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Syntheses of Cyclopentane, Cyclohexene and Olefin Oxazoles as Thromboxane A_2/Endoperoxide Receptor Antagonists

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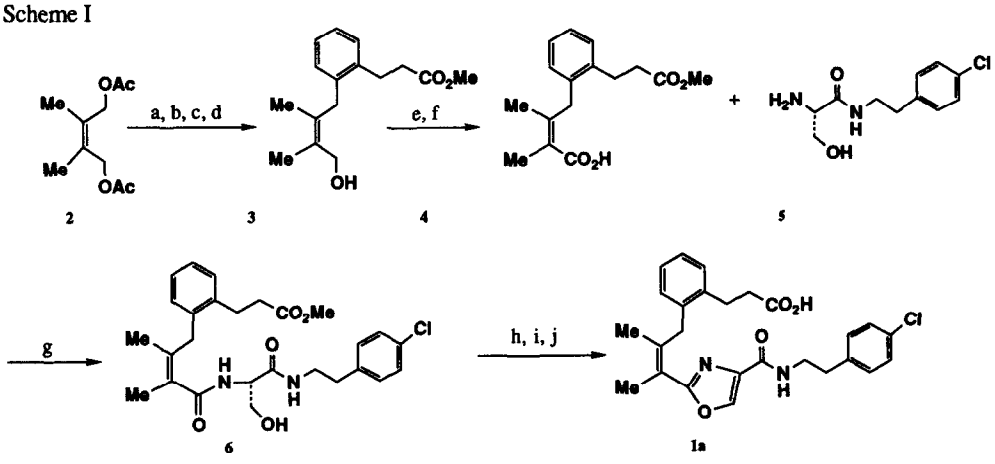
Abstract: Synthesis and antiplatelet activity of a series of structurally simple thromboxane A_2 receptor antagonists are described. The *cis*-cyclopentane analog (-)-**1c** was the most potent compound in this series with I_{50} and K_d values of 15 nM and 4.3±0.0 nM, respectively. In radioligand binding assay, *trans*-cyclopentane analog (-)-**1d** was the most potent ligand with a K_d value of 0.5±0.3 nM.

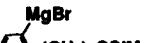
In the accompanying papers[1,2] we described the syntheses and pharmacology of pyrrolidine and 1,3-dioxane, 1,3-dioxolane oxazole derivatives as TxA_2/PGH_2 receptor antagonists at the platelet receptor. Our continued efforts to identify structurally simple analogs led to the syntheses of cyclopentane, cyclohexene and more importantly simple olefin derivatives **1a-d** whose syntheses and pharmacological activities *in vitro* are the subject of this communication.

Synthesis

Olefin analog **1a** was prepared from readily available diacetate **2** and the synthetic route is outlined in Scheme I. Diacetate **2** was coupled with 2-(3-thexyldimethylsilyloxypropyl)phenyl magnesium bromide in THF in presence of catalytic dilithium copper tetrachloride[3] to form a monoacetate which was further elaborated to alcohol-ester **3** following the methodology described earlier for the synthesis of BMS 180,291.[4] Oxidation of alcohol **3** with activated manganese oxide in hexane afforded an aldehyde which was further oxidized with sodium chlorite[5] in butanol-water to form acid **4** which was coupled with (S)-serine amide **5**[6] to form bis-amide **6**. Cyclization of **6** in acetonitrile with triphenyl phosphine and carbon tetrachloride in presence of Hunig's base,

Scheme I



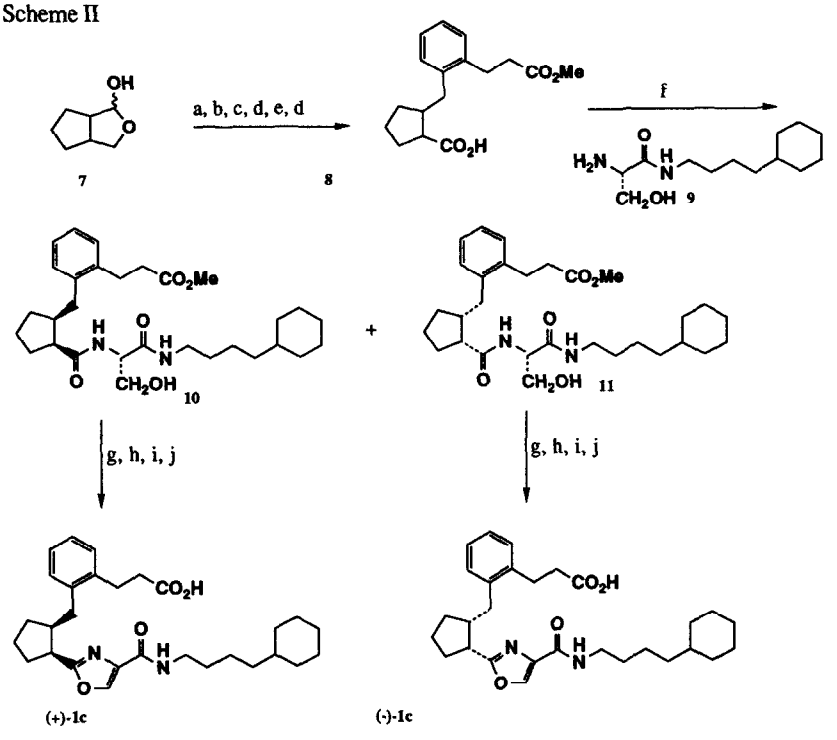
(a) 

