Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 3279–3283
Bioorganic & Medicinal Chemistry Letters

Discovery of new diphenyloxazole derivatives containing a pyrrolidine ring: Orally active prostacyclin mimetics. Part 2

Kouji Hattori,[a,*] Osamu Okitsu,[a] Seiichiro Tabuchi,[a] Kiyoshi Taniguchi,[a] Mie Nishio,[b] Satoshi Koyama,[b] Jiro Seki[b] and Kazuo Sakane[a]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd, 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan*
[b]*Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd, 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan*

Received 18 February 2005; revised 11 April 2005; accepted 22 April 2005

Abstract—Synthetic and biological evaluation of novel diphenyloxazole derivatives containing a pyrrolidine ring, as a prostacyclin mimetic without the PG skeleton, are described. Asymmetric reduction of a ketone using a chiral Ru complex and reductive amination by $NaBH_4$ produces four isomers of the tetrahydronaphthalene ring and the pyrrolidine ring with high stereoselectivity. FR193262 (**4**), (*R*,*R*)-diphenyloxazolyl pyrrolidine derivative, displays high potency and agonist efficacy at the IP receptor and has good bioavailability in rats and dogs.

1. Introduction

Prostacyclin (PGI_2) is primarily derived from vascular endothelium and plays an extremely important inhibitory role in platelet aggregation and as a vasodilator in maintaining homeostatic circulation.[1] Despite fascinating pharmacological properties, the inherent instability of prostacyclin limits its therapeutic applicability. Several groups have already disclosed novel PGI_2 analogs without a PG skeleton, which led us to design a novel PGI_2 mimetics with improved chemical and metabolic stability.[2] Hamanaka and co-workers proposed the tetrahydronaphthalene-5-oxyacetic acid skeleton such as AP-227 (**2**) in which the cyclopentane ring in the PG structure is removed to construct a new skeleton.[3] Recently, we have also disclosed the non-prostanoid structure FR181157: (*S*)-**3** having potent PGI_2 activity with improved pharmacokinetic properties.[4] After extensive optimization of this series, we found the more rigid structure FR193262 (**4**), which had improved potency for PGI_2 and affinity for the IP receptor. Herein, we disclose a stereoselective synthesis and biological evaluation of diphenyloxazole derivatives as novel PGI_2 mimetics. Our design strategy is shown in Figure 2, and involved construction of the tetrahydronaphthalene skeleton from the cyclohexene skeleton of **3**, and the diphenyloxazole part as an important pharmacophore for PGI_2 activity was modified by incorporation to a pyrrolidine ring to fix to the best position (Fig. 1).

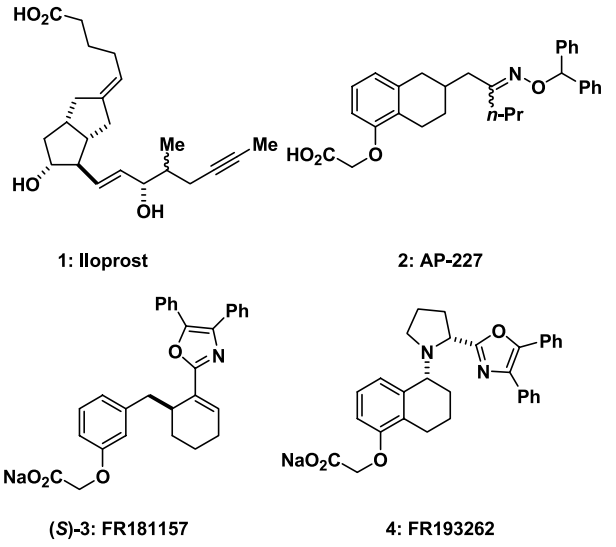


Figure 1.

