NOVEL NONPROSTANOID PROSTACYCLIN (PGI_2) MIMETICS WITH HETEROCYCLIC MOIETY†

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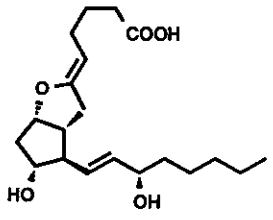
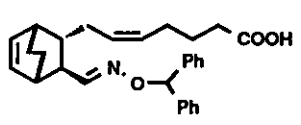
Abstract - Structural modification of [2-(2-benzhydryloxyiminopentyl)-1,2,3,4-tetrahydro-5-naphthyloxy]acetic acid (**4**), previously identified as a PGI_2 agonist without a PG skeleton, was examined. Conversion of the oxime moiety in **4** to the pyrazole led to [2-(4-benzhydrylpylazoyl)methyl-1,2,3,4-tetrahydro-5-naphthyl-oxy]acetic acid (**34**) which strongly inhibited ADP-induced aggregation of human platelets *in vitro*.

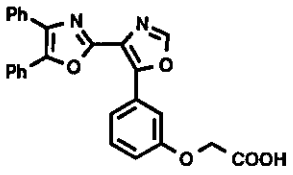
Many prostacyclin (PGI_2, **1**) analogues have been synthesized to search for the chemically stable, biologically potent and tissue specific agonists for potential medical utility,[1] since PGI_2[2] was identified in 1976 as a powerful endogenous stimulator of blood platelet adenylate cyclase. The carboxylic acid, the cyclopentane ring and the allylic alcohol moieties have been believed to be essential for expression of the biological activities of PGs.[3] Accordingly, approaches to their specific agonists have so far been limited to the structural modifications of the α and ω-chains in PGs. Recently, an Edinburgh University group and



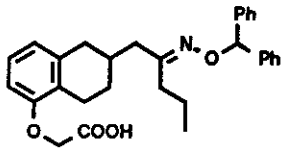
1 PGI_2



2 EP-157



3 BMY 45788



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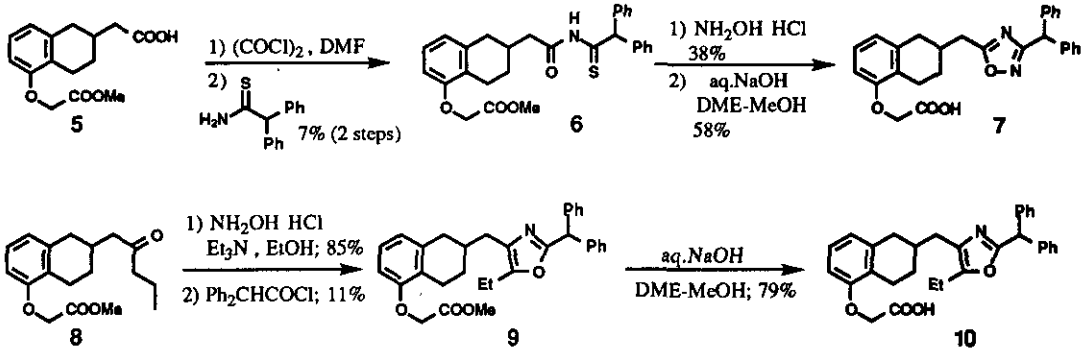
the Bristol-Myers Squibb group proposed EP-157 (**2**)[4] and BMY 45788 (**3**)[5], respectively, as the nonprostanoid prostacyclin mimetics. We also demonstrated that the oxime derivative (**4**)[6] was an especially potent and orally active PGI_2 agonist. Despite the favorable profile of **4**, this series of compounds has the *anti* (more active) and *syn* (less active) interconvertable oxime part.[6] 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**)[7] was treated with oxalyl chloride, and then the product was coupled with diphenylthioacetamide to afford **6**. Cyclization of **6** with hydroxylamine hydrochrolide followed by hydrolysis provided **7**. The ketone (**8**)[6] was first reacted with hydroxylamine hydrochrolide and then cyclized with diphenylacetyl chloride in the manner of Bhatt *et al* .[8] to give **9**. Saponification of **9** furnished the target compound (**10**).

