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OXA-PROSTANOID ANALOGS. IDENTIFICATION OF AN ORALLY EFFECTIVE, DUAL THROMBOXANE RECEPTOR ANTAGONIST /THROMBOXANE SYNTHASE INHIBITOR

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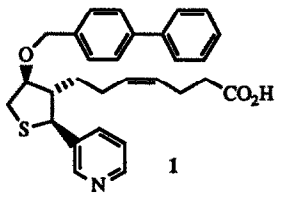
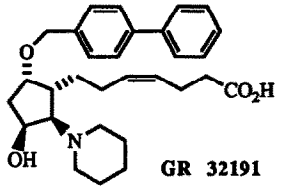
Abstract: The synthesis and pharmacological evaluation of oxa-prostanoid analogs with dual thromboxane receptor antagonist (TxRA)/thromboxane synthase inhibitor (TxSI) activities are described. One analog **6** with the desirable long lasting oral TxRA/TxSI activity has been identified.

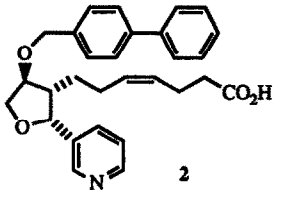
In the preceding paper, we described the synthesis of the thia-prostanoid analog **1** that exhibited potent TxRA/TxSI activities *in vitro*. This compound, however, was found to have short duration of action *in vivo*.[1] In view of the undesirable pharmacokinetic profile of this compound, we turned our attention to the study of the corresponding oxa-prostanoid analogs. In this report, we would like to describe the synthesis and biological evaluation of the oxa-prostanoid analogs **2** to **7** which in contrast to their sulfur isosters were expected to exhibit a desirable biological profile.



1



GR 32191



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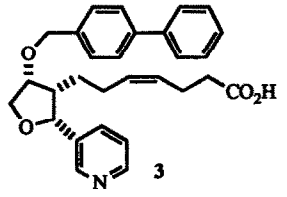

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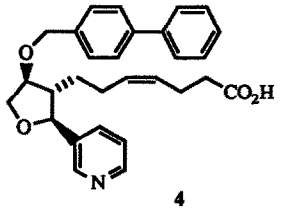

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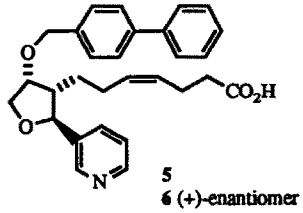
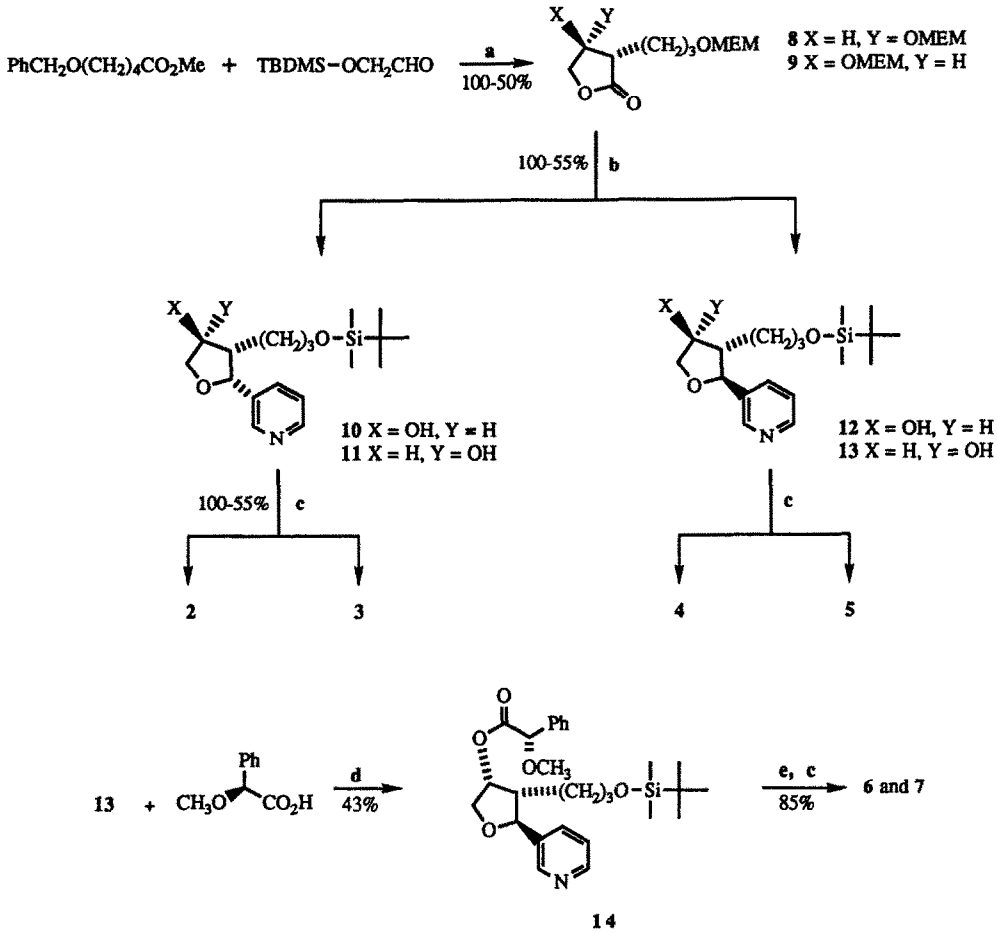


5
6 (+)-enantiomer
7 (-)-enantiomer

Compounds such as **5** to **7** with stereochemistry similar to the model thromboxane receptor antagonist, GR 32191,[2] were expected to preserve the receptor antagonist profile of the parent molecule. In addition, compounds **2** to **7** incorporated the 3-pyridyl moiety at the appropriate distance from the side chain carboxylic acid which is the structural requirement for thromboxane synthase inhibitor activity.[3]

Scheme I



Reagents and Conditions: **a**) (1) LDA, THF, (2) Conc. HCl, (3) 10% Pd/C, [H], 48 psi, (4) MEM-Cl, Et_3N; **b**) (1) 3-lithiopyridine, ether, (2) $NaBH_4$, EtOH, (3) Diethyl azodicarboxylate, Ph_3P, (4) MeOH, HCl, (5) TBDMS-Cl, Imidazole, DMF, **c**) (1) KH, ICH_2-(4-biphenyl), (2) MeOH, HCl, (3) Swern oxidation, (4) $Ph_3C{=}CH(CH_2)_2CO_2CH_3$, THF, (5) NaOH, MeOH; **d**) DCC, DMAP and separation of diastereomers; **e**) NaOH, MeOH

The synthesis of compounds **2** to **7** is illustrated in Scheme I. Aldol condensation of methyl 5-benzyloxyvalerate[4] and *t*-butyldimethylsilyloxy acetaldehyde[5] gave, after lactonization of the product followed by hydrogenolysis of the benzyl group and reprotection of the hydroxyl groups with MEM chloride, the isomeric

Table I. TxSI/TxRA Activities *In Vitro*[a]

Compound	TxSI[b] (IC_{50} nM)	TxRA	
		WP[c] (IC_{50} nM)	PA_2[d]
2	65	820	N.T.
3	32	795	N.T.
4	22	88	7.13
5	17	28	7.66
6	4.3	26.5	7.98
7	120	510	7.15
R 68070	3	1,280	6.35
CGS 22652	2	18	8.9

a) For description of methods see reference 8.
b) Thromboxane synthase Inhibition. Values represent an average of two determinations.
c) Inhibition of U-46619 induced aggregation of washed human platelets. Values represent a single determination.
d) Inhibition of U-46619 induced contraction of dog saphenous vein (slope ±95% confidence limit).

Table II. *Ex Vivo* Inhibition of U 4669-Induced Guinea Pig Platelet Aggregation 1 hr Post Oral Administration.[a]

Compound	Dose mg/kg	N	Aggregation Ratio[b]
6	2.0	5	>100
	0.3	5	65.6 ± 19
R 68070	10	3	4.4
CGS 22652	10	5	24.5

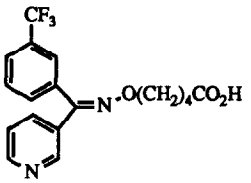
a) For description of methods see Reference 10.
b) Aggregation ration = EC_{50} for drug/EC_{50} for control

lactones **8** and **9** which were easily separated by chromatography on silica gel. Each isomer **8** and **9** was reacted with 3-pyridyllithium[6] in ether to give the corresponding hydroxy ketones which were reduced without isolation with $NaBH_4$. The corresponding diols were then cyclized to the tetrahydrofuranes using the Mitsunobu reagent.[7] The MEM protecting groups were removed and the primary hydroxy groups were selectively protected with *t*-butyldimethylsilyl chloride to give two pairs of 4-hydroxy-2-(3-pyridyl)tetrahydrofuranes **10, 11** and **12, 13,** which were separated by chromatography on silica gels. The pure isomers **10** to **13** were converted to the end products **2** to **5** in five well known reaction steps.

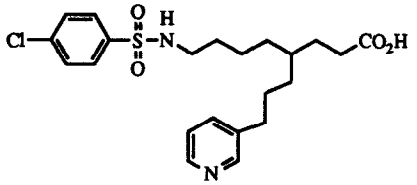
The two enantiomers of the intermediate **10** were prepared via the diastereomeric isomers **14** (100% de) and each enantiomer **10** was converted to the corresponding enantiomeric compounds **6** and **7**. The absolute streochemistry of **6** was determined by X-ray crystallography and found to be identical to GR 32191.

The *in vitro* biological profile of compounds **2** to **7** is summarized in Table I. Two reference dual TxRA/TxSI compounds, R 68070[9] and CGS 22652[10,11] were tested for comparison. All racemic isomeric compounds **2** to **5** were found to be potent inhibitors of the human platelet thromboxane synthase in isolated enzyme preparations. In a functional thromboxane receptor assay using aspirinated human washed platelets only isomer **5** strongly inhibited the thromboxane mimetic U-46619 (IC_{50}=28 nM) while isomers **2** and **3** were essentially inactive. With respect to the activity of the enantiomers of isomer **5**, all thromboxane synthase inhibitor and thromboxane receptor antagonist activities resided with the (+)-enantiomer **6** (IC_{50}'s of 4.3 and 26.5 nM respectively) while the (-)-enantiomer **7** exhibited weak activity in both TxSI and TxRA assays. As in the case of the thia-prostanoid analogs[1], none of the compounds in this report exhibited partial agonist activity when assessed for TxR-antagonism in vascular tissue such as canine saphenous veins and rabbit aortas.

When administered orally at a dose of 0.3 mg/kg to conscious guinea pigs enantiomer **6** effectively inhibited *ex vivo* U-46619 induced platelet aggregation 1 h following administration (Table II). A calculated dose of 0.23 mg/kg of **6** increased the concentration of U-46619 needed to induce 50% maximal platelet aggregation by 50-fold. In cynomolgous monkey a single 30 mg/kg oral dose of compound **6** resulted in total inhibition of U-46619-induced *ex vivo* platelet aggregation for at least 8 h with a return to predose values at 24 h. Likewise, thromboxane synthase inhibition was measured by the effect of compound **6** on serum thromboxane B_2 (TxB_2, the principal metabolite of TxA_2) synthesis which was inhibited for 24 h with concomitant significant elevations of 6-keto-$PGF_{1\alpha}$ (the stable metabolite of PGI_2) and PGE_2 levels.[11]



R 68070



CGS 22652

In synopsis, the (+)-enantiomer **6** exhibited a desirable biological profile for an orally active thromboxane receptor antagonist/thromboxane synthase inhibitor agent.

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