

DUAL-ACTING THROMBOXANE RECEPTOR ANTAGONIST/SYNTHASE INHIBITORS: HETEROCYCLIC VARIATIONS

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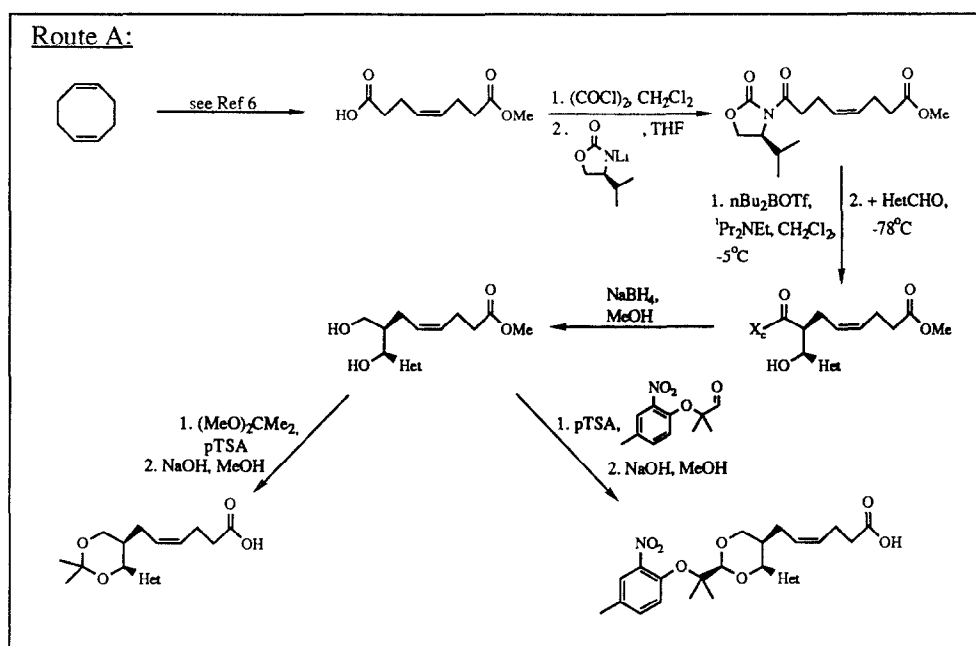
Abstract: The ability of 1,3-dioxanes bearing a variety of aromatic heterocycles at C4 to inhibit thromboxane synthase has been examined. Potent dual-acting thromboxane receptor antagonist/thromboxane synthase inhibitors have been discovered.

Activated human platelets convert arachidonic acid to thromboxane A₂ (TXA₂), a potent aggregating agent and vasoconstrictor. Inhibition of TXA₂ synthase alters the metabolic fate of arachidonate in a variety of cells and results in an increase in the amount of prostaglandin (PG) D₂ and PGI₂ formed from the common precursor PGH₂. Unfortunately the potentially beneficial effects (platelet inhibition, vasodilatation) resulting from increased levels of PGD₂ and PGI₂ can be negated by PGH₂-mediated activation of platelet and vascular TXA₂ receptors. Hence the combination of a thromboxane synthase inhibitor (TXSI) and a thromboxane receptor antagonist (TXRA) provides a superior anti-thrombotic effect than either drug alone³. Several groups have reported the discovery of agents which exhibit both activities in the same molecule⁴.

A structural feature of thromboxane synthase inhibitors common to otherwise disparate series is an aromatic heterocycle (usually 3-pyridine or 1-imidazole) which is believed to co-ordinate to the haem iron in the enzyme active site⁵. A previous communication from this department has described the development of dual-acting

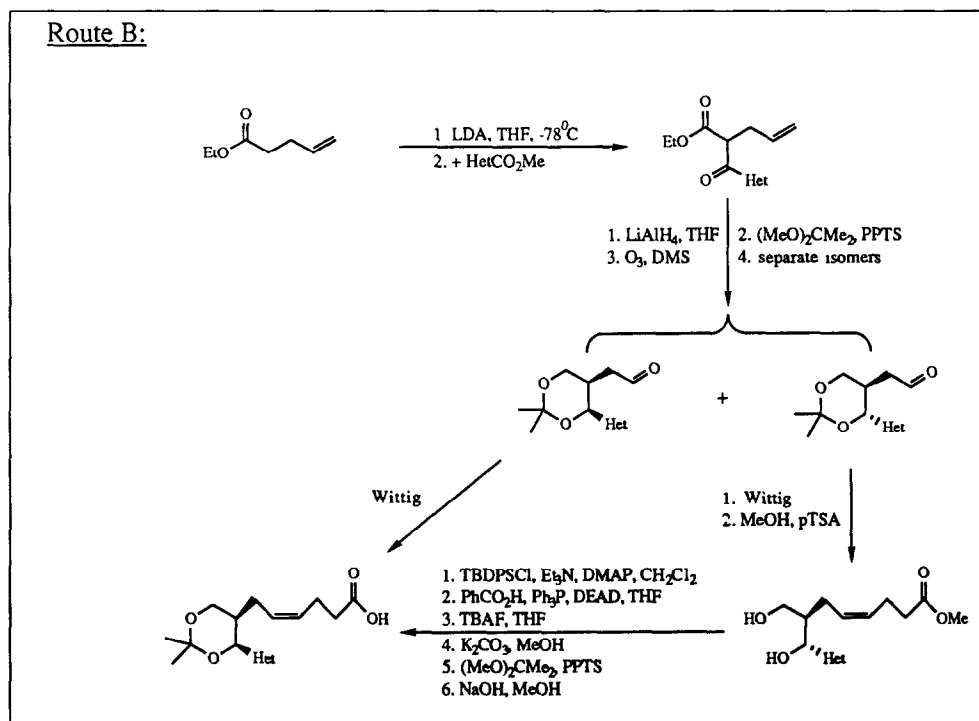
agents from the family of 1,3-dioxanes which are known to be potent TXRAs by incorporation of a 3-pyridyl residue at C4^{4a}. In such a framework, incorporation of a 1-imidazolyl group at C4 of the dioxane ring would lead to an unstable aminal derivative. We wished to establish whether 1,3-dioxanes containing other heterocyclic substituents at C4 could be effective as thromboxane synthase inhibitors. This report describes our preliminary results.

The synthesis of the analogues described herein was achieved by one of the two routes shown. The preferred option was route A in which the C4 substituent was introduced at a late stage in an enantioselective aldol condensation of an acyl oxazolidinone with a heterocyclic aldehyde⁷. The formation of the dioxane ring was achieved under thermodynamic control leading to a single diastereoisomer in each case.

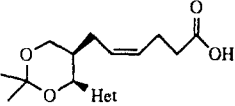











If, however, the heterocyclic ester was more readily available we adopted the racemic route B. Here reduction of the ketoester generated a mixture of diastereoisomers whose ratio varied with the heterocycle.

In the case of the pyrazine analogue the undesired isomer was formed almost exclusively and a Mitsunobu inversion⁸ sequence was used to provide the required diol.



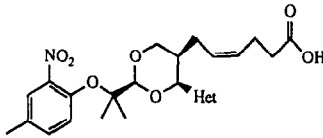
Initially the readily accessible 2,2-dimethyl-1,3-dioxanes were prepared in order to assess the thromboxane synthase (TXS) inhibitory properties of each C4 variant (Table 1)⁹. These derivatives did not show potent TXR antagonism. Compared to the pyridyl derivative (1), most of the heterocyclic variants were relatively inactive as TXS inhibitors, as has been noted in other series¹⁰. However, encouraging results were obtained with the 5-thiazolyl (5) and the two N1-substituted 5-imidazolyl (8,9) derivatives. In passing, it is interesting to note that a molecule which does not contain nitrogen (7) can still exhibit weak activity.





TABLE 1: 2,2-DIMETHYL-4-HETEROARYL-1,3-DIOXANES: TXA₂ SYNTHASE INHIBITION *IN VITRO*


Entry	Het	Form	IC ₅₀ (μM) ^a
1		(±)	0.12
2		(-)	7.4
3		(-)	>10
4		(±)	>10
5		(±)	0.08
6		(±)	>10
7		(-)	4.1
8		(-)	0.07
9		(-)	0.90

^a Inhibition of arachidonic acid-stimulated human platelet microsomal TXB₂ formation.

It has been shown that a variety of C2 substituents in 1,3-dioxanes can lead to potent TXR antagonists^{4a;11}. By analogy with the 3-pyridyl series, we hoped that modification of the substituent at C2 would lead to compounds exhibiting dual TXRA/TXSI activity. To that end, single enantiomers were prepared. The efficacy of the derivatives as dual-acting agents *in vitro* was then established (Table 2).

TABLE 2: DUAL ACTION DERIVATIVES: TXA₂ RECEPTOR ANTAGONISM AND SYNTHASE INHIBITION *IN VITRO*


Entry	Het	Form	TXA ₂ ANTAGONISM	TXA ₂ SYNTHASE INHIBITION
			pA ₂ ^{a, b}	IC ₅₀ (μM)
10		(-)	8.4	0.019
11		(-)	8.3	0.018
12		(-)	8.4	0.050
13		(-)	6.7	0.49

^a Apparent pA₂ values based on at least two determinations. Schild analysis gave slopes which differed significantly from unity.

^b Inhibition of U 46619-induced platelet aggregation in human platelet rich plasma.

The use of the 5-thiazolyl as an alternative to the 1-imidazolyl residue in TXSIs is preceded in other structural series¹⁰. Compound (11) is, however, notable for its high selectivity for TXS; the affinity for prostacyclin synthase (a closely-related haem-containing enzyme) is approximately four orders of magnitude less. It is gratifying to observe that the high antagonist potency is also maintained. The antagonism is not competitive; this is also true of the pyridine-containing analogue and other series of antagonists^{4a, b}. The N-methyl imidazole derivative (12) is noteworthy in that few examples of 5-substituted imidazoles have been reported as effective TXSIs¹².

The thiazole derivative (11) was further evaluated *ex vivo*. Oral administration to the conscious dog (1mg/kg) produced significant dual activity (concentration ratio >50 for blockade of U46619-induced platelet aggregation¹³; >60% inhibition of serum TXB₂ formation) for a duration of at least eight hours. In the rat (5mg/kg) the effects were less long-lived (ca. 5 hours).

In summary, the key points demonstrated above are that a variety of substituted heterocycles can be used to confer TXSI properties to the 1,3-dioxane TXRA series without loss in antagonist potency, and that the dual-acting thiazole derivative (**11**) has potential for use in the treatment of thromboembolic disease.

References and Notes:

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13. 'Concentration ratio' refers to the ratio of agonist EC₅₀ values before and after administration of the drug.