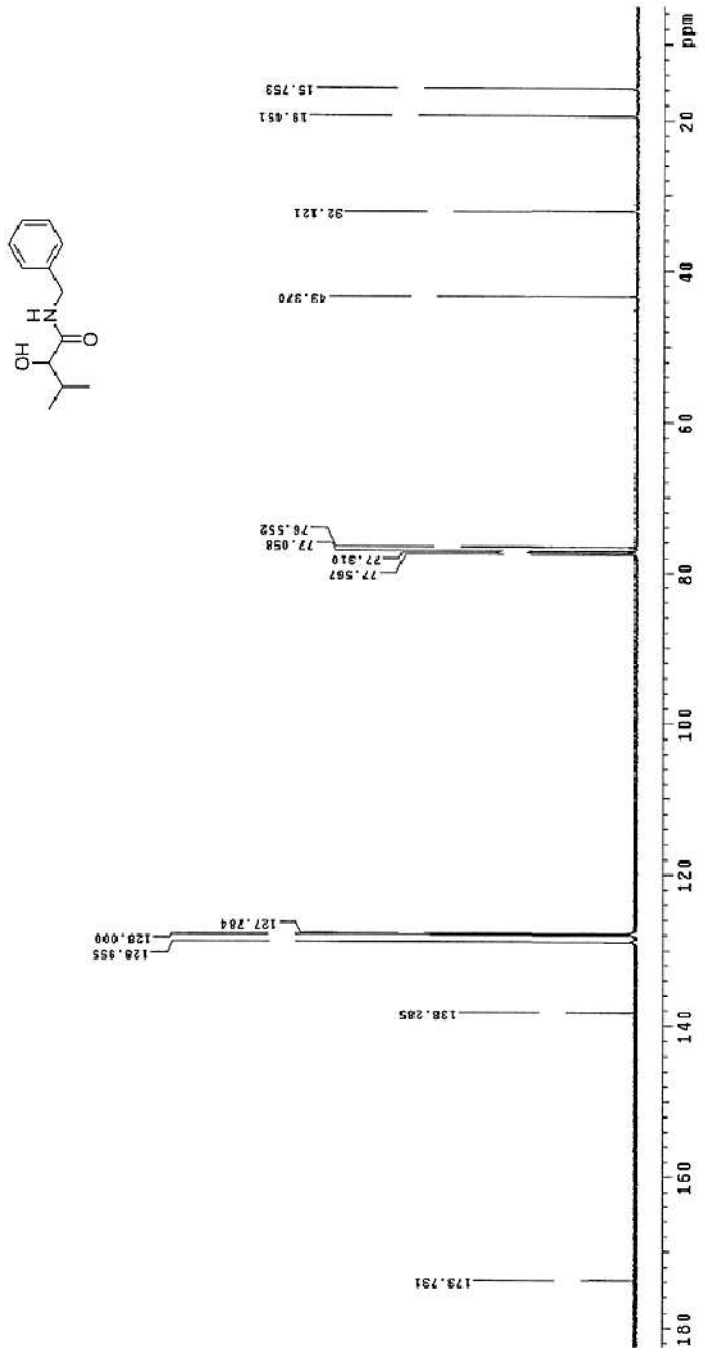

OH
H
N
O
ppm
1
2
3
4
5
6
7
3.14
1.78
1.15
1.40
1.05
1.00
0.97

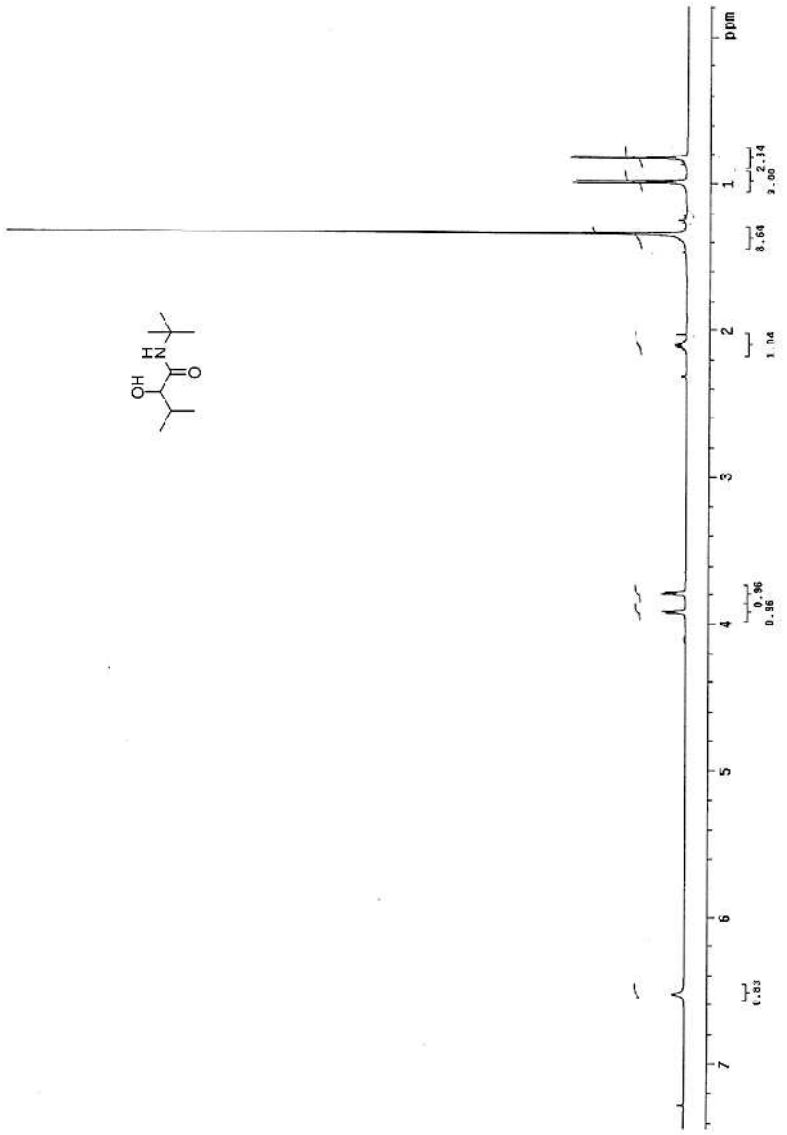

OH
NH
O
174.013
77.578
77.325
77.069
73.041
51.012
28.902
28.800
28.774
27.859
9.100
ppm
180
160
140
120
100
80
60
40
20

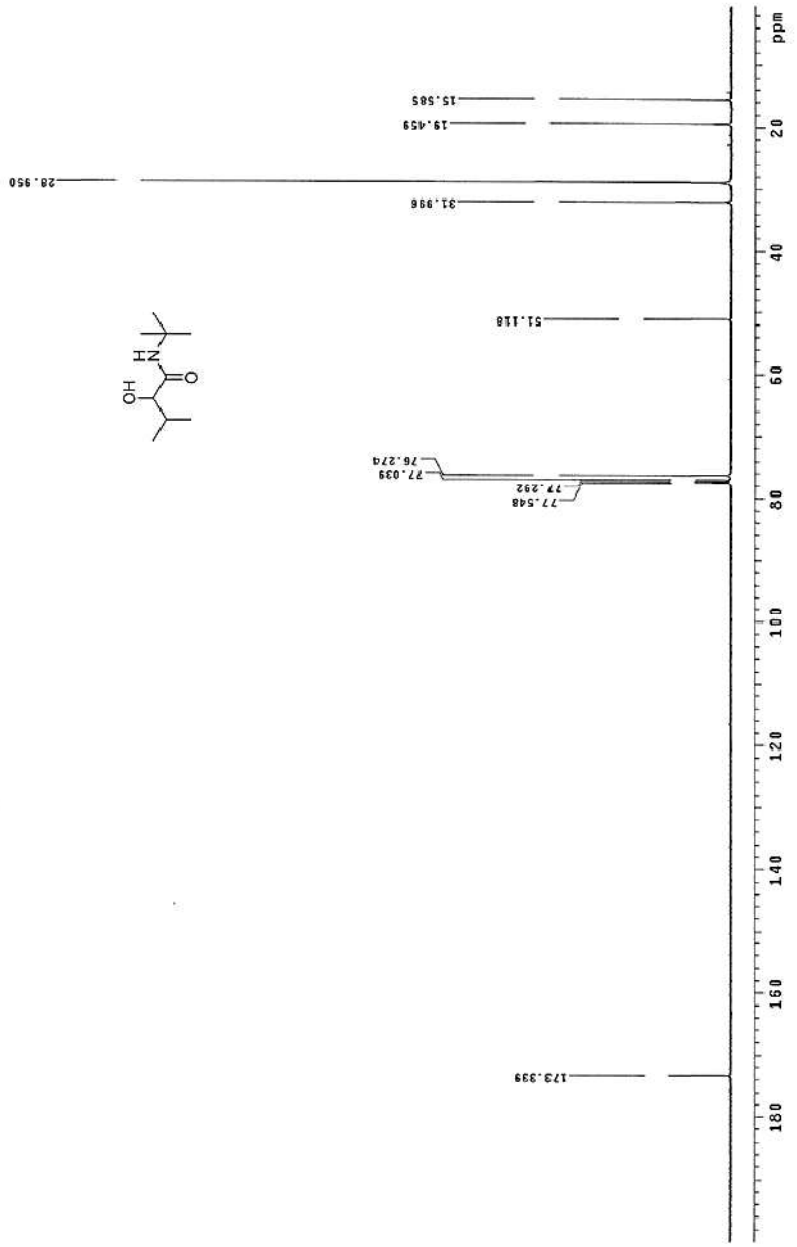

OH
H
N
O
ppm
1
2
3
4
5
6
7
3.33
3.43
4.52
2.10
1.00
1.31

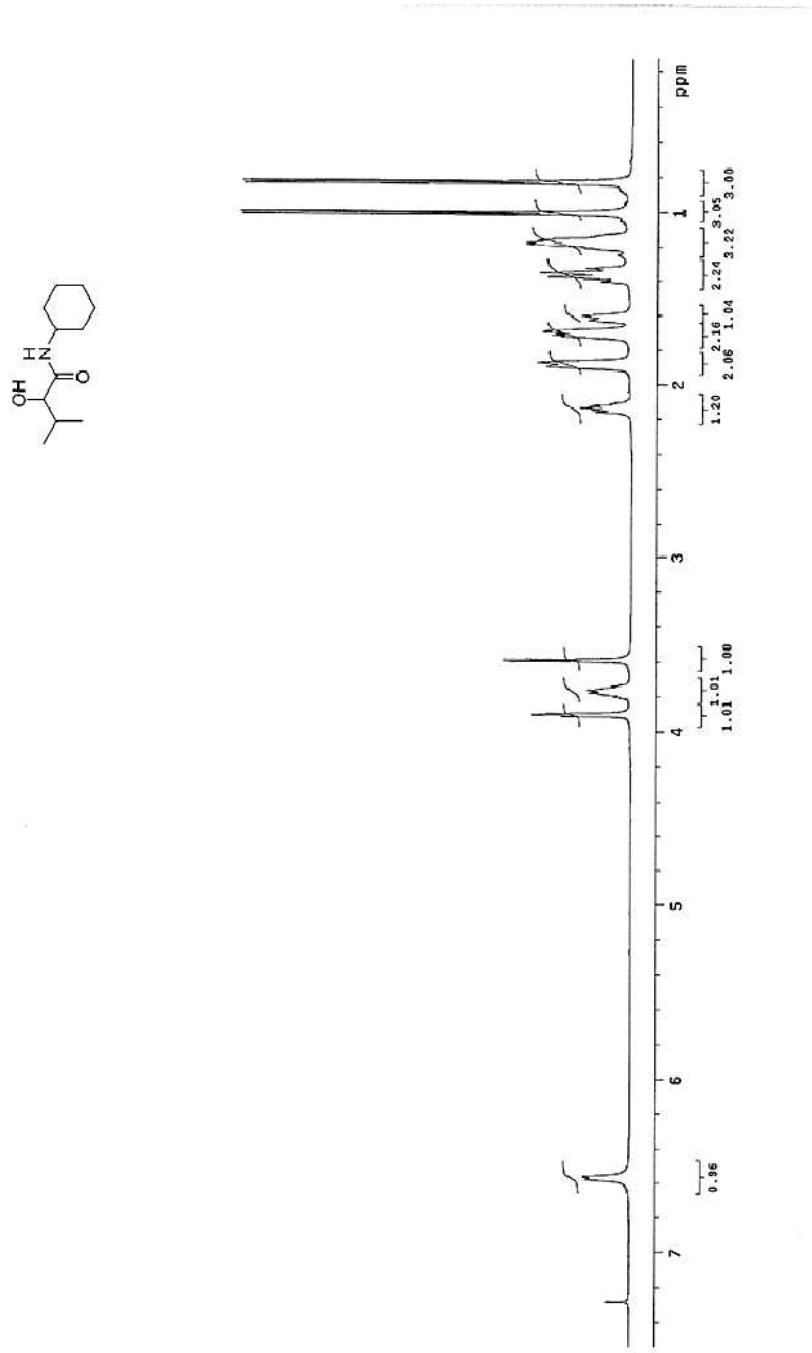

9.191
25.025
25.043
25.724
28.126
33.855
33.234
48.075
73.022
77.047
77.299
77.556
179.310
ppm
20
40
60
80
100
120
140
160
180
OH
H
N
O

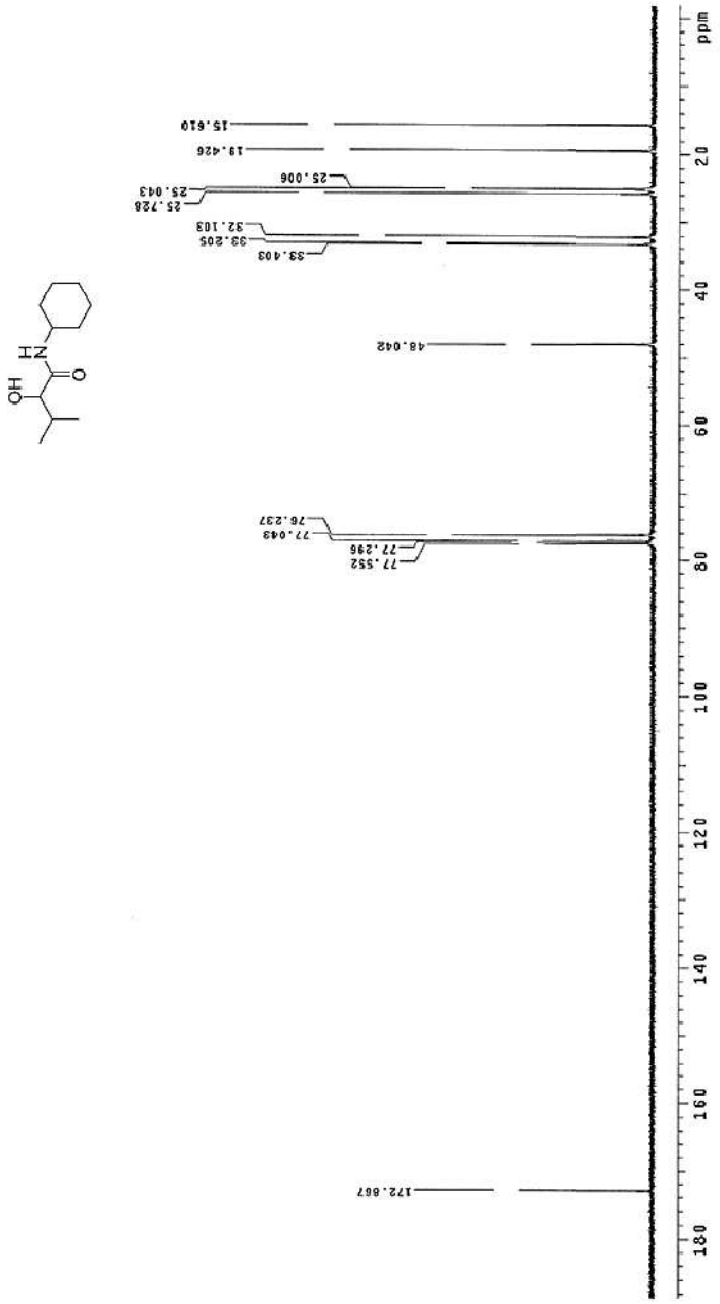

HN
O
OH
ppm
1
2
3
4
5
6
7
6.15
1.15
0.81
1.00
2.05
4.57
0.96

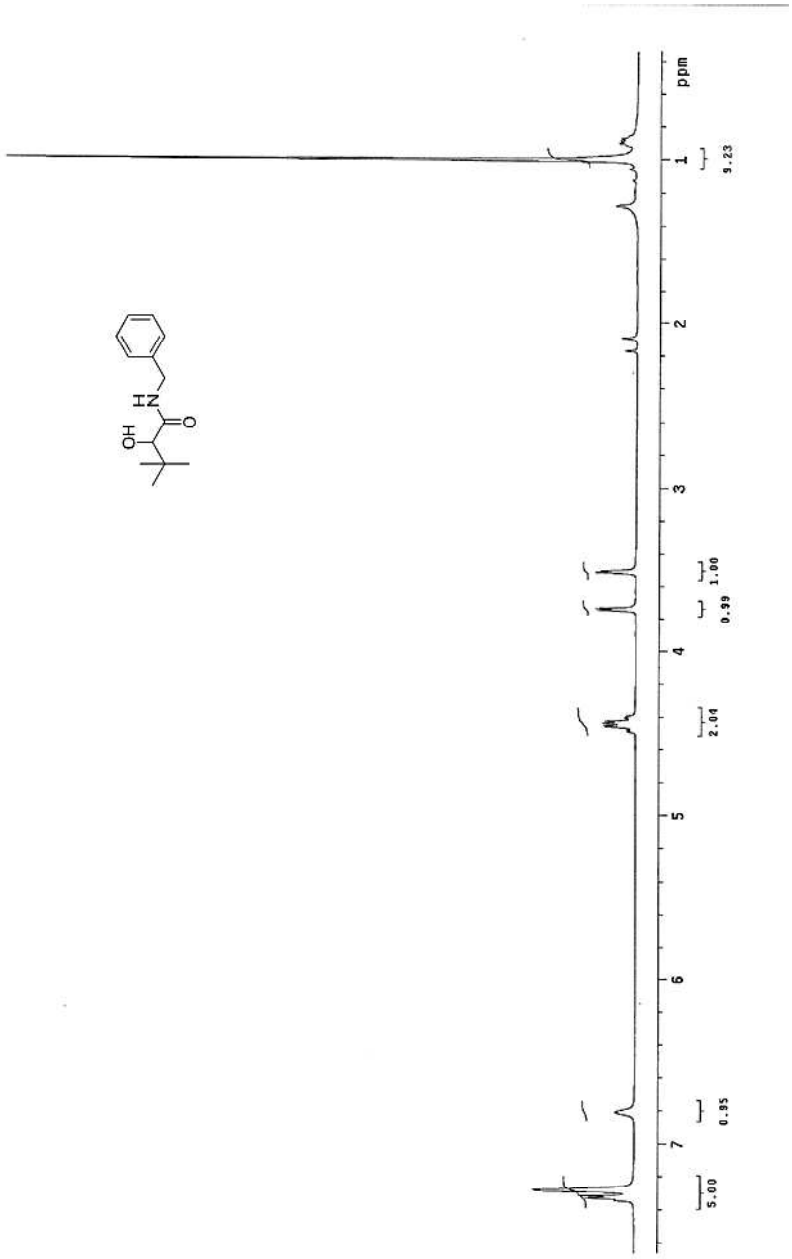

15.753
19.451
32.121
49.370
76.552
77.058
77.319
77.567
127.764
128.099
128.955
138.285
173.731
ppm