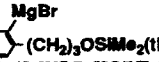
, Li_2CuCl_4, THF; (b) Jone's reagent; (c) MeOH, AcCl; (d) MeOH, K_2CO_3 (e) Hexane, MnO_2; (f) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, BuOH-H_2O; (g) WSC, HOBT, NMM, DMF; (h) Ph_3P, i-Pr_2NEt, CCl_4, AcCN; (i) CH_2Cl_2, NiO_2; (j) LiOH, MeOH-H_2O.

followed by oxidation of the oxazoline with nickel peroxide and subsequent hydrolysis of methyl ester furnished oxazole-acid **1a**. This route was also used for preparation of cyclohexene derivative **1b**.

Cis-cyclopentane analogs **1c,d** were prepared from hemi-acetal **7**[7] and the synthetic route is outlined in Scheme II. Elaboration of **7** to carboxylic acid **8** followed the methodology described previously for the synthesis of BMS 180,291.[4] Coupling of racemic **8** with (S)-serine amide **9**[8] provided a diastereomeric mixture of bis-amides **10** and **11** which could be readily separated by silica gel chromatography. Bis-amides **10** and **11** were transformed to (+)-**1c** and (-)-**1c**, respectively following the methodology used in the preparation of BMS 180,291.[4] Although (+)-**1c** and (-)-**1c** were obtained in enantiomerically pure form, their absolute configurations are at present undetermined. The related *trans*- cyclopentane derivatives (+)-**1d** and (-)-**1d** were synthesized in a similar fashion starting from the corresponding *trans*-acid of **8**.

Scheme II

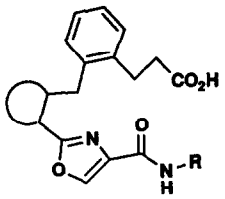


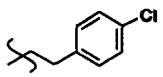
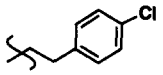
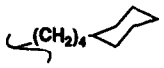
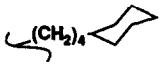
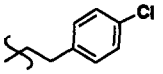
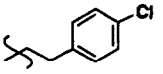
(a) Mg, THF,  ; (b) $Pd(OH)_2$, AcOH, H_2; (c) Py, Ac_2O; (d) Jone's reagent; (e) MeOH, AcCl; (f) WSC, HOBT, NMM, DMF; (g) CH_2Cl_2, MsCl, Et_3N; (h) Acetone, K_2CO_3; (i) EtOAc-$CHCl_3$, DBU, $CuBr_2$; (j) LiOH, MeOH-H_2O

Pharmacology

All compounds were tested for their ability to inhibit arachidonic acid (AA, 800 μM) and ADP-induced (20 μM) platelet aggregation of human platelet rich plasma[9] and the results are reported as I_{50} values in Table I. Consistent with their selective TxA_2 receptor antagonist activity, none of these compounds were effective in inhibiting ADP-induced platelet aggregation.

Table 1



Compound	Ring	R	AAIPA I50 (μM)	K_d (nM)	Slope
1a			0.235	37.3±5.9	1.52±0.06
1b			0.194	63.5±4.5	1.23±0.23
(-)-1c			0.015	4.3±0.0	1.4±0.06
(+)-1c			0.107	23.8±0.9	1.7±0.21
(-)-1d			0.338	0.5±0.3	0.77±0.03
(+)-1d			5.163	3.3±0.5	0.71±0.03

The olefin and cyclohexene analogs (**1a** and **1b**) were roughly equipotent as inhibitors of AA-induced platelet aggregation with I_{50} values of 235 nM and 194 nM, respectively. Although less potent than the corresponding 7-oxabicyclo[2.2.1]heptane analog (SQ 34,943; I_{50} = 7 nM), **1a** and **1b** are significantly more potent than a well characterized antagonist BM 13.505 (I_{50} = 730 nM).[10] Both antagonists, (+)-**1c** and (-)-**1c**, derived from 1,2-*cis*-cyclopentane were effective platelet aggregation inhibitors, the (-)-enantiomer being 7-fold more potent. A similar trend was observed with the 1,2-*trans*-cyclopentane analogs (+)-**1d** and (-)-**1d**. However, the more active *trans*-enantiomer (-)-**1d** was about twenty fold less potent than the corresponding *cis*-analog (-)-**1c**.