Keywords: Diphenyloxazole; Prostacyclin mimetic; IP receptor.
* Corresponding author. Tel.: +81 6 6390 1220; fax: +81 6 6304 5435; e-mail: kouji_hattori@po.fujisawa.co.jp

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.04.042

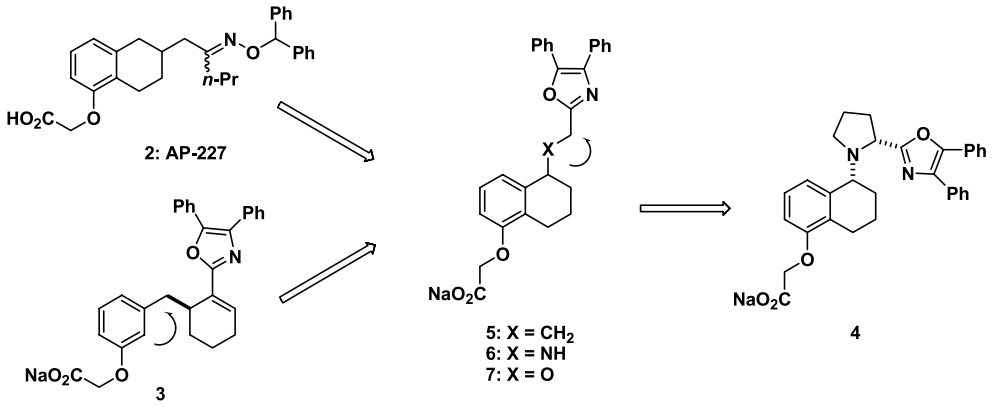
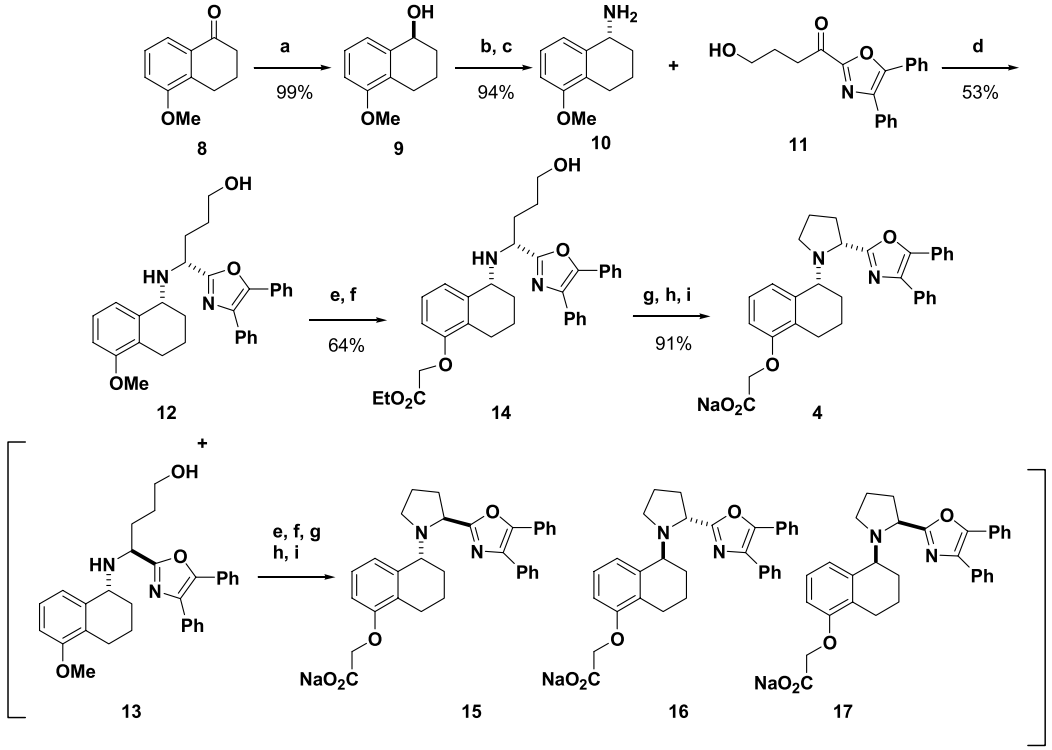