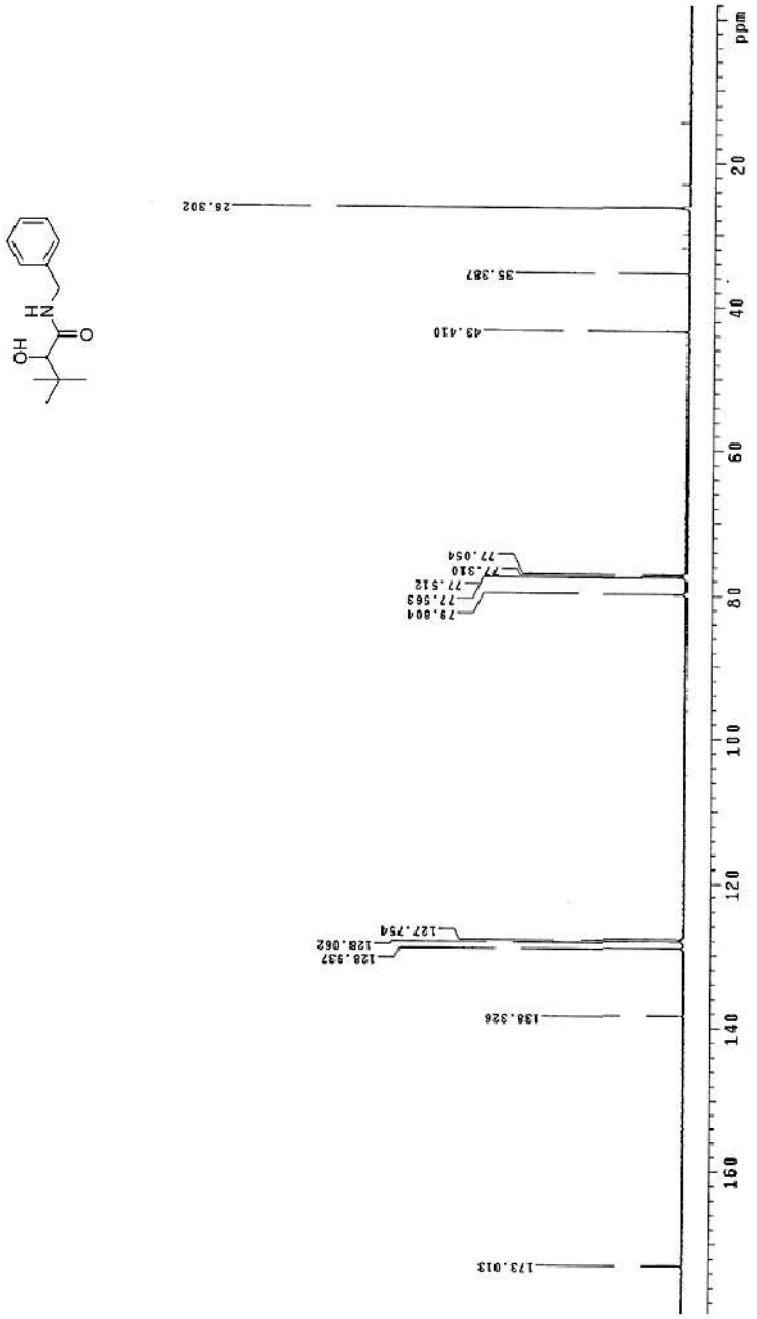

ppm
1
2
3
4
5
6
7
2.14
3.00
8.64
1.04
0.96
0.96
6.83

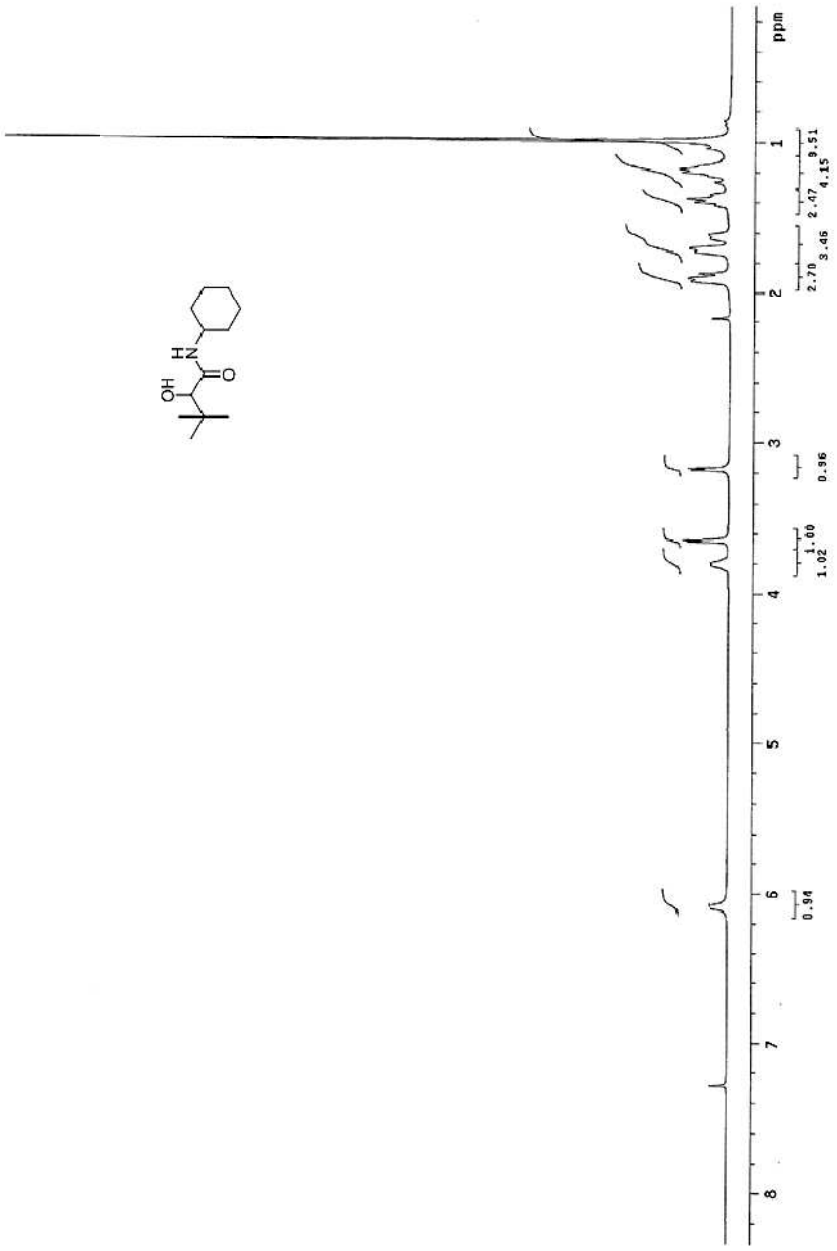

15.585
19.459
28.950
31.998
51.118
76.274
77.039
77.548
173.399
ppm
20
40
60
80
100
120
140
160
180
OH
H
N
O

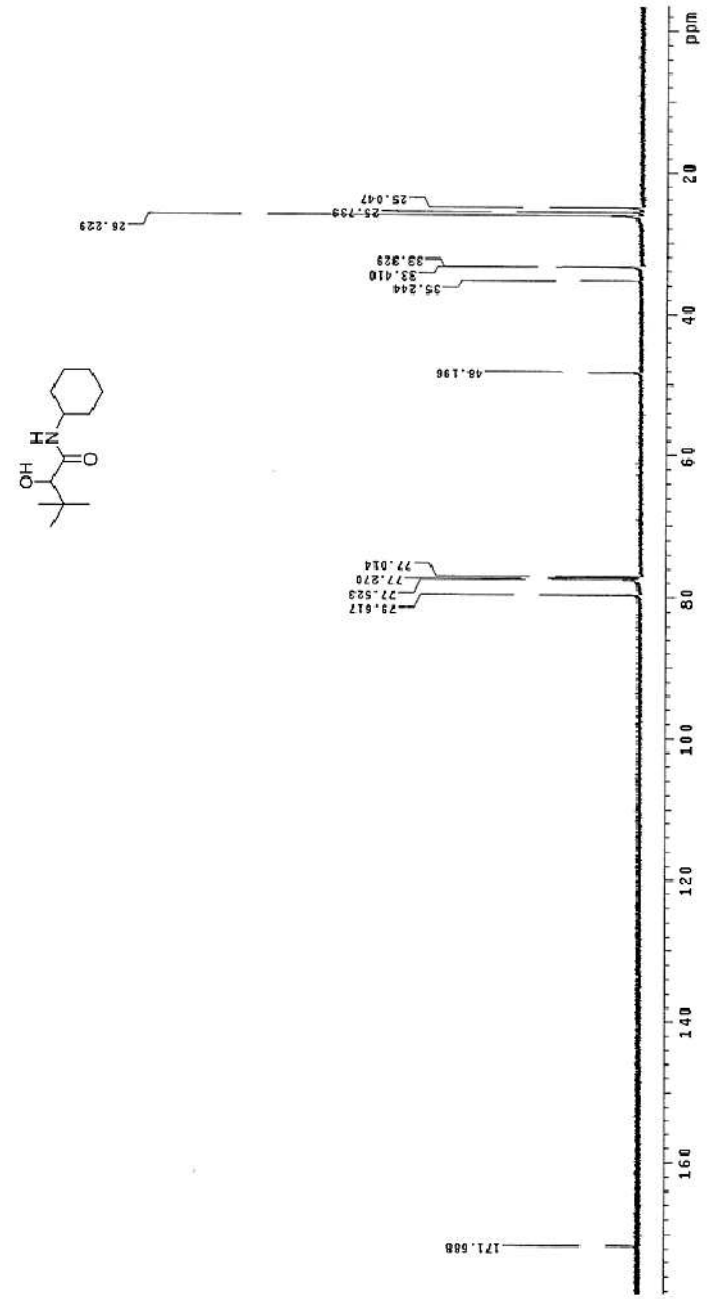

OH
H
N
O
ppm
1
2
3
4
5
6
7
0.96
1.01
1.00
1.20
2.16
2.06
1.04
2.24
3.22
3.05
3.00


172.867
77.552
77.296
77.043
76.237
48.042
33.403
32.103
25.728
25.043
25.006
19.426
15.619
ppm


HN
O
OH
ppm
1
2
3
4
5
6
7
9.23
1.00
0.99
2.04
0.85
5.00


26.302
35.387
43.410
77.054
77.310
77.512
77.569
79.004
127.754
128.062
128.537
136.326
173.013
ppm


OH
H
N
O
ppm
1
2
3
4
5
6
7
8
9.51
4.15
2.47
3.46
2.70
0.96
1.00
1.02
0.94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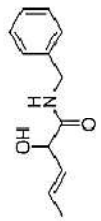
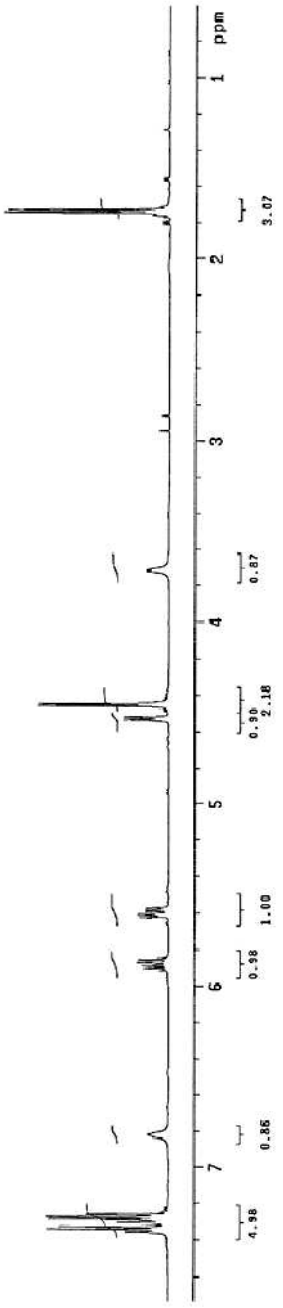
79.617
77.523
77.270
77.014
48.196
35.244
33.410
33.329
28.229
25.739
25.047
ppm
20
40
60
80
100
120
140
160
NH
O
OH




ppm
1
2
3
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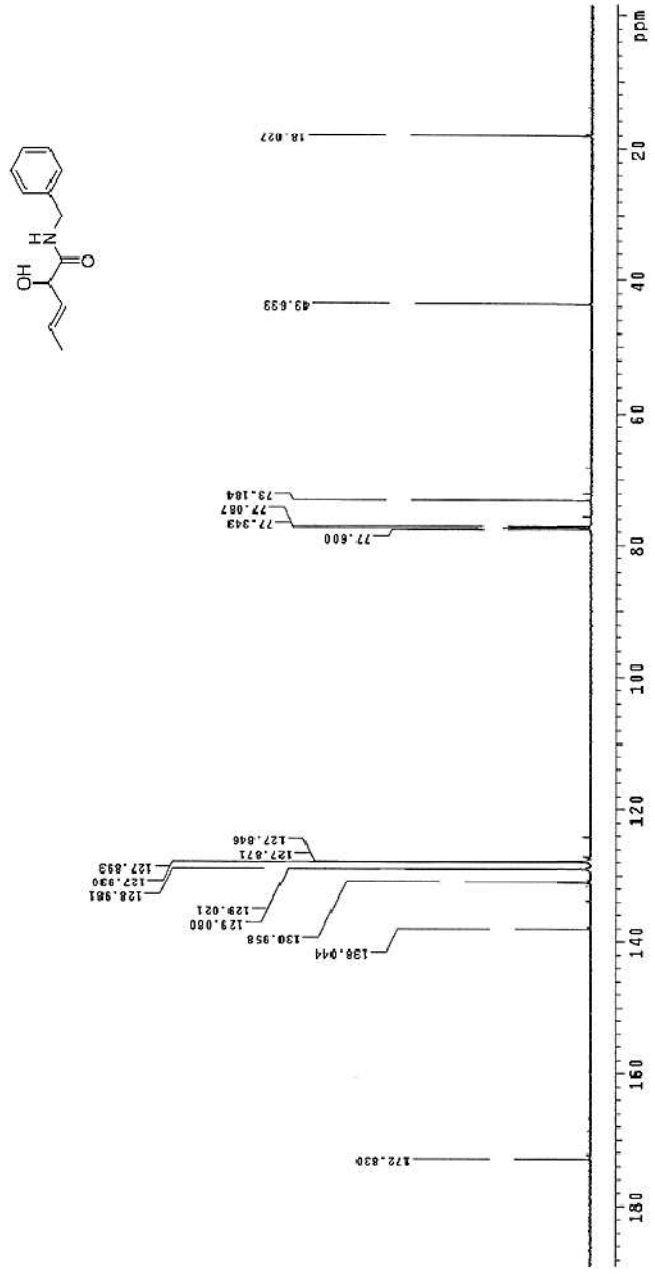
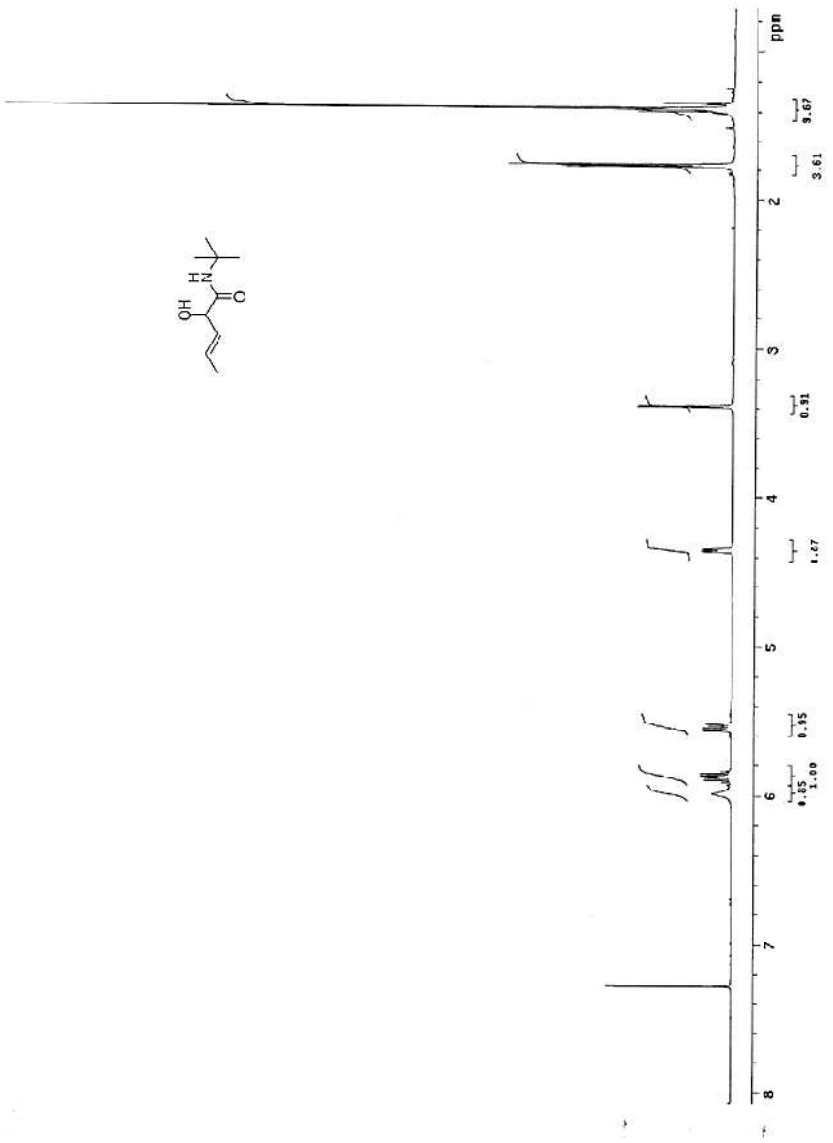
5
6
7
3.07
0.87
0.90
2.18
0.98
1.00
0.86
4.98


ppm
20
40
60
80
100
120
140
160
180
18.027
43.639
73.184
77.087
77.343
77.600
127.646
127.871
127.893
127.930
128.981
129.021
129.080
130.958
138.044
172.830
HN
O
OH


