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MOLECULAR DESIGN OF NOVEL PGI_2 AGONISTS WITHOUT PG SKELETON. I

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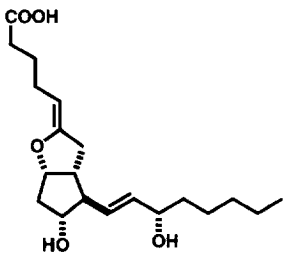
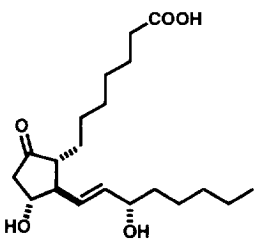
Abstract. Syntheses of novel prostaglandin (PG) mimetics without PG skeleton are described, and the structure-activity relationships are discussed. Highly potent compounds could be obtained when the PG analog **3** was modified by removing and reconstructing the cyclopentane ring, and changing the allylic alcohol in the natural PGs.

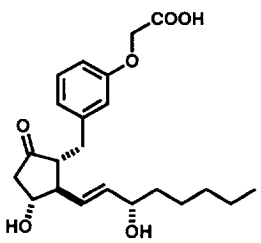
Since the discovery of prostacyclin (PGI_2, **1**),[1] many efforts have been devoted to the search for the chemically stable, biologically potent and tissue specific agonists for potential medical utility.[2] PGI_2 and PGE_1 (**2**) have a different structure, however, they bind to the same platelet PGI_2 receptors and show qualitatively the same biological activities.[3] For these biological activities of PGs, the carboxylic acid, the cyclopentane ring and the allylic alcohol moieties have been demonstrated to be essential.[4] Accordingly, approaches to their specific agonists were so far limited to the structural modifications of the α and ω-chains in PGs. Recently, an Edinburgh University group and the Bristol-Myers Squibb group, respectively, proposed EP-157[5] and BMY 42393[6] as the PGI_2 agonists without PG skeleton.



1 PGI_2



2 PGE_1



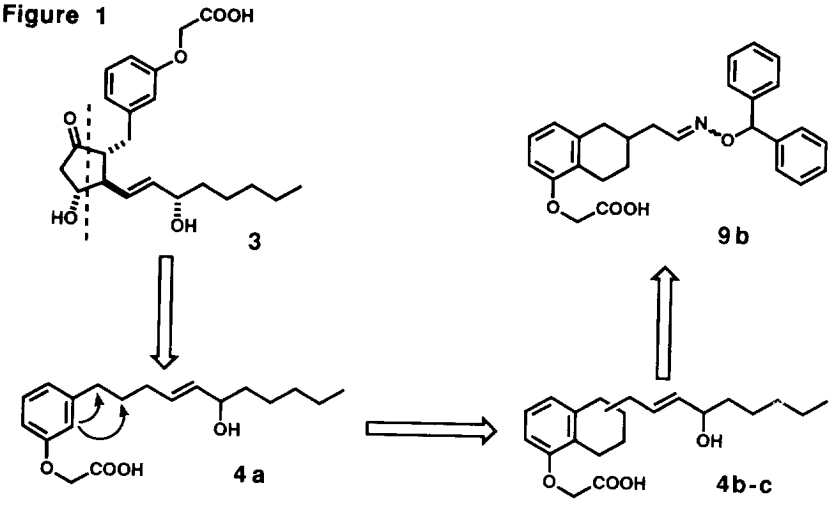
3

We were greatly concerned with the role of the cyclopentane ring. The cyclopentane ring involving the 11-hydroxyl group, 9-oxygenated function, and 8*R* and 12*S* configurations of PGI_2 and PGE_1 have been considered to bind to the receptors. At first, we assumed that the cyclopentane ring controlled the geometrical relationship between the carboxylic acid and the allylic alcohol functions in PGs. If the new structures are able to consist of the same spatial arrangement as that of the active conformer in PGs, it would be reasonable to assume that they should show the biological activities comparable to those of PGs.

We began a research program with the goal of identifying a new PGI_2 agonist without these cyclopentane ring and allylic alcohol parts. We selected the PGE_1 analog **3**[7] for the study of a non PG-like structure. Our

strategy as shown in Figure 1 is to design molecules in which the cyclopentane ring part in PG is removed to construct a new skeleton (**4a-c**), and in which the allylic alcohol part in PG is modified to show the PGI_2-like activities (**9b**).

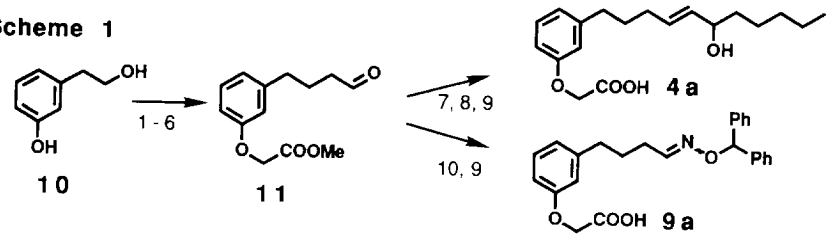
Figure 1



Chemistry

The compounds were synthesized by the routes shown in Schemes 1, 2 and 3. The synthesis of **4a** and **9a** is depicted in Scheme 1. Commercially available 3-hydroxyphenyl ethanol **10** was converted in six steps to ester aldehyde **11**. Wadsworth-Emmons reaction[8] of **11** produced enone, which was converted to **4a** by the reduction with sodium borohydride in the presence of catalytic amount of acetic acid followed by saponification. Oximization of **11** with benzhydryloxy amine[9] and saponification gave **9a**.

Scheme 1

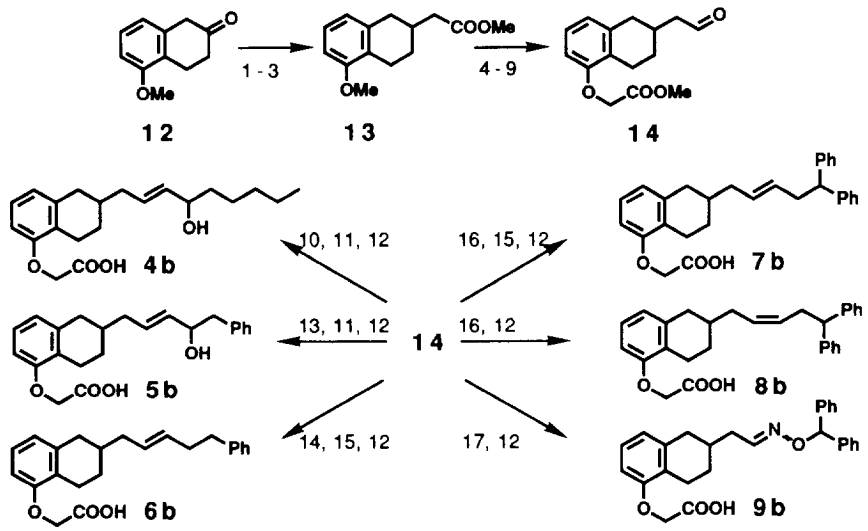


(1) SO_3•pyridine, Et_3N, DMSO; (2) $Ph_3PCHCOOMe$, $CHCl_3$; (3) H_2, Pd-C, AcOEt; (4) $LiAlH_4$, THF; (5) K_2CO_3, $BrCH_2COOMe$, MeCN; (6) Swern Ox.; (7) LiCl, *i*-Pr_2NEt, $(MeO)_2POCH_2CO(CH_2)_4CH_3$, MeCN; (8) $NaBH_4$, cat.AcOH, MeOH, -20°C; (9) aq.NaOH, MeOH; (10) $H_2NOCHPh_2$, EtOH.

2-Substituted-tetrahydronaphthalene-5-oxyacetic acids **4b-9b** were prepared as shown in Scheme 2. Compound **13** was easily accessible starting from 5-methoxy-2-tetralone **12**[10] by Reformatsky reaction[11] followed by dehydration and hydrogenation. Key intermediate **14** was obtained by the following series of

reactions: (i) reduction of **13** with lithium aluminum hydride to afford alcohol; (ii) acylation; (iii) demethylation; (iv) saponification; (v) *O*-alkylation; and (vi) oxidation. Compounds **4b**, **5b**, and **9b** were easily prepared by the same preceding procedure. Wittig reactions of **14** with two types of the ylide furnished stereoselectivly *cis*-compounds which were contaminated with a trace of *trans*-isomers. This *trans*-isomers were readily isomerized by the reaction of light. Saponification gave **6b**, **7b**, and **8b**.

Scheme 2



(1) Zn, $BrCH_2COOEt$, C_6H_6; (2) $POCl_3$, pyridine; (3) H_2, Pd-C, AcOEt; (4) $LiAlH_4$, THF; (5) Ac_2O, pyridine; (6) BBr_3, CH_2Cl_2; (7) aq.NaOH, MeOH; (8) K_2CO_3, $BrCH_2COOMe$, MeCN; (9) Swern Ox.; (10) $(MeO)_2POCH_2CO(CH_2)_4CH_3$, LiCl, *i*-$Pr_2NEt$, MeCN; (11) $NaBH_4$, cat.AcOH, MeOH, -20°C; (12) aq.NaOH, MeOH; (13) $(MeO)_2POCH_2COCH_2Ph$, LiCl, *i*-Pr_2NEt, MeCN; (14) $Ph_3P(CH_2)_3Ph$, *n*-BuLi, THF; (15) hv, $(PhS)_2$; (16) $Ph_3P(CH_2)_2CHPh_2$, *n*-BuLi, THF; (17) $H_2NOCHPh_2$, EtOH.

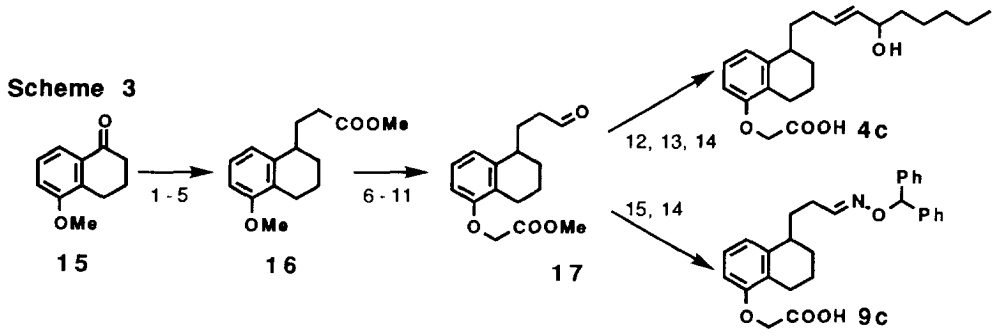
Scheme 3 illustrates the preparation of 1-substituted-tetrahydronaphthalene-5-oxyacetic acids **4c** and **9c**. Conversion of commercially available 5-methoxy-1-tetralone **15** into **16** was achieved by (i) treatment with trimethylsilyl nitrile to give cyanohydrin; (ii) dehydration with phosphorous oxychloride to α,β-unsaturated nitrile; (iii) diisobutylaluminum hydride reduction; (iv) Wittig reaction; and (v) hydrogenation. **16** was transformed to ester-aldehyde **17** in six steps. Compounds **4c** and **9c** were easily prepared by the same preceding procedure.

Biological Results and Discussion

In order to assess the affinities of the target compounds for platelet PGI_2 receptors, radioligand binding assays were performed in human platelets using [^{3}H]-iloprost.[3]

Table 1 shows the affinities of simple allylic alcohol compounds. Normal alkyl compound **4a**, in which the ring was removed from the structure **3**, bound weakly to the PGI_2 receptors. This weakness can be

Scheme 3

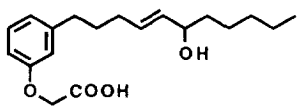
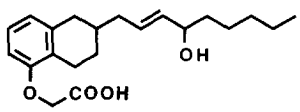
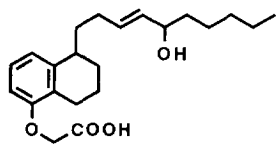


(1) Me_3SiCN; (2) $POCl_3$, pyridine; (3) DIBAL, $PhCH_3$, and then H_2SO_4; (4) $Ph_3PCHCOOMe$, $CHCl_3$; (5) H_2, Pd-C, AcOEt; (6) $LiAlH_4$, THF; (7) Ac_2O, pyridine; (8) BBr_3, CH_2Cl_2; (9) aq.NaOH, MeOH; (10) K_2CO_3, $BrCH_2COOMe$, MeCN; (11) Swern Ox.; (12) LiCl, *i*-Pr_2NEt, $(MeO)_2POCH_2CO(CH_2)_4CH_3$, MeCN; (13) $NaBH_4$, cat.AcOH, MeOH, -20°C; (14) aq.NaOH, MeOH; (15) $H_2NOCHPh_2$, EtOH.

