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PHARMACOLOGICAL EVALUATION OF COMBINED PGI_2 AGONISTS/THROMBOXANE SYNTHASE INHIBITORS. I

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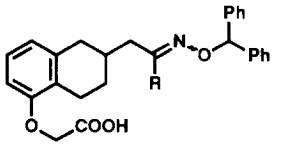
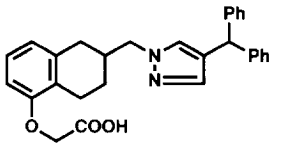
Abstract. By incorporation of a pyridine moiety into compounds shown to be PGI_2 agonists, we have synthesized a series of compounds which also show potent thromboxane synthase inhibitory activity. Agents **9** and **14** with the 3-substituted pyridine moiety show a combined properties of PGI_2 agonist and TXA_2 synthase inhibitor.

Vane and his collaborators proposed an interesting homeostatic hypothesis whereby the prostaglandin endoperoxides H_2 and G_2 serve as substrates for the generation of two labile substances, thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) with diametrically opposite biological effects.[1,2] TXA_2 generated by blood platelets promotes platelets aggregation while PGI_2 produced by the vascular endothelium inhibits aggregation. In addition to its effects on platelets, PGI_2 may play an important role in preventing gastric ulceration by inhibiting secretion, in inflammation by inhibiting protease secretion of polymorphonuclear leukocytes, and in blood pressure regulation by control of vascular tone. These and other crucial physiological processes may be regulated by the opposing actions of TXA_2 and PGI_2. There has therefore been considerable interest in generating agents that modulate the action of TXA_2 or PGI_2; an agent that might adjust the action of TXA_2 and PGI_2 at the same time and in the one molecule.



1 R = Me
2 R = *n*-Pr



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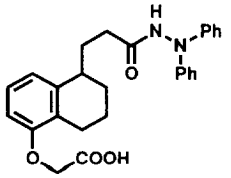

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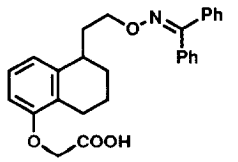

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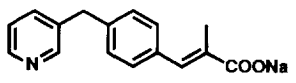
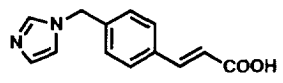


6 ONO-1581



7 OKY-046

We already reported the design of new PGI_2 agonists **1**-**5**.[3] Since the structures of our PGI_2 agonists are far from those of PGI_2 analogs, it would be easy to incorporate the another function which is essential to show the additional activity. Several compounds, such as **ONO-1581** (**6**)[4] and **OKY-046** (**7**)[5], have been reported to be effective TX synthase inhibitors. In the process of our design of PGI_2 agonists, we have postulated that the affinity of binding to the PGI_2 receptors is dependent on the geometrical relationship between carboxylic acid and terminal phenyl groups. With regard to TXA_2 synthase inhibitors, there is the most important engagement of the spatial position between the carboxylic acid and the pyridine (or imidazole) unit. Our strategy was based on the incorporation of a pyridine group into one of the terminal phenyl groups of the PGI_2 agonists in expectation of present a superior anti-thrombic effect by combination of PGI_2 agonists and TXA_2 synthase inhibitors.

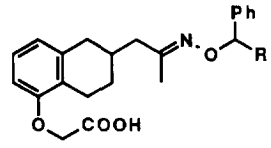
Biological Results and Discussion

Tables 1 and 2 show the PGI_2 agonistic activity and TXA_2 synthase inhibitory activity of chosen structures. Evaluation of PGI_2 agonistic activity was undertaken by measuring inhibition of 4 μM ADP-induced human platelet aggregation. TXA_2 synthase activities in human platelet microsome were measured by TXB_2 assay unit obtained from Cayman using PGH_2 as a substrate, IC_{50} values were determined.

