Development of light-activatable farnesyltransferase inhibitor

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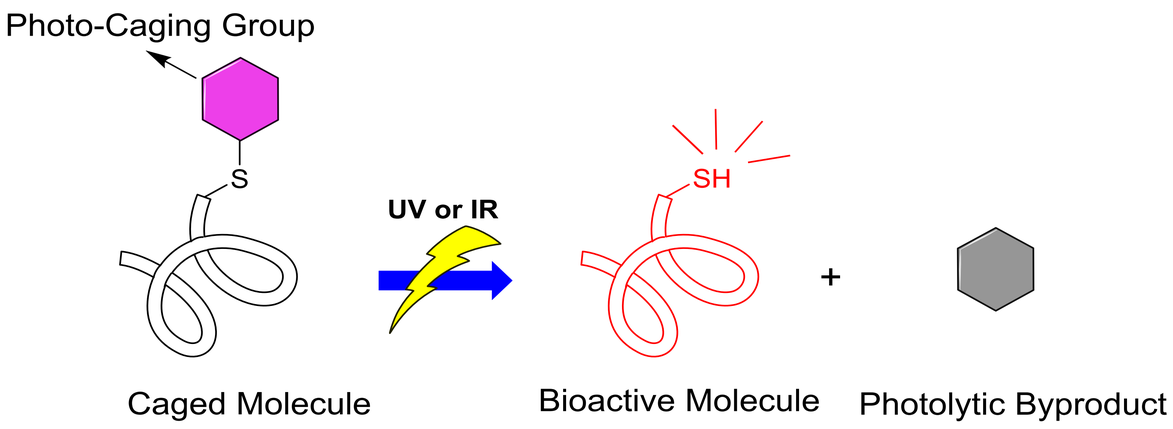
Abstract

One of the main efforts in the area of drug delivery is to release controlled amount of drug in specific location inside the body where the drug is supposed to affect certain target receptors or cells. The goal of this research project was to synthesize a photo-caged transferase inhibitor (FTI), which is a potential cancer drug. To accomplish this project, nitrodibenzofuran was synthesized as a PPG in order to mask the FTI via attachment to the thiol functionally of the drug. Before working with actual inhibitor, NDBF was synthesized and used for caging cysteamine as a model thiol containing molecule. The goal is to study the photolysis of NDBF-cysteamine via UV and IR irradiation.

Background

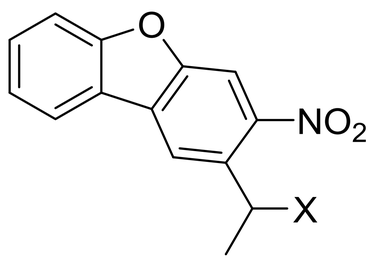


❖Photocaging techniques involve protection of a key functionality in a bioactive molecule using a photocleavable protecing group, so called caging group. This protection renders the molecule inactive. Upon irradiation, the active molecule is released only at the time and position where the light is irradiated.

❖ Thiol containing compounds play vital roles in various aspects of biology (enzymatic activity, controlling cellular redox state), protein and peptide chemistry (e.g. protein and peptide folding, native chemical ligation).

❖ Although dozens of photo-caging groups have been developed so far, there is not a unique one that could be used for protection of all types of functionalities. Moreover, several factors have to be considered while selecting a caging group such as absorption maxima (**λmax**), one-photon absorptivity (**ε**), quantum yield (**Φ**) and two photo cross section (**δ**).

Use of Nitrodibenzofurane for Caging Thiols

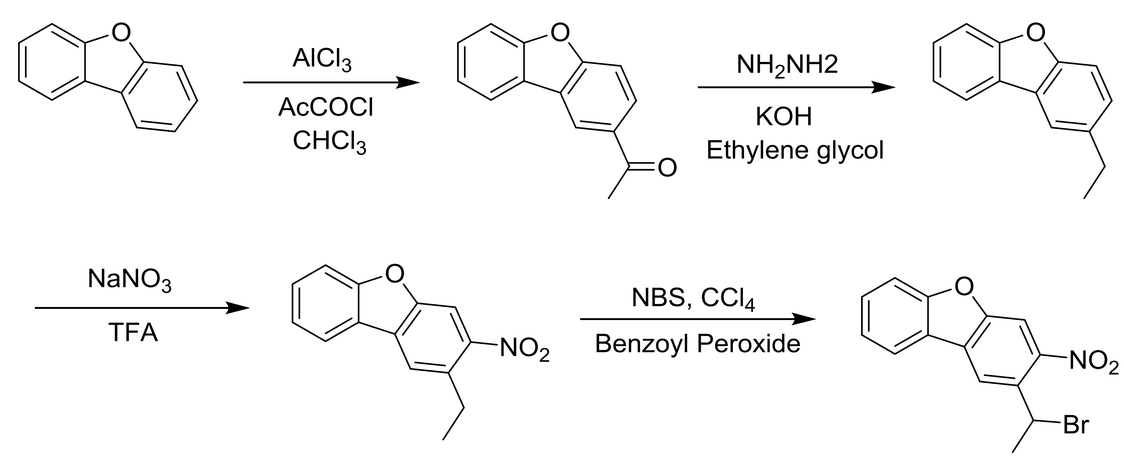


λmax = 330 nm
Φ = 0.1-0.6
ε ~ 18000 $M^{-1}cm^{-1}$
δ= 0.6 GM

Synthesis of NDBF

❖ In order to prepare enough amount of NDBF to perform our desired experiment, the first step was to synthesize bulk amount of this compound through via a four step synthesis procedure.

