

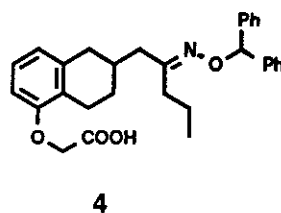
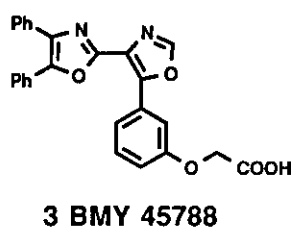
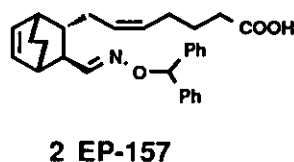
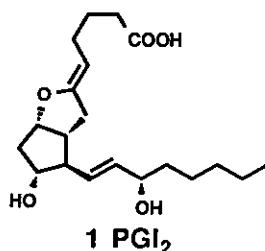
# NOVEL NONPROSTANOID PROSTACYCLIN (PGI<sub>2</sub>) MIMETICS WITH HETEROCYCLIC MOIETY†

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**Abstract** - Structural modification of [2-(2-benzhydryloxyiminopentyl)-1,2,3,4-tetrahydro-5-naphthyloxy]acetic acid (**4**), previously identified as a PGI<sub>2</sub> agonist without a PG skeleton, was examined. Conversion of the oxime moiety in **4** to the pyrazole led to [2-(4-benzhydrylpyrazoyl)methyl-1,2,3,4-tetrahydro-5-naphthyl-oxy]acetic acid (**34**) which strongly inhibited ADP-induced aggregation of human platelets *in vitro*.

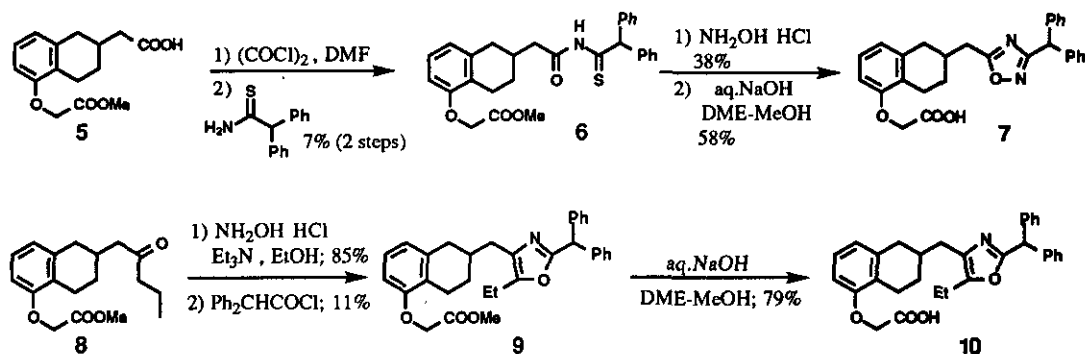
Many prostacyclin (PGI<sub>2</sub>, **1**) analogues have been synthesized to search for the chemically stable, biologically potent and tissue specific agonists for potential medical utility,<sup>1</sup> since PGI<sub>2</sub><sup>2</sup> was identified in 1976 as a powerful endogenous stimulator of blood platelet adenylate cyclase. The carboxylic acid, the cyclopentane ring and the allylic alcohol moieties have been believed to be essential for expression of the biological activities of PGs.<sup>3</sup> Accordingly, approaches to their specific agonists have so far been limited to the structural modifications of the  $\alpha$  and  $\omega$ -chains in PGs. Recently, an Edinburgh University group and



the Bristol-Myers Squibb group proposed EP-157 (2)<sup>4</sup> and BMY 45788 (3)<sup>5</sup>, respectively, as the nonprostanoid prostacyclin mimetics. We also demonstrated that the oxime derivative (4)<sup>6</sup> was an especially potent and orally active PGI<sub>2</sub> agonist. Despite the favorable profile of 4, this series of compounds has the *anti* (more active) and *syn* (less active) interconvertable oxime part.<sup>6</sup> Therefore, to search for the substitutable functions for the oxime moiety, we synthesized and evaluated a series of diphenylmethylated heterocyclic derivatives.