OH
H
N
O
ppm
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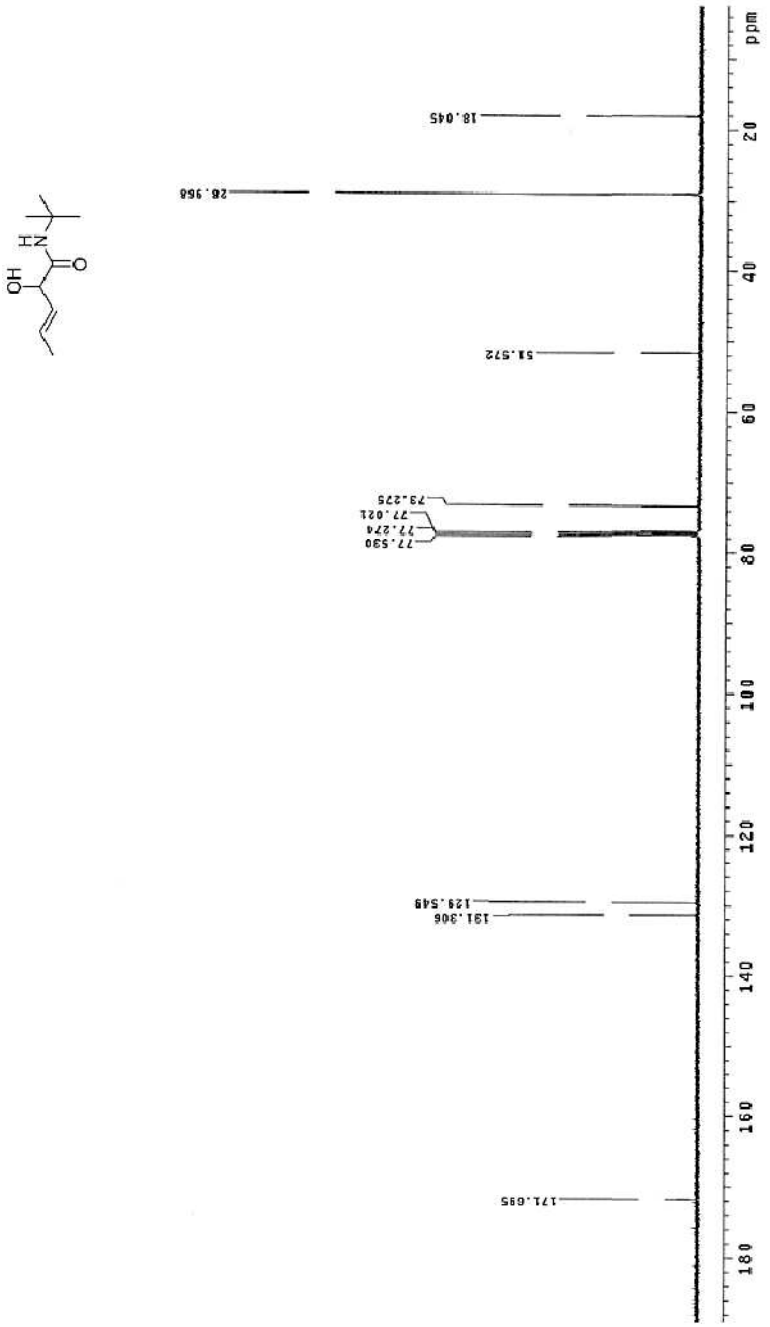
2
3
4
5
6
7
8
3.67
3.61
0.91
1.47
1.95
1.00


OH
H
N
O
18.045
28.968
53.572
79.225
77.021
77.274
77.590
129.549
131.306
171.695
ppm
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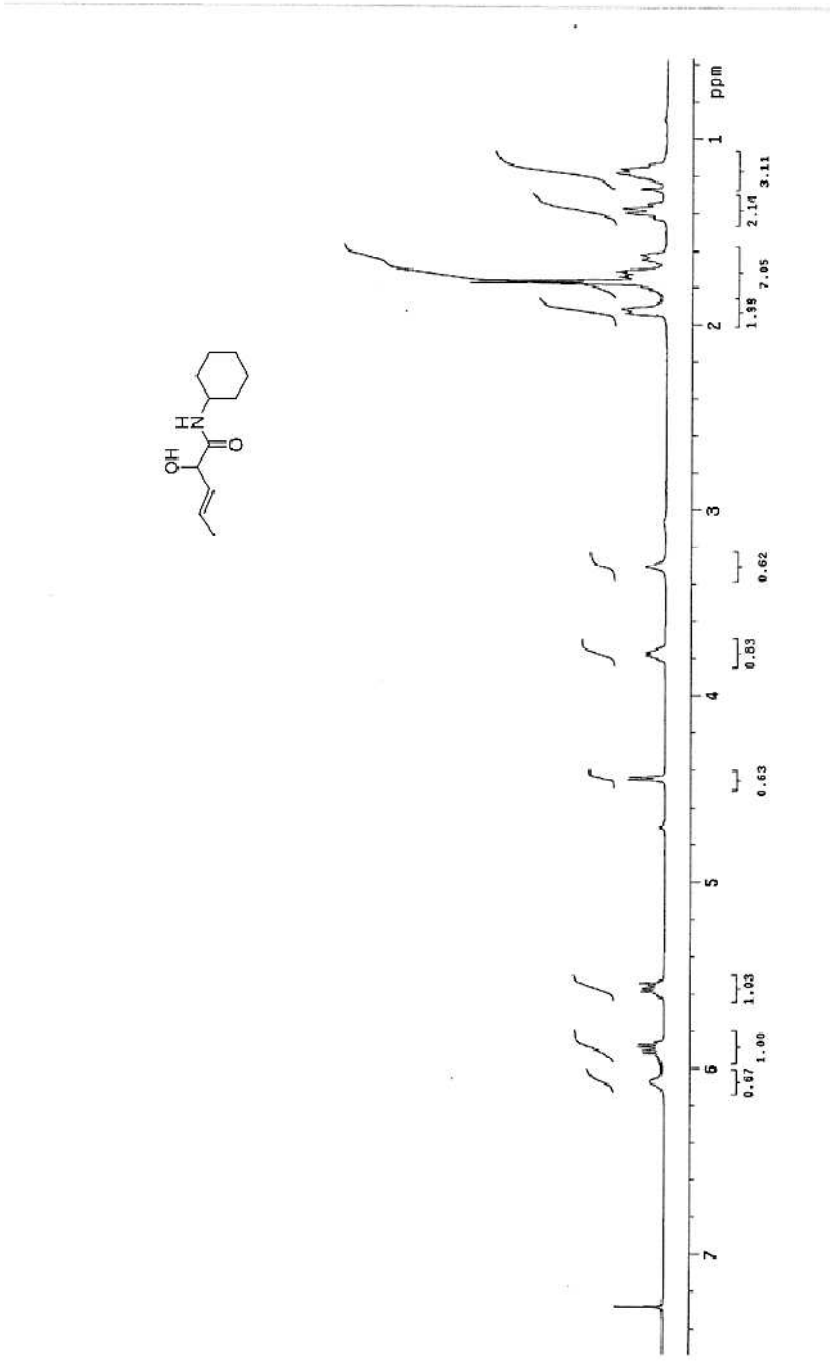
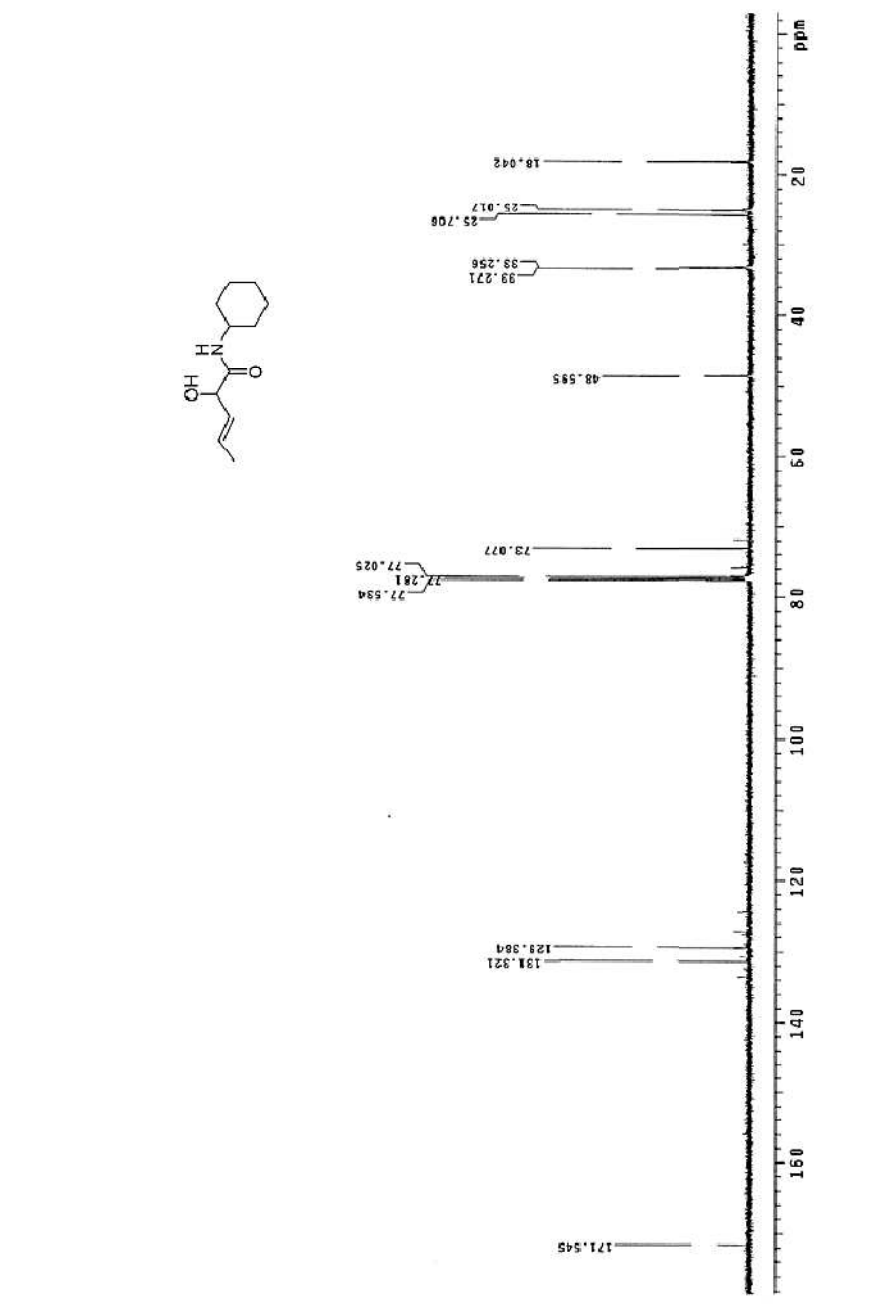
40
60
80
100
120
140
160
180


OH
H
N
O
ppm
1
2
3
4
5
6
7
3.11
2.14
7.05
1.99
0.62
0.83
0.63
1.03
1.00
0.67


ppm
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40
60
80
100
120
140
160
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25.708
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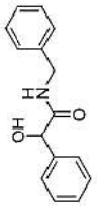
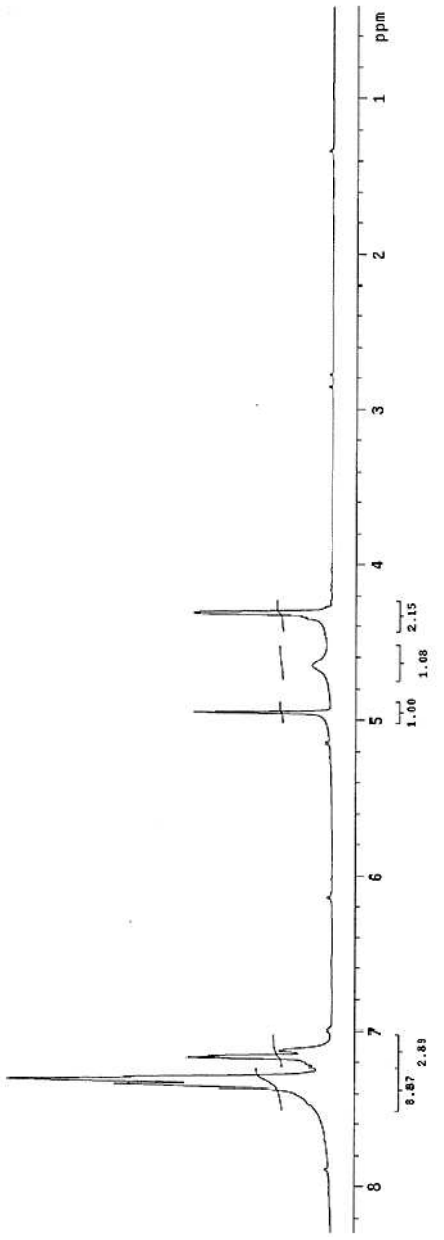
48.595
73.077
77.025
77.281
77.594
129.364
131.921
171.545
OH
H
N
O