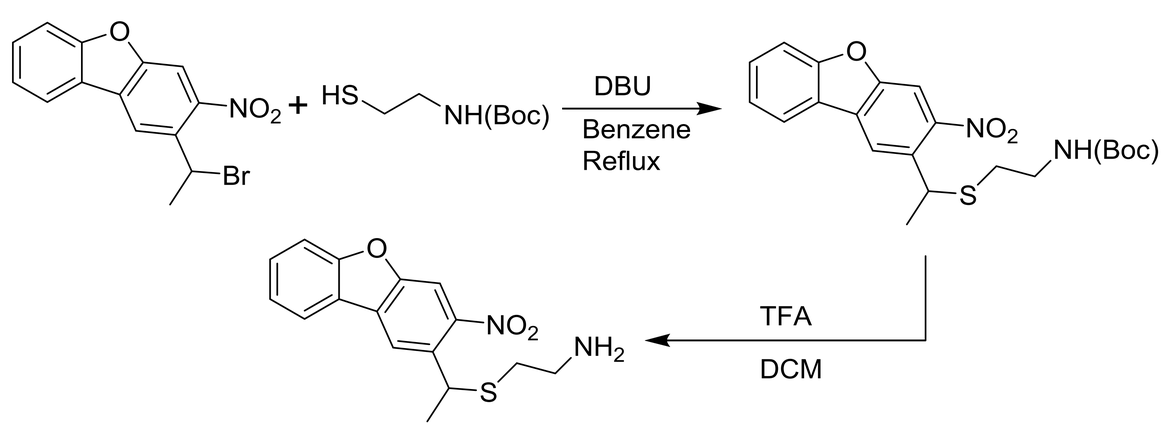
Synthesis of NDBF



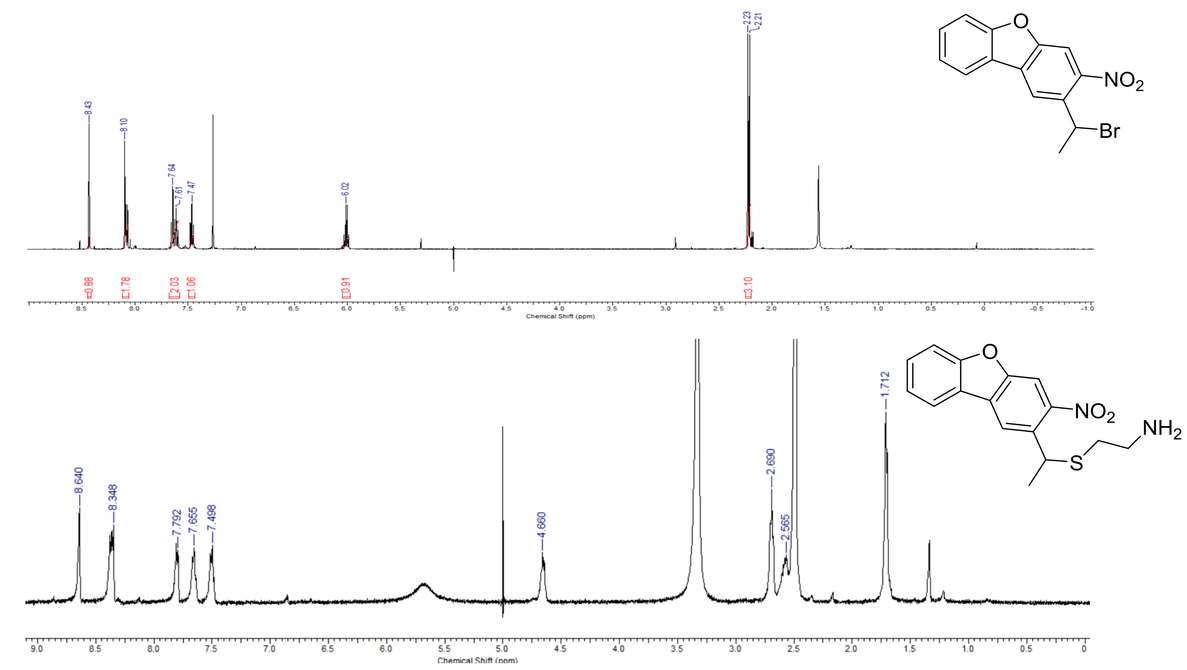
❖ Through Extensive solid phase synthesis I have managed to synthesize 4 g of NDBF-Br.

Caging Cysteamine as a model molecule

❖ Before using FTI which is an expensive drug we decided to test our caging molecule on a model thiol containing small molecule, therefore we synthesized NDBF-Cysteamine.



NMR Data



Future Directions

❖ Study the photolysis rate of NDBF Cysteamine via HPLC analysis

❖ Synthesize NDBF-FTI.

❖ Photolyze caged FTI and evaluate the release of free FTI via HPLC analysis.

References

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(3) Abate-Pella, D.; Zeliadt, N. A.; Ochocki, J. D.; Warmka, J. K.; Dore, T. M.; Blank, D. A.; Wattenberg, E. V.; Distefano, M. D. *ChemBioChem* **2012**, *13*, 1009.

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