ABSTRACT

Name of Research Scholar: **Mr. Sunny Goon** Index no:**67/21/Chem/27**
Degree for which submitted: **Ph.D.** Department: **Chemistry**
Name of the Research Guide: **Dr. Mohabul Alam Mondal** (Assoc. Professor, Dept. of Chemistry, J.U), **Dr. Arindam Talukdar** (Sr. Pr. Scientist, CSIR-IICB)
Thesis Title: **Design and exploration of small molecule modulators targeting metabolic disorders and T-cell activation.**

Chapter-I:

The E3 ubiquitin ligase, Constitutive Photomorphogenic 1 (COP1), plays a critical role in lipid metabolism within hepatocytes by regulating the stability and turnover of Adipose Triglyceride Lipase (ATGL), the rate-limiting enzyme in lipolysis. Dysregulation of the COP1-ATGL axis disrupts hepatic lipid homeostasis, leading to pathological conditions such as simple steatosis. In this study, we report the design and development of quinazolinone-based modulators targeting the COP1-ATGL pathway. Comprehensive structure-activity relationship (SAR) studies guided the rational incorporation of functional groups at key positions (C2, C5 and N1) of the quinazolinone scaffold to optimize molecular interactions and bioactivity. The biological activity of the synthesized compounds was evaluated through in vitro assays, which demonstrated their efficacy in modulating ATGL stability and function. The lead compound **58**, exhibited a significant ability to enhance ATGL protein levels, inhibit ATGL ubiquitination, and reduce intracellular lipid accumulation in hepatocytes in a dose-dependent manner. Pharmacokinetic properties were further assessed through ADME profiling, confirming compound **58** as a candidate with favorable drug-like properties. This study highlights quinazolinedione as a promising chemotype for the therapeutic modulation of COP1-ATGL activity. By targeting this pathway, these compounds offer a novel approach for managing lipid-related disorders, particularly in the context of non-alcoholic fatty liver disease (NAFLD) and associated metabolic syndromes.

Chapter-II:

PPARγ plays a key role in managing non-alcoholic fatty liver disease (NAFLD) by regulating lipid metabolism, glucose homeostasis, and inflammation. It mitigates oxidative stress by enhancing antioxidant defenses, improving mitochondrial function, and upregulating enzymes like superoxide dismutase (SOD) and glutathione peroxidase. While thiazolidinediones (TZDs) have shown efficacy as PPARγ activators, their clinical use is limited by adverse effects. This study presents a novel purine-based PPARγ activator, compound **30**, designed to target the PPARγ-NRF2 pathway and reduce ROS-induced hepatocellular dysfunction. Compound **30** selectively elevated PPARγ expression and downstream genes such as NRF2, NQO1, and SOD1. In CellRox assays, it significantly reduced ROS levels, and CETSA experiments confirmed strong binding affinity with PPARγ. Furthermore, it demonstrated superior efficacy (EC_{50} = 214.6 nM)

compared to the marketed activator rosiglitazone (EC_{50} = 257.3 nM) in PPARγ Transcription Factor Kit assays. In summary, the purine-based compound 30 offers a promising therapeutic approach to ameliorate ROS-driven hepatocellular proteotoxicity in NAFLD.

Chapter-III:

Piezo1, a mechanosensitive ion channel, is crucial for numerous physiological functions and has garnered significant attention for its therapeutic relevance. The development of selective agonists has provided insights into how cells respond to mechanical cues, offering promising therapeutic strategies. In this work, we analyzed the structural components of Yoda1, a well-characterized Piezo1 agonist, to unravel its structure–activity relationship (SAR) and facilitate the creation of improved agonists. Using Piezo1-mCherry-transfected HEK293A cells, we conducted initial screening assays with Yoda1 serving as the reference agonist. Through these efforts, we identified a novel Piezo1 agonist, Yaddle1 (**34**), featuring a trifluoromethyl substitution. Yaddle1 exhibited potent activity with an EC_{50} of 0.40 μM and showed marked improvements in solubility. Its kinetic solubility at physiological pH (26.72 ± 1.8 μM at pH 7.4) was approximately 22 times greater than that of Yoda1 (1.22 ± 0.11 μM at pH 7.4), addressing the solubility issues associated with Yoda1. Computational studies as well as density functional theory (DFT) analysis revealed that Yaddle1 leverages tetrel interactions to stabilize Piezo1's domain interface, functioning as a dynamic wedge to support its activation. Furthermore, Yaddle1 demonstrated the ability to induce calcium ion (Ca^{2+}) influx in primary human $CD4^+$ T cells, highlighting its potential as a novel vaccine adjuvant to enhance T cell activation. In summary, Yaddle1 emerges as a next-generation Piezo1 agonist with superior solubility and bioactivity, providing a valuable tool for studying Piezo1-mediated functions and exploring its therapeutic applications

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