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2
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4
5
6
7
8
1.00
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2.15
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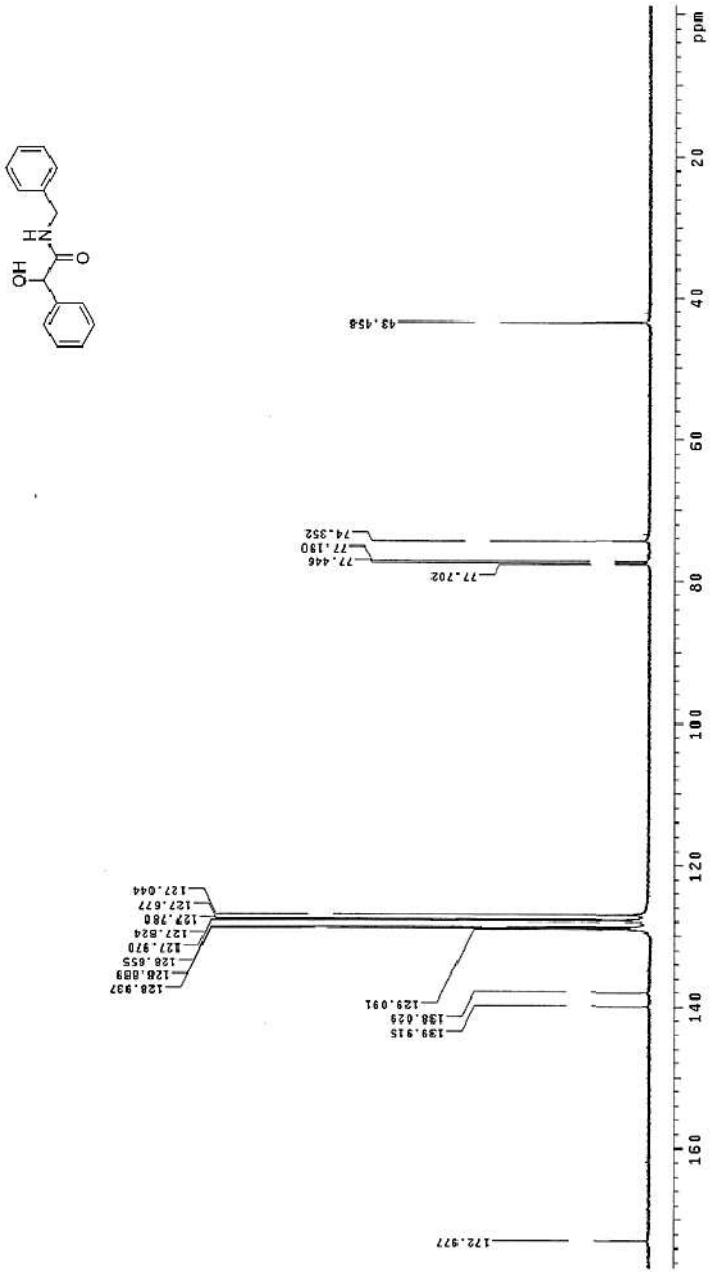
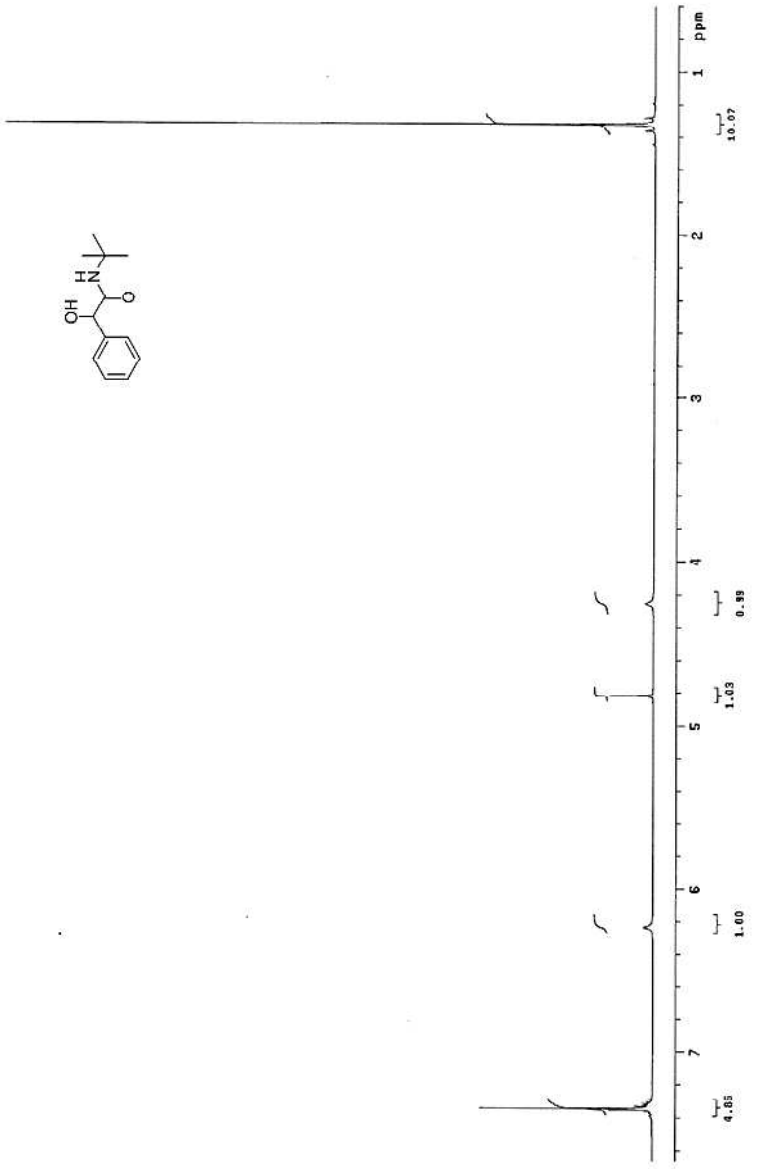
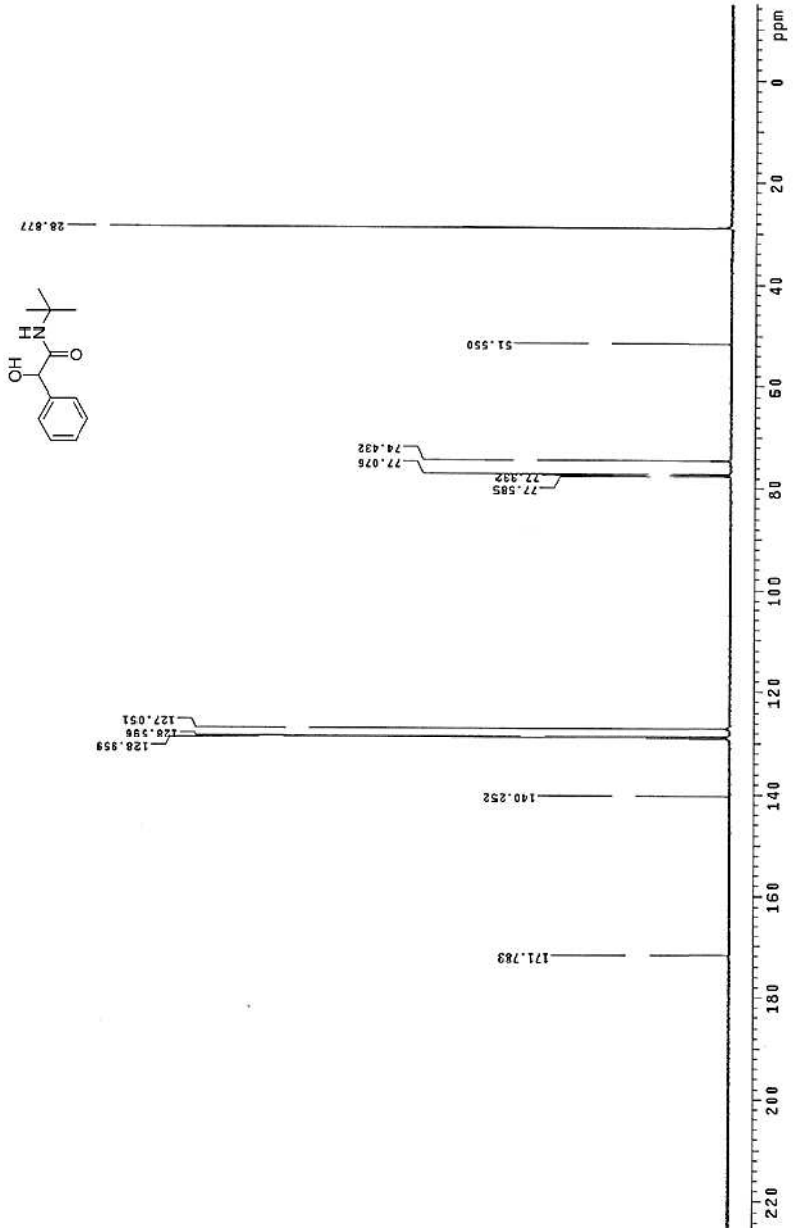
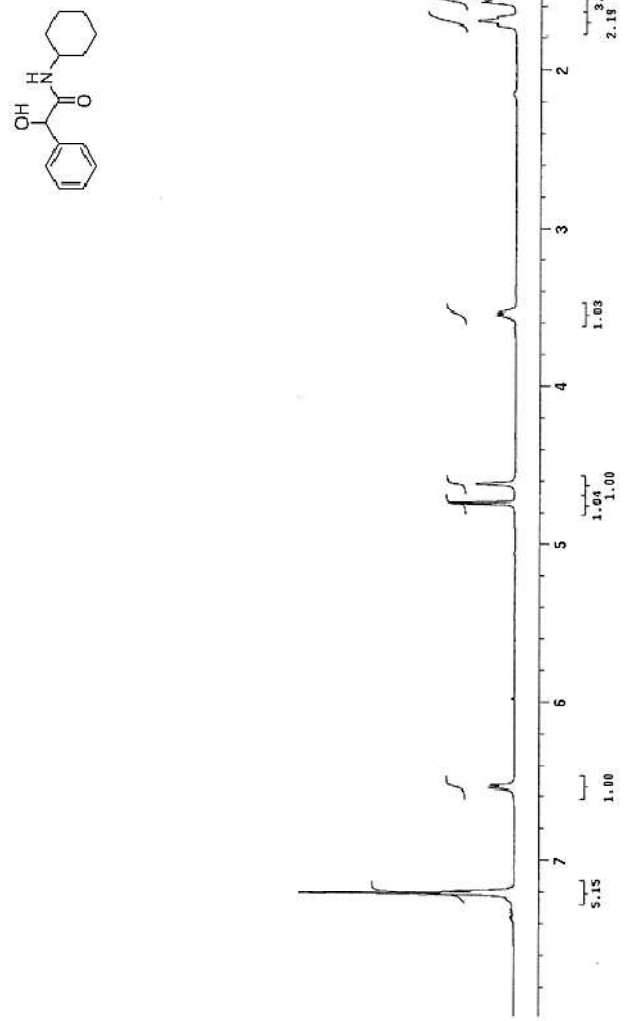
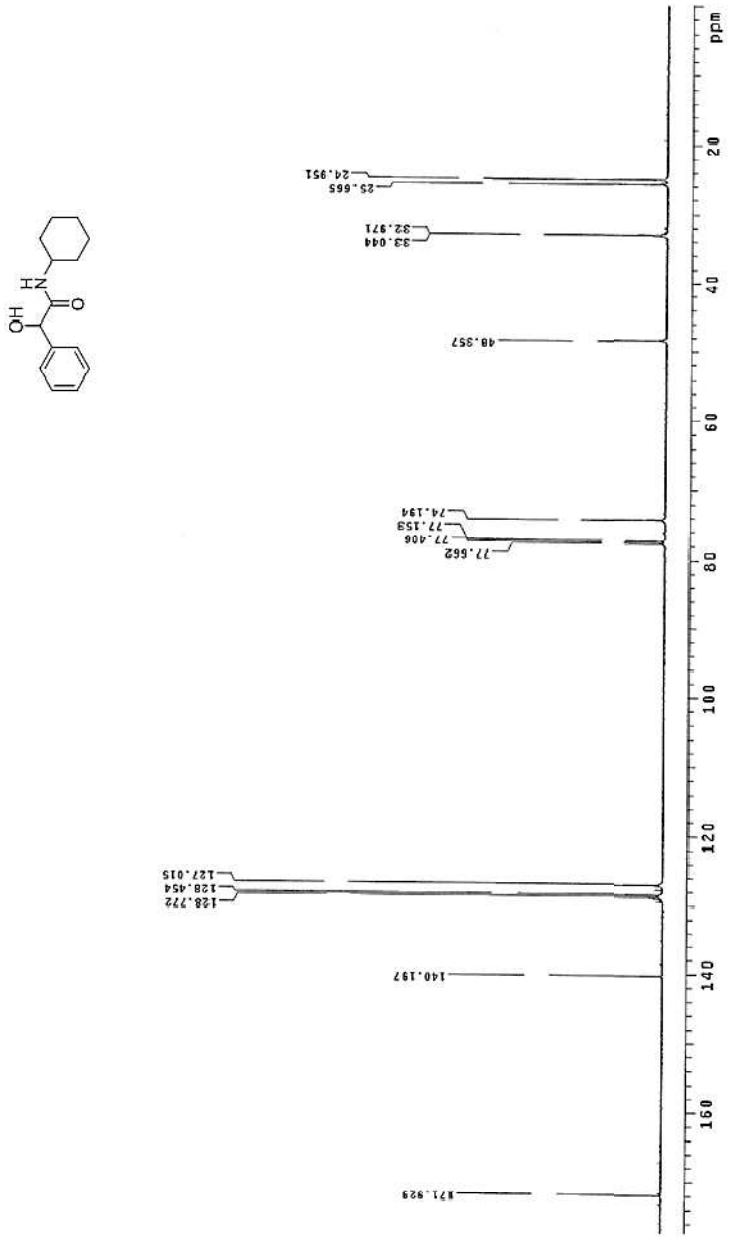
2.89

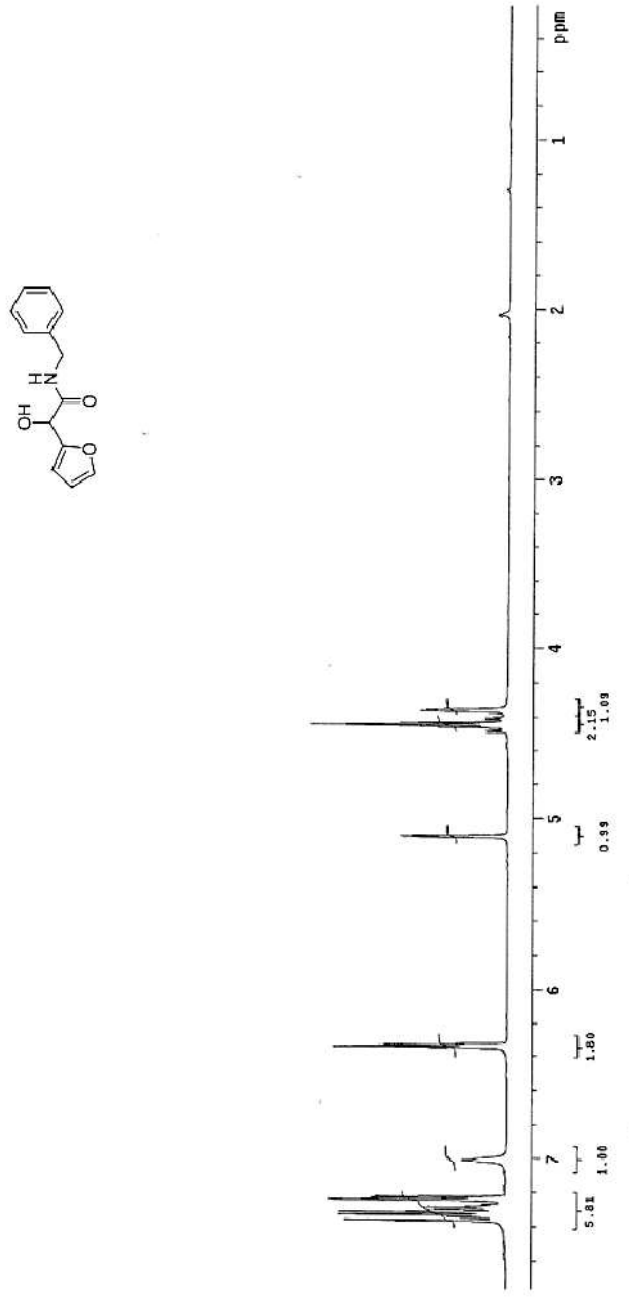

ppm
20
40
60
80
100
120
140
160
43.458
74.352
77.190
77.446
77.702
127.044
127.677
127.780
127.824
127.970
128.655
128.889
128.937
129.091
138.029
139.915
172.977

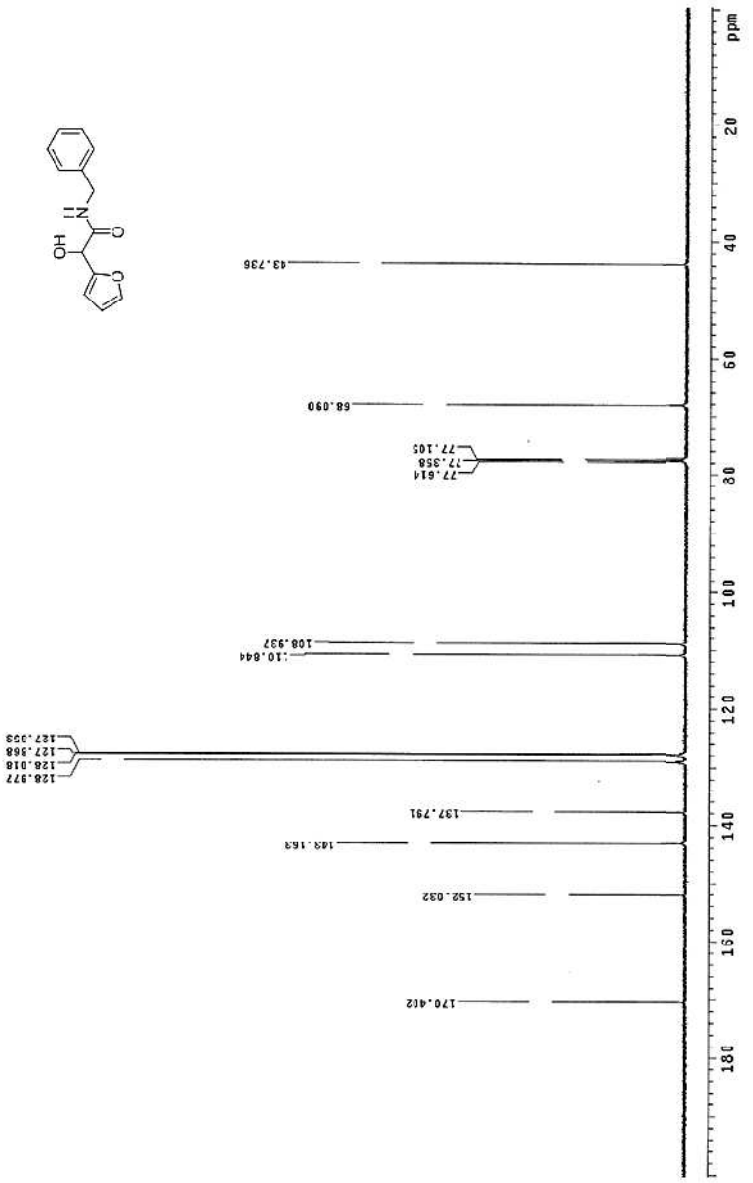

OH
H
N
O
ppm
1
2
3
4
5
6
7
10.07
0.99
1.03
1.00
4.85

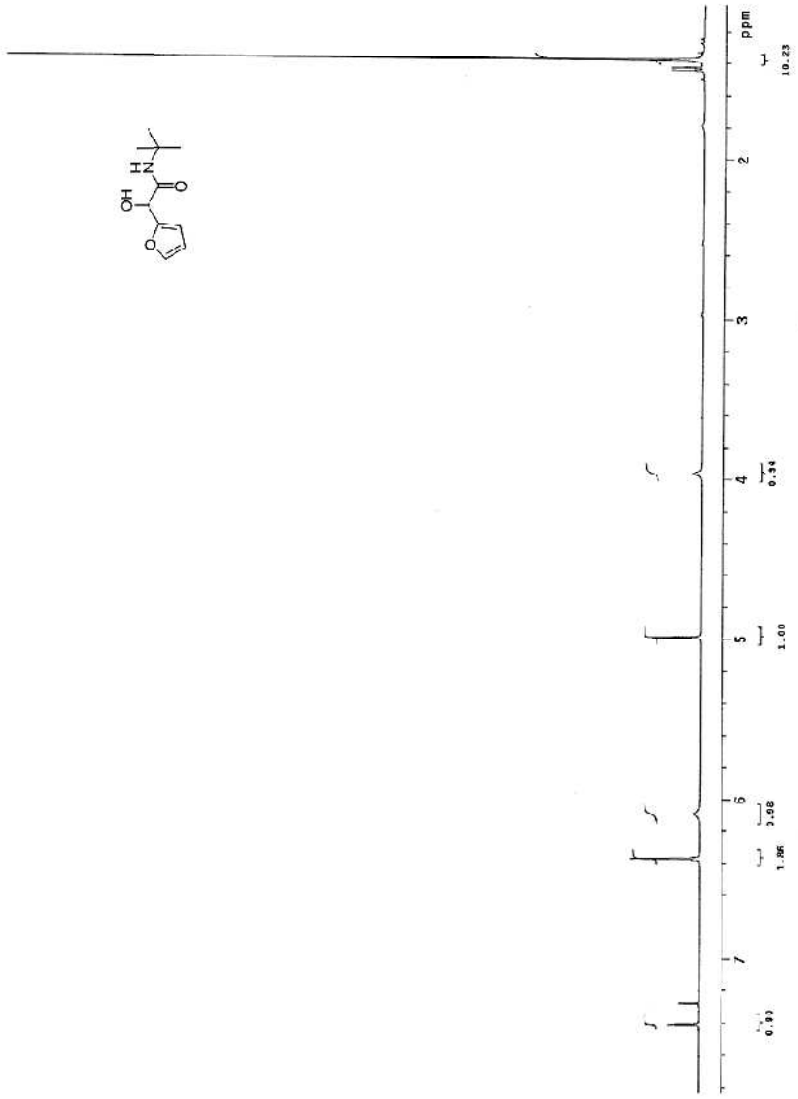

28.877
51.550
74.432
77.076
77.585
77.992
127.051
128.398
128.959
140.252
171.783
ppm
0
20
40
60
80
100
120
140
160
180
200
220
NH
O
OH