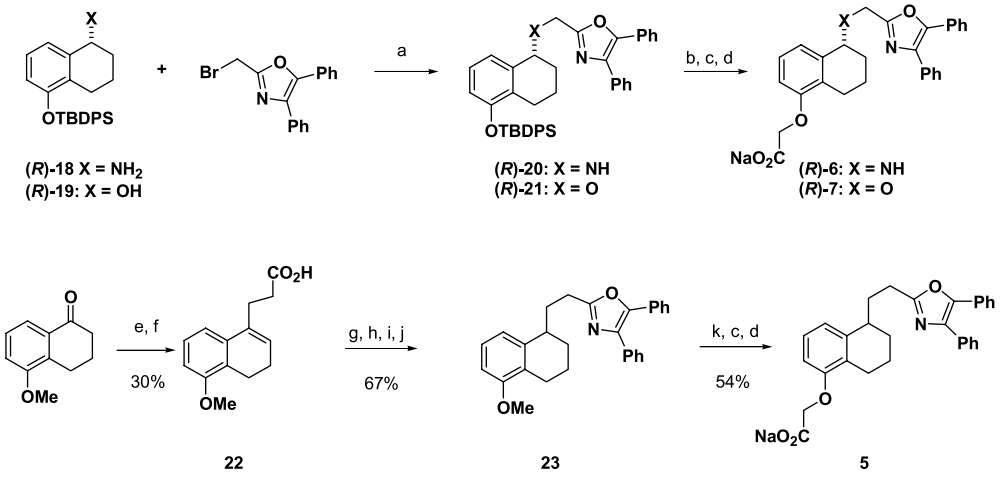
Figure 2.

2. Chemistry

Our synthetic strategy for the diphenyloxazole derivatives is illustrated in Scheme 1. We need to make this compound by controlling stereochemistry at two benzyl centers. The required optically active alcohol **9** was obtained via the chiral Ru complex reported by Noyori and co-workers.[5] Asymmetric reduction of commercially available 5-methoxy-1-tetralone **8** by the standard procedure in a 5:2 formic acid–triethylamine azeotrope containing 0.5 mol % of the chiral Ru complex, which was prepared by reacting $[RuCl_2(\eta^6\text{-mesitylene})]_2$, (*S*,*S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN), and triethylamine, provided the optical pure alcohol **9** in 99% yield and 99% ee. The optically pure alcohol **9** was smoothly converted to the corresponding azide with inversion of configuration using diphenyl phosphorazidate and DBU,[6] which was followed by catalytic hydrogenation with Pd/C to afford the amine **10** in 94% yield. Treatment of amine **10** with acyldiphenyloxazole derivative **11** in the presence of catalytic *p*-toluenesulfonic acid under reflux gave the intermediate imine, which was immediately reduced to a mixture of the amine **12** and **13** in a 4:1 ratio (as determined by NMR) using $NaBH_4$ in 53% yield. The mixture was purified by column chromatography to separate the



Scheme 1. Reagents and conditions: (a) $[RuCl_2(\eta^6\text{-mesitylene})]_2$, (*S*,*S*)-TsDPEN, HCO_2H–$(C_2H_5)_3N$; (b) DPPA, DBU, Tol; (c) Pd/C, MeOH; (d) cat. *p*-TsOH, Tol, then $NaBH_4$MeOH–THF; (e) BBr_3, CH_2Cl_2; (f) ethyl bromoacetate, K_2CO_3, DMF; (g) $SOCl_2$, CH_2Cl_2; (h) K_2CO_3, DMF; (i) NaOH, EtOH.



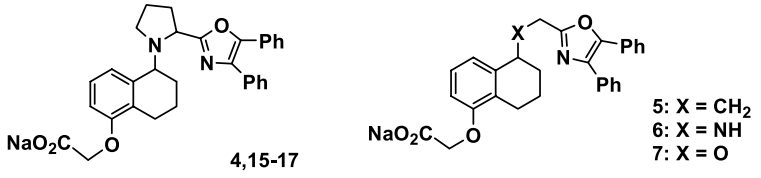
Scheme 2. Reagents and conditions: (a) K_2CO_3, DMF for **18** (95%), *n*-BuLi, THF for **19** (75%); (b) *t*-BuNF, THF; (c) ethyl bromoacetate, K_2CO_3, DMF; (d) NaOH, EtOH; (e) diethylsuccinate, *t*-BuOK, *t*-BuOH; (f) HCl, AcOH; (g) $SOCl_2$, CH_2Cl_2; (h) benzoin, Et_3N, CH_2Cl_2; (i) $AcONH_4$, AcOH; (j) Pd/C, MeOH; (k) BBr_3, CH_2Cl_2.

