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Identification of novel anti-diabetic Agents

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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. The 2-thio-imidazole derivative 6g was identified as a novel, potent and selective TGR5 agonist (hTGR5 EC50 = 57 pM, mTGR5 = 62 pM) with a favorable pharmacokinetic profile. The compound 6g was found to have potent glucose lowering effects in vivo during an oral glucose tolerance test in DIO C57 mice with ED50 of 7.9 mg/kg and ED90 of 29.2 mg/kg. GPR40 / FFAR1 is another G protein-coupled receptors predominantly expressed in pancreatic β-cells and activated by long-chain free fatty acids, mediates enhancement of glucose-stimulated insulin secretion. A series of novel substituted 3-(4-aryloxyaryl) propanoic acid derivatives were prepared and evaluated for their activities as GPR40 agonists, leading to the identification of compound 5, which is highly potent in in vitro assays and exhibits robust glucose lowering effects during an oral glucose tolerance test in nSTZ rats (ED50 = 0.8 mg/kg; ED90 = 3.1 mg/kg) with excellent pharmacokinetic profile, and devoid of cytochromes P450 isoforms inhibitory activity.

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