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Unique Binding Mode of Evogliptin with Human Dipeptidyl Peptidase IV

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Abbreviations: dipeptidyl peptidase–IV; DPP4; PDB, glp-1; protein data bank; RMSD, root-mean-square deviation

Abstract

Evogliptin ((*R*)-4-((*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl)-3-(*tert*-butoxymethyl)piperazine-2-one)) is a highly potent selective inhibitor of dipeptidyl peptidase IV (DPP4) that was approved for the treatment of type 2 diabetes in South Korea. In this study, we report the crystal structures of Evogliptin, DA-12166, and DA-12228 (*S,R* diastereomer of Evogliptin) complexed to human DPP4. Analysis of both the structures and inhibitory activities suggests that the binding of the trifluorophenyl moiety in the *S*₁ pocket and the piperazine-2-one moiety have hydrophobic interactions with Phe357 in the *S*₂ extensive subsite, and that the multiple hydrogen bonds made by the (*R*)- β -amine group in the *S*₂ pocket and the contacts made by the (*R*)-*tert*-butyl group with Arg125 contribute to the high potency observed for Evogliptin.

Keywords: dipeptidyl peptidase IV, DPP4, Evogliptin, diabetes, inhibitor; complex structure;

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