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Discovery and development of novel DPP IV inhibitor

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Type 2 diabetes mellitus (T2DM) is the most common form of the diabetes disease, accounting for about 90-95% of all diagnosed North American cases of diabetes. The main goal of the treatment of type 2 diabetes is to achieve glycemic control as close to the non-diabetic range as practicable, in order to reduce the risk of late-stage complications. The incretin hormone glucagon-like peptide 1 (GLP-1) is a potent simulator of endogenous insulin release. GLP-1 possesses several physiological properties, such as increasing insulin secretion, beta cells mass, and insulin gene expression, inhibiting acid secretion and gastric emptying in the stomach, decreasing food intake by increasing satiety in brain, and promoting insulin sensitivity. Unfortunately, GLP-1 is rapidly degraded *in vivo* by the serine protease dipeptidyl peptidase-4 (DPP-4); therefore, DPP-4 inhibitors have emerged as a new therapeutic option to treat type 2 diabetes. A novel series of thienopyrimidine derivatives was designed and synthesized, and found to be dipeptidyl peptidase-4 (DPP-4) inhibitors. Among them, compound DC291407 was identified as efficacious, safe, and selective inhibitor of DPP-4 resulting in decreased blood glucose *in vivo*. Compound DC291407 showed high DPP-4 inhibitory activity (IC_{50}=0.011 μM), good selectivity against DPP-4 (selective ratio: DPP-8/DPP-4>10000; DPP-9/DPP-4>10000), and good efficacy in an oral glucose tolerance test in ICR mice (Fig. 1). DC291407 (0.6 mg/kg, 2 mg/kg, and 6 mg/kg) displayed significant DPP IV inhibition in ob/ob mice at 4 weeks (Fig. 1). The onset dose (2 mg/kg) is much better than alogliptin. Compound DC291407 showed a high clearance (i.e.), high AUC, and a high maximal concentration (C_{max}), long half-life, and safety when dosed orally in SD rats and dogs. DC291407 is much better than alogliptin in terms of half-life and AUC in SD rats and dogs. The *in vivo* antidiabetic studies and desirable pharmacokinetic properties in rat of compound DC291407 showed that it might be a promising new hit for further development of antidiabetic agents.

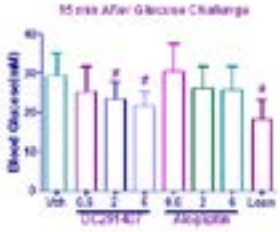

Fig. 1. Glucose responses during an OGTT in ICR mice and ob/ob mice following treatment with DC291407 or Alogliptin.

Recent publications

1. Kim D, Wang L, Beconi M, Eiermann G J, Fisher M H et al. (2005) (2R)-4-oxo-4[3-(trifluoromethyl)-5,6-dihydro [1, 2, 4]triazolo[4, 3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine: a potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem 48:141-151.
2. Weber A E (2004) Dipeptidyl peptidase IV inhibitors for the treatment of diabetes. J Med Chem 47:4135-4141.
3. Rasmussen H B, Branner S, Wiberg F C and Wagtmann N (2003) Crystal structure of human dipeptidyl peptidase IV/CD26 in complex with a substrate analog. Nat Stru Bio 10:19-25.

Biography

Jiang Wang received her PhD degree in Medicinal Chemistry under the supervision of Professor Hong Liu at the Center for Drug Discovery and Design, Shanghai Institute of Materia Medica, Shanghai, China. In 2011, she worked as a Postdoctoral Fellow in Professor Hualiang Jiang's group at the Shanghai Institute of Materia Medica. Her research interests are focused on asymmetric synthesis of pharmacologically active molecules for treatment of type 2 diabetes and applications of nickel (II) complexes in asymmetric synthesis of enantiopure amino acids.

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