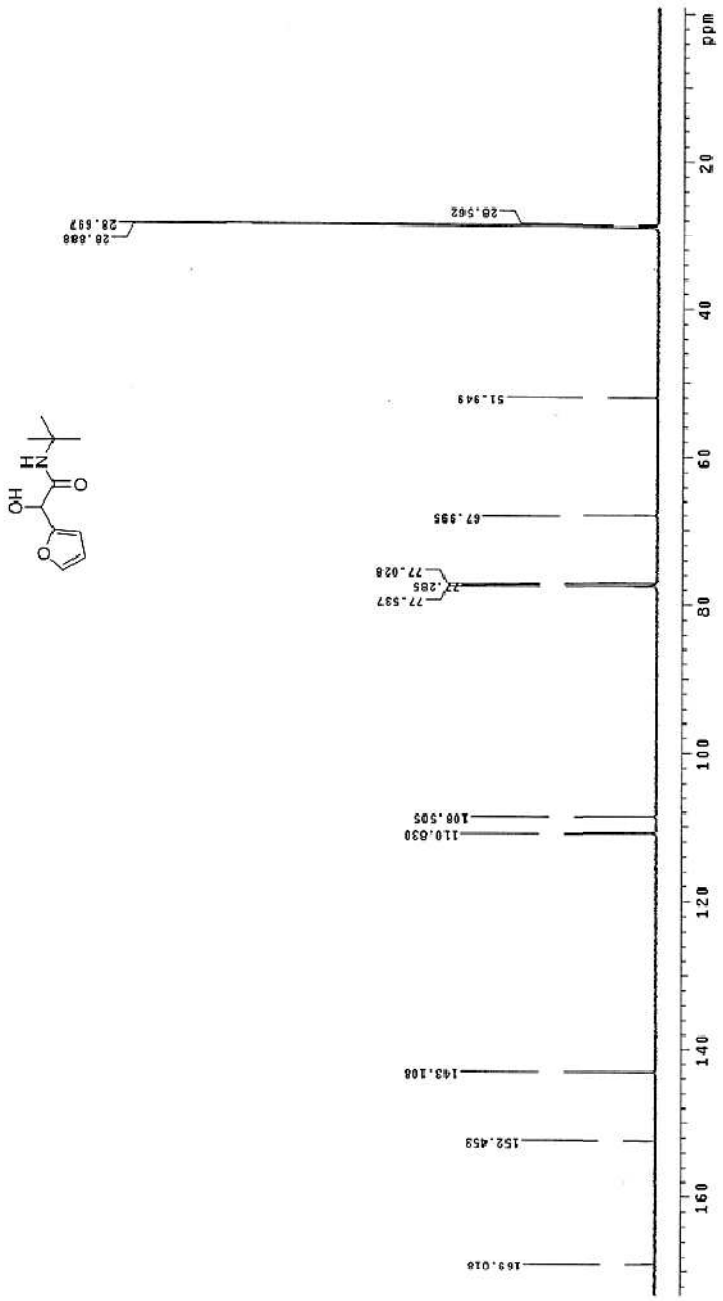

OH
H
N
O
ppm
1
2
3
4
5
6
7
5.15
1.00
1.04
1.00
1.03
2.19
3.41
2.30
3.30


OH
N
H
O
24.951
25.665
32.971
33.044
48.357
74.194
77.153
77.406
77.662
128.454
128.772
140.197
171.929
ppm
20
40
60
80
100
120
140
160

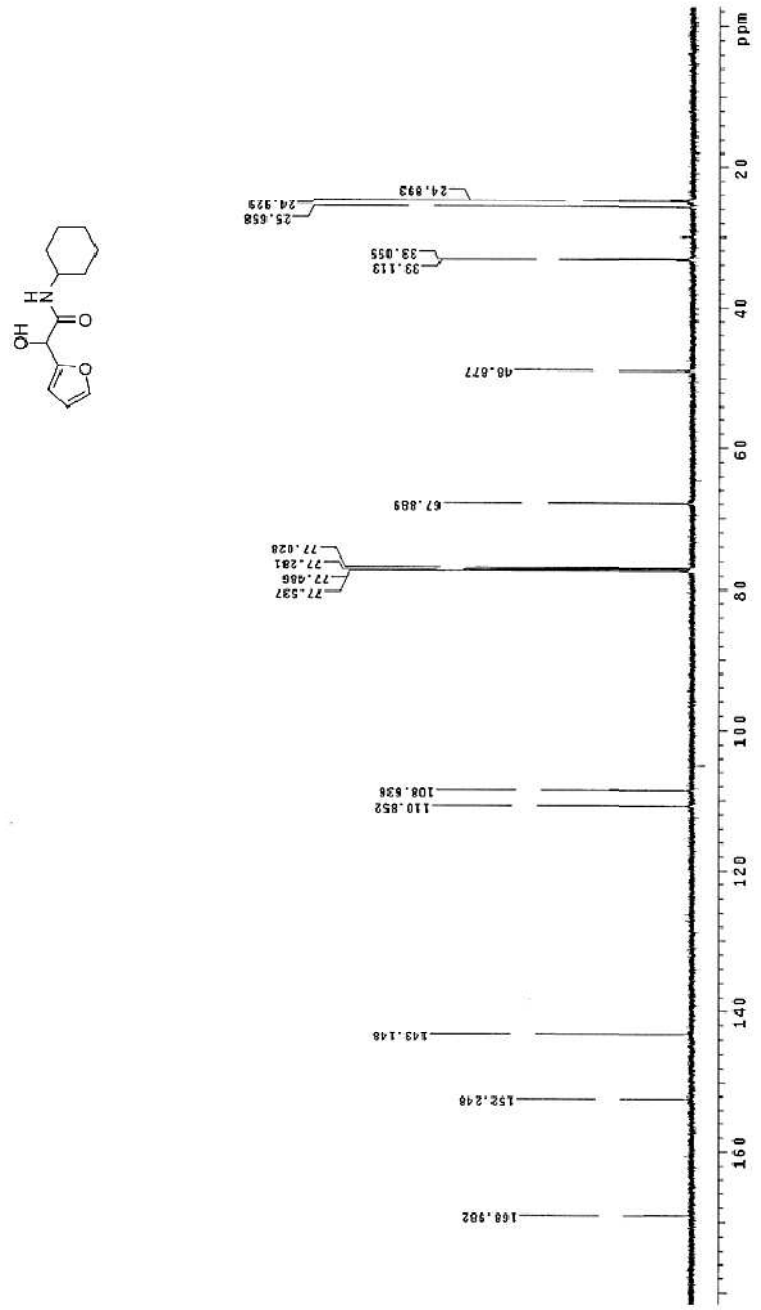

H
N
O
OH
O
ppm
1
2
3
4
5
6
7
2.15
1.09
0.99
1.80
1.00
5.81

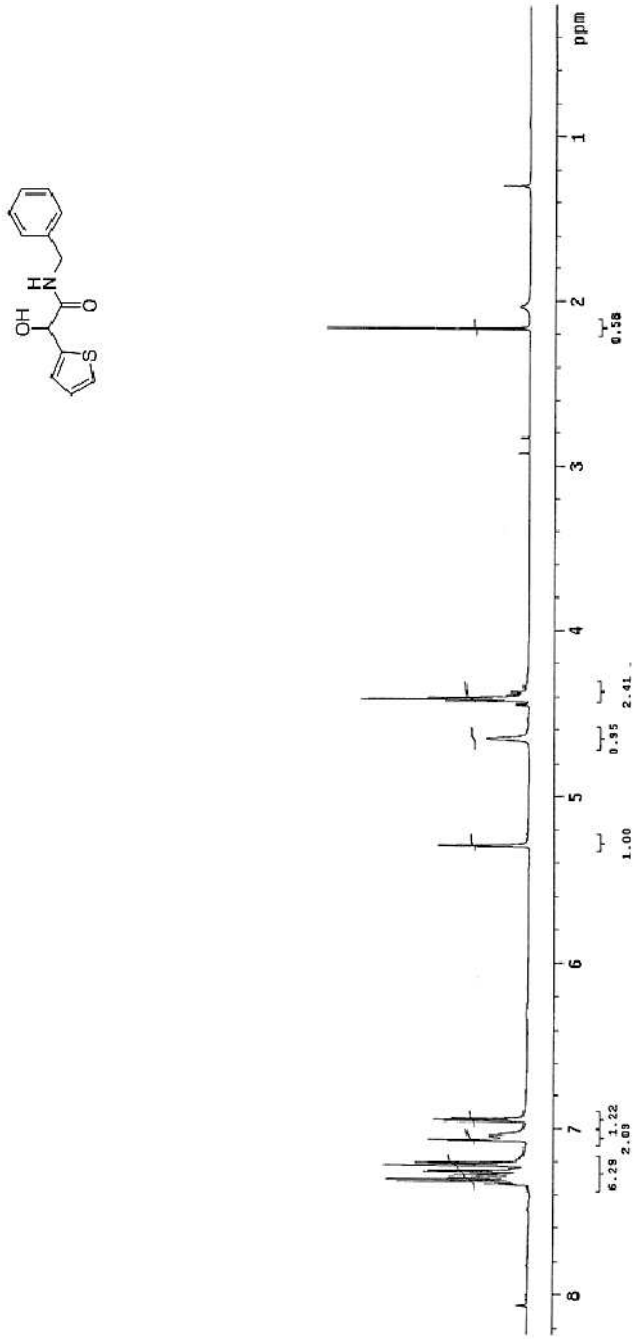

43.736
68.090
77.614
77.358
77.105
108.937
110.644
128.977
128.018
127.368
127.035
137.791
149.169
152.032
170.402
ppm

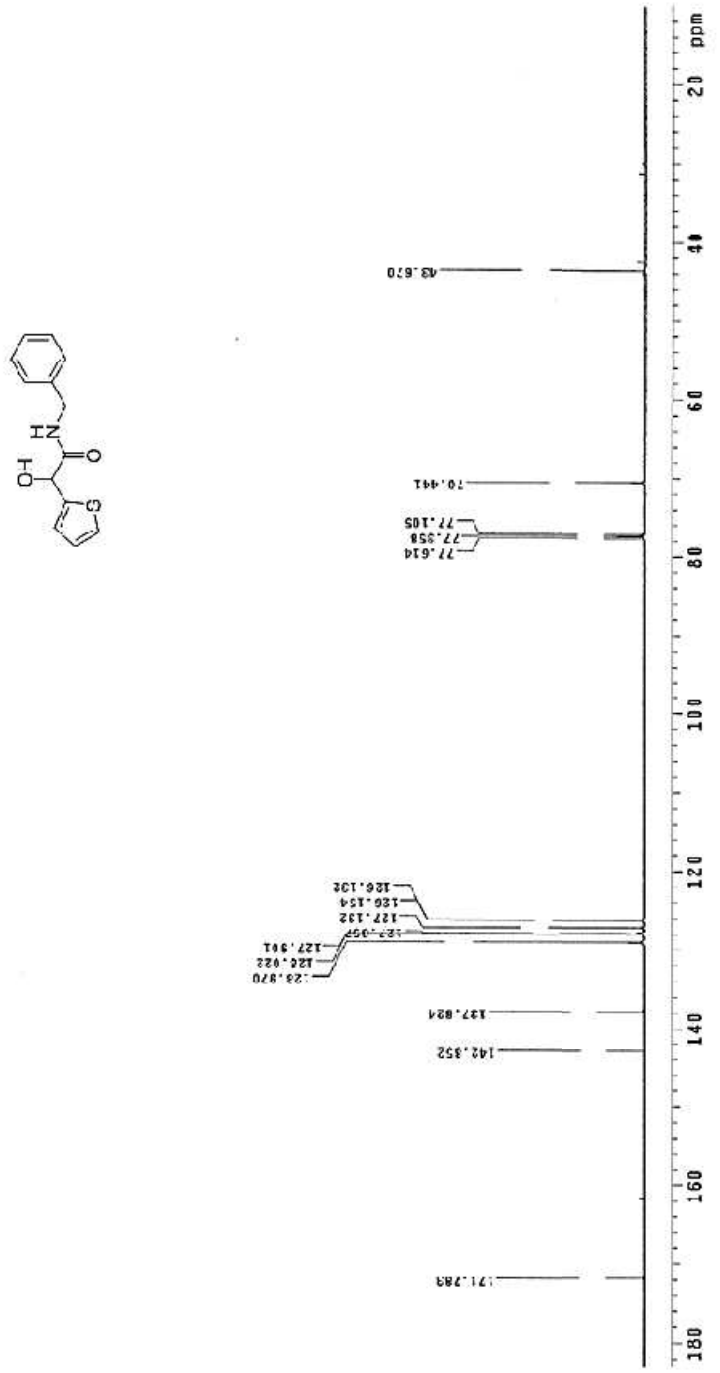



26.562
26.686
28.697
51.949
67.995
77.028
77.285
77.537
108.505
110.630
143.108
152.459
169.016
ppm
20
40
60
80
100
120
140
160
HO
N
H
O
O

OH
H
N
O
O
ppm
1
2
3
4
5
6
7
0.90
0.34
1.03
1.08
1.00
0.99
1.20
2.72
5.05
2.66
0.48


24.893
24.929
25.658
33.055
33.113
48.677
67.889
77.028
77.281
77.466
77.537
108.636
110.852
143.148
152.249
168.902
ppm