These antagonists displaced [^{3}H]-SQ 29,548 from its specific binding site in human platelet membranes[11] with K_d values ranging from 0.5 nM - 64 nM. With the exception of the enantiomeric pair (+)-**1d** and (-)-**1d**,

oxazole derivatives **1a-c** displayed receptor binding affinities consistent with their platelet inhibitory activity *in vitro*. Despite its modest antiplatelet activity (I_{50} = 338 nM), (-)-**1d** (K_d = 0.5±0.3 nM) displayed a high affinity for the platelet receptor which was comparable to the corresponding 7-oxabicylo[2.2.1]heptane analog SQ 34,943 (K_d = 1.3±0.07 nM). The large difference between I_{50} and K_d values for (+)-**1d** and (-)-**1d** may be attributed in part to their overall molecular lipophilicities (estimated logP = 4.28) that aid in selective partition of these compounds inside the phospholipid membrane where the putative TxA_2 receptor is postulated to be localized.[12]

In conclusion, replacement of the 7-oxabicyclo[2.2.1]heptane nucleus with structurally simple ring systems have led to identification of several potent TxA_2 receptor antagonists *in vitro*.

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Notes and References

1. Hall, S. E.; Han, W-C; Harris, D. N.; Goldenberg, H.; Michel, I. M.; Monshizadegan; Webb, M. L. *BioMed. Chem. Lett.*, preceding paper in this issue.
2. Das, J.; Reid, J. A.; Harris, D. N.; Goldenberg, H.; Michel, I. M.; Monshizadegan; Webb, M. L. *BioMed. Chem. Lett.*, preceding paper in this issue.
3. Fouquet, G; Schlosser, M. *Angew. Chem., Internat. Edit.* **1974**, *13*, 82-83.
4. Misra, R. N.; Brown, B. R.; Sher, P. M.; Patel, M. M.; Hall, S. E.; Han, W.-C.; Barrish, J. C.; Floyd, D. M.; Sprague, P. W.; Morrison, R. E.; Ridgewell, R. E.; White, R. E.; DiDonato, G. C.; Harris, D. N.; Hedberg, A.; Schumacher, W. A.; Webb, M. L.; Ogletree, M. L. *BioMed. Chem. Lett.* **1992**, *2* (1), 73-76.
5. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091-2096.
6. Serine amide **5** (white solid, mp. 193-7°C) was prepared as an hydrochloride salt in two steps from t-BOC-L-serine by coupling with p-chlorophenethyl amine [Ethyl-3-(3-dimethylamino)propyl carbodiimide (WSC), 1-hydroxybenzotriazole (HOBT), Et_3N or 4-Methylmorpholine (NMM), DMF, 0 to 25°C, 79%], followed by t-BOC-deprotection (CH_2Cl_2, TFA; Et_2O, HCl, 90%).
7. Hemiacetal **7** was prepared in three steps from *trans*-1,2-cyclopentane dicarboxylic acid: (i) Δ, 81%, (ii) $NaBH_4$, THF, 0°C, 62% and (iii) DIBALH, Toluene, -78°C, 69%.
8. Misra, R.N.; Brown, B. R.; Sher. P. M.; Patel, M. M.; Goldenberg, H. J.; Michel, I. M.; Harris, D. N. *BioMed. Chem. Lett.* **1991**, *1* (9), 461-464.
9. (a) Assay as described by Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Heikes, J. E.; Sprague, P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, *22* (2), 295-307; the I_{50} for BM13.505 and GR 32,191 were 730 nM and 33 nM, respectively, under identical assay conditions.
(b) Ogletree, M. L.; Harris, D. N.; Schumacher, W. A.; Hall. S. E.; Brown, B. R.; Misra, R. N. *Circulation*, **1991**, *84*, II-79.
10. Lefer, A. M. *Drugs Future* **1988**, *13*, 999-1005.
11. Assay as described by Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Harris, D. N.; Liu, E. C.-K. *J. Pharmacol. Exp. Ther.* **1988**, *245* (3), 786-792.
12. Saussy, D. L. Jr.; Mais, D. E.; Baron, D. A.; Pepkowitz, S. H.; Halushka, P. V. *Biochem. Pharmacol.* **1988**, *37* (4), 647-654.