attributed to the high flexibility of **4a**, which presumably prevented it from binding. To circumvent this, the introduction of an additional ring to diminish the flexibility of **4a** gave the 2,5- and 1,5-disubstituted tetrahydro naphthalene derivatives **4b** and **4c** with IC_{50}'s of 7.8 μM and 9.6 μM, respectively.

These results gave an argument that the cyclopentane ring part would control the relationship between the carboxylic acid and the allylic alcohol moieties in PG, and the relative relationship between the carboxylic acid and the allylic alcohol moieties in **4b** and **4c** would be similar to that in PGI_2 and PGE_1.

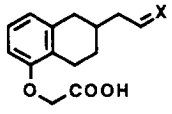
Table 1. The Effect without Cyclopentane Ring on the Displacement of [^{3}H]-Iloprost from Human Platelet PGI_2 Receptor

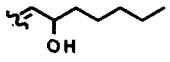
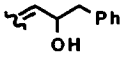
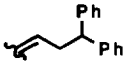
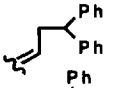
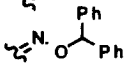
No.		IC_{50} (μM)
4a		23
4b		7.8
4c		9.6

We next turned our attention to the allylic alcohol moiety as shown in Table 2. In order to examine whether **4b** would show PG-like behavior, **4b** was first modified in a classical way as in PGs. A phenyl ring

was introduced to the ω-chain to afford **5**. As in the case of PG, this modification caused a little change in the receptor binding affinity. The IC_{50} value of compound **5** was 4.9 μM. However, the removal of the hydroxyl group in **5** gave the interesting compound **6** with the IC_{50} value of 5.3 μM. As opposed to prostaglandins, it is still active without the allylic alcohol. Further modifications of compound **6** led to compound **7** with the IC_{50} value of 3.1 μM. At this stage, its *cis* isomer **8** showed the same binding potency. Therefore, we considered that the binding affinity should be dependent on the geometrical relationship between the carboxylic acid and the terminal phenyl groups. This prompted us to search for other functional groups with more potent binding affinity than the double bond. When the double bond in compound **8** was replaced by an oxime moiety, the potency of resulting compound **9b** remarkably increased to IC_{50} of 0.65 μM !

Table 2. The Effect of Variation of the Allylic Alcohol Part on the Displacement of [^{3}H]-Iloprost from Human Platelet PGI_2 Receptor



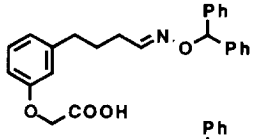
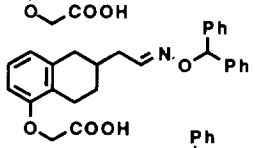
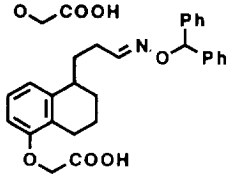
No.	X	IC_{50} (μM)
4b		7.8
5b		4.9
6b		5.3
7b		3.1
8b		3.0
9b		0.65

The skeletal changes of the oxime analogs gave IC_{50} values of 3.9 μM for **9a** and 0.60 μM for compound **9c** in Table 3. It is interesting to note the similarity in the binding tendency of these oxime ethers, as compared to those of compounds possessing the allylic alcohol, as we mentioned before.

The IC_{50} values of inhibition of 4 μM ADP-induced human platelets aggregation were 1.1 μM for **9b**, and 2.1 μM for **9c**.

Notably, the agents detailed herein lack the cyclopentane ring and the allylic alcohol in PGs have been which have been long considered essential for the biological activity. Thus, though a reassessment of the role of each functionality included in the PG skeleton, we succeeded in the design of the new PGI_2 agonists.

Table 3. The Effect of Skeletal Change on the Displacement of [^{3}H]-Iloprost from Human Platelet PGI_2 Receptor

No.		IC_{50} (μM)
9a		3.9
9b		0.65
9c		0.60
Iloprost		0.027

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