OH
H
N
O
S
ppm
1
2
3
4
5
6
7
8
0.58
2.41
0.95
1.00
6.29
1.22
2.69


ppm
20
40
60
80
100
120
140
160
180
43.670
70.491
77.614
77.358
77.105
126.132
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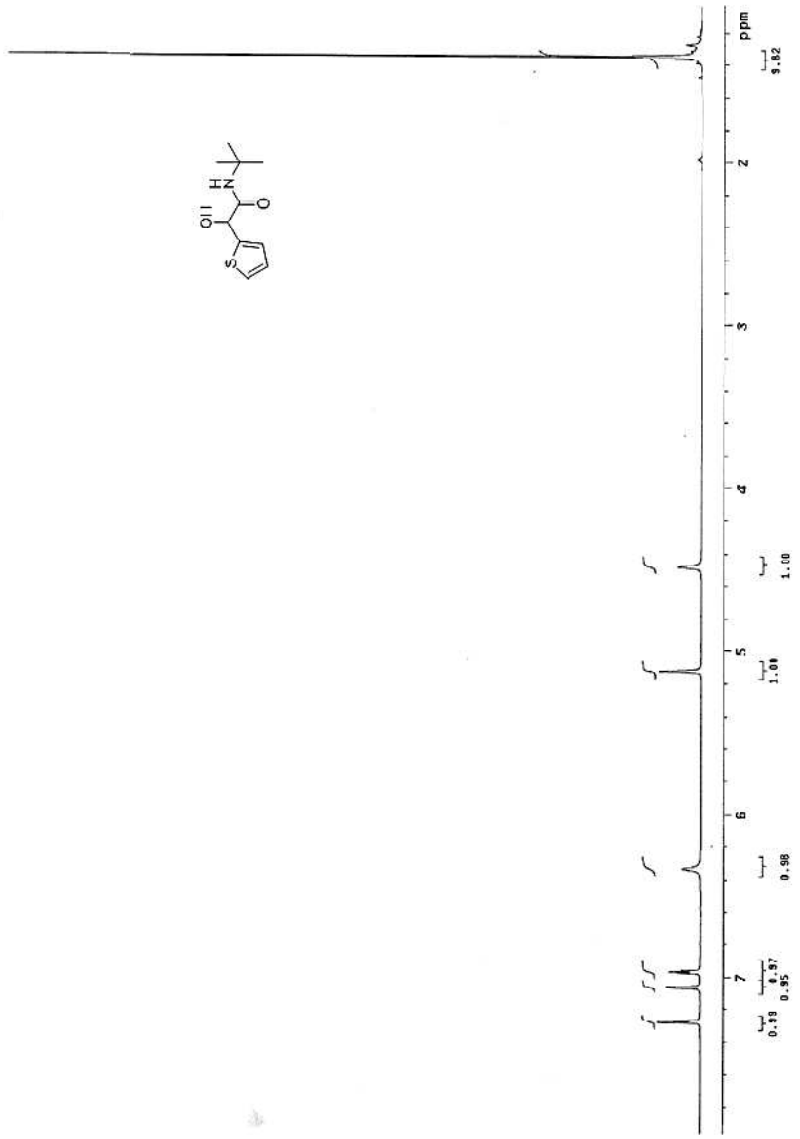
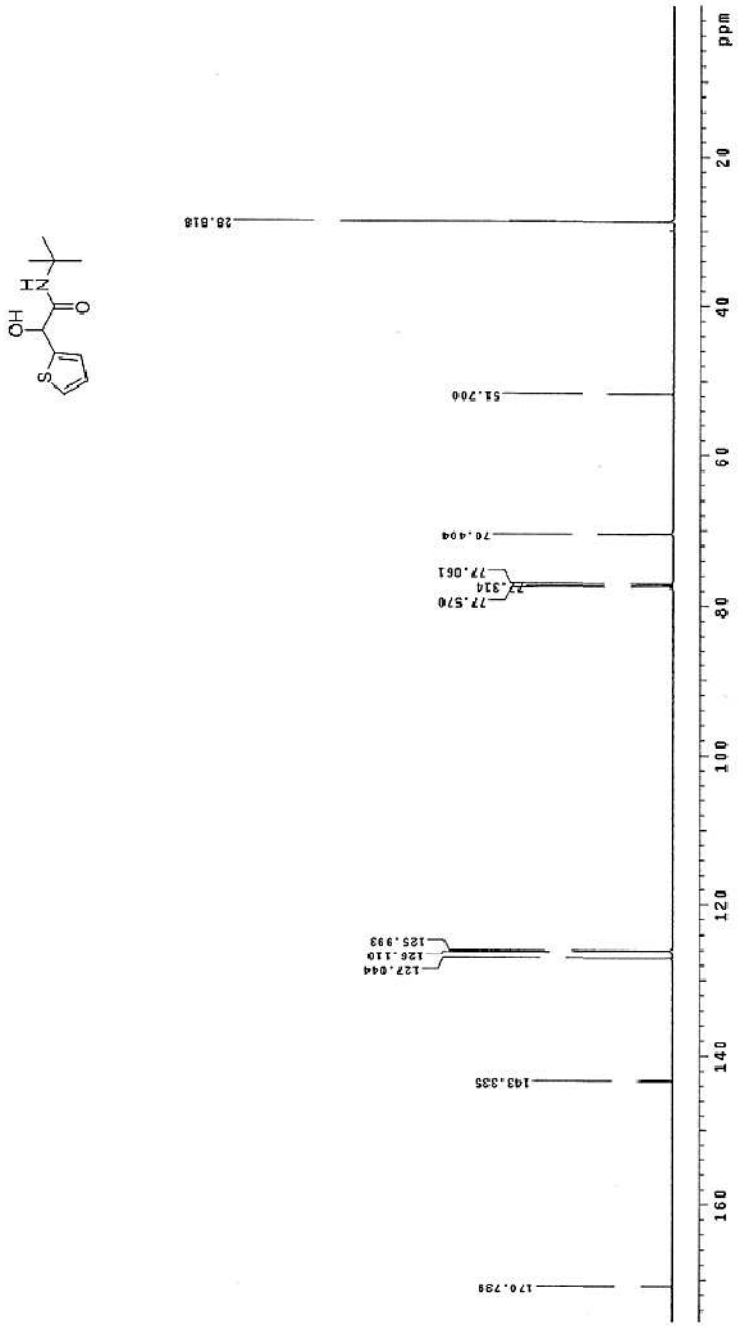
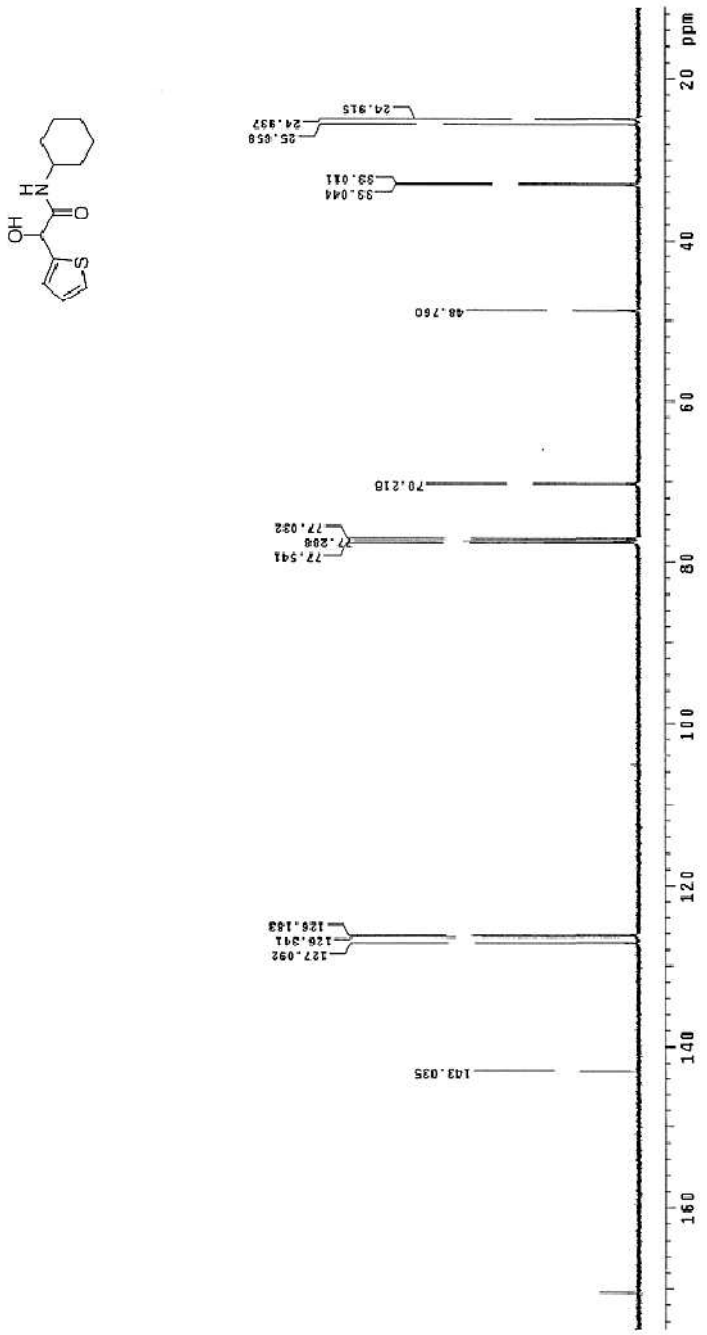
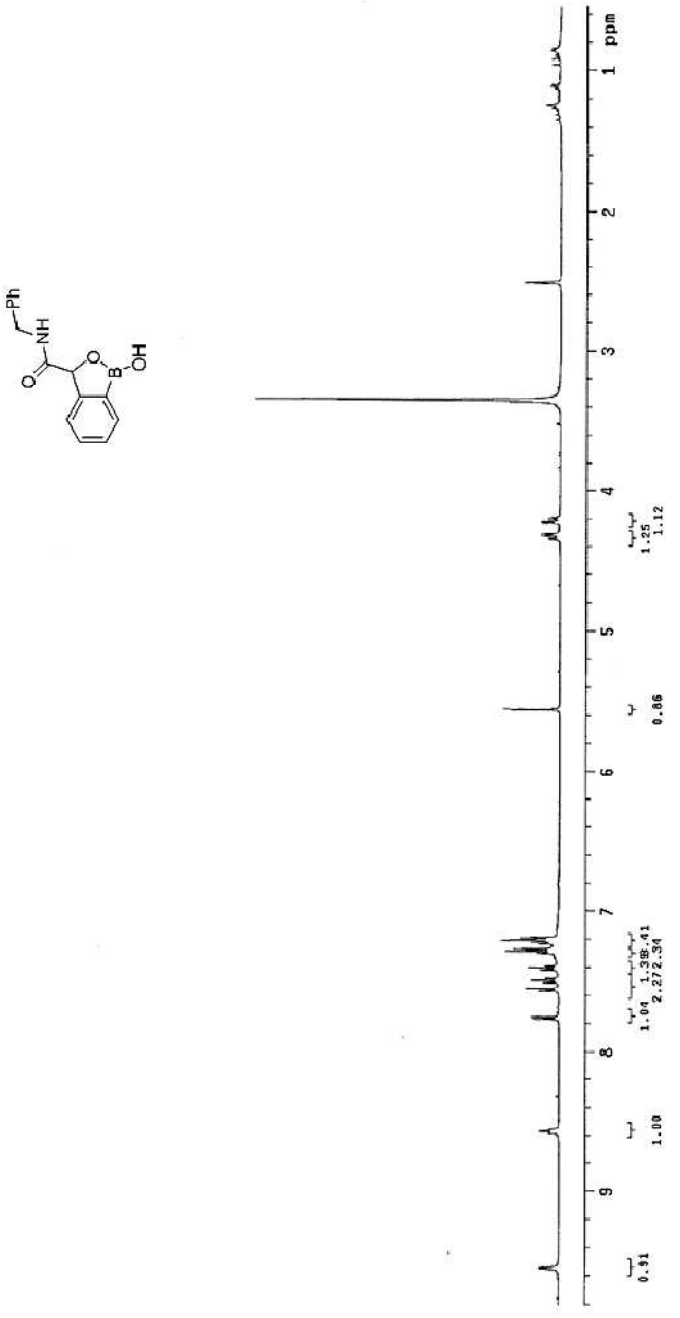
128.022
128.970
137.824
142.352
171.783

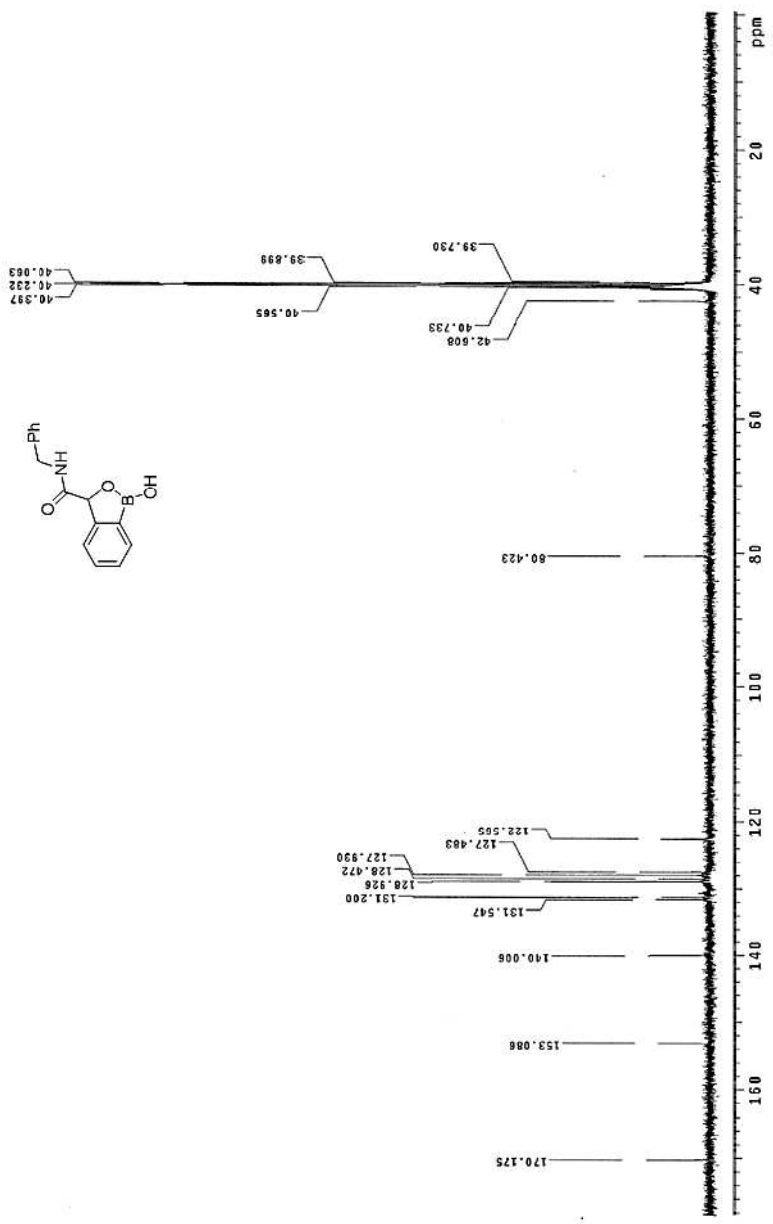

OH
H
N
O
S
ppm
9.82
1.00
1.01
0.98
4.97
0.95
0.19


28.818
51.700
70.404
77.570
77.314
77.061
125.993
126.110
127.044
143.335
170.789
ppm
20
40
60
80
100
120
140
160
HN
O
OH
S

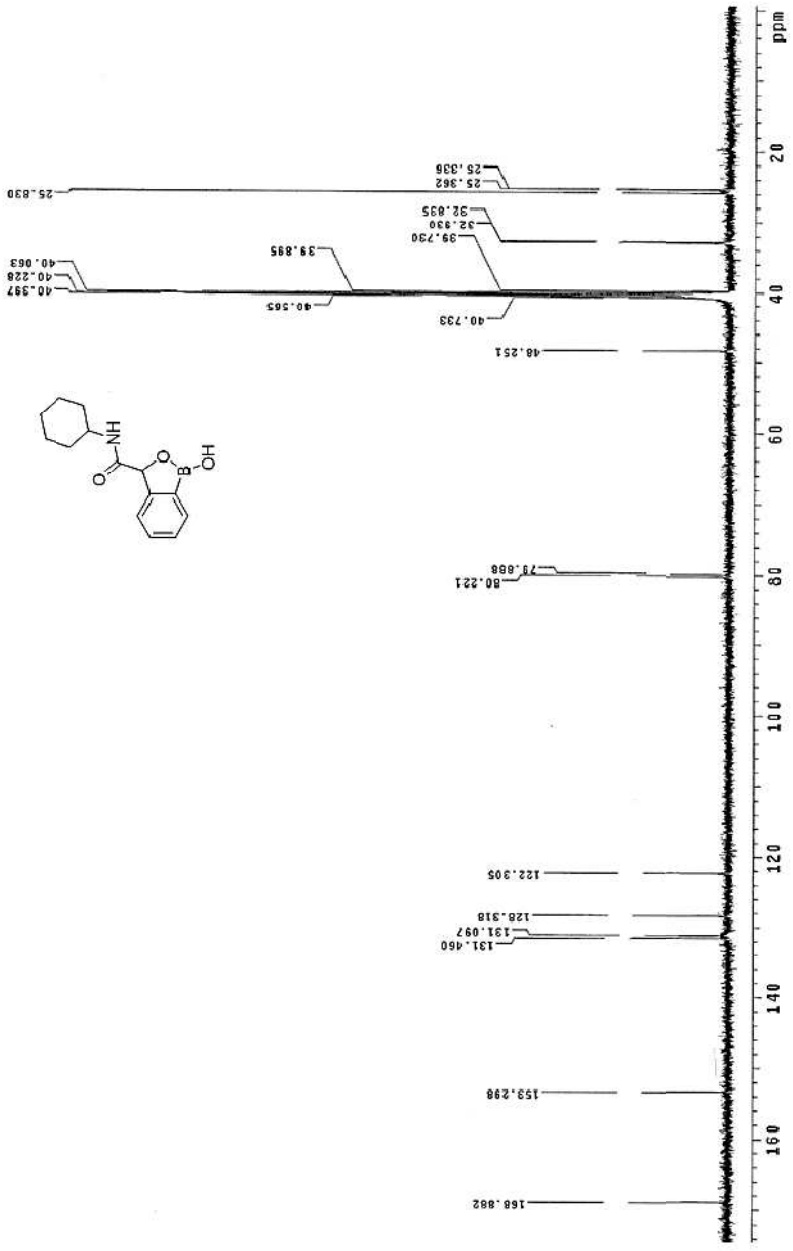
ppm


24.815
24.997
25.059
33.041
33.044
48.760
70.218
77.041
77.208
77.082
126.141
127.092
126.183
143.035
20
40
60
80
100
120
140
160
ppm


Ph
NH
O
O
B
OH
1 ppm
2
3
4
5
6
7
8
9
0.91
1.00
1.04
1.38
2.27
2.34
0.86
1.25
1.12


39.730
39.898
40.063
40.232
40.397
40.565
40.733
42.608
60.423
122.565
127.463
127.930
128.472
128.926
131.200
131.547
140.006
153.086
170.175
Ph
NH
O
O
B
OH
ppm
20
40
60
80
100
120
140
160

NH
O
O
B
OH
ppm
1
2
3
4
5
6
7
8
9
1.01
0.44
1.19
2.25
1.38
1.33
1.00
1.62
6.03
8.66
1.82
3.61
2.94


ppm
20
40
60
80
100
120
140
160
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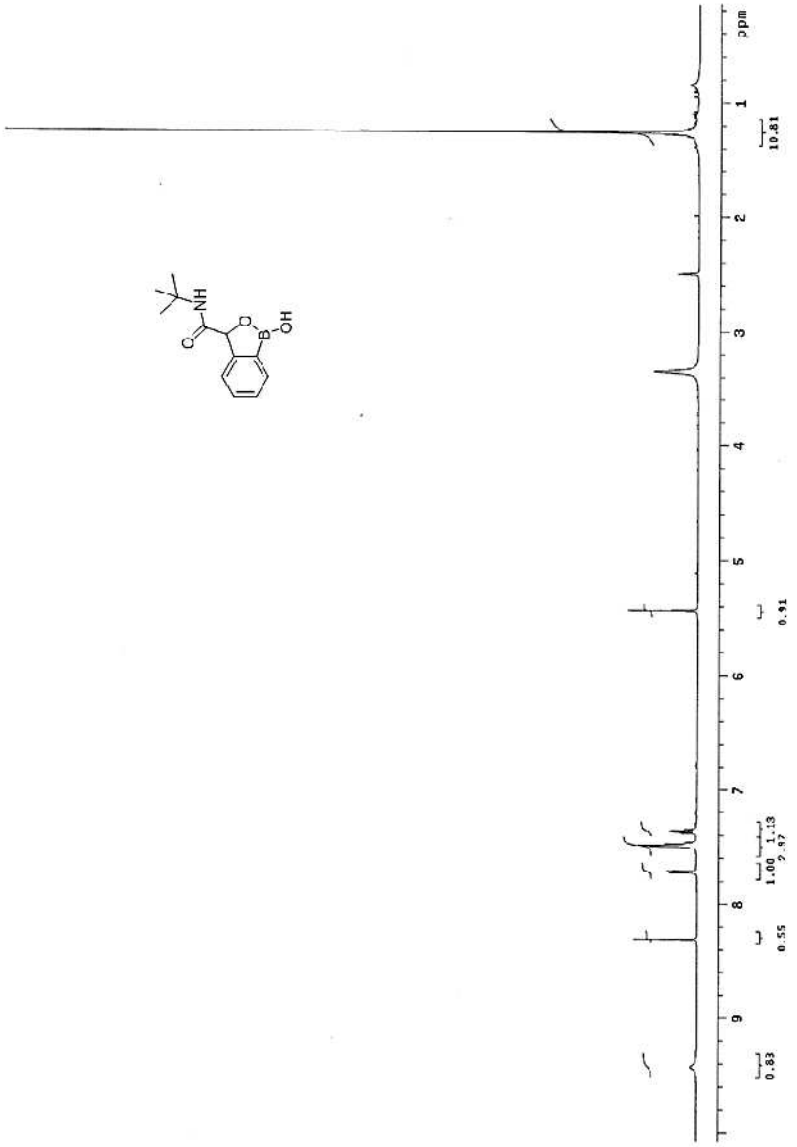
153.298
131.460
131.097
128.318
122.305
80.221
79.868
48.251
40.733
40.563
39.885
39.730
32.930
32.835
25.862
25.338
25.830
40.397
40.228
40.063
NH
O
O
B
OH