The results in Table 1 show that introduction of one pyridine group instead of a phenyl group in **1** to afford **8**-**10** results in success in combination of PGI_2 agonistic activity and TXA_2 synthase inhibitory activity. For example, 3-substituted pyridine derivative **9** possesses weak PGI_2 activity but potent TXA_2 synthase inhibitory activity, relative to the 2 or 3-substituted pyridine derivatives **8** and **10**. It is apparent that the structure-activity relationship for the two biological effects do not parallel each other and a compromise on the two activities is necessary; 3-substituted pyridine compound **9** was chosen for further evaluation.[6]

The evaluation of a series of structurally varied agents possessing the 3-substituted pyridine moiety revealed the structure-activity correlation between PGI_2 agonistic activity and TXA_2 synthase activity as shown in Table 2. The comparable activity between diphenyl derivatives and 3-pyridyl phenyl derivatives suggests that the pyridine function contributes a little to the productive PGI_2 activity. While it is essential for TXA_2 activity, compounds **9** and **14** showing the most potent TXA_2 synthase inhibitory activity. In this way, we succeeded in the design of structurally novel agent which display a combined PGI_2 agonism and TXA_2 synthase inhibition.

Table 1 The Effect of Pyridine Derivatives on PGI_2 Agonistic and TXA_2 Synthase Inhibitory Activity

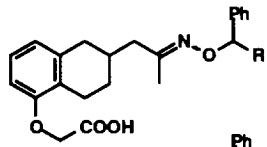
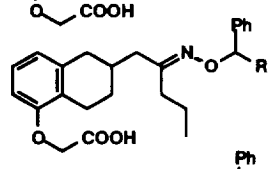
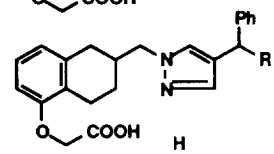
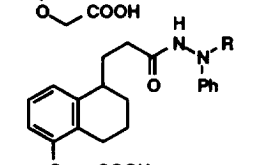
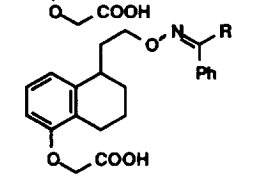


No.	R	PGI_2 Agonistic Activity IC_{50} (μM)	TXA_2 Inhibitory Activity IC_{50} (nM)
1		0.23	inactive
8		0.57	>1000
9		1.4	20
10		0.48	210
Iloprost		0.0014	inactive
6 ONO1581		inactive	3
7 OKY046		inactive	10

References and Notes

1. (a) Bunting, S.; Gryglewski, R.; Moncada, S.; Vane, J. R. *Prostaglandins*, **1976**, *12*, 897. (b) Dusting, G. J.; Moncada, S.; Vane, J. R. *ibid*, **1977**, *13*, 3.
2. Hamgerg, M.; Svensson, J.; Samuelsson, B. *Proc. Nat. Acad. Sci. USA*, **1975**, *72*, 2994.
3. Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.*, preceding paper in this issue.
4. Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Miyamoto, T.; Taniguchi, K.; Hayashi, M.; Iizuka, K.; Nakazawa, M. *J. Med. Chem.*, **1981**, *24*, 1149.

Table 2 The Effect of Pyridine Derivatives on PGI_2 Agonistic and TXA_2 Synthase Inhibitory Activity

No.		R	PGI_2 Agonistic Activity IC_{50} (μM)	TXA_2 Inhibitory Activity IC_{50} (nM)
1		Ph	0.23	inactive
9		3-pyridine	1.4	20
2		Ph	0.15	inactive
11		3-pyridine	0.32	85
3		Ph	0.13	inactive
12		3-pyridine	0.15	320
4		Ph	0.057	inactive
13		3-pyridine	0.44	940
5		Ph	0.25	inactive
14		3-pyridine	0.24	40

5. Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. *ibid.*, **1981**, *24*, 1139.

6. Details will be reported in a separate paper.

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