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THROMBOXANE MODULATING AGENTS. 1. DESIGN OF 1-[(ARYLSULFONYL)AMINO] ALKYLINDOLE DERIVATIVES AS DUAL THROMBOXANE SYNTHASE INHIBITOR/THROMBOXANE RECEPTOR ANTAGONISTS.

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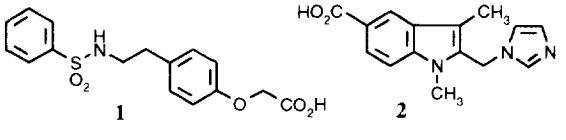
Abstract: The design of a series of dual thromboxane synthase inhibitor/thromboxane receptor antagonists based on an indole thromboxane synthase inhibitor template is described. The indole-5-propanoic acid derivatives **17**, **22** and **23** were found to be potent dual agents *in vitro*.

Introduction:

There has been considerable interest in recent years in the design of agents to prevent the vasoconstrictor and platelet aggregatory actions of thromboxane A_2 (TxA_2).[1-6] TxA_2 synthase inhibitors prevent formation of TxA_2 from the substrate PGH_2, and offer the additional potential advantage that accumulated substrate may be utilised by PGI_2 synthase to form the vasodilator and anti-aggregatory PGI_2.[7,8] Unfortunately, TxA_2 synthase inhibitors have shown disappointing clinical efficacy. This is believed to be due, at least in part, to the fact that PGH_2 itself is a potent agonist at the TxA_2 receptor.[9] Thromboxane receptor antagonists have also attracted interest[1-5] as they are able to block the action of both TxA_2 and PGH_2, but do not promote the diversion of PGH_2 to PGI_2. A compound with the ability both to inhibit TxA_2 synthase and to block the action of PGH_2 and TxA_2 at the TxA_2 receptor should therefore have a superior profile to either type of agent alone.[6,10,11] This communication describes our preliminary efforts to design such a dual agent.



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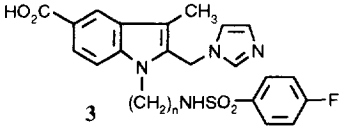

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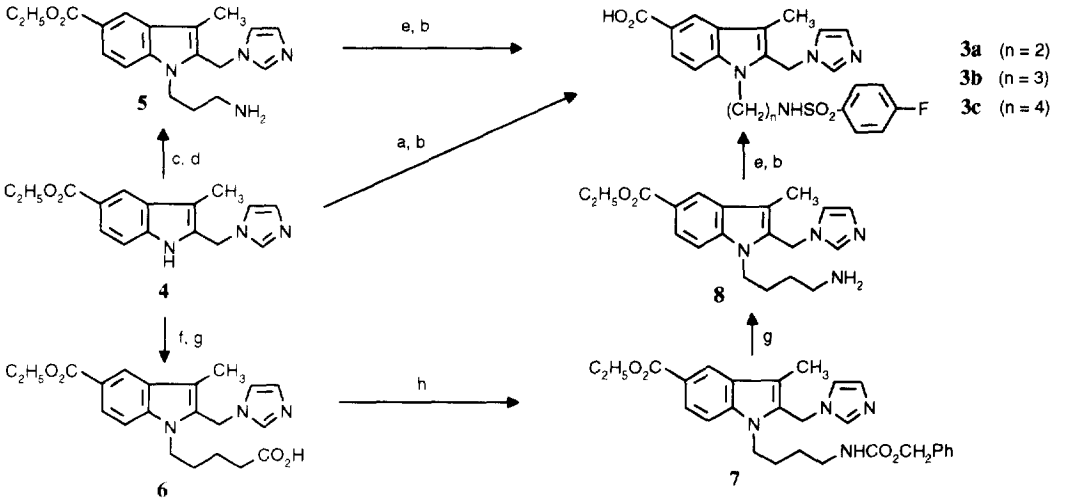
Several groups have reported the design of dual TxA_2 synthase inhibitor/TxA_2 receptor antagonists by combining the key structural features for each activity into one molecule.[6] We have previously described the design of

