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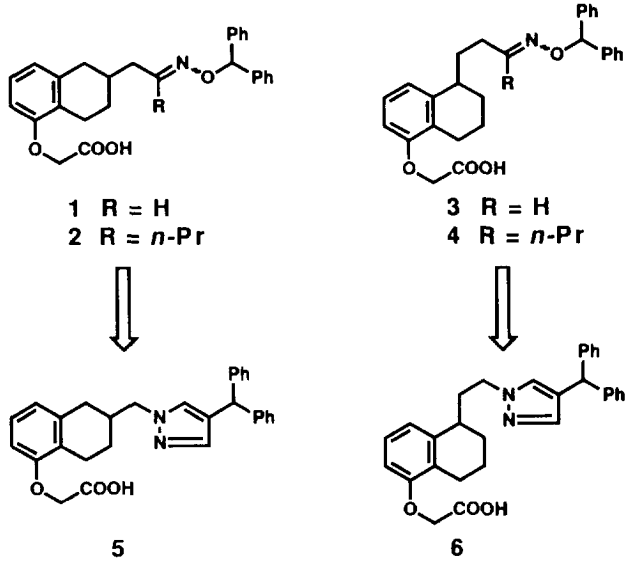
MOLECULAR DESIGN OF NOVEL PGI_2 AGONISTS WITHOUT PG SKELETON. IV

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

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

Abstract. The synthesis and biological evaluation of a novel series of di or tetrahydronaphthalene-5-oxyacetic acid derivatives with the 4-benzhydryl pyrazole group is described. Among these compounds, **7** has been identified as a highly potent PGI_2 agonist with an exceptionally long *in vivo* duration of action.

In the previous papers[1] we described the design, synthesis and pharmacology of tetrahydronaphthalene-5-oxyacetic acid derivatives with the benzhydryloxyimine group (**1-4**), as the PGI_2 agonists to the human platelet receptor. Compound **2** was found to be an especially potent and orally active PGI_2 agonist.



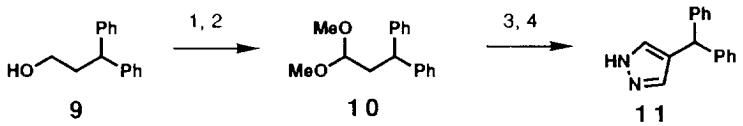
Despite the favorable biological profile of **2**, we have a problem in this series due to the *anti* (more active) and *syn* (less active) interconversion of the oxime moiety. However, it provided a novel tetrahydronaphthalene-5-oxyacetic acid substructure with a potential for potency, oral activity and duration of action which we anticipated could be employed in conjunction with the *anti* form of the oxime surrogate. We

report here in preliminary form the synthesis of novel and very potent PGI_2 agonists **5-8**, in which the benzhydryl oxime moiety in **1-4** has been replaced by the 4-benzhydryl pyrazole group.

Chemistry

The key intermediate **11** for synthesis of compounds **5-8** was prepared as shown in Scheme 1. Oxidation of commercially available 3,3-diphenyl-1-propanol (**9**) gave aldehyde which was converted to acetal **10**. Formylation of **10** by the method of Vilsmeier-Haack-Arnold acylation[2], followed by reaction with hydrazine monohydrochloride and potassium carbonate afforded 4-benzhydryl pyrazole (**11**).

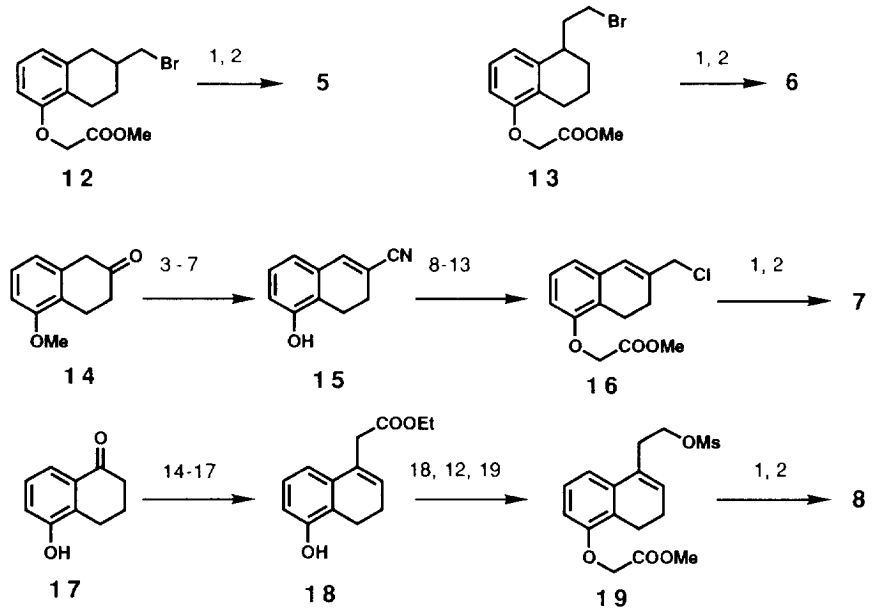
Scheme 1



9 10 11

(1) Swern Ox.; (2) MeOH, TsOH; (3) $POCl_3$, DMF; (4) N_2H_4·HCl, K_2CO_3.