NH
O
B
OH
ppm
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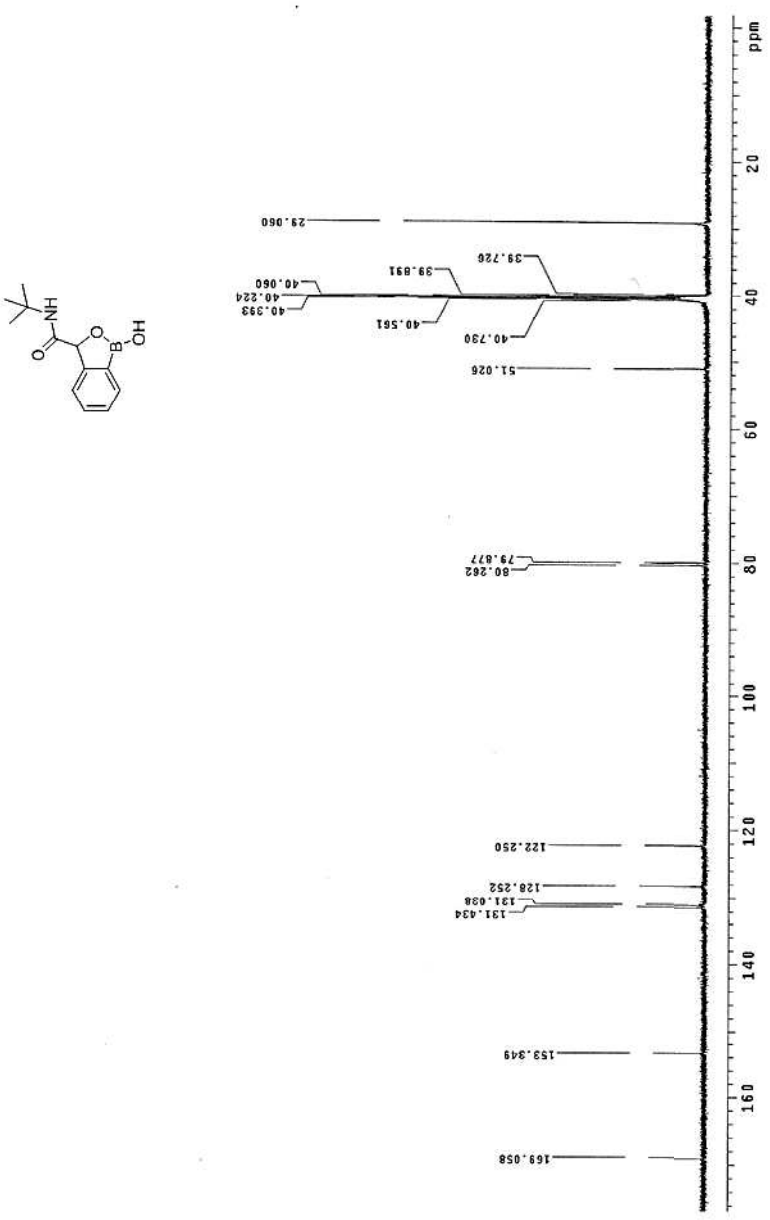
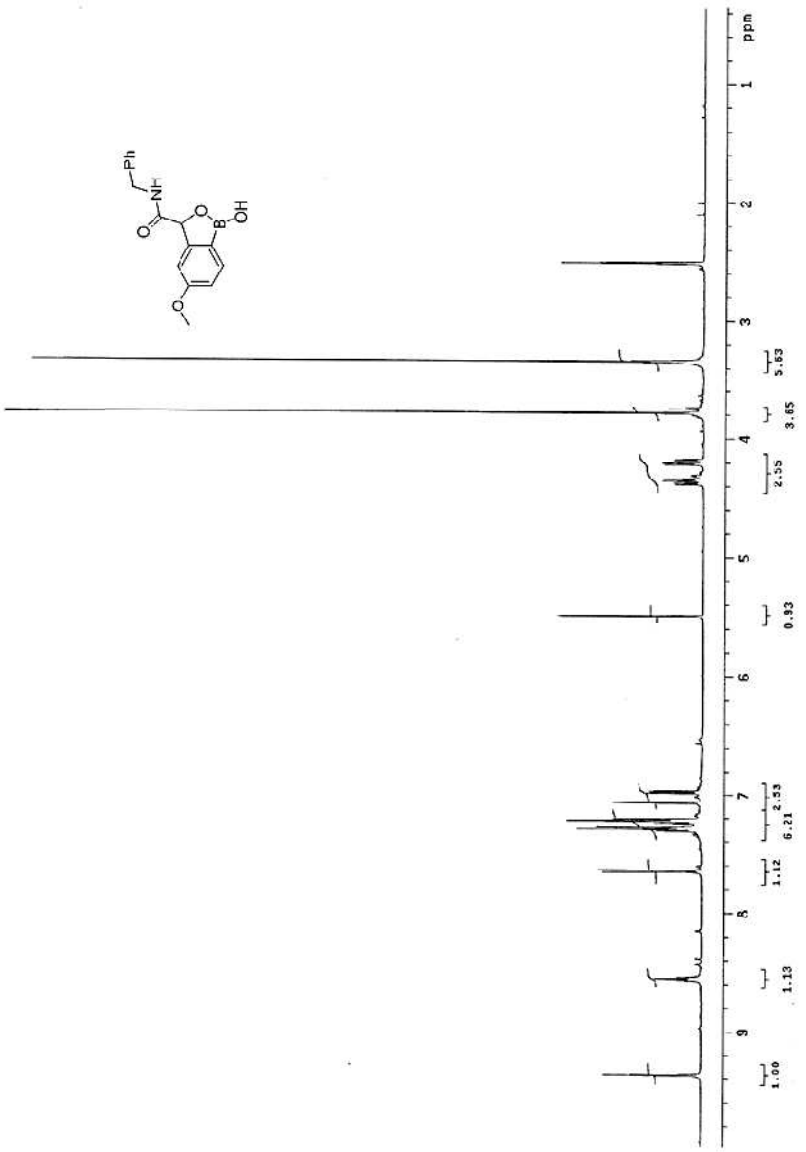
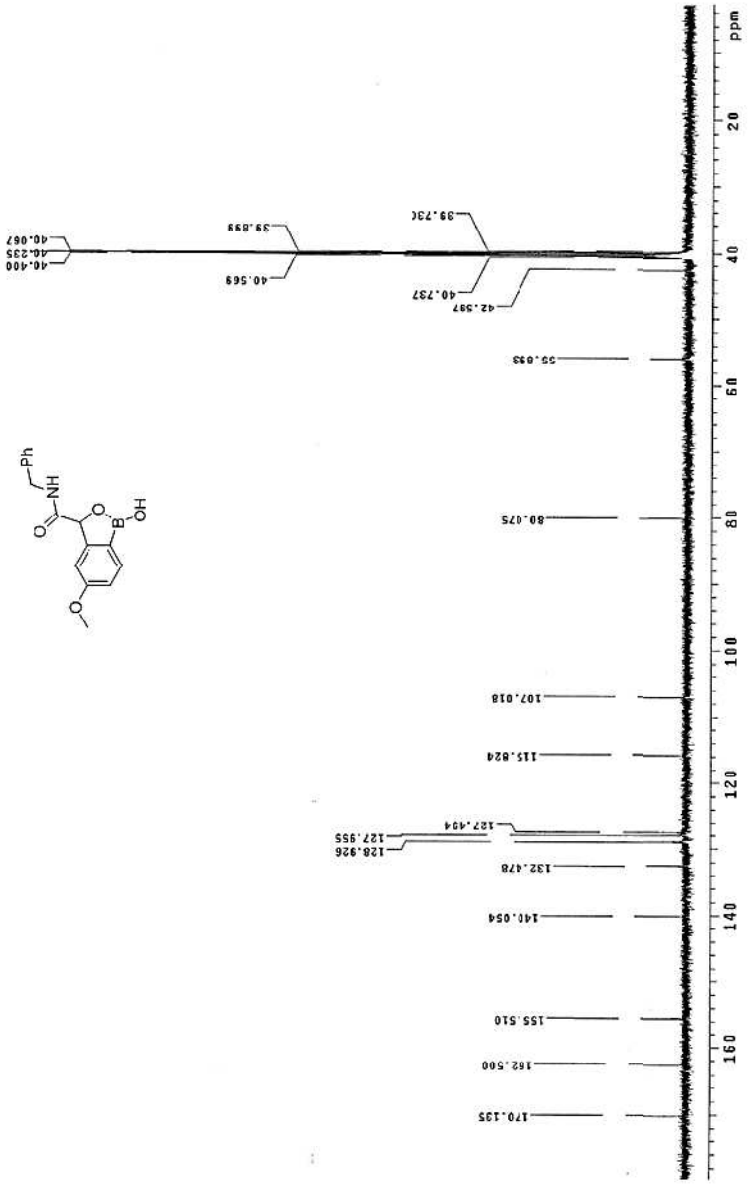
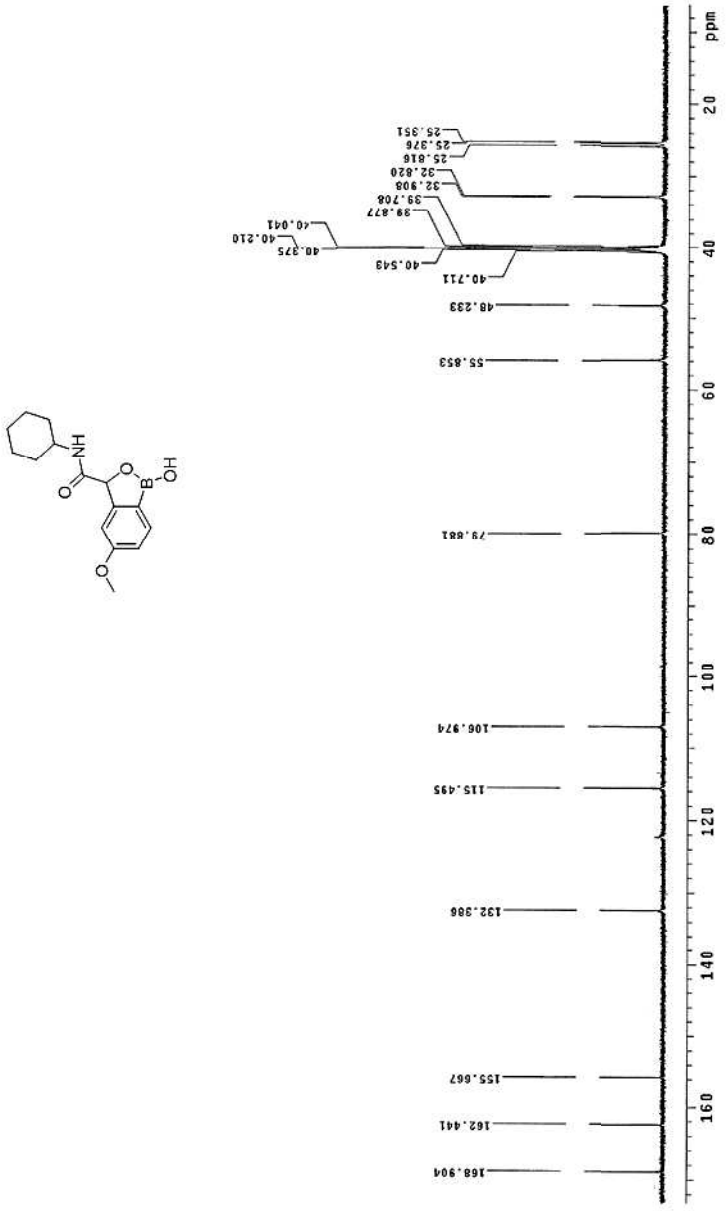
0.91
1.00
1.13
9.17
0.55
0.83

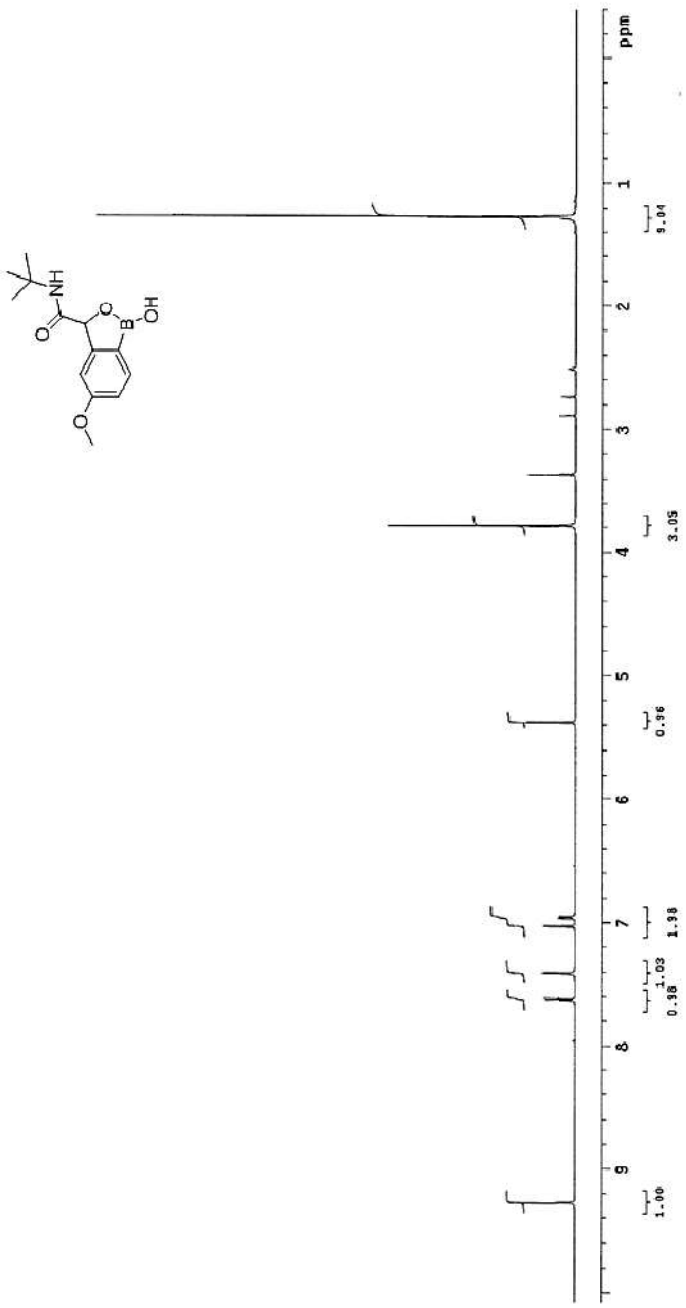

29.060
39.726
39.891
40.060
40.224
40.393
40.561
40.730
51.026
79.877
80.262
122.250
128.252
131.038
131.434
153.349
169.058
ppm
20
40
60
80
100
120
140
160
NH
O
O
B
OH

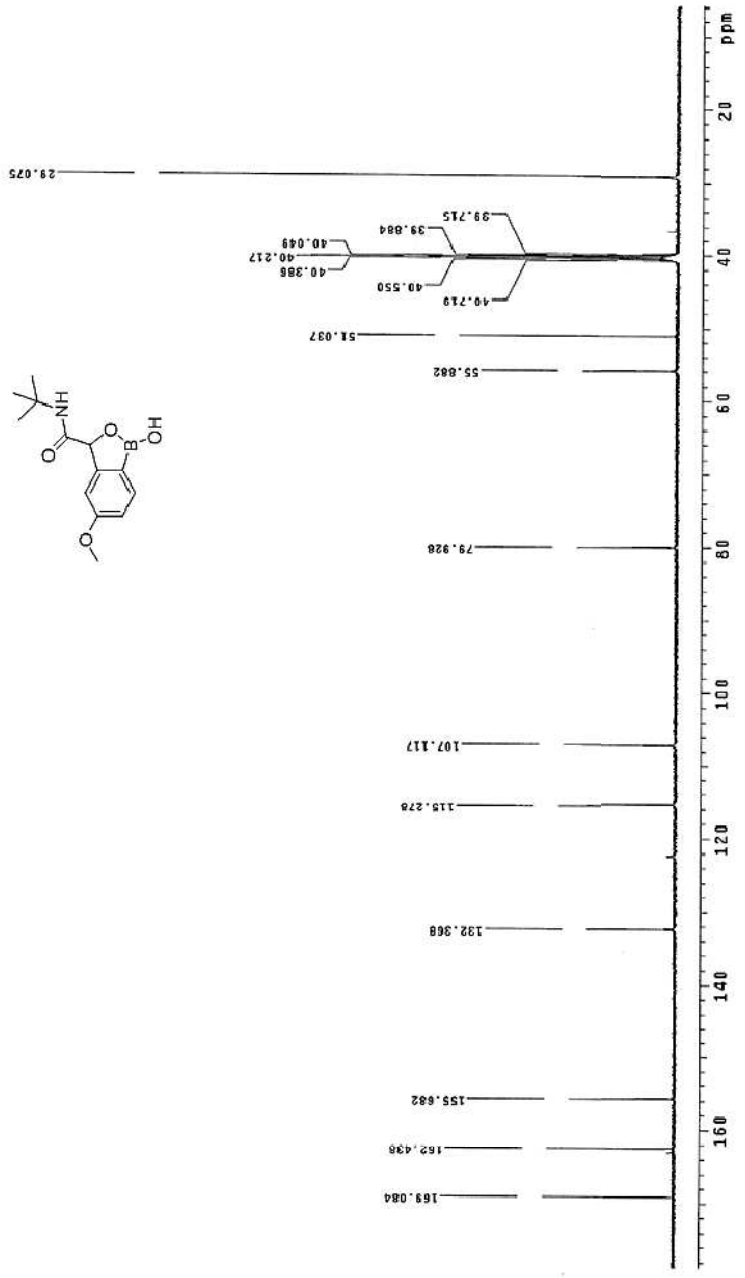

Ph
NH
O
O
B
OH
O
ppm
1
2
3
4
5
6
7
8
9
5.63
3.65
2.55
0.93
2.53
6.21
1.12
1.13
1.00

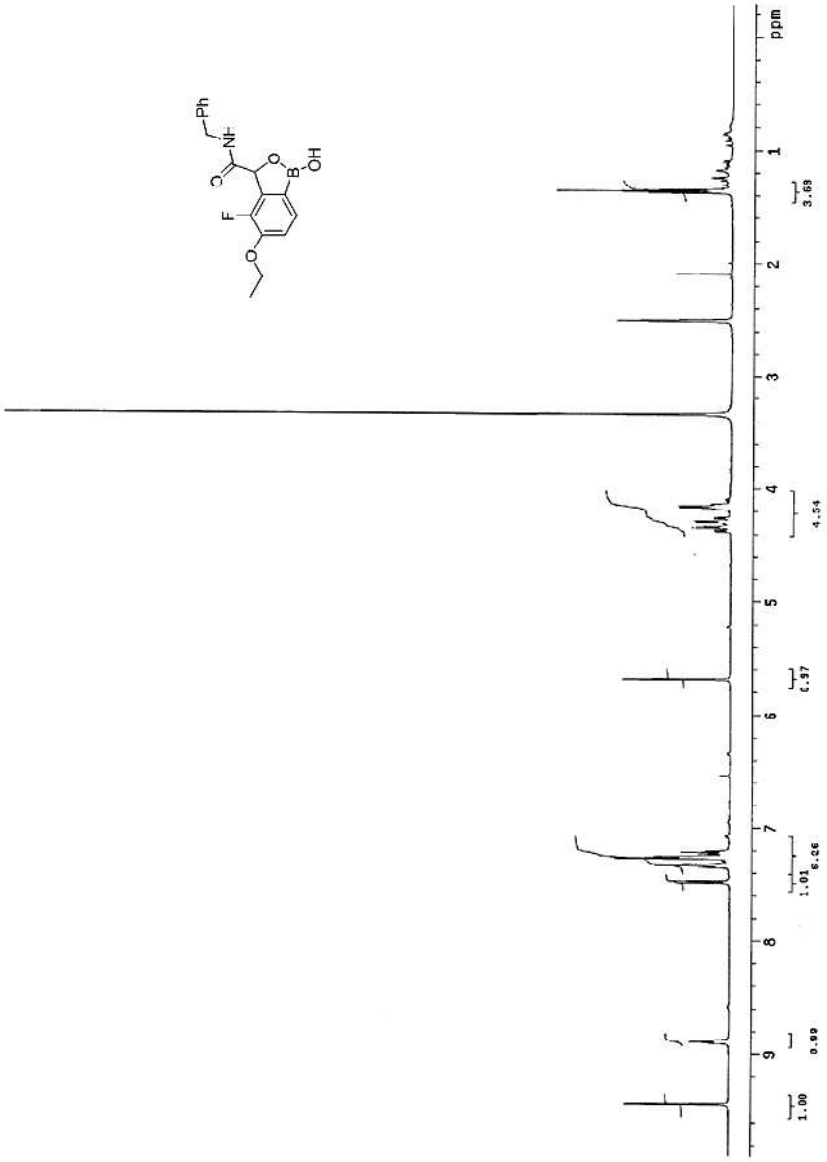

ppm
20
40
60
80
100
120
140
160
39.730
39.899
40.067
40.235
40.400
40.569
40.737
42.587
55.035
80.075
107.018
115.824
127.494
127.955
128.926
132.478
140.054
155.510
162.500
170.135
Ph
NH
O
O
B
OH
O

