**INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI**
**SHORT ABSTRACT OF THESIS**


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Programme of Study : **Ph.D.**


Thesis Title:
***Development of ROS-responsive Turn-on Fluorogenic Prodrugs for the Delivery of Anti-inflammatory and Anti-cancer Drugs along with Hydrogen Sulfide***


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Key words for description of Thesis Work : **ROS, $H_2S$, Anti-cancer drug, Anti-inflammatory drug, Fluorogenic prodrug**.


## SHORT ABSTRACT


My PhD thesis titled "***Development of ROS-responsive Turn-on Fluorogenic Prodrugs for the Delivery of Anti-inflammatory and Anti-cancer Drugs along with Hydrogen Sulfide***" comprises of five chapters.

In **chapter 1**, the mechanism of reactive oxygen species (ROS) production and detoxification in biological systems have been highlighted. In addition, the development of ROS-responsive fluorogenic probes, non-fluorogenic anti-inflammatory and anti-cancer prodrugs, and fluorogenic anti-cancer prodrugs have been reviewed elaborately. Moreover, the biological function, detection techniques, and enzymatic production of $H_2S$ have been discussed briefly. Several synthetic donors of $H_2S$ such as hydrolysis-based, biothiol-triggered, ROS-responsive, and so on have been reviewed briefly.

In search of understanding the importance of fluorophores and different linkers for connecting the boronate ester moiety to the fluorophore before developing a prodrug, total nine probes, where three different fluorophores (coumarin, naphthalimide, and fluorescein unit) were connected with boronate ester using three different linkers (direct, ether, and carbonate) have been developed as shown in **chapter 2**. According to the spectroscopic studies in aqueous medium, directly-coupled boronate ester probes are more sensitive than linker-based probes towards $H_2O_2$, whereas self-immolative probes are capable of releasing the fluorophore sustainably. Fluorescence microscopic studies also further confirmed the higher sensitivity of the directly-coupled probe than self-immolative-based probes.

In **chapter 3**, a peroxide-responsive fluorogenic prodrug (**DCI-ROS**) of NSAID (diclofenac) have been developed, where the drug is released sustainably with turn-on NIR fluorescence in the presence of $H_2O_2$ confirmed by spectroscopic studies. Moreover, Fluorescence microscopic studies in MDA-MB-231 cells confirmed the release of the fluorophore in the presence of endogenous ROS. The cellular studies in inflammation-induced macrophage cells RAW 264.7 indicated that the prodrug **DCI-ROS** is more selective towards inflammatory cells over normal cells. Finally, western blot analysis confirmed the release of the active drug from the prodrug in the presence of endogenous ROS by inhibiting COX-2 as the parent drug **DCF**.

Next, in **chapter 4**, a peroxide-responsive turn-on fluorogenic prodrug (**DCF-HS**) of diclofenac along with the delivery of $H_2S$ have been developed. Spectroscopic and HPLC studies confirmed the release of the fluorophore and drug in a sustainable manner. Moreover, cellular studies confirmed the release of fluorophore and $H_2S$. In addition, the anti-inflammatory effect was observed from western blot analysis, where prodrug **DCF-HS** inhibited the COX-2 as the parent drug diclofenac.

In **chapter 5**, a ROS-responsive fluorogenic prodrug (**AM-TCB**) of the anti-cancer drug amonafide along with the delivery of $H_2S$ have been developed. Several studies such as spectroscopic, HPLC, and cellular studies supported the release of the drug and $H_2S$ in the presence of $H_2O_2$. Most importantly, the designed prodrug **AM-TCB** showed selectivity towards cancer cells (HeLa) over normal cells (HEK-293), where cytotoxicity of the prodrug **AM-TCB** for cancer cells similar to free drug amonafide, less toxic towards normal cells as compared to amonafide.

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