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Application of classic medicinal chemistry strategies in the rapid generation of novel dipeptidylpeptidase-IV inhibitors (Postprint)

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Abstract

The marketed DPP-IV inhibitors represented by Vildagliptin, Saxagliptin, and Alogliptin trigged the discovery of tens thousands of novel DPP-IV inhibitors. Inspired by the good potency and easily structural modification, we initiated a series of modification of Aloglitpin with classic medicinal chemistry strategies. Herein, we reviewed how we generated diverse and highly potent inhibitors X (IC50= 0.3 nM), Y (IC50= 3.6 nM), Z (IC50= nM), and E (IC50= 1.4 nM) through scaffold hopping triggered optimization, B (IC50= 0.7 nM), C (IC50= 0.4 nM), A (IC50= nM) through pharmacophorehybridization based lead generation, F (IC50= nM) via the extendedcombination of these strategies.In this way, the development of DPP-IV inhibitors will eventually become the classic case in themedicinal chemistry history like COX-2 inhibitors and sulfonamides.

Full Text

Preamble

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Abstract

The marketed DPP-IV inhibitors represented by Vildagliptin, Saxagliptin, and Alogliptin have triggered the discovery of tens of thousands of novel DPP-IV

inhibitors. Inspired by their potent activity and ease of structural modification, we initiated a series of modifications of Alogliptin using classic medicinal chemistry strategies. Herein, we review how we generated diverse and highly potent inhibitors X (IC50= 0.3 nM), Y (IC50= 3.6 nM), Z (IC50= nM), and E (IC50= 1.4 nM) through scaffold hopping-triggered optimization, and inhibitors B (IC50= 0.7 nM), C (IC50= 0.4 nM), and A (IC50= nM) through pharmacophore hybridization-based lead generation, as well as inhibitor F (IC50= nM) via extended combination of these strategies. In this way, the development of DPP-IV inhibitors may eventually become a classic case in medicinal chemistry history, much like COX-2 inhibitors and sulfonamides.

Keywords: DPP-IV inhibitor, medicinal chemistry strategy, scaffold, pharmacophore

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia caused by either insulin deficiency or insufficient response to the hormone1. According to the International Diabetes Federation (IDF), more than 371 million people were affected by this disease worldwide in 20122. Its epidemic places a great burden on patients and society. The disease itself, associated with multi-system complications, accounts for a substantial proportion of premature mortality and morbidity and cost over 471 billion dollars in healthcare last year. Type 2 diabetes (T2D, formerly referred to as non-insulin-dependent or adult-onset diabetes) results from the body' s insufficient response to insulin. Although T2D comprises over 90% of diabetes patients, its progression is potentially preventable through proper lifestyle alterations and medical treatments. Thus, continuous effort has been devoted to anti-diabetic research and drug development.

The incretin effect, induced by enteric glucose, contributes to more than 70% of insulin stimulation3, which has proven to be a feasible mechanism for anti-diabetic research and drug development. Glucagon-like peptide-1 (GLP-1) is one of the important incretin hormones that increases insulin secretion and sensitivity, beta cell mass, and satiety, while reducing glucagon secretion and gastric emptying4. Distinct from other incretin hormones, GLP-1 retains glucose regulatory function in T2D patients. However, under normal physiological conditions, GLP-1 is rapidly cleaved by dipeptidyl peptidase IV (DPP-IV) and loses its function4. Understanding of GLP-1' s inactivation process revealed the role of dipeptidyl peptidase IV (DPP-IV) and contributed to the development of orally bioavailable DPP-IV inhibitors5.

Herein, we review our structure modifications based on Alogliptin, a DPP-IV inhibitor developed by Takeda Pharmaceutical Company. By adopting classic medicinal chemistry strategies, we rapidly generated various novel DPP-IV inhibitors as lead compounds. Together with further activity- or pharmacokinetic property-driven optimization processes, we successfully acquired several DPP-

IV inhibitors with either excellent in vitro biological activity or in vivo efficacy. In this way, we present a successful and effective workflow for rapid candidate generation with drug-like properties based on specific marketed drugs.

2. Promiscuity of Dipeptidyl Peptidase-IV and DPP-IV Inhibitors

To date, several DPP-IV inhibitors have been marketed and become first-line therapy for T2D worldwide, represented by Sitagliptin16, Vildagliptin27, Saxagliptin38, Alogliptin49, Linagliptin510, Gemigliptin611, and Teneligliptin712 (Fig. 1 [Figure 1: see original paper]). These inhibitors can be divided into peptidomimetics and non-peptidomimetics. Besides Sitagliptin and Gemigliptin, one class of peptidomimetics is pyrrolidine analogs, which have been widely studied and are represented by Vildagliptin and Saxagliptin13. As non-peptidomimetics, Alogliptin and Linagliptin were developed based on high-throughput screening and displayed very fine pharmacokinetic and pharmacodynamic profiles9-10.

