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SYNTHESIS OF A NOVEL SERIES OF 3-OXO-2,4-DIOXOBICYCLO[3.2.1]OCTANES: ADDITIONAL EVIDENCE FOR TWO THROMBOXANE RECEPTOR SUBTYPES.

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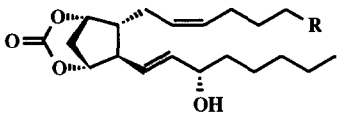
Abstract: A series of 3-oxo-2,4-dioxobicyclo[3.2.1]octanes (**1-4**) was synthesized and identified as potent thromboxane (TXA_2) receptor agonists. Replacement of the terminal -COOH group resulted in an unexpected change in biological activity: platelet aggregation, which typically occurs in response to TP-receptor stimulation, did not occur although potent contractile properties on vascular smooth muscle were retained.

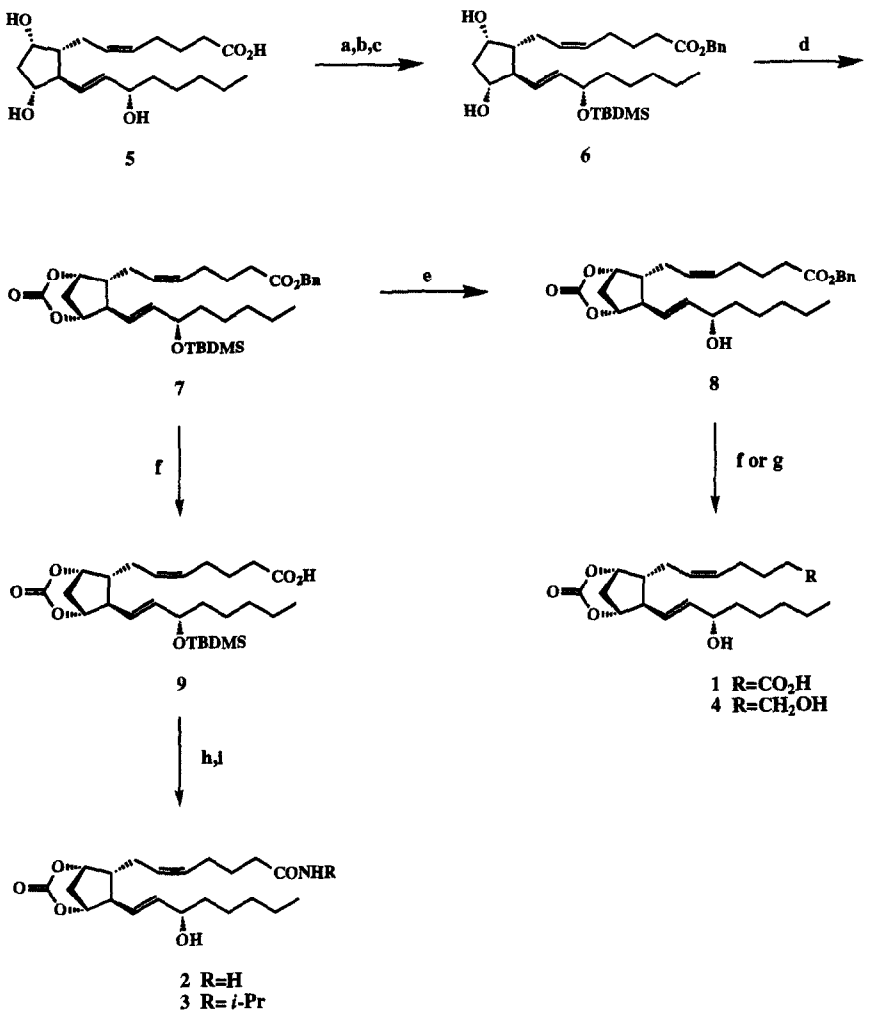
Currently, the concept of heterogeneous thromboxane A_2 (TP-) receptor populations in smooth muscle and platelets is not generally recognized. Although heterogeneity has been suggested in some instances, comprehensive review of the TP receptor pharmacology has favored the existence of a single receptor subtype.[1] Furthermore, studies involving purification of the human platelet receptor, receptor cloning from the human placenta,[2] and chromosomal mapping,[3] categorically find in favor of only one type of TP receptor, despite some previous claims[4] that suggested TP receptor heterogeneity. In this communication we wish to report the synthesis and biological evaluation of a new series of TXA_2 mimetics (**1-4**) which provide substantial evidence for the existence of two TP receptor subtypes.



1 R=CO_2H **3** R=CONH*i*-Pr
2 R=$CONH_2$ **4** R=CH_2OH

The synthesis of this novel series of TP-agonists, which incorporate a 3-oxo-2,4-dioxobicyclo[3.2.1] ring system, is illustrated in Scheme 1. Prostaglandin $F_{2\alpha}$ (**5**) was converted to its corresponding 15-*t*-butyldimethylsiloxy benzyl ester **6** by the following three step sequence: (1) esterification with O-benzyl-N,N′-diisopropylisourea[10] in toluene at 65 °C for 2 h; (2) reaction with 1-butaneboronic acid[11] in toluene at 110 °C for 24 h to form the 9,11-cyclic carbonate; and (3) silylation with *t*-butyldimethylsilyl triflate[12] and 2,6-lutidine in CH_2Cl_2 at 23 °C for 12 h with cleavage of the cyclic boronate occurring during aqueous work-up provided ester **6**[13] in 62% overall yield. Diol **6** was transformed to cyclic carbonate **7** in 94% yield upon treatment with

Scheme 1



Reagents and conditions: (a) *i*-PrN=C(OBn)NH*i*-Pr, toluene, 65 °C, 2 h; (b) $BuB(OH)_2$, toluene, 110 °C, 24 h; (c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 12 h; (d) triphosgene, pyridine, CH_2Cl_2, -70 °C (1 h) → 23 °C; (e) Bu_4NF, THF, 23 °C, 12 h; (f) 10% Pd/C, 1-methyl-1,4-cyclohexadiene, MeOH, 35 °C, 0.25 h; (g) $LiBH_4$, Et_2O, 23 °C, 6 h; (h) $SOCl_2$, 23 °C, 16 h; (l) RNH_2, CH_2Cl_2, 0 °C, 1 h.

triphosgene[14] and pyridine in CH_2Cl_2 at -70 °C for 1 hr followed by gradual warming to room temperature. Deprotection of **7** (Bu_4NF, THF, 23 °C, 90%) furnished alcohol **8** which upon subjection to chemoselective transfer hydrogenation (10% Pd-C, 1-methyl-1,4-cyclohexadiene, MeOH, 35 °C, 0.25 h) or reduction ($LiBH_4$, Et_2O, 23°C, 6 h) afforded the corresponding carboxylic acid **1** or alcohol **4**[15] in 99% and 35% yields, respectively. Hydrogenation of **7** as described above for benzyl ester **8** gave a 99% yield of carboxylic acid **9**. Amidation of **9** was conducted by the following procedure: reaction of **9** with neat thionyl chloride at 23 °C for 16 h, removal of excess $SOCl_2$ *in vacuo*, dilution with anhydrous CH_2Cl_2 and addition of the ammonia gas or isopropyl amine at 0 °C (1 h) afforded the deprotected amides **2** and **3** in 20-30% yields.[15]

Biological evaluation of this series of 3-oxo-2,4-dioxobicyclo[3.2.1]octanes (**1-4**) in two standard TP-receptor assays, aggregation of human platelets and contraction of isolated rat thoracic aorta, revealed some striking differences in activity (see Table 1). Compound **1** was a potent stimulant in both bioassays, with EC_{50} values 24 and 0.23 nM in the platelet and aorta preparations, respectively. Compound **4** potently contracted the rat aorta (EC_{50}=1 nM) but was completely devoid of either TP agonist or antagonist activity in human platelets. This pair of compounds represent the only ligands thus far reported to absolutely discriminate between platelet and vascular TP-receptors.

Table 1. Effect Of C1-Substituents of 3-Oxo-2,4-dioxobicyclo[3.2.1]octanes On TP Receptor Activity.

Compound	R	Rat Aorta EC_{50}(nM)	Human Platelet Aggregation EC_{50}(nM)
1	CO_2H	0.23	24
2	$CONH_2$	58	3110
3	CONH*i*Pr	324	NA*
4	CH_2OH	1.0	NA*

*Not active at concentrations tested up to 10 μM.

In summary, we have described the synthesis of a novel class of TP-receptor agonists whose activity profiles provide evidence for the existence of two TP-receptor subtypes. The pharmacological results apparently indicate that combination of the 3-oxo-2,4-dioxobicyclo[3.2.1]octane ring system with the proper C1-substituents may play a key role in identifying ligands that differentiate between TP receptor populations in human platelets and rat aorta smooth muscle.

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15. Reported yields are representative of non-optimized conditions.

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