desired amine **12** and isomers **13**. The enantiomerically pure **12** was subsequently treated with BBr_3 followed by alkylation with ethyl bromoacetate to give the ethyl ester **14**. Treatment of **14** with $SOCl_2$ and then K_2CO_3 formed the corresponding pyrrolidine ring. Finally, hydrolysis of the ester furnished **4** in 91% yield and >99% ee from **14**. The stereoisomer **15** was prepared from **13** and the other isomers **16** and **17** were prepared using similar methods except for using (*R*,*R*)-TsDPEN.[7] The assignment of the absolute configuration of **4** was confirmed by the alternative synthetic.[8] The synthetic route of acyclic derivatives is illustrated in Scheme 2. The enatiomerically pure **6** and **7** were prepared from alkylation of the optically active amine **18** and alcohol **19** with diphenyloxazolylmethyl bromide, followed by the similar method. Compound **5** was also prepared as a mixture of isomers from **22** using standard method.

3. Biological activity

FR193262 (**4**) displayed potent PGI_2 agonist activity and especially good pharmacokinetic properties. Table 1 shows the in vitro SAR results for the diphenyloxazole derivatives. PGI_2 receptor binding was examined by the conventional ligand binding assay based on the displacement of [^{3}H]-Iloprost from the cloned human IP receptor.[9] IC_{50} values in the functional assay were obtained by measuring inhibition of ADP-induced platelet aggregation using human, rat, dog, and monkey platelet rich plasma. Compound **4** exhibited high binding affinity for

Table 1. SAR of diphenyloxazole derivatives[a]



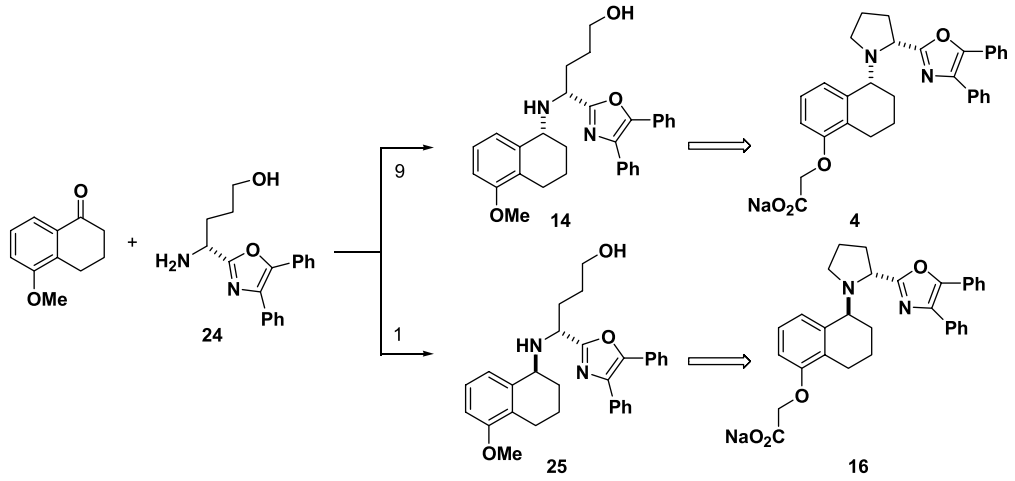
Compounds	Function assay: IC_{50} (nM)				Binding assay: K_i (nM)
	Human	Rat	Dog	Monkey	Human
4	19 ± 3.8	630 ± 71	780 ± 72	59 ± 0.25	12 ± 0.25
15	640 ± 21	>10,000			
16	870 ± 41	>10,000			
17	63 ± 9.7	2200			
5	1000	>10,000			
(*R*-**6**)	190	5000			
(*S*-**6**)	1500				
(*R*-**7**)	140				
(*S*-**7**)	1400				
1: Iloprost	2.5 ± 0.14				6.5 ± 0.12
2: AP-227	150 ± 17	5600 ± 470			
3: FR181157	60 ± 5.2	1200 ± 170	1300 ± 180		54 ± 0.36

[a] Results are the average of two or three experiments.

Table 2. Pharmacokinetic profile of **4**[a,b]

	po (fasted) $n = 3$			iv $n = 3$		Ba (%)
	Dose (mg/kg)	Cmax (ng/mL)	AUC (ng h/mL)	$t_{1/2}\beta$ (h)	CLtot (mL/min/kg)	
Rat	3.2	187 ± 0.057	172 ± 0.01	0.21 ± 0.01	89.25 ± 5.6	31
Dog	0.032	61.2 ± 9.3	327 ± 11.7	2.25 ± 0.13	1.00 ± 0.10	66

[a] Result were shown as the mean ± SE.
[b] Administration of **4** as the HCl salt.