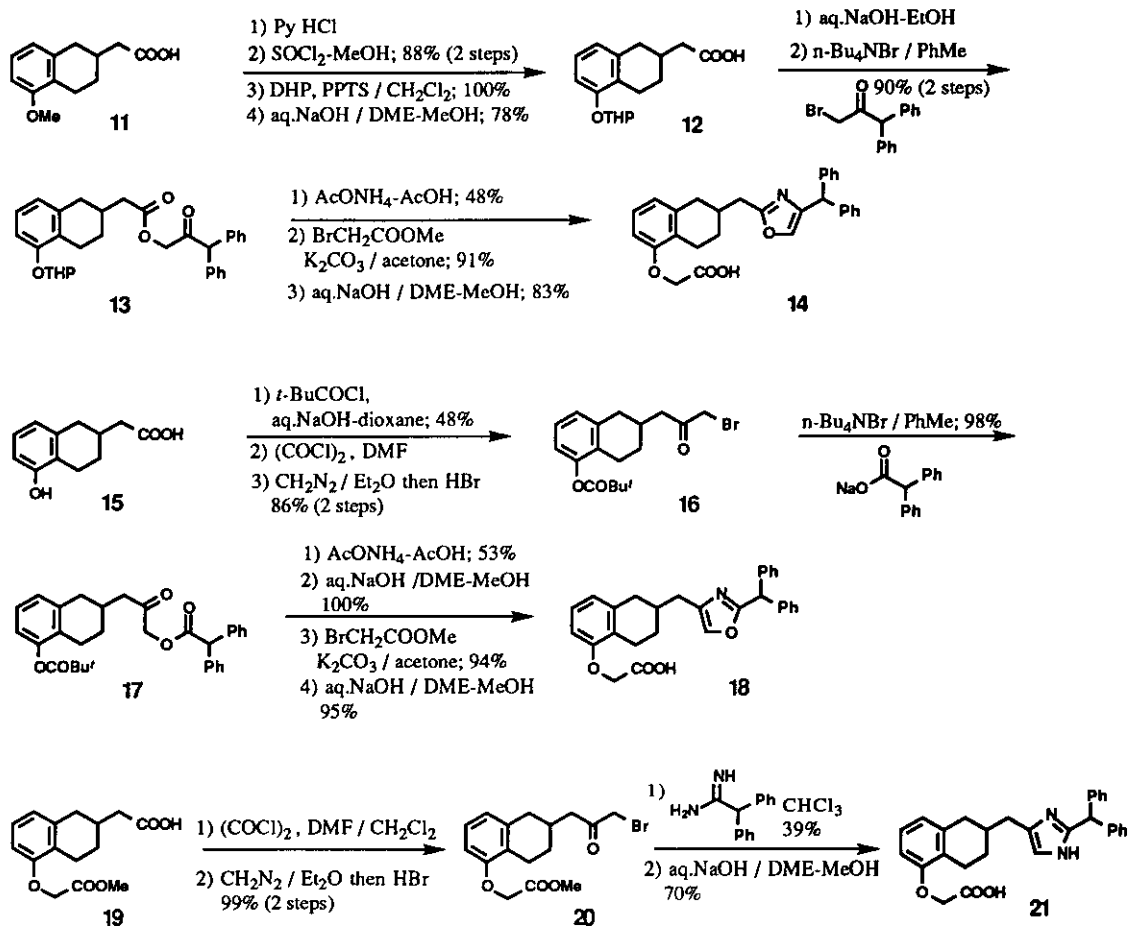
Scheme I



Scheme II illustrates the preparations of **14**, **18** and **21**. Intermediate (**12**) was obtained from **11**[9] 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[10] in the presence of a catalytic amount of *n*-Bu4NBr in toluene afforded the keto ester (**13**). Compound (**13**) was exposed to an excess of NH4OAc 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 α-bromoketone; and (iii) ketoesterification.

Compound (**21**) was available by reaction of the keto ester (**20**) derived from **19** with benzhydrylamidine in $CHCl_3$ at reflux followed by saponification.

