NOVEL FLUOROPROSTACYCLIN ANALOGS WITH MODIFIED CYCLOALKYLENYL CHAINS. HIGHLY POTENT AND ORALLY ACTIVE ANTI-ANGINAL AGENTS

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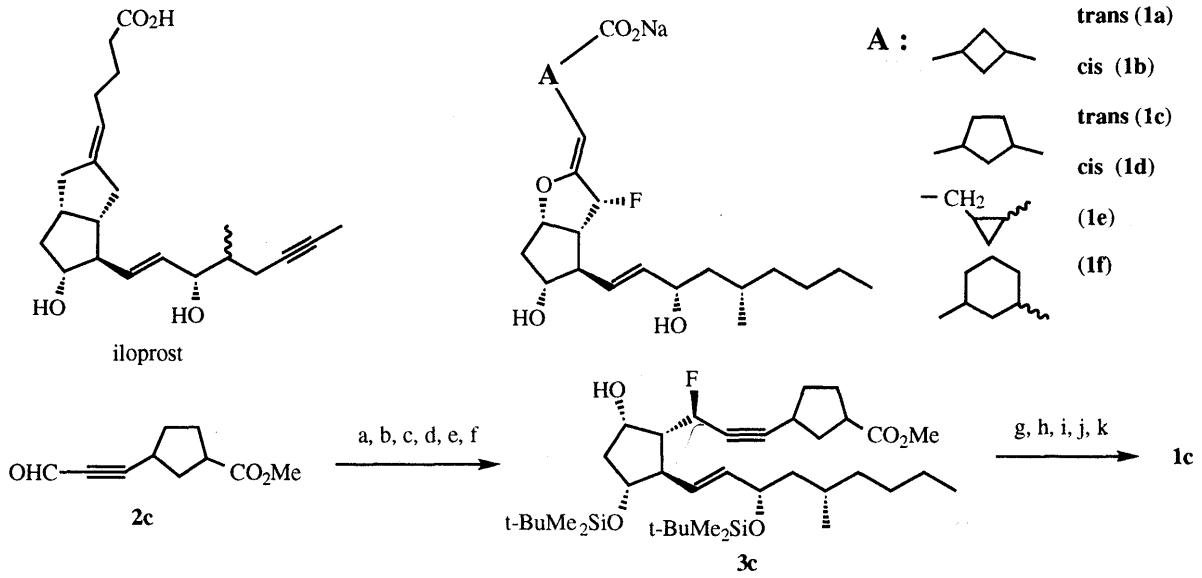
Novel fluoroprostacyclin analogs (**1a-f**) have been synthesized and pharmacologically evaluated. Compounds **1a-c** given intravenously or orally showed potent and long-lasting anti-anginal activities in an animal model.

KEY WORDS fluoroprostacyclin; anti-anginal activity; platelet aggregation inhibition; hypotensive effect; β-oxidation; iloprost

Prostacyclin is one of the unstable metabolites of arachidonic acid which exerts a variety of actions such as inhibition of platelet aggregation and induction of vasodilation to maintain homeostasis in circulation, and its stable analogs have been regarded as potential drugs for thrombotic diseases, myocardial infarction, and arteriosclerosis.[1)]



(a) (3*S*,5*S*)-3-*t*-butyldimethylsiloxy-5-methyl-(*E*)-nonenyl lithium,[7)] $C_3H_7C{\equiv}CCu$, $(Me_2N)_3P$, ether; (3*R*)-3-*t*-butyldimethylsiloxycyclopentenone,[7)] -78 to -40°C, 63% (b) Me_3SiCl, Py, 0°C (c) $NaBH_4$, MeOH, -20°C (d) Et_3SiCl, Py, CH_2Cl_2, 0°C, 81% (3 steps) (e) piperidinosulfur trifluoride, $ClCF_2CFCl_2$, r.t., 75% (f) pyridinium *p*-toluenesulfonate, EtOH, r.t., 64% (g) 1atm H_2, Pd-$CaCO_3$-Pb, 0°C (h) NIS, CH_3CN, 40°C (i) DBU, toluene, 110°C (j) Bu_4NF, THF, r.t. (k) NaOH, EtOH, r.t., 10% (5 steps).