Scheme 3.

the IP receptor with a K_i of 12 nM and high antiaggregative potency in the functional assay with an IC_{50} of 19 nM. The enatiomer **17** was 3-fold less potent and other isomers **15** and **16** were also approximately 30-fold less potent under the same conditions. In general, the acyclic analogs **5**, **6**, and **7** had decreased activity compared to the pyrrolidine analogs. It is well known that this class of PGI_2 mimetic has significant species difference. Compound **4** also displayed similar results, since inhibition of ADP-induced platelet aggregation using rat, dog, and monkey platelet rich plasma was less potent than human (rat: IC_{50} = 630 nM, dog: IC_{50} = 780 nM, monkey: IC_{50} = 59 nM). Table 2 shows the pharmacokinetic profiles in rats and dogs. Compound **4** without a PG skeleton displayed good oral bioavailability (rat: F = 31%, dog: F = 66%) in both species. The detailed SAR results and pharmacological properties of **4** will be published in the future.

In summary, we designed a series of diphenyloxazole derivatives with tetrahydronaphthalene skeleton as a prostacyclin mimetic compound **4**, containing a pyrrolidine ring, which was prepared by stereoselective synthesis at two chiral centers and exhibited high potency and agonist efficacy at the IP receptor and good bioavailability in rats and dogs. The detailed pharmacological work will be published in the near future.

Acknowledgments

We express our thanks to Dr. David Barrett for his critical reading of the manuscript.

References and notes

1. (a) Bley, K. R.; Hunter, J. C.; Eglen, R. M.; Smith, J. A. M. *TIPS* **1998**, *19*, 141; (b) *Therapeutic Applications of Prostaglandins*; Vane, J., O'Grady, J., Eds.; Edward Arnold: London, 1993; (c) Dusting, G. J.; MacDonald, P. S. *Pharmacol. Ther.* **1990**, *48*, 323.
2. (a) DeLeval, X.; Hanson, J.; David, J.-L.; Masereel, B.; Pirotte, B.; Dogne, J.-M. *Curr. Med. Chem.* **2004**, *11*, 1243; (b) Benoit, P.; DeLeval, X.; Pirotte, B.; Dogne, J.-M. *Expert Opin.* **2002**, *12*, 1225; (c) Meanwell, N. A.; Romine, J. L.; Seiler, S. M. *Drugs Future* **1994**, *19*, 361; (d) Wise, H.; Jones, R. L. *TIPS* **1996**, *17*, 17.
3. (a) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Toritsu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1065; (b) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Toritsu, K.; Takada, H.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1071; (c) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Toritsu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1077; (d) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Toritsu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1083; (e) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Toritsu, K.; Shigeoka, S.; Hamada, S.; Kato, H.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1087.
4. Hattori, K.; Tabuchi, S.; Okitsu, O.; Taniguchi, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4277.
5. Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, N. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
6. Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, J. J. *J. Org. Chem.* **1993**, *58*, 5886.
7. The purity of each isomer was determined by HPLC (Chiralcel OD-R, 25 cm × 0.46 cm I.D., flow rate 0.8 mL/min, 40% acetonitrile/0.02 M, pH 6.0, phosphate buffer) R_t = 7.2 min for **4**, 10.3 min for **15**, 10.9 min for **16**, and 15.2 min for **17**. These compounds should be handled with

extreme caution because of potent PGI_2 agonist activity and high skin permeability.
8. Compounds **4** and **16** were prepared from the optical active amine **24**, which was transformed from D-pyrroglutamic acid, with a ratio 9:1 (Scheme 3).
9. (a) Katsuyama, M.; Sugimoto, Y.; Namba, T.; Irie, A.; Negishi, M.; Narumiya, S.; Ichikawa, A. *FEBS Lett.* **1994**, *344*, 74; (b) Boie, Y.; Ruchmore, T. H.; Darmon-Goodwin, A.; Grygorczyk, R.; Slipetz, D. M.; Metters, K.; Abramovitz, M. *J. Biol. Chem.* **1994**, *269*, 12173.