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Name of the Scholar: Sonam Roy

Name of the Supervisor: Md. Imtaiyaz Hassan

Name of the Department/Centre: Centre for Interdisciplinary Research in Basic Sciences

Topic of Research: Structure-guided Design and Development of Potent and Selective Inhibitors of Human Sphingosine Kinase-1 for Lung Cancer Therapy.

Finding

Summary of Abstract in 200 words: SphK1 is found to be highly upregulated in non-small cell lung cancer (NSCLC) and is responsible for the resistance to currently available chemotherapeutic drugs. The SphK1 gene was successfully cloned, expressed,and the protein was purified in a single chromatography step with a single 45 kDa band on SDS-PAGE. The secondary and tertiary structural changes in the SphK1 on treatment with buffers at different pH and at different urea concentrations were studied to find the optimum pH for maximum catalytic activity and to understand the unfolding mechanism of SphK1. We also studied a series of natural compounds for their inhibitory activity against SphK1. Among them, harmaline, quercetin, cinchonine, and colcemid, exhibited potent inhibitory activity against SphK1. Quercetin and harmaline also hindered the growth of NSCLC cell lines. Further, we synthesized small molecules withan unorthodox architecture concerning the natural substrate of SphK1 to develop the specific and highly potent SphK1 inhibitors. We found that novel urea, sulfonyltriurea, and thiazolyl benzenesulfonamides small molecule compounds inhibited the SphK1 ATPase activity with high potency. Our study has expanded the structural diversity of scaffolds that can be used as a potent SphK1 inhibitory molecule to generate highly SphK1 selective inhibitors for lung cancer therapy.