Chart 1

We have studied the synthesis of 7-fluoroprostacyclin derivatives[2)] to stabilize chemically labile vinyl ether by introducing electron-withdrawing fluorine atom. Subsequently, our modifications have been focused on the upper side chain in order to prevent it from being metabolized by β-oxidation.[3)] The modifications of the chain of prostacyclin

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analogs have been limited to a few reports,[4] probably due to the subtlety of their activities and the difficulty of the synthesis. We have concentrated on the synthesis of the derivatives bearing cycloalkylene groups, and recently discovered cyclobutylene analogs **1a** and **1b** as potent anti-anginal agents.[5] We herein report the synthesis, pharmacological evaluation, and structure-activity relationship of a series of novel cycloalkylene fluoroprostacyclin analogs **1a-f** which have been demonstrated to exhibit potent and orally active anti-anginal activities for a long duration.

Synthesis of 7-fluoroprostacyclins **1c-f**[6] has been achieved according to the reported procedure,[5] which is representively shown by **1c** in Chart 1. After three-component coupling reaction[7] starting from the corresponding racemic *trans* aldehyde **2c**,[8] protection and subsequent stereospecific fluorination[4a] afforded 7-fluoroprostaglandin **3c** in 25% yield (6 steps). Selective hydrogenation of **3c** with Lindlar catalyst, followed by cyclization and deprotection, furnished **1c**[9] in 10 % overall yield (5 steps) after separation of the undesired diastereomer.[10]

Table I. Inhibitory Effects of **1a-f** and Iloprost on ADP-Induced Guinea Pig Platelet Aggregation *in Vitro* (ADP=1 μM)

Substance	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	Iloprost
Inhibition of platelet aggregation (PGE_1=1)[a]	3.4	13.3	7.0	0.85	0.34	0.6	10.8

a) Relative potency to PGE_1.

Table II. Preventive Effects on ST-Depression and Changes in Blood Pressure of **1a-c** and Iloprost in Rats

Substance	Preventive effect on vassopressin-induced ST-depression[a]		Changes in mean blood pressure[b]	
	i.v. (MED, μg/kg)	*p.o.* (MED, mg/kg)	*i.v.* (μg/kg, ΔmmHg)	*p.o.* (mg/kg, ΔmmHg)
1a	0.1	0.01	0.1, -19 0.01, -5	0.1, -19 0.01, 0
1b	0.1	0.1	0.1, -19 0.01, -5	1.0, -27 0.1, -9
1c	1.0	0.1	1.0, -10 0.1, 0	1.0, -29 0.1, 0
Iloprost	1.0	1.0	1.0, -34 0.1, 0	1.0, -3

a) Substances were intravenously or orally administered before vassopressin injection.
b) Changes in mean blood pressure in anesthetized rats (*i.v.*) and conscious rats (*p.o.*).

The results of pharmacological evaluation of **1a-f** are summarized in Table I and Table II. Cyclobutylene compounds **1a,b** and *trans* cyclopentylene derivative **1c** had a potent inhibitory effect on ADP-induced platelet aggregation *in vitro*, which was comparable to iloprost[1a] (Table I). In contrast, *cis* cyclopentylene analog **1d** exerted considerably weaker action. The derivatives having a smaller or larger cyclic side chain, **1e** and **1f**, also had weak potency, which implies that the distance and angle between the carboxyl group and the vinyl ether should be important for the affinity to platelet prostacyclin receptor.[11] Conformational rigidity of the side chains in **1a-f** should significantly influence the sensitive nature of the receptor.

Anti-anginal potency of **1a-c** given intravenously (*i.v.*) and orally (*p.o.*) were evaluated by their preventive effect on vassopressin-induced ST-depression of rat electrocardiogram.[12] As demonstrated in Table II, minimum

effective doses (MED) in intravenous and oral administration of **1a** were 0.1 μg/kg and 0.01 mg/kg, respectively, which means that **1a** has 10 - 100-fold more potency in comparison with iloprost. It should be noted that the effect of **1a** lasted 3 h after the oral administration (0.01 mg/kg), whereas iloprost (1.0 mg/kg) was only effective within 0.5 h. The long-lasting action should be attributed to the chemical and metabolic stability of **1a**. The isomer **1b** and the cyclopentylene analog **1c** were both 10-fold more potent than iloprost but 10-fold less potent than compound **1a** in preventing ST-depression. Compounds **1a-c** had little or no hypotensive effect at the doses exerting anti-anginal effect. Thus, compounds **1a-c** have remarkable potency in comparison with iloprost as selective anti-anginal agents.

