Piperidine derivatives as nonprostanoid IP receptor agonists 2

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ABSTRACT

We searched for a strong and selective nonprostanoid IP agonist bearing piperidine and benzanilide moieties. Through optimization of substituents on the benzanilide moiety, the crucial part of the agonist, **43** (2-((1-(2-(N-(4-tolyl)benzo[d][1,3]dioxole-5-carboxamido)ethyl)piperidin-4-yl)oxy)acetic acid monohydrate monohydrochloride) was discovered and exhibited strong platelet aggregation inhibition (IC_{50} = 21 nM) and 100-fold selectivity for IP receptor over other PG receptors. The systemic exposure level and bioavailability after oral administration of **43** were also good in dog.

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Prostacyclin inhibits platelet activation and acts as a vasodilator.[1,2] Prostacyclin also plays an important role in biological homeostasis as an endogenous autacoid widely distributed in various tissues. Interest in prostacyclin as an antithrombotic agent has prompted an intensive search for mimics or other prostaglandin I_2 receptor (IP receptor) agonists with high chemical and metabolic stability. Our original approach led us to create the stable prostacyclin mimic beraprost (**1**, Fig. 1), which is used to treat chronic occlusive disease and primary pulmonary hypertension.[3–6]

On the other hand, novel IP agonists that are structural different from prostacyclin, nonprostanoid prostacyclin mimetic, have been sought in order to obtain metabolically stable IP agonists (Fig. 2).[7–13]

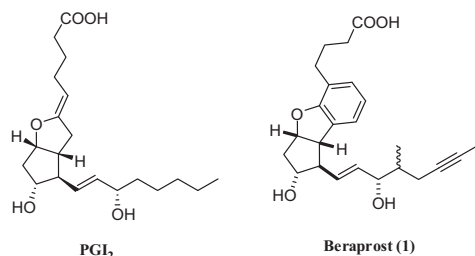

Octimibate   **ONO-1301**
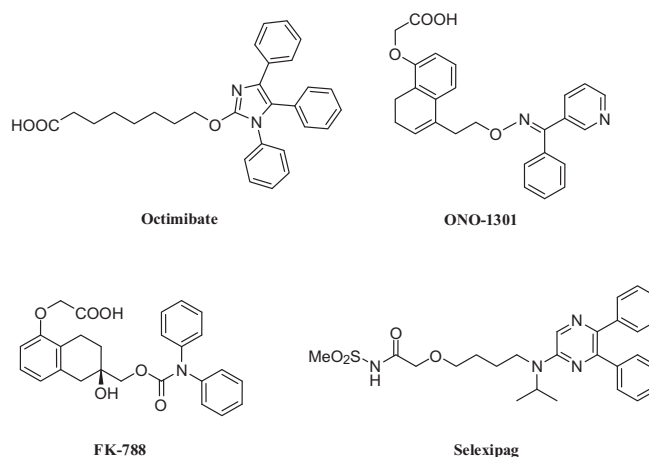

FK-788   **Selexipag**

Figure 2. Nonprostanoid IP agonists.

We have been investigating not only prostacyclin mimics but also nonprostanoid IP agonists. We previously reported novel IP agonists bearing a piperidine moiety, such as **2** and **3** (Fig. 3).[14]

The unique piperidine derivative **2** ((2-((1-(2-(N-(4-tolyl)benzamido)ethyl)piperidin-4-yl)oxy)acetic acid)) was a good IP receptor agonist and was 50-fold more selective for the human IP receptor than for other human prostanoid receptors. In addition, the pharmacokinetic profile of **2** is particularly favorable, but its platelet aggregation inhibition activity resulting from its IP agonistic action

PGI₂   **Beraprost (1)**

Figure 1. Structure of beraprost.