Scheme 2



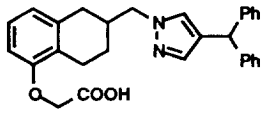
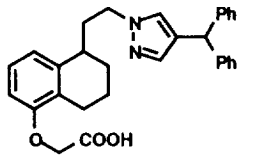
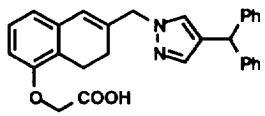
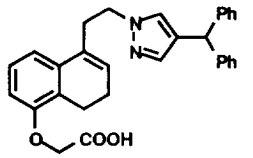
(1) **11**, *t*-BuOK, DMF; (2) NaOH, MeOH; (3) $NaHSO_3$; (4) NaCN; (5) MsCl, Et_3N; (6) DBU, $PhCH_3$; (7) BBr_3; (8) *t*-$BuMe_2SiCl$, imidazole; (9) DIBAL; (10) *n*-Bu_4NF; (11) $NaBH_4$, MeOH, cat.AcOH; (12) $BrCH_2COOMe$, K_2CO_3, MeCN; (13) CCl_4, Ph_3P; (14) Me_3CCOCl, pyridine; (15) Zn, $BrCH_2COOEt$, C_6H_6; (16) HCOOH; (17) EtOH, EtONa; (18) $LiBH_4$, MeOH, THF; (19) MsCl, Et_3N.

Scheme 2 illustrates the preparation of compounds **5**-**8**. Treatment of ester bromides **12** and **13** with the potassium salt of **11** gave the pyrazole esters which were hydrolyzed to afford **5** and **6**.

Compound **16** was obtained from **14** by following series of reactions; (i) treatment with sodium bisulfite to give bisulfite addition product; (ii) cyanation; (iii) mesylation; (iv) dehydration to afford α,β unsaturated nitrile; (v) demethylation to give **15**; (vi) protection of phenol with t-butyldimethylsilyl chloride; (vii) reduction with DIBAL to afford aldehyde; (viii) deprotection of silyl ether; (ix) reduction of aldehyde; (x) O-alkylation; and (xi) chlorination with carbon tetrachloride and triphenylphosphine.

Conversion of **17** into **18** was achieved by (i) pivalylation of the phenol; (ii) Reformatsky reaction with ethyl bromoacetate; (iii) dehydration to afford the α,β and β,γ unsaturated esters (the ratio was 1:9); (iv) ethanolysis of pivaloyl ester to afford **18** which was purified by recrystallization. Reduction of **18** with lithium borohydride gave diol compound. The mesylate **19** was prepared by selective *O*-alkylation of phenol followed by mesylation. Alkylation of **16** and **19** with **11** furnished pyrazole derivatives which were hydrolyzed to afford **7**[3] and **8**.

Table 1 The Effect of Pyrazole Derivatives on the Binding and Functional Assays

No.		Binding Assay IC_{50} (μM)	Functional Assay IC_{50} (μM)
5		0.040	0.13
6		0.018	0.093
7		0.008	0.026
8		2.0	8.6

Biological Results and Discussion

Evaluation of PGI_2 binding was undertaken using conventional ligand binding assay based on the displacement of [^{3}H]-iloprost from human platelets. All compounds were tested for their ability to inhibit 4 μM

ADP-induced platelet aggregation of human platelet rich plasma (PRP) and the results are reported as IC_{50} values.

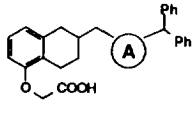
As shown in Table 1, **5** and **6**, which were designed based on compound **1** and **3**, showed high affinities for human platelet PGI_2 receptors and potent PGI_2 agonistic activities. Surprisingly, even the dihydronaphthalene derivative **7**, lucking chirality, exhibited potent PGI_2 agonistic property. Replacement of the pyrazole group by other five membered heterocyclic functions resulted in decrease in PGI_2 agonistic potencies.[4] In particular, **7** was found to be an potent PGI_2 agonist in human platelets and was further evaluated for its *in vitro* duration of action.

Compound **7** showed ADP-induced antiaggregation of guinea pig, rat and dog platelets less effective than human platelets with IC_{50}'s of 1.0, 27, and 1.1 μM, respectively. Oral administration of **7** (1 and 3 mg/kg) inhibited ADP- or collagen-induced platelet aggregation and this inhibition lasted more than four hours in dog.

These results suggested that **7** inhibits platelet aggregation *in vitro* and *in vivo* by acting as an agonist for the PGI_2 receptors although its structure is completely different from that of PGI_2.

References and Notes

1. For Part II, see: Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Takada, H.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.*, preceding paper in this issue.
2. Jutz, C. *Advances in Organic Chemistry: Method and Results*: Taylor, E. C. Ed.; 1976, vol. 1, Part 1, pp. 225-342.
3. Characterization of **7**: white powder, 155-156° (ethyl acetate-hexane); IR (KBr): 2913, 1735, 1575, 1467, 1219 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 8.00 (1 H, brs), 7.37-7.12 (11 H, m), 7.06 (1 H, s), 7.04 (1 H, t, J = 8 Hz), 6.66 (1 H, d, J = 8 Hz), 6.62 (1 H, d, J = 8 Hz), 6.18 (1 H, s), 5.35 (1 H, s), 4.78 (2 H, s), 4.58 (2 H, s), 2.84 (2 H, t, J = 8 Hz), 2.13 (2 H, d, J = 8 Hz); 125 MHz ^{13}C-NMR ($CDCl_3$) δ 171.87, 154.31, 143.91, 138.98, 136.20, 134.86, 129.32, 128.57, 128.42, 126.78, 126.44, 125.21, 125.01, 123.15, 120.35, 111.25, 65.61, 57.19, 47.57, 24.06, 20.11; MS (EI) *m/z* 450 (M^+).
4. The PGI_2 agonistic potencies of other five membered heterocyclic derivatives are shown below.



A	Functional Assay IC_{50} (μM)	A	Functional Assay IC_{50} (μM)	A	Functional Assay IC_{50} (μM)
	1.0		1.0		0.67
	5.1		12		0.53

(*Received in Japan* 8 *March* 1995; *accepted* 10 *April* 1995)