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## Discovery of novel 2-thio-imidazole derivatives as potent and orally efficacious TGR5 receptor agonists

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TGR5 is a G protein-coupled receptor (GPCR), activation of which promotes secretion of glucagon-like peptide-1 (GLP-1) and modulates insulin secretion. In our pursuit of novel drugs with distinct mechanism of action for type 2 diabetes we report here the discovery of 2-((2-(4-(1H-imidazol-1-yl) phenoxy) ethyl)thio)-5-(2-(3,4-dimethoxyphenyl)propan-2-yl)-1-(4-fluorophenyl)-1H-imidazole as a novel, potent, selective and orally bioavailable TGR5 agonist. Using computer aided modeling studies we designed a series of novel 2-thio-imidazole derivatives, and then experimentally established a structure-activity relationship (SAR). The mentioned compound was identified as a TGR5 agonist with EC<sub>50</sub> of 57pM and 62pM against the human TGR5 and mouse TGR5 receptors, respectively, in recombinant CRE-directed luciferase reporter gene assays. The compound showed a favorable pharmacokinetic profile. Further, this compound showed *in vivo* GLP-1 secretion in a C57 mouse model, and it potently reduced glucose excursion in oral glucose tolerance test (OGTT) in DIO C57 mice (ED<sub>50</sub> = 7.9 mg/kg; ED<sub>90</sub> = 29.2 mg/kg).

### Biography

Sameer Agarwal has obtained Master's in Chemistry from IIT, Delhi and was awarded DAAD (German Govt. Scholarship) fellowship to pursue research project at Karlsruhe University, Germany. He has received PhD degree from Technical University, Dresden, Germany in the field of Synthetic and bio-organic chemistry under direction of Prof. Dr. Hans-Joachim Knölker, FRSC, a well-known scientist of present times for his contribution towards Alkaloid Chemistry. He worked as Research Scientist (Post-Doc), JADO Technologies, (collaboration with Max Planck Institute (MPI) of Molecular Cell Biology and Genetics and Chemistry Department, Technical University), Germany. He then decided to return to his home country and working with Zydus Research Centre, Cadila Healthcare Ltd., Ahmedabad as Principal Scientist / Group Leader in the area of basic drug discovery and his research interest includes discovery of cardio metabolic, anti-inflammatory and oncology drugs. He has large number of publications in international journals and patents and is a reviewer of many prestigious journals including American Chemical Society.

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