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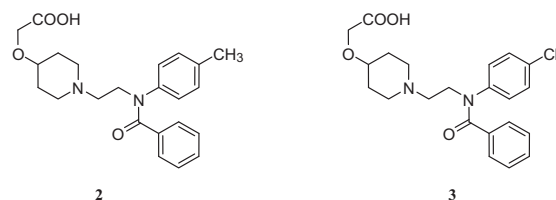
Figure 3. Our nonprostanoid IP agonists.
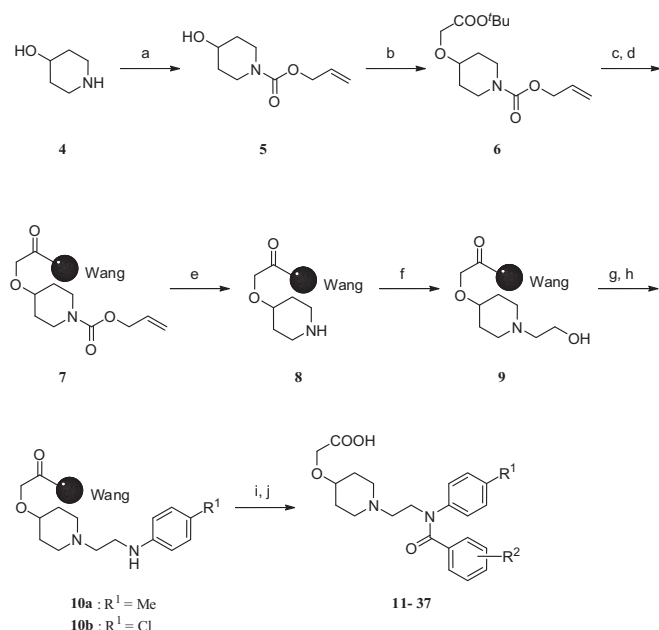
Scheme 1. Synthesis of compounds **11–37**. Reagents and conditions: (a) allyl chloroformate, NEt$_3$, CH$_2$Cl$_2$, rt, 15 h, 74%; (b) BrCH$_2$COO^{t}Bu, Bu$_4$NBr, toluene, 10 M NaOH aq, 50 °C, 14 h, 62%; (c) TFA, CH$_2$Cl$_2$, rt, 3 h; (d) Wang resin, DMP, DIC, DMF, rt, 15 h; (e) 1,3-dimethylbarbituric acid, Pd(PPh$_3$)$_4$, THF, rt, 15 h; (f) 2-bromoethanol, K$_2$CO$_3$, DMF, rt, 12 h; (g) MsCl, NEt$_3$, CH$_2$Cl$_2$, rt, 2 h; (h) substituted aniline, KI, CH$_3$CN, 70 °C, 12 h; (i) substituted BzCl, NEt$_3$, THF, rt, 12 h; (j) TFA, CH$_2$Cl$_2$, rt, 1 h.

Table 1
In vitro platelet inhibitory activity of **11–21**[a]

Compound	R^2	Inhibition of human platelet aggregation IC$_{50}$[b,c] (nM)
11		220
12	F	970
13	Cl	690
14	OCH$_3$	1200
15	CF$_3$	>10,000
16	Ph	>10,000
17	F	160
18	Cl	100
19	CH$_3$	160
20	OCH$_3$	32
21	CF$_3$	20,000

[a] IC$_{50}$ represents the concentration that inhibited induced platelet aggregation by 50%.
[b] Platelet aggregation was induced by ADP (5 μM) in human platelet rich plasma.
[c] Values are means of two experiments.

is unsatisfactory (IC$_{50}$ = 130 nM). To obtain promising drug candidates, the inhibitory activity of IP agonists needs to be improved. In this letter, we report the design and synthesis of compounds that maintained the favorable pharmacokinetic profile of **2** while exhibiting higher platelet aggregation inhibitory activity (IC$_{50}$ <100 nM).

We previously showed that replacement of substituents on the aniline moiety of **2** affected the level of platelet aggregation inhibitory activity, but the same approach was not tested for the benzoyl moiety, although a similar effect was expected. Accordingly, in this study, we aimed to discover compounds with substituted benzoyl moieties that increased platelet aggregation inhibitory activity.

Various substituents (e.g., halogen, electron-donating, electron-withdrawing, and aromatic groups) at several positions on the benzoyl moiety were tested. As in the case of **2** and **3**, the 4-position of the aniline moiety was substituted with a methyl or chloro. We used the same solid-phase approach as in our previous study to efficiently obtain a variety of compounds bearing the above-mentioned substituents (Scheme 1).

After protecting the nitrogen atom of commercially purchased 4-hydroxypiperidine by treatment with allyl chloroformate, the bromoacetic acid t-butyl ester structure was introduced by O-alkylation to produce **6**. The ester moiety of **6** was hydrolyzed, and **7**

was immobilized on Wang resin. Compound **9** was obtained from **7** by nitrogen deprotection and then hydroxyethylation. The hydroxyl group of **9** was mesylated, and an aniline moiety and a benzoyl moiety were sequentially introduced. The final compounds (**11–37**) were obtained by the cleaved from the Wang resin. All compounds were purified by HPLC and identified by LC/MS. Platelet aggregation inhibition activities of synthesized compounds are shown in Tables 1 and 2.[15]

The type of substituent on the aniline moiety (4-methyl or 4-chloro) did not influence the effect of substituents on the benzoyl moiety, and introduction of a 4-methoxy or 4-chloro substituent on the benzoyl moiety reduced the inhibitory activity. Introduction of a CF$_3$ or phenyl substituent on the benzoyl moiety resulted in an especially strong reduction in the inhibitory activity (Table 1, 15 and 16; Table 2, 26 and 27). On the other hand, substitution at the 3-position of the benzoyl moiety, except introduction of a CF$_3$ substituent, increased the inhibitory activity. Since introduction of a strongly electron-withdrawing CF$_3$ group at any position resulted in substantially decreased the inhibitory activity, lower electron density in the benzoyl moiety possibly induced the decreases in platelet aggregation inhibition activity (Table 1, 15 and 21; Table 2, 26 and 32).

Also, an electron-donating methoxy group increased the inhibitory activity of the compound when introduced at the 3-position, but decreased it when introduced at the 4-position (Table 1, 14 and 20; Table 2, 25 and 31). Tables 1 and 2 showed that the 3-substituted benzoyl derivatives were more potent than the