The target compounds were synthesized by the routes shown in Schemes I, II and III. The syntheses of 7 and 10 are described in Scheme I. The carboxylic acid (5)<sup>7</sup> was treated with oxalyl chloride, and then the product was coupled with diphenylthioacetamide to afford 6. Cyclization of 6 with hydroxylamine hydrochloride followed by hydrolysis provided 7. The ketone (8)<sup>6</sup> was first reacted with hydroxylamine hydrochloride and then cyclized with diphenylacetyl chloride in the manner of Bhatt *et al.*<sup>8</sup> to give 9. Saponification of 9 furnished the target compound (10).

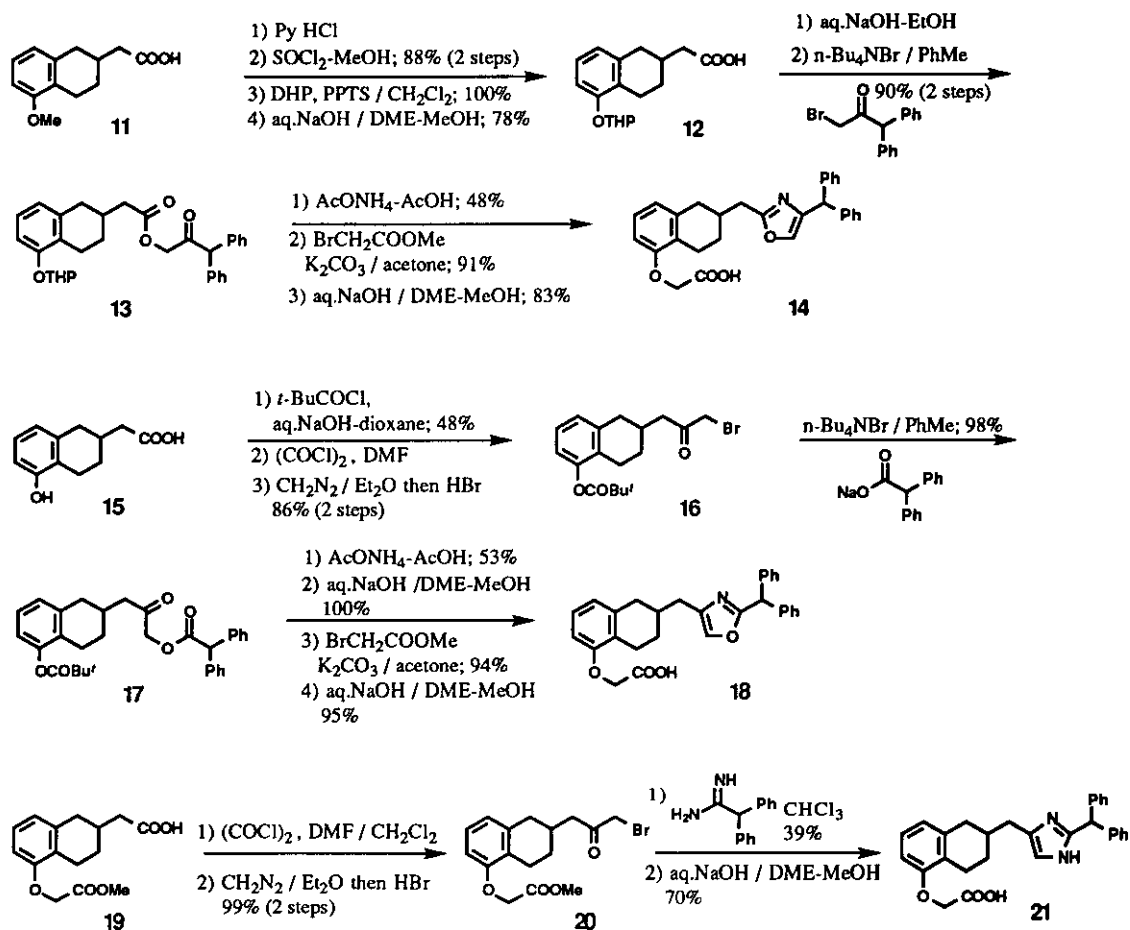
Scheme I



Scheme II illustrates the preparations of 14, 18 and 21. Intermediate (12) was obtained from 11<sup>9</sup> by (i) demethylation with pyridine hydrochloride; (ii) esterification; (iii) THP-protection of the phenol; and (iv) saponification. Coupling of the anhydrous sodium salt of 12 with 3-bromo-1,1-diphenyl-2-propanone<sup>10</sup> in the presence of a catalytic amount of *n*-Bu<sub>4</sub>NBr in toluene afforded the keto ester (13). Compound (13) was exposed to an excess of NH<sub>4</sub>OAc in AcOH to give the cyclized compound which was alkylated with methyl bromoacetate and then hydrolyzed to provide 14. The oxazole derivative (18) was also obtained by the same preceding procedure from 17, which was easily prepared by the following series of reaction: (i) protection of the phenol on 15; (ii) conversion to the  $\alpha$ -bromoketone; and (iii) ketoesterification.

Compound (21) was available by reaction of the keto ester (20) derived from 19 with benzhydrylamidine in  $\text{CHCl}_3$  at reflux followed by saponification.

