

## 28AB-ISMS34 **Discovery of 1,2,4-oxadiazolidine-3,5-dione Derivatives as Novel GPR40 Agonists**

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GPR40, a Gq-coupled GPCR that binds to medium- and long-chain fatty acids, is highly expressed in pancreatic  $\beta$  cells and involved in glucose-stimulated insulin secretion from the pancreas. Therefore, GPR40 has emerged as an attractive target for the treatment of type 2 diabetes. We describe herein our exploration of the design, synthesis, and SAR of a novel series of 1,2,4-oxadiazolidine-3,5-dione derivatives as potent and selective GPR40 agonists. Optimization of this series generated a clinical compound ASP4178 with potent GPR40 agonistic activity and good PK profiles. Furthermore, ASP4178 demonstrated an excellent antidiabetic effect in diabetic ob/ob mice after repeated administration.