DPP-4 Inhibitors for the Treatment of Type 2 Diabetes

Diandian Shen

ABSTRACT

The current therapies for Type 2 diabetes may suffer from insulin resistance, impaired glucose tolerance and progressive loss of β-cell function. Dipeptidyl peptidase 4 (DPP-4) inhibitors have recently emerged as a promising approach in the treatment of Type 2 diabetes\(^1\).\(^2\). DPP-4 enzyme is a serine protease that modulates the biological activities of numerous peptides, including glucagon-like peptide-1 (GLP-1), which plays an essential role in the control of post-prandial glucose levels by potentiating insulin release, inhibiting the release of glucagon and improving pancreatic β-cell function. The rapid clearance of active GLP-1 (in vivo \(t_{1/2} \sim 2\)min) through DPP-4-mediated cleavage poses challenges to the development of exogenous GLP-1 based therapy. The reduction of endogenous GLP-1 degradation by inhibiting DPP-4 activity is becoming an emerging strategy for blood glucose control in Type 2 diabetic patients.

The development of small-molecule DPP-4 inhibitors has attracted increasing attention in recent years by both university and pharmaceutical researchers. Among these new inhibitors, vildagliptin (GALVUS\textsuperscript{TM}), a potent, selective, and orally active DPP-4 inhibitor, has recently been approved by FDA for the treatment of Type 2 diabetes. Several other DPP-4 inhibitors are currently being evaluated in late stage human clinical trials, including sitagliptin and saxagliptin\(^3\). Pei et al. (2006) reported the discovery, structure-activity relationship (SAR) of a series of (5-substituted pyrrolidinyl-2-carbonyl)-2-cyanopyrrolidine analogs as potent DPP-4 inhibitors\(^4\). The C5-substituents led to various interactions with human DPP-4 and could be optimized to reach a potency with subnanomolar Ki's. A series of methanoprolinenitrile-containing DPP-4 inhibitors were synthesized and evaluated for SAR\(^5\). It has been reported that installation of a cyclopropyl moiety at either the 3,4- or 4,5- position of the cyanopyrrolidine parent structure led to compounds with potent inhibition, enhanced chemical stability and good selectivity.

References:


