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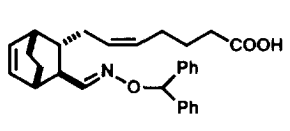
# MOLECULAR DESIGN OF NOVEL $PGI_2$ AGONISTS WITHOUT PG SKELETON. II

Nobuyuki Hamanaka,* Kanji Takahashi, Yuuki Nagao, Kazuhiko Torisu, Hideo Takada, Hidekado Tokumoto, and Kigen Kondo

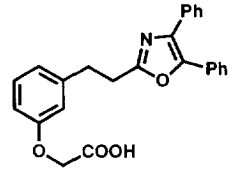
*Minase Research Institute, Ono Pharmaceutical Co., Ltd.*
*Shimamoto, Mishima, Osaka 618, Japan*

**Abstract.** Introduction of alkyl groups at the oximium carbon of the $PGI_2$ agonists **3a** and **4a** has led to a series of potent $PGI_2$ mimetics. The most effective compounds are **3c** and **3d**, whose agonistic activity for human platelet $PGI_2$ receptors is almost the same as that of $PGE_1$.

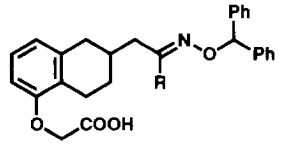
Several years ago, an Edinburgh University group showed that EP-157 (**1**)[1], which had been designed to act as a $TXA_2/PGH_2$ antagonist, rather a $PGI_2$ agonist. The Bristol-Myers Squibb group also proposed the $PGI_2$ mimetic, BMY 42393 (**2**)[2], which had been modified from Octimibate[3] as an ACAT (cholesterol acyl transferase) inhibitor. However, these groups could not show the structural relationship between $PGI_2$ and its mimetics. New $PGI_2$ agonists, **3a** and **4a**, have been designed[4], replacing the cyclopentane ring and allylic alcohol functionalities of PG with a new tetrahydronaphthalene skeleton and an oxime functionality modified to show $PGI_2$-like activities, respectively. It should be noted that there is no need for our $PGI_2$ agonists **3a** and **4a** to possess the cyclopentane ring and the allylic alcohol moieties as we postulate the binding affinity to the $PGI_2$ receptors to be dependent on the geometrical relationship between the carboxylic acid and the terminal phenyl groups. These agonists, similar in functionality, still display weaker agonistic activity than PGE1, therefore, we further explored the structural requirements for activity using 3a and 4a as model.



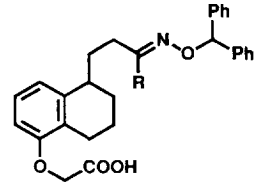

**1 EP-157**




**2 BMY 42393**




**3a R = H**

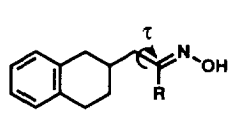


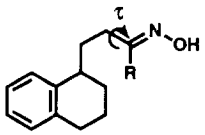

**4a R = H**

In order to design even more potent compounds, we focused our attention on the active conformations of **3a** and **4a**. There are many free-rotating bonds in the stereochemical structures of **3a** and **4a**. Among these

free-rotating bonds, we focused especially on the bond represented by the arrow (τ) (Figure 1). The rotation of this bond would be easily restricted by introducing a bulky group at R. For information on the conformations of the simple compounds **5a** and **5b**, favorable conformers about bond τ were calculated by molecular dynamics. Since there are no generally accepted parameters at present for the oxime function, CHARMm was utilized in the molecular dynamics. A rough approximation was enough for our primary aim, and in order to eliminate the effects of the minor conformational mobility, the oxyacetic acid and benzhydryl moieties in **3a** and **4a** were excluded from the calculation. The results are shown in Figure 1. With regard to τ there are three preferred conformations in **5a** (**I**, **II**, **III**) and two in **5b** (**II**, **III**). Thus, introduction of a methyl group in position R forbade the *anti* conformer between Cα-$R^1$ and C=N bond (τ = 180 °, **I**), therefore leading to an increase in the population of the Cα-$R^1$ bond perpendicular to the plane of the oxime group (τ = ±90 °, **II** and **III**). With regard to **6a** and **6b**, almost the same phenomenon was observed as that of **5a** and **5b**. If the difference in the population of the rotation τ affects the receptor binding, we can conclude that the active conformation of **3a** and **4a** would be either conformer **I** or conformers **II** and **III**. For this purpose, we introduced alkyl groups at the R position in **3a** and **4a**.

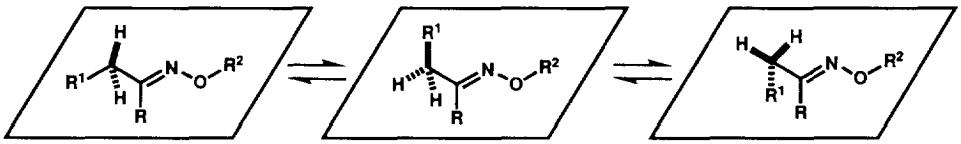
**Figure 1**




**5a** R = H
**5b** R = Me

**6a** R = H
**6b** R = Me



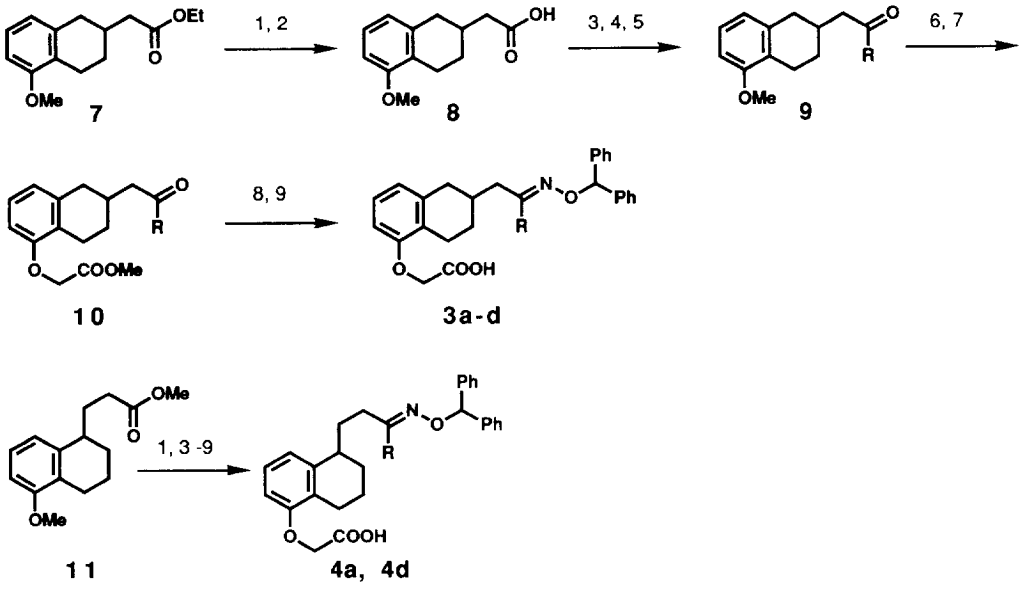

**I** **II** **III**

## Chemistry

The synthesis of compounds **3b**, **3c**, and **3d** (Scheme 1) began with ethyl 5-methoxy tetrahydronaphthalene-2-acetate **7**,[4] which was hydrolyzed (quantitative yield) to give carboxylic acid **8**. Resolution of **8** was conveniently carried out at this stage by means of *d*- or *l*-phenethylamine.[5] Conversion to the acid chloride, followed by amination with *N,O*-dimethylhydroxylamine afforded the active amine, which underwent nucleophilic attack by alkyl magnesium halides[6] to give the corresponding alkyl ketones **9**. After deprotection of the methyl ether group, the phenol compound was treated with ethyl bromoacetate in the presence of $K_2CO_3$ to obtain ester **10**. Formation of the oxime[7] with benzhydryloxy amine and saponification of the ester produced compounds **3b**, **3c**, and **3d**.

Compound **4d** was synthesized in a similar fashion starting from methyl 5-methoxy tetrahydronaphthalene-1-propionate **11**.[4]

**Scheme 1**




(1) aq.NaOH, MeOH; (2) optical resolution using *d*- or *l*-phenethylamine; (3) $(COCl)_2$; (4) HNMe(OMe)·HCl, $Et_3N$; (5) RMgX or $LiAlH_4$; (6) pyridine·HCl, Δ; (7) $BrCH_2COOMe$, $K_2CO_3$, MeCN; (8) $H_2NOCHPh_2$, EtOH.

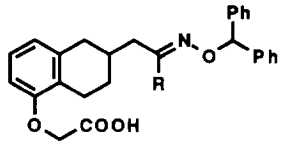
## Biological Results and Discussion

Evaluation of $PGI_2$ binding was undertaken using the conventional ligand binding assay based on the displacement of [$^3$H]-iloprost from human platelets. $IC_{50}$ values of the functional assay were obtained by measuring inhibition of 4 μM ADP-induced platelet aggregation using human platelet rich plasma.

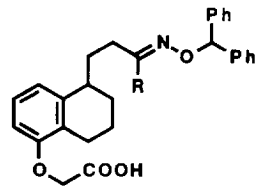
As can be seen from the results in Table 1, the introduction of methyl, ethyl, or propyl group in **3a** led to the compounds **3b**, **3c**, and **3d**, respectively. It is interesting to note that their binding potencies to the human platelet $PGI_2$ receptors are 0.38 μM for **3b**, 0.15 μM for **3c**, and 0.15 μM for **3d**. Furthermore, functional assay showed that **3b**, **3c**, and **3d** were potent $PGI_2$ agonists having $IC_{50}$ values of 0.23 μM, 0.07 μM, and 0.15 μM, respectively.

However, modification of **4a** to **4d** did not result in the same effect on potency as that of **3a** as shown in Tables 1. The binding potency of **4d** was about three times lower than that of **4a** ($IC_{50}$ values of 2.1 μM and 0.60 μM, respectively). The $IC_{50}$ values in the functional assay were 2.1 μM for **4a** and 2.4 μM for **4d**.

**Table 1 The Effect of Alkyl Substitutions in 1 or 2-Substituted Tetrahydronapthalene Derivatives**




**2 Substituted Series**

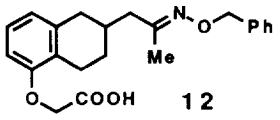



**1 Substituted Series**

| No. | 1 or 2 Substitution | R | Binding Assay $IC_{50}$ (μM) | Functional Assay $IC_{50}$ (μM) |
|---|---|---|---|---|
| **3a** | 2 | H | 0.65 | 1.1 |
| **3b** | 2 | Me | 0.38 | 0.23 |
| **3c** | 2 | Et | 0.15 | 0.07 |
| **3d** | 2 | *n*-Pr | 0.15 | 0.15 |
| **4a** | 1 | H | 0.60 | 2.1 |
| **4d** | 1 | *n*-Pr | 2.1 | 2.4 |
| **Iloprost** | | | 0.027 | 0.0014 |
| **$PGE_1$** | | | 1.4 | 0.07 |

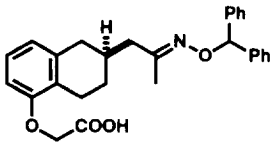
It is interesting to note that the restriction of the rotation (τ) in **3a**, by introduction of some alkyl groups, led to the increase in binding potency. This result gave the insight that the active conformer of **3a-d** in the rotation (τ) should be the conformer **II** or **III**. However, a similar restriction of the rotation (τ) in **4a** gave the reduction of binding potency. This would imply that the active conformer of **4a** in the rotation (τ) should be the conformer **I**. These results prompted us to search for the other functional groups giving more potent binding affinity than the oxime moiety.

Removal of a phenyl ring in **3b** led to **12**, which showed weak binding potency and platelet inhibitory activity with $IC_{50}$'s of 5.3 μM and 12 μM, respectively. The terminal diphenyl group appeared to be an important functional group for biological activity.

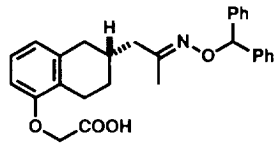



**12**

Thus far, our studies were conducted on isomeric mixtures. At this point, it is important to know which isomer is more active. The geometrical isomers of the oxime **3b** were separated by HPLC (YMC). The *anti*-isomer was found to be more potent than the *syn*-isomer. However, since the inversion energy barrier between the *anti* and *syn* isomers is very low, these two isomers are interconverted easily at room temperature. With regard to the enantiomers, the binding potencies were 0.22 μM for *S* isomer **3b**, and 2.2 μM for *R* isomer **3b**. The $IC_{50}$ values of functional assay were 0.13 μM for *S* isomer **3d**, and 1.9 μM for *R* isomer **3b**. The *S*-isomer of **3b** is about ten times more active than the *R*-isomer in the human platelet antiaggregation. Now we can conclude that among compounds **3a-d** *S*-configuration and *anti*-form are very important for increasing the binding potency.