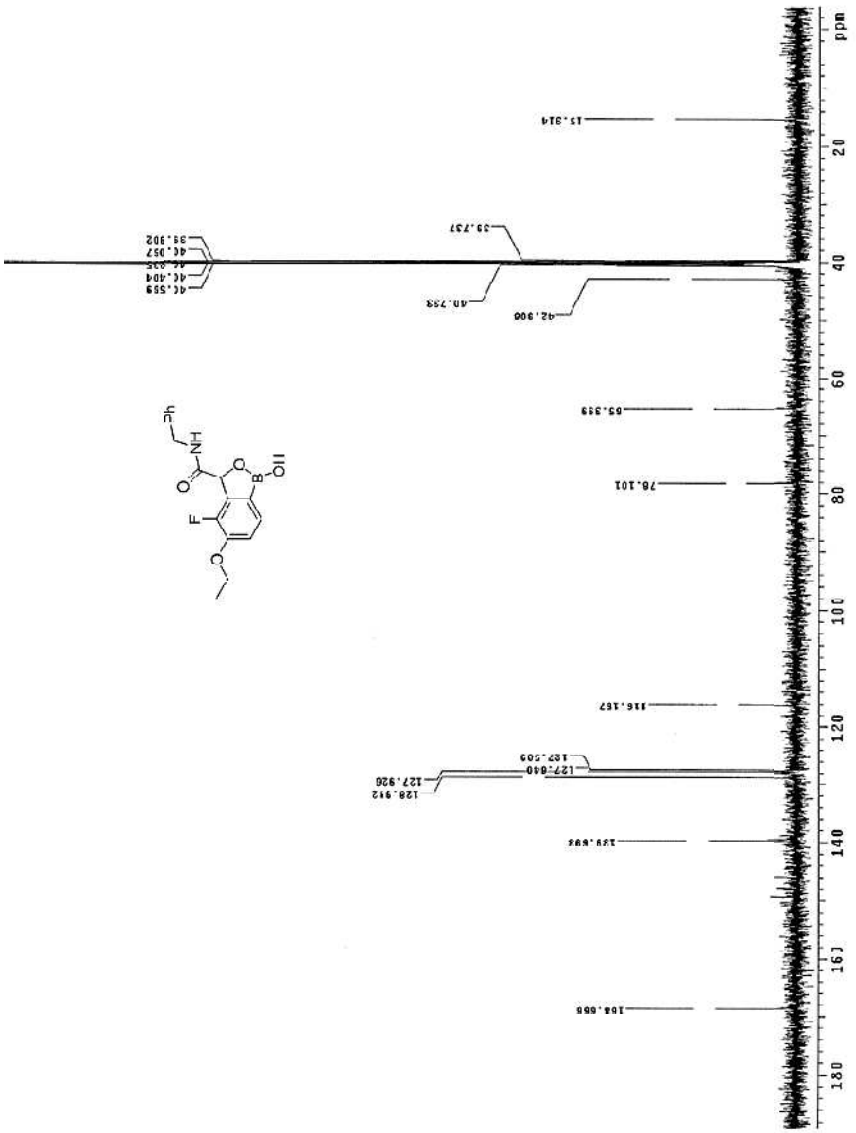
NH
O
B
OH
O
ppm
10
9
8
7
6
5
4
3
2
1
0
3.32
1.40
0.95
1.91
0.87
3.36
1.15
5.61
6.67


25.351
25.376
25.818
32.820
32.906
39.706
39.877
40.041
40.210
40.375
40.549
40.711
48.233
55.853
79.881
106.974
115.495
132.386
155.667
162.441
168.904
ppm


NH
O
O
B
OH
O
ppm
1
2
3
4
5
6
7
8
9
9.04
3.05
0.96
1.98
1.03
0.98
1.00


29.075
39.715
39.884
40.049
40.217
40.386
40.550
49.719
51.037
55.882
79.928
107.117
115.276
132.368
155.682
162.436
169.084
ppm
20
40
60
80
100
120
140
160
NH
O
O
B
OH
O


Ph
NH
O
O
B
OH
F
O
ppm
1
2
3
4
5
6
7
8
9
3.69
4.54
1.97
1.01
6.26
1.00
0.99


ppm
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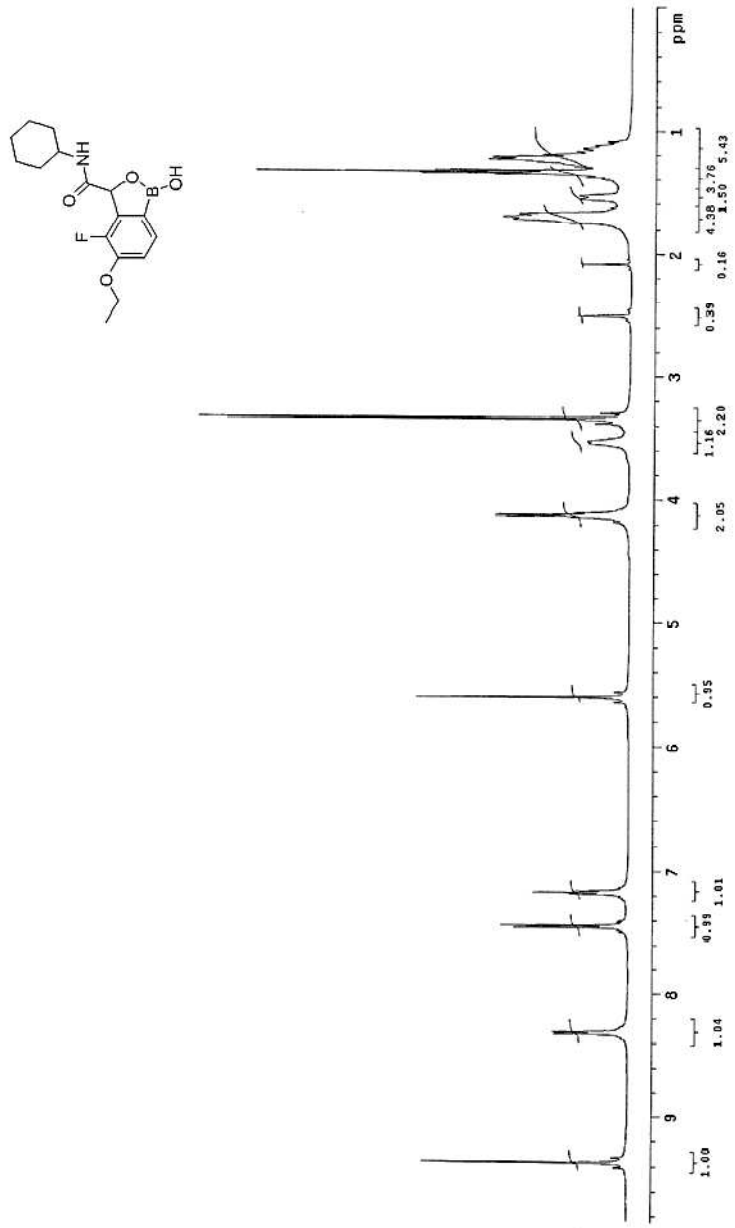
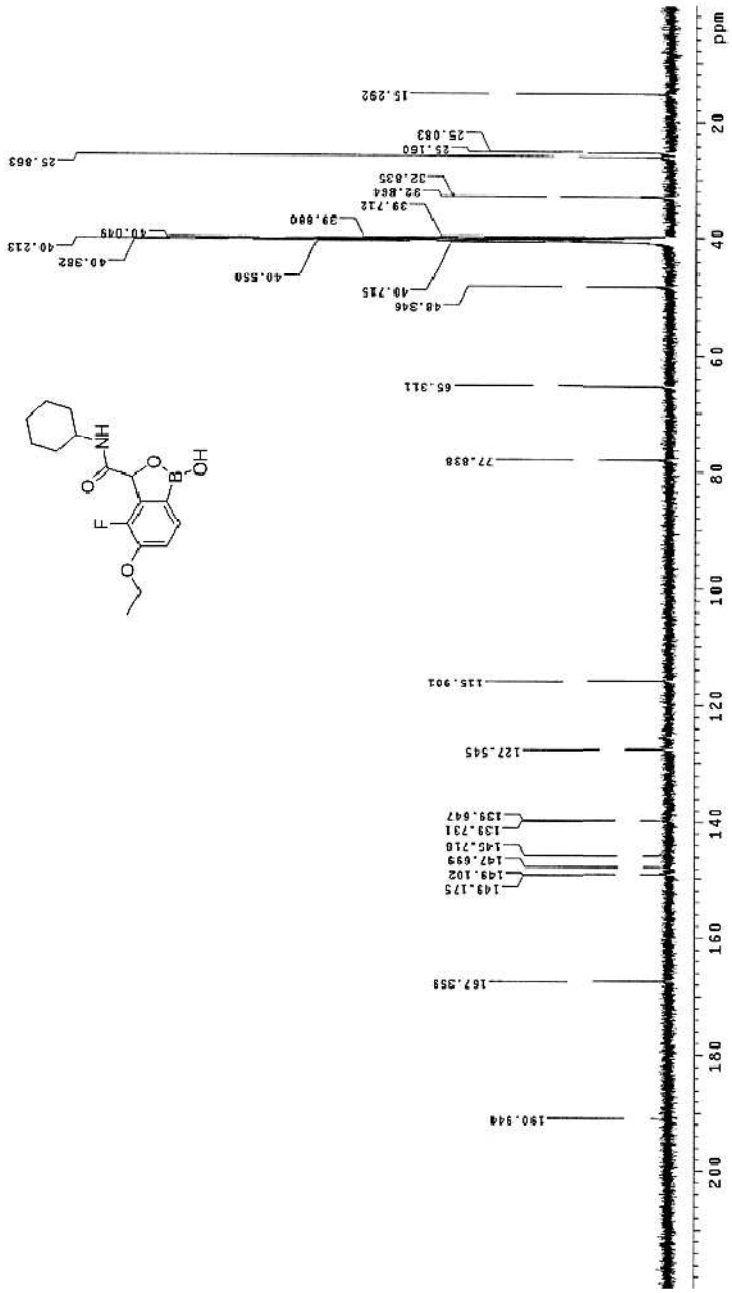
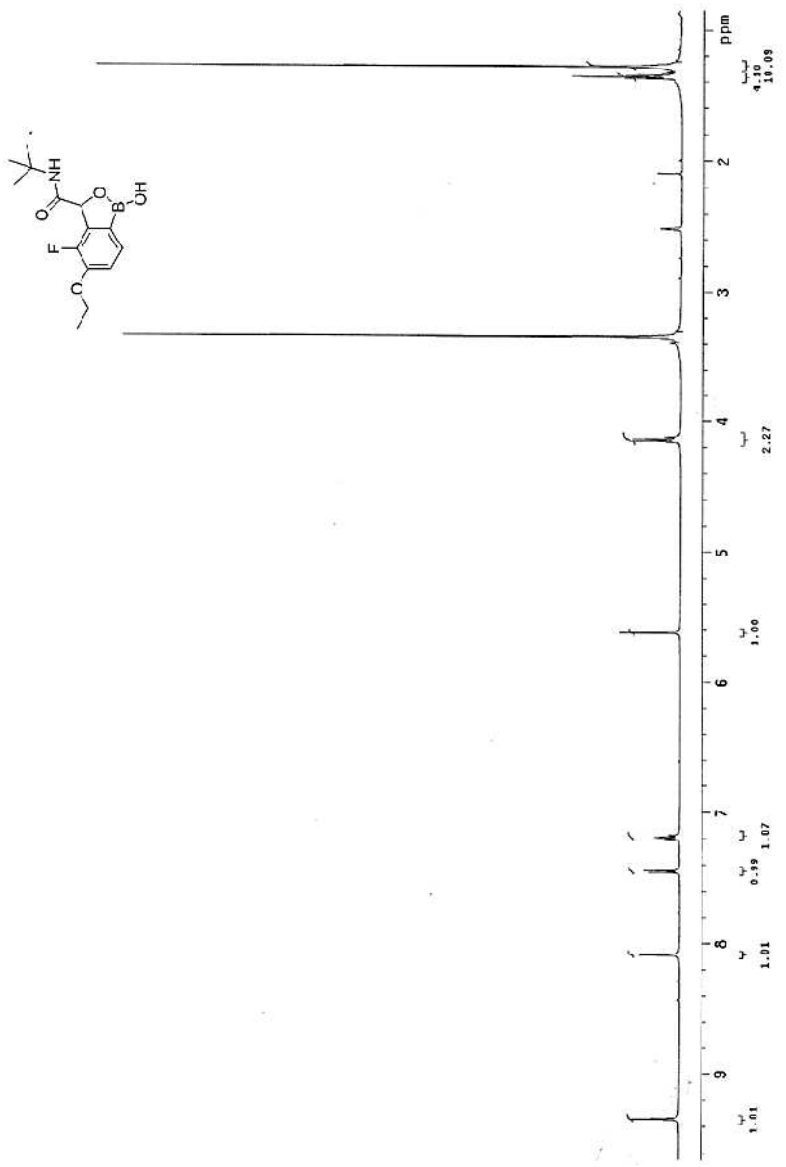
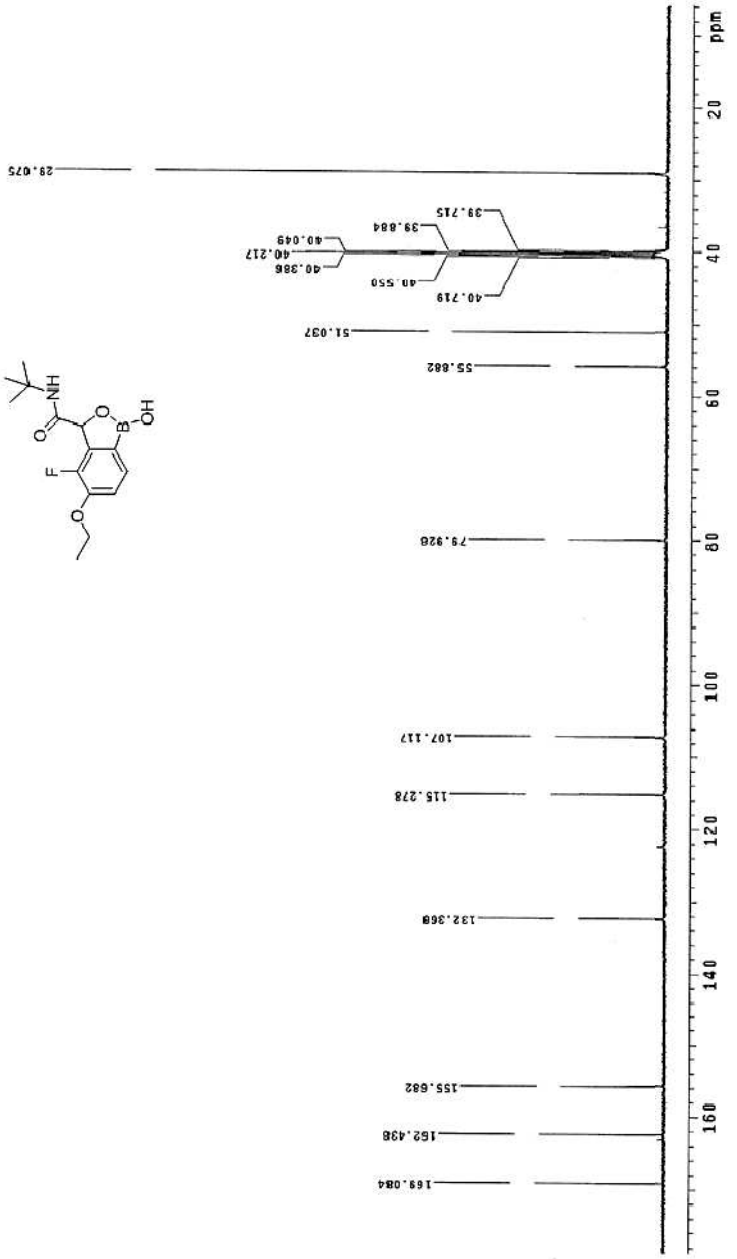
39.737
41.733
42.900
65.339
76.101
116.167
127.650
127.920
128.942
129.695
158.666


NH
O
O
B
OH
F
O
ppm
1
2
3
4
5
6
7
8
9
5.43
3.76
4.38
1.50
0.16
0.39
2.20
1.16
2.05
0.95
1.01
0.99
1.04
1.00


15.292
25.083
25.160
25.863
32.035
32.864
39.732
39.990
40.049
40.213
40.382
40.550
40.745
48.346
65.311
77.038
135.901
127.545
139.647
139.731
145.710
147.699
149.102
149.175
167.359
190.944
ppm
20
40
60
80
100
120
140
160
180
200
NH
O
O
B
OH
F
O


NH
O
O
B
OH
F
O
ppm
1
2
3
4
5
6
7
8
9
4.10
10.09
2.27
1.00
1.07
0.39
1.01
1.01


28.075
39.715
39.884
40.049
40.217
40.386
40.550
40.719
51.037
55.682
79.928
107.117
115.278
132.368
155.682
162.438
169.084
ppm
20
40
60
80
100
120
140
160
NH
O
O
B
OH
F
O