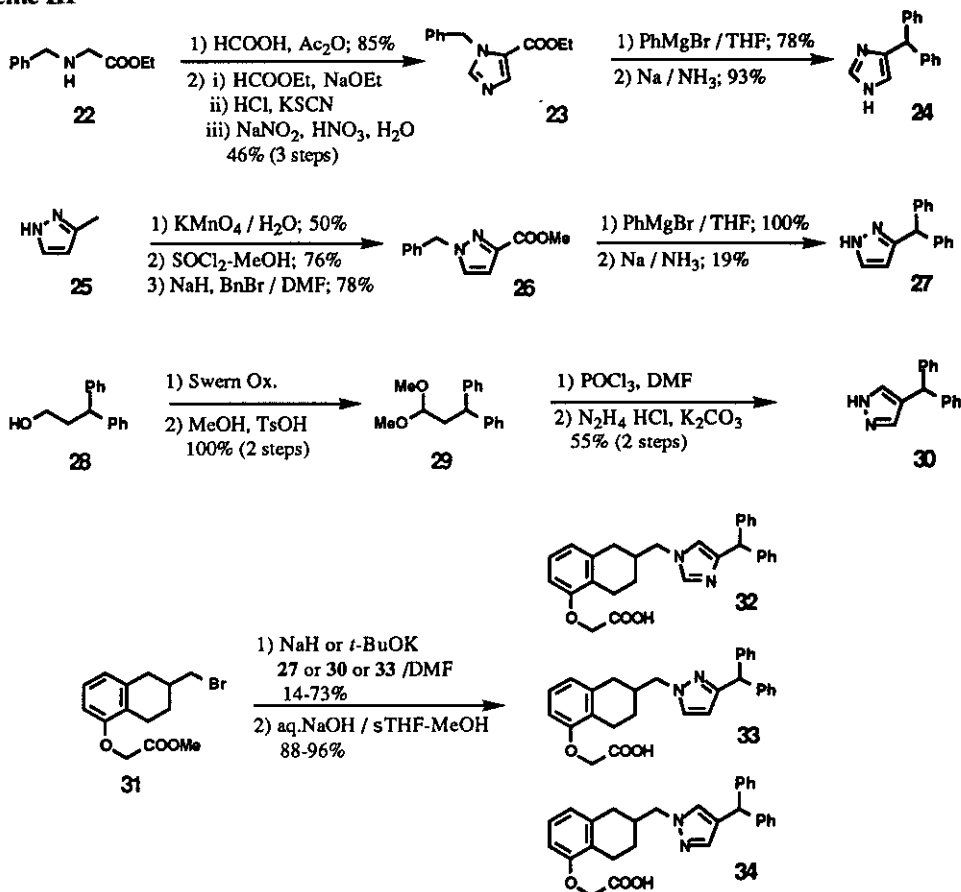
## Scheme II



Compounds (32, 33 and 34) were prepared by the synthetic procedures summarized in Scheme III. Treatment of compound (23), which was obtained from *N*-benzylglycine ethyl ester (22) by the sequence of four step reactions, with 6 equiv. of phenylmagnesium bromide in THF followed by reduction and deprotection in a single operation gave 4-diphenylmethylimidazole (24). Synthesis of intermediate (27) was achieved by (i) oxidation of methyl moiety by potassium permanganate; (ii) esterification; (iii) *N*-benzylation; (iv) treatment with phenylmagnesium bromide in THF; and v) debenzoylation and dehydroxylation. Oxidation of commercially available 3,3-diphenyl-1-propanol (28) gave the corresponding aldehyde which was converted to acetal (29). Formylation of 29 by the method of

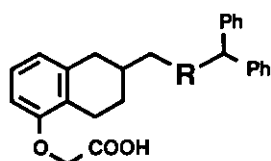
Vilsmeier-Haack-Arnold acylation,<sup>11</sup> followed by reaction with hydrazine monohydrochloride in the presence of potassium carbonate afforded 4-benzhydrylpyrazole (30). Coupling of the bromide (31) with 24, 27 or 30 in DMF followed by saponification furnished the desired compounds (32-34).

Scheme III



PGI<sub>2</sub> receptor binding was examined by the conventional ligand binding assay based on the displacement of [<sup>3</sup>H]-iloprost<sup>12</sup> from human platelet membrane. IC<sub>50</sub> values of the functional assay were obtained by measuring the inhibition of 4 μM ADP-induced platelet aggregation using human platelet rich plasma.

Table 1 shows the results of these assays. Among these compounds<sup>13</sup> evaluated, the platelet inhibitory activity of the *N*-alkylated heterocyclic derivatives (32, 33 and 34) was greater than that of the others. Especially, the 1,4-dialkylated pyrazole (34) exhibited high binding affinity for the PGI<sub>2</sub> receptor with an IC<sub>50</sub> of 0.04 μM and antiaggregative potency with an IC<sub>50</sub> of 0.13 μM, the agonistic ability of 34 was the same as that of 4 and PGE<sub>1</sub>.

**Table 1.** Physical Properties and Biological Activities of Heterocyclic Derivatives

compound	R	mp °C	IC <sub>50</sub> μM	
			displacement of [ <sup>3</sup> H]iloprost from human platelet membrane	inhibition of ADP-induced human platelet aggregation
7		oil	0.26	1.0
10		150.5-151.5	1.2	1.6
14		129.5-131.5	1.8	5.1
18		158.0-159.5	0.050	1.0
21		170 (decomposition)	6.8	12
32		amorphous solid	0.35	0.67
33		130.0-133.0	0.36	0.53
34		160.0-163.0	0.040	0.13
4			0.15	0.15
PGE <sub>1</sub>			1.4	0.07
iloprost			0.027	0.0014

## REFERENCES AND NOTES

† This work is dedicated to the memory of Professor Yoshio Ban.

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13. All new compounds have physical and spectroscopic data consistent with their structures. For **34**: Ir (KBr) 3423, 2927, 1708, 1586, 1467, 1273  $\text{cm}^{-1}$ ; ms (EI)  $m/z$  452 ( $\text{M}^+$ );  $^1\text{H}$  nmr (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-7.12 (11 H, m), 7.06-6.90 (2 H, m), 6.64 (1 H, d,  $J = 8.0$  Hz), 6.60 (1 H, br s), 6.53 (1 H, d,  $J = 8.0$  Hz), 5.35 (1 H, s), 4.57 (2 H, br s), 4.14-3.90 (1 H, m), 3.05-2.86 (1 H,

m), 2.75-2.08 (4 H, m), 1.92-1.73 (1 H, m), 1.43-1.19 (1 H, m);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ )  $\delta$  177.75, 155.34, 144.03, 138.78, 136.90, 129.53, 128.59, 128.41, 126.43, 126.01, 125.59, 124.65, 122.47, 108.21, 65.42, 57.13, 47.57, 35.23, 33.44, 26.20, 22.44.

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