**3b *S* Isomer**




**3b *R* Isomer**

Propyl derivative **3d** showed ADP-induced antiaggregation of guinea pig and dog platelets less effective human platelets with $IC_{50}$'s of 1.9, and 7.3 μM, respectively. Compound **3d** also elevated cAMP contents in human platelet in a dose dependent manner under similar condition that they inhibit platelet aggregation. Oral administration of **3d** inhibited *ex vivo* platelet aggregation ($EC_{50}$: 0.82 mg/Kg) and this inhibition lasted more than four hours in guinea pigs. In addition, the inhibitory effects on platelet adhesion was also observed in guinea pigs. In anesthetized dogs, **3d** (1 and 3 mg/Kg, i.d.) inhibited ADP or collagen induced aggregation and lowered the blood pressure.

These results suggested that **3d** inhibits platelet aggregation *in vitro* and *in vivo* by acting as an agonist for the $PGI_2$ receptors linked to adenylate cyclase although its structure is completely different from that of $PGI_2$.

## References and Notes

1. (a) Armstrong, R. A.; Jones, R. L.; MacDermot, J.; Wilson, N. H. *Br. J. Pharmacol.*, **1986**, *87*, 543. (b) Muir G., Jones R.L., Will S.G., Winwick T., Peesapatil V., Wilson N.H., Griffiths N., Nicholson W.V., Taylor P., Sawyer L., Blake A.J., *Eur. J. Med. Chem.*, **1993**, *28*, 609.

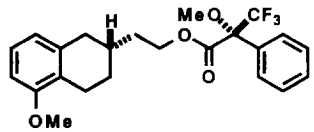
2. (a) Meanwell, N. A.; Rosenfild, M. J.; Trehan, A. K.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming J. S.; Gamberdella, M.; Zavoico, G. B.; Seiler, S. M. *J. Med. Chem.*, **1992**, *35*, 3483. (b) Meanwell, N. A.; Rosenfild, M. J.; Trehan, A. K.; Romine, J. L.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming J. S.; Gamberdella, M.; Zavoico, G. B.; Seiler, S. M. *ibid.*, **1992**, *35*, 3498.

3. (a) Lautenschlager, H. H.; Prop, G.; Niemann, R. *Drugs of the Future*, **1986**, *11*, 26. (b) Rucker, W.; Prop, G.; Huther, A. M. *Atherosclerosis*, **1988**, *69*, 155.

4. For Part I, see: Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.*, preceding paper in this issue.

5. The absolute configuration of **8** was established from an X-ray structure of phenethyl amide **13**. General procedure of X-ray crystallographic analysis: Diffraction data were collected with graphite-monochromated Cu-Kα radiation on a Rigaku AFC-5R automatic four-cycle diffractometer and 2θ/ω-scan mode up to 120° in 2θ at room temperature. TEXAN, structure analysis software package, with micro VAX 3800, was used for all computations. The structure was solved by direct methods using SHELXS in combination with difference Fourier recycling. The full-matrix least-squares refinement was carried out using ORFLS with non-H atoms treated anisotropically. The ideal position for hydrogen atoms were calculated, and were verified on a difference Fourier map. Then they included further refinement and structure factor calculation $Rw = (\Sigma s^2(|Fo|-|Fc|)^2/\Sigma s^2|Fo|^2)^{1/2}$.

*X-ray crystallographic determination of* ***11*** $C_{23}H_{25}O_4F_3$ ( mol. wt 422.43) A colorless crystal recrystallized from ethanol, space group $P2_1$, $a$ = 8.6690 (11) Å, $b$ = 7.6005 (8) Å, $c$ = 16.278 (2) Å, β = 101.50 (1)° $Z$=2, $Dc$ = 1.33 g/cm$^3$. 1568 independent reflections were collected. The scan width was 1.2° and scan speed 8.0°/s. The final refinement converged to $R$ = 0.048 and $Rw$ = 0.050 for 370 variables and 1501 (I>3σ(I)) refractions. The highest residual peak in a difference Fourier map is 0.20 Å$^{-3}$.




**13**

6. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.*, **1981**, *22*, 3815.

7. All oxime derivatives **3a-d**, **4a**, and **4d** were identified by spectroscopy. The ratios of *anti* : *syn* were 6:4 for **3a**, 7:3 for **3b-d**, 5:5 for **4a**, and 6:4 for **4d**.

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