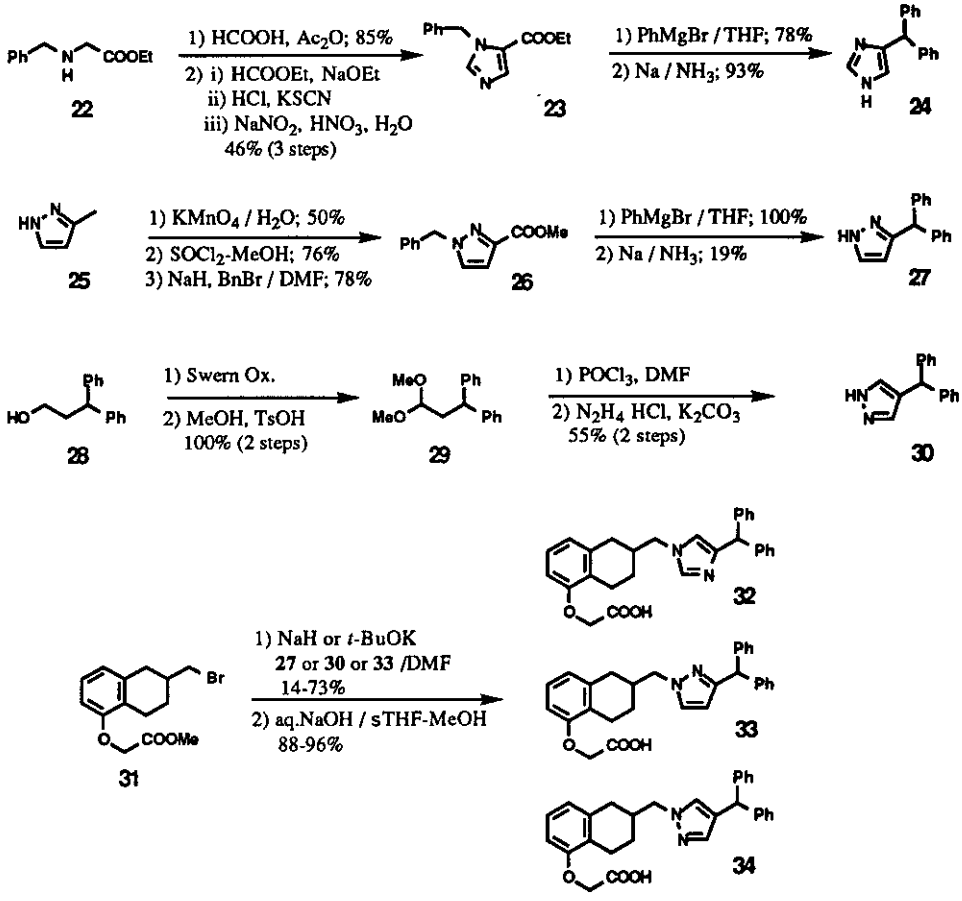
Scheme II



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) debenzylation 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

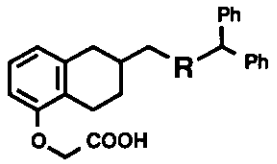
Vilsmeier-Haack-Arnold acylation,[11] followed by reaction with hydrazine monohydrochloride in the presence of potassium carbonate afforded 4-benzhydrylpyrazole (**30**). Coupling of the bromide (**31**) with **24**, **27** or **30** in DMF followed by saponification furnished the desired compounds (**32-34**).

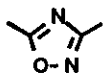
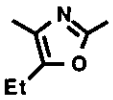
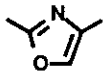
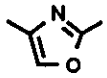
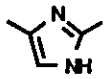
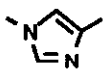
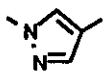
Scheme III



PGI_2 receptor binding was examined by the conventional ligand binding assay based on the displacement of [^{3}H]-iloprost[12] from human platelet membrane. IC_{50} 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[13] 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 pylazole (**34**) exhibited high binding affinity for the PGI_2 receptor with an IC_{50} of 0.04 μM and antiaggregative potency with an IC_{50} of 0.13 μM, the agonistic ability of **34** was the same as that of **4** and PGE_1.

Table 1. Physical Properties and Biological Activities of Heterocyclic Derivatives



compound	R	mp °C	IC_{50} μM: displacement of [^{3}H]iloprost from human platelet membrance	IC_{50} μM: 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
PGE1			1.4	0.07
iloprost			0.027	0.0014

REFERENCES AND NOTES

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

1. J. M. Muchowski, *Handbook of Eicosanoids: Prostaglandins and Related Lipids*, Willis, A. L., Ed., 1987, Vol. 1 (Part B), pp. 42-81.
2. (a) S. Moncada, R. J. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, 1976, **263**, 663. (b) R. J. Gryglewski, S. Bunting, S. Moncada, R. J. Flower, and J. R. Vane, *Prostaglandins*, 1976, **12**, 685. (c) R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, 1976, **12**, 915.
3. R. C. Nickolson, M. H. Town, and H. Vorbrüggen, *Med. Res. Rev.*, 1985, **5**, 1.
4. G. Muir, R. L. Jones, S. G. Will., T. Winwick, V. Peesapatil, N. H. Wilson, N. Griffiths, W. V. Nicholson, P. Taylor, L. Sawyer, and A.J. Blake, *Eur. J. Med. Chem.*, 1993, **28**, 609.
5. N. A. Meanwell, J. L. Romine, M. J. Rosenfeld, S. W. Martin, A. K. Trehan, J. J. K. wright, M. F. Malley, J. Z. Gougoutas, C. L. Brassard, J. O. Buchanan, M. E. Federici, J. S. Fleming, M. Gamberdella, G. B. Zavoico, and S. M. Seiler, *J. Med. Chem.*, 1993, **36**, 3884.
6. N. Hamanaka, K. Takahashi, Y. Nagao, K. Torisu, H. Takada, H. Tokumoto, and K. Kondo, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1071.
7. N. Hamanaka, K. Takahashi, Y. Nagao, K. Torisu, H. Tokumoto, and K. Kondo, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1077.
8. G. S. Reddy and M. V. Bhatt, *Indian J. Chem.*, Sect. B, 1981, **20**, 322.
9. N. Hamanaka, K. Takahashi, Y. Nagao, K. Torisu, H. Tokumoto, and K. Kondo, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1065.
10. C. L. Stevens and C. T. Lenk, *J. Org. Chem.*, 1954, **19**, 538.
11. C. Jutz, *Advances in Organic Chemistry: Method and Results*, Taylor, E. C. Ed.; 1976, Vol. 1, Part 1, pp. 225-342.
12. A. I. Schafer, B. Copper, D. O'Hara, and R. I. Handin, *J. Biol. Chem.*, 1979, **254**, 2914.
13. All new compounds have physical and spectroscopic data consistent with their structures. For **34**: Ir (KBr) 3423, 2927, 1708, 1586, 1467, 1273 cm^{-1}; ms (EI) *m/z* 452 (M^+); ^1H nmr (200 MHz, $CDCl_3$) δ 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}C nmr ($CDCl_3$) δ 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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