potent TxA_2 synthase inhibitors, [12,13] and our approach was to incorporate known structural features for TxA_2 receptor antagonism into a suitable synthase inhibitor template. One of the earliest non-prostanoid TxA_2 receptor antagonists was sulotroban (**1**), [14] and many subsequent antagonists contain the same structural features, i.e. an [(arylsulfonyl)amino]alkyl side chain linked *via* a ring system to a carboxylic acid substituent.[3-5] We therefore sought a suitable TxA_2 synthase inhibitor template into which to introduce an [(arylsulfonyl)amino]alkyl substituent at an appropriate distance from the acid group. The indole derivative **2** was selected since it is a potent inhibitor *in vitro* and *in vivo*, [13] and allows the prospect of convenient substituent modification at the indole 1-position to give structures of type **3**.

Chemistry:

The required analogues of **2** were prepared by alkylation of the ester **4** followed by hydrolysis (Scheme I). Alkylation of the anion of **4** with 1-[(4-fluorophenyl)sulfonyl]aziridine[15] followed by base hydrolysis gave **3a**. The homologue **3b** was prepared by N-alkylation of **4** with acrylonitrile followed by reduction to give the amine **5**. Sulfonylation of **5** with 4-fluorobenzenesulfonyl chloride followed by hydrolysis gave **3b**. Alkylation of the anion of **4** with benzyl 5-bromovalerate followed by hydrogenolysis gave the acid **6** which was converted to the benzyl carbamate **7** *via* a Curtius reaction using diphenylphosphoryl azide. Hydrogenation of **7** gave the amine **8** which was converted to the acid **3c** by sulfonylation followed by base hydrolysis.

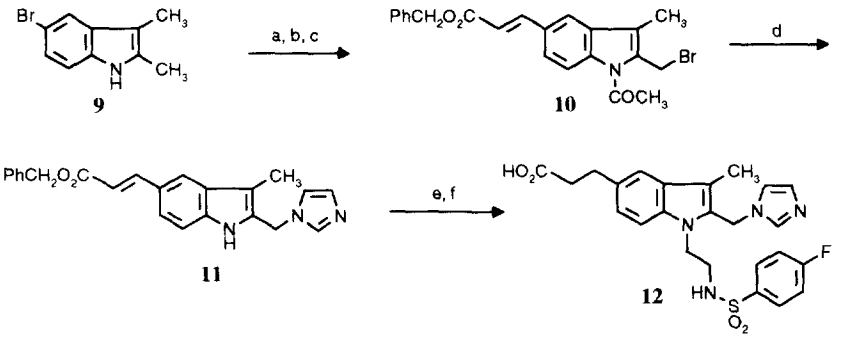
Scheme I



Conditions: (a) NaH, 1-[(4-fluorophenyl)sulfonyl]aziridine, DMF; (b) NaOH, EtOH, H_2O; (c) $H_2C{=}CHCN$, $PhCH_2NMe_3^+OH^-$, dioxan; (d) $NaBH_4$, $CoCl_2$, EtOH; (e) $4\text{-}FC_6H_4SO_2Cl$, DMAP, CH_2Cl_2; (f) NaH, $Br(CH_2)_4CO_2CH_2Ph$, DMF; (g) H_2, Pd/C, THF; (h) $(PhO)_2P(O)N_3$, $PhCH_2OH$, dioxan.

Extension of the 5-carboxyl substituent was achieved using Pd-catalysed coupling (Scheme II). Thus, the 5-bromoindole derivative **9** was treated with benzyl acrylate under Heck conditions and the resulting 5-propenoate ester was N-acetylated and then brominated to give **10**. This bromo compound was treated with imidazole to give **11** following loss of the acetyl group during work up. Alkylation using 1-[(4-fluorophenyl)sulfonyl]aziridine followed by hydrogenation gave the acid **12**.

