28AB-ISMS25 **Discovery of a Potent and Orally Bioavailable GPR40 Agonist DS-1558**

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GPR40 is a G protein-coupled receptor that is predominantly expressed in pancreatic β-cells. GPR40 agonists stimulate insulin secretion only under the presence of high glucose concentration. Based on this mechanism, GPR40 agonists are believed to be novel insulin secretagogues with low risk of hypoglycemia. Our derivatizations of 3-aryl-3-ethoxypropanoic acids were performed to improve *in vitro* activity and pharmacokinetics. We discovered an orally available insulin secretagogue DS-1558, (3*S*)-3-ethoxy-3-(4-{[(1*R*)-4-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]oxy}phenyl)propanoic acid, which was confirmed to have an enhancing effect on glucose-dependent insulin secretion after intravenous glucose injection in SD rats and potent glucose-lowering effects during oGTT on ZF rats. The docking study of DS-1558 and hGPR40 receptor could explain the result of SAR study reasonably. The details of design, synthesis, and biological activities of the 3-aryl-3-ethoxypropanoic acid derivatives will be presented.