These different classes of DPP-IV inhibitors can effectively inhibit the DPP-IV enzyme regardless of their distinct structures. Thus, the DPP-IV enzyme exhibits great substrate promiscuity, which provides room for us to conduct various molecular operations on marketed drugs. On the other hand, extensive research on the DPP-IV enzyme has confirmed this promiscuity. In the crystal structure, DPP-IV is a dimer. Each subunit consists of an / -hydrolase domain and an eight-bladed -propeller domain with the N-terminus located at the same position in the dimer14. These two domains form a large cavity as the active catalytic site that binds with the substrate or inhibitor15. The cavity within the subunit contains three active sites. The S1 site has the catalytic triad (Ser-630, Asp-708, and His-740) which interacts with the substrate at the Ser-630 elbow. The side chains of Tyr-666, Tyr-662, Val-711, Val-656, Trp-659, and Tyr-631 form the hydrophobic S1 pocket, which is responsible for the proline specificity of DPP-IV. The crystal structure of human DPP-IV in complex with diprotin A suggested that the unprotected and protonated N-terminus of the substrate strongly interacts with Glu-205 and Glu-206 of the S2 pocket16. Meanwhile, the S3 pocket formed by Ser-209, Arg-358, and Phe357 is responsible for DPP-IV selectivity against DPP-8/917. These cavities allow for large diversity and variations in substrates. In other words, this means that modifications to a specific drug have a greater chance of acquiring candidates with fine drug-like properties. Thus, we initiated systematic modifications on Alogliptin using classic medicinal chemistry strategies to generate more candidates as potent and effective DPP-IV inhibitors.

3. Scaffold Hopping-Based Generation of DPP-IV Inhibitors

For target-based drug development, most lead compounds face attrition due to the gap between in vitro activity and in vivo efficacy. To reduce such attrition rates and obtain more compounds with balanced drug-like properties, systems biology/pathology/pharmacology18, fragment-based approaches19, and scaffold hopping strategies20 have been developed for lead discovery. Among them, scaffold hopping has proven to be an efficient way to identify active compounds while avoiding poor physicochemical and pharmacokinetic properties. Scaffold hopping, initially introduced in 1999 to identify structurally novel compounds with similar biological activities to known active compounds20c,21, has been widely used in lead optimization22. Many marketed drugs were derived from other known drugs or natural products23, indicating that this operation predates the term "scaffold hopping." A typical example of scaffold hopping is represented by the COX-2 inhibitors rofecoxib (Vioxx) and valdecoxib (Bextra), which were separately sold by two pharmaceutical giants with only a difference in five-membered hetero rings (Fig. 3a [Figure 3: see original paper], 3b)24. Another scaffold hopping process can be elucidated between morphine and tramadol (Fig. 3c, 3d)25. With quite different 2D structures, these two drugs display a similar layout in 3D superposition (Fig. 3e). Scaffold hopping by ring opening of morphine led to tramadol with reduced activity but better pharmacokinetic and toxicological profiles. Thus, while keeping key pharmacophore features conserved, backbone variation can acquire drug-like compounds, even with improved pharmacokinetic (PK) and toxic properties.

During the discovery process of Alogliptin, its precursor quinazolinone analog indicated the key binding sites: the aminopiperidinyl group binds Glu-205 and Glu-206 with the N-terminus; the cyanobenzyl group locates in the S1 pocket; the carbonyl binds Tyr-631 as a hydrogen bond donor9. Thus, for our starting drug Alogliptin, we first conducted scaffold hopping to search for novel compounds by keeping these key functional groups conserved. Pyrimidone analogs were rapidly generated and screened for inhibitory activity (Fig. 4 [Figure 4: see original paper], Tab. 1), represented by the thienopyrimidine compound 8 (IC50=0.3 nM vs. 3.4 nM for Alogliptin)26. Generally, this scaffold hopping operation maintained the activity profiles as expected, except for compounds 12 and 13.

Inspired by the scaffold hopping from morphine to tramadol with improved ADME-tox properties, we further launched a PK-driven optimization on compound 8 for its insufficient in vivo glucose-lowering efficacy. At this stage, we identified the intrinsic metabolic instability within compound 8 and determined the thienyl group as the soft fragment through in vitro microsomal incubation and metabolite identification (data not shown). Further replacement of the thienyl with a pyrrolyl group significantly increased metabolic stability, yet reduced oral bioavailability due to high efflux during the absorptive process (compound 11). Modifications on the pyrrolopyrimidine scaffold eventually yielded

compound 10a, exhibiting compatible in vitro indicators (IC50=1.3 nM, F=41%) and better in vivo efficacy than Alogliptin (Fig. 5 [Figure 5: see original paper])27.

Meanwhile, optimization on other backbones was carried out as well. Although limited achievement was obtained, screening of target-derived by-products from compound 12 still provided confidence for further optimization of scaffold hopping products that had lost activity (Fig. 6 [Figure 6: see original paper]). The nanomolar activity of compound 12b may provide a potential explanation for the large decrease in activity observed for compounds 12 and 13, suggesting that large substituents support better accommodation between backbones and the DPP-IV enzyme.

4. Pharmacophore Hybridization-Triggered Hit-to-Lead Optimization

With pharmacophores fixed, we rapidly generated two series of pyrimidone analogs as potent and orally bioavailable DPP-IV inhibitors according to pharmacophore-based scaffold hopping. Although key pharmacophore features played a critical role in activity, this did not mean the pharmacophore had to maintain exactly the same structure. Moreover, the large cavities within the DPP-IV protein provided ample room for pharmacophores with varied structures. The emergence of Linagliptin well supported this concept. The butynyl group of Linagliptin and the cyanobenzyl group of Alogliptin occupy the S1 pocket in 3D superposition (Fig. 7 [Figure 7: see original paper])28. Thus, pharmacophore hybridization should also be a viable approach for generating DPP-IV inhibitors.

In this section, we first conducted pharmacophore variations directly on the pyrimidinedione scaffold of Alogliptin (Fig. 8 [Figure 8: see original paper]). Hit compound 14 was rapidly synthesized and evaluated with an IC50 of 198 nM. Based on previous experience with optimization of compounds obtained from scaffold hopping, we selected compound 14 as the hit compound and initiated conventional hit-to-lead optimization, represented by compound 14a (IC50=3.1 nM, F=63%, T1/2=4.2 h)28.

Further optimization of compound 14a focused primarily on the quinoline group. Our previous work examined several substituents at different positions on the quinoline, leading to compound 14aa (Fig. 9 [Figure 9: see original paper], IC50=0.3 nM, F=73%, T1/2=5.0 h)28. Parallel work on bicyclic variations was conducted and is listed in Table 2 . Compound 14ai, substituted with the 4-methylquinazolinyl group of Linagliptin, increased the activity to 0.7 nM with moderate PK profiles compared to compound 14aa. However, both compounds demonstrated that pharmacophore hybridization is a feasible approach for rapid lead generation of DPP-IV inhibitors.

5. Extension of Scaffold Hopping and Pharmacophore Hybridization

Much of our work focused on Alogliptin and most efforts have yielded promising preclinical candidates. During this process, we also attempted to extend the application of these molecular operations. Based on our initial scaffold hopping analog 10, we incorporated a butynyl group and generated hit compound 15. Furthermore, hybridization of the quinazoline moiety from Linagliptin onto compound 15 gave compound 15a (Fig. 10 [Figure 10: see original paper], IC50=1.6 nM, F=83%, T1/2=4.9 h)29, the second pyrrolopyrimidine candidate with a much better pharmacokinetic profile than both Alogliptin and compound 10a.

Molecular modifications to Linagliptin were also investigated (Fig. 11 [Figure 11: see original paper]). Replacement of the butynyl group of Linagliptin with the cyanobenzyl group from Alogliptin led to compound 16 (IC50=5.0 nM). Compound 16 might be a potential starting point for further optimization. However, its lower activity compared to Linagliptin and the compounds mentioned above, as well as patent considerations, halted further development. Nevertheless, this simple reverse pharmacophore hybridization supported the notion that these operations are applicable to other compounds without causing large deviations from known active compounds.

6. Conclusion

In this paper, we reviewed our medicinal chemistry efforts on the marketed DPP-IV inhibitor Alogliptin and presented several highly potent DPP-IV inhibitors with improved pharmacokinetic profiles or in vivo efficacy. This work demonstrates the utility of classic medicinal chemistry strategies for the efficient generation of DPP-IV inhibitors. As DPP-IV inhibitors have become more widely used, our understanding of their development has deepened. Longer-acting DPP-IV inhibitors are also making their way to market. The classic and applicable methods described here not only review our efforts on Alogliptin but may also serve as a strategy to accelerate the development and diversification of DPP-IV inhibitors based on any known molecules.

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