DISCOVERY OF NOVEL ORALLY ACTIVE, NON-COVALENT DPP-IV INHIBITORS

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Inhibition of the serine protease dipeptidyl peptidase-IV (DPP-IV) leads to increased levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) which play a central role in insulin release and glucose homeostasis. The use of DPP-IV inhibitors as potential therapeutic agents for the treatment of type 2 diabetes has been receiving increasing attention in recent times. Many of the early DPP-IV inhibitors have been designed as irreversible or reversible covalent substrate analogues, amongst them Novartis' phase III clinical compound Vildagliptin (LAF237). The received opinion for identification of potent DPP-IV inhibitors for a long time included the requirement of a serine trap within the inhibitor structure. However, more recently progress has been reported in this field culminating in the discovery of non-covalent DPP-IV inhibitors, such as Merck's phase III compound MK-0431 being the most advanced of this cohort.

Herein, we present two novel series of non-covalent DPP-IV inhibitors. After screening of Santhera's fragment collection, two β-phenylethylamine fragments were uncovered as weak DPP-IV inhibitors (DPP-IV IC_{50} 37 and 40 μM). By the x-ray structure of one of these inhibitors complexed with porcine enzyme, we discovered an unexpected non-substrate like reverse-binding mode for this DPP-IV inhibitor. This discovery laid the foundation for the design of several novel DPP-IV inhibitor series, two of which are reported here. The medicinal chemistry optimization process ultimately led to potent non-covalent small molecule DPP-IV inhibitors (IC_{50} sub-10 nM), that are highly selective over related DPP-like enzymes, and exhibit oral bioavailability. Inhibition data for DPP-IV, selectivity data, efficacy data in ob/ob mice and an x-ray structure showing the non-substrate like reverse-binding mode are given here.