REFERENCES AND NOTES

1) a) W. Skuballa, H. Vorbrüggen, *Angew. Chem. Int. Ed. Engl.*, **20**, 1046 (1981); b) M. Shibasaki, Y. Torisawa, S. Ikegami, *Tetrahedron Lett.*, **24**, 3493 (1983); c) K. Ohno, H. Nishiyama, H. Nagase, K. Matsumoto, M. Ishikawa, *Tetrahedron Lett.*, **31**, 4489 (1990); d) P. W. Collins, S. W. Djuric, *Chem. Rev.*, **93**, 1533 (1993); e) J. Vane, J. O'Grady (eds.), "Therapeutic Applications of Prostaglandins", Edward Arnold, London 1993.

2) a) A. Yasuda,"Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications" ed. by R. Filler, Y. Kobayashi, L. M. Yagupolskii Y. Elsevier Amsterdam, 1993, pp. 275-308; b) K. Bannai, T. Toru, T. Oba, T. Tanaka, N. Okamura, K. Watanabe, A. Hazato, S. Kurozumi, *Tetrahedron*, **39**, 3807 (1983).

3) M. Hamberg, *Eur. J. Biochem.*, **6**, 135 (1968).

4) a) L. Flohe, H. Böhlke, E. Frankus, S. M. A. Kim, W. Lintz, G. Loschen, G. Michel, B. Müller, J. Schneider, U. Seipp, W. Vollenberg, K. Wilsmann, *Arzneim. Forsh.*, **33(II)**, 1240 (1983); b) K. Kojima, K. Koyama, S. Amemiya, S. Saito, *Chem. Pharm. Bull.*, **34**, 948 (1987); c) K. Iseki, T. Kanayama, Y. Hayasi, M. Shibasaki, *Chem. Pharm. Bull.*, **38**, 1769 (1990).

5) Preliminary communication for the synthesis of **1a** and **1b**. T. Asai, Y. Morizawa, T. Shimada, T. Nakayama, M. Urushihara, Y. Matsumura, A. Yasuda, *Tetrahedron Lett.*, in press.

6) All new compounds were fully characterized by physicochemical properties.

7) M. Suzuki, T. Kawagishi, T. Suzuki, R. Noyori, *Tetrahedron Lett.*, **23**, 4057 (1982); R. Noyori, M. Suzuki, *Angew. Chem. Int. Ed. Engl.*, **23**, 847 (1984); R. Noyori, "Asymmetric Catalysis in Organic Synthesis", John Wiley & Sons, New York, 1994.

8) The aldehyde **2c** was prepared from methyl 3-cyclopentenecarboxylate as follows: 1) thexyl borane, $THPOCH_2C{\equiv}CLi$, then MeOH, I_2, NaOH-H_2O_2, (56%) 2) p-TsOH-MeOH, (78%) 3) Swern oxidation, (68%). **2c**: ^1H NMR ($CDCl_3$) δ 1.80-2.35 (m, 6H), 2.95-3.10 (m, 2H), 3.69 (s, 3H), 9.19 (s, 1H). The cis aldehyde **2d** was obtained by epimerization of **2c** in the presence of $LiNPr^i_2$ in THF. **2d**: ^1H NMR ($CDCl_3$) δ 1.80-2.42 (m, 6H), 2.75-2.95 (m, 2H), 3.70 (s, 3H), 9.19 (s, 1H).

9) A white powder, mp: 218.0-219.0 °C (dec). IR (KBr): 3385, 2960, 2930, 2850, 1555, 1420, 1290, 1235, 1045, 1028, 965 cm^{-1}. ^1H-NMR (CD_3OD) δ 0.90-1.05 (m, 6H), 3.88-4.02 (m, 1H), 4.14-4.24 (m, 1H), 4.58-4.72 (m, 2H), 5.45 (dd, J = 64, 8.4 Hz, 1H), 5.56-5.80 (m, 2H). ^{19}F NMR (CD_3OD) δ -185.4 (d, J = 64 Hz). HPLC (reverse phase); t_R = 10.5 min (YMC AM-312 ODS 5 μm 150 x 6.0 mm, CH_3CN- 1% Et_3N (addjusted to pH 6.3) 40 / 60 v/v, 1.0 ml/min, UV 210nm).

10) The undesired less polar diasteromer (HPLC; t_R = 13.4 min, under the same conditions as above) has no effect for inhibition of platelet activation.

11) a) A. Tsai, K. K. Wu, *Eicosanoids*, **2**, 131 (1989); b) A. Tsai, E. Strobel-Jager, K. K. Wu, *J. Comput.-Aided Mol. Design*, **5**, 135 (1991).

12) T. Yamamoto, K. Nakatsuji, K. Hosoki, T. Karasawa, *Clin. Exp. Pharmacol. Physiol.*, **20**, 673 (1993).

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