INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: Benzylic Organosulfides and Analogues: Greener Synthesis, Anti-cancer Activities and the Feasibilities of H_2S Donation

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SHORT ABSTRACT

The thesis comprises four chapters. Chapter 1 highlights the general introduction of H_2S and its role in biological systems. This chapter briefly discusses the production, metabolism, and biochemical pathways of H_2S regulation and its detection techniques. Additionally, a brief and concise review has been made on the reported synthetic and natural donors of H_2S and their biological implications in different diseases, notably cancer. In chapter 2, we presented a series of 4-substituted benzylic derivatives of DADS as well as their diselenide analogues for detailed structure-activity relationship (SAR) studies regarding their anti-cancer properties against ER+ breast cancer cell lines (MCF-7) and other organ-specific cancer cells. The SAR study revealed that the anti-cancer activity of the benzylic disulfides/diselenides could be enhanced significantly upon the incorporation of 4-cyano group on the benzene ring. Further investigations revealed the notable increase in intracellular ROS level upon the administration of diselenides towards MCF-7 cells correlating with their anti-proliferative activity. Treatment of 4-cyanobenzyl diselenide in MCF-7 cells induced prominent nuclear fragmentation and induced the apoptosis pathway, confirmed by evaluating the expression level of several oncogenic marker proteins (Bcl2, Survivin, and Procaspase 3). In chapter 3, we described a very simple and convenient method for the selective synthesis of garlic-derived allyl sulfides and related derivatives utilizing a wide variety of alkyl, alkenyl, and benzyl halides as precursors under a greener and catalyst-free condition. We show for the first time that, the selectivity among symmetrical trisulfides, disulfides, and monosulfides could be achieved by variation of several reaction parameters. Our study further revealed that the reaction temperature and solvent were two crucial parameters for an effective selectivity toward trisulfides over disulfides. The detailed mechanistic studies by experimental and computational methods indicated that the co-formation of disulfides along with trisulfides is due to the formation of sodium sulfite (Na_2SO_3) as a by-product that interfere in the reaction. Furthermore, results from the preliminary anti-proliferative activities by trisulfides towards MCF-7 revealed potent anti-cancer activities of most of the trisulfides in general. Importantly, the 4-methyl substituted trisulfide exhibited the highest anti-proliferative activity in MCF-7 cells and it was capable of donating H_2S in a sustained manner in the presence of biothiols. The mechanistic investigations on the potent anti-proliferative activity

of the benzylic organotrisulfide (3,5-dimethoxybenzyl) against the highly aggressive triple-negative breast cancer cells (MDA-MB-231) was carried out in chapter 4. From the pool of different substituted benzylic organotrisulfides, 3,5-dimethoxybenzyl trisulfide (**4.0**) exhibited highest selectivity towards the MDA-MB-231 over the normal cells (HEK-293). The selected trisulfide compound further studied the detailed mechanistic aspects for evaluating its anti-proliferative activity. Trisulfide **4.0** exhibited the anti-cancer activity mainly by targeting and suppressing the Wnt/β-catenin signaling pathway. The detailed mechanistic studies revealed that compound **4.0** facilitated the GSK-3β-induced phosphorylation of β-catenin and subsequent proteasomal degradation, which was supported by the G2/M phase arrest of the cell cycle and the significant down-regulation of downstream signaling genes such as Cyclin D1 and c-Myc. Unlike the disulfide and monosulfide moieties, the presence of a trisulfide functionality facilitated the release of H_2S, which was found to be important for the desired inactivation of β-catenin expression. Surprisingly, combination with DATS and our synthesized sustained donor **4.0** exhibited cytoprotective effect due to the optimum level of H_2S donation. Moreover compound **4.0** or the released H_2S induced down-regulation of the p53 protein, possibly through S-sulfhydration process observed by western blot experiment.