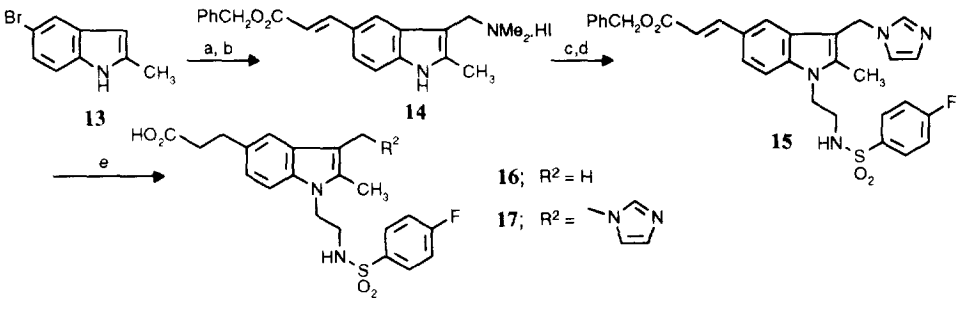
Scheme II



Conditions: (a) $H_2C{=}CHCO_2CH_2Ph$, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Et_3N, MeCN, reflux; (b) Ac_2O, cat. camphorsulfonic acid, reflux; (c) Br_2, CH_2Cl_2; (d) imidazole (10 eq.), K_2CO_3, Me_2CO; (e) NaH, 1-[(4-fluorophenyl)sulfonyl]aziridine, DMF; (f) H_2, Pd/C, THF.

The 3-(1-imidazolylmethyl) isomer **17** was prepared from the indole **13** by a Heck reaction with benzyl acrylate followed by a Mannich reaction of the product to give **14** (Scheme III). The latter was heated with imidazole to displace the dimethylamino group and the product was alkylated using 1-[(4-fluorophenyl)sulfonyl]aziridine to give **15**. Hydrogenation of **15** in THF was slow, but was more rapid in acetic acid, giving a mixture of the 3-methyl analogue **16** (11%) as well as **17** (39%).

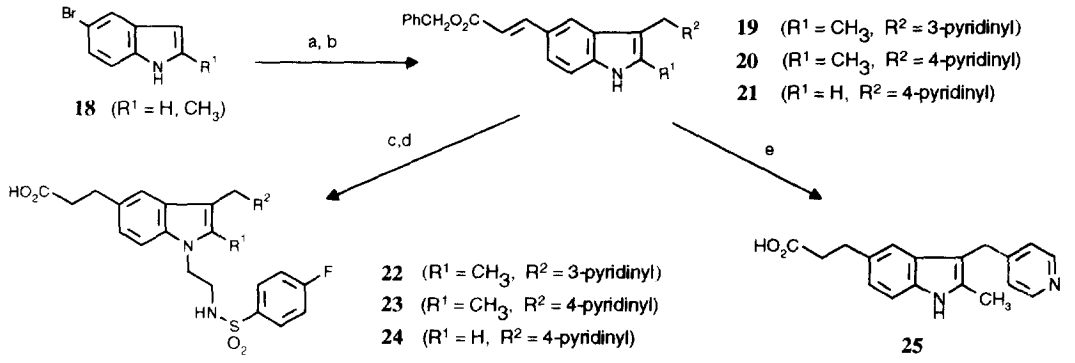
Scheme III



Conditions: (a) $H_2C{=}CHCO_2CH_2Ph$, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Et_3N, MeCN, reflux; (b) $H_2C{=}NMe_2{}^+I^-$, MeCN; (c) imidazole (3 eq.), MeCN, reflux; (d) NaH, 1-[(4-fluorophenyl)sulfonyl]aziridine, DMF; (e) H_2, Pd/C, AcOH.

3-(Pyridinylmethyl) analogues were prepared from a 5-bromoindole derivative **18** according to Scheme IV. Reaction of the indole Grignard derivative with a (chloromethyl)pyridine followed by a Heck reaction of the products with benzyl acrylate gave the indolepropenoate esters **19**, **20** and **21**. The anions of these products were treated with with 1-[(4-fluorophenyl)sulfonyl]aziridine, and the products were hydrogenated to give **22**, **23** and **24** respectively. Hydrogenation of the indolepropenoate **20** gave the propanoic acid **25**.

Scheme IV



Conditions: (a) MeMgI, R^2CH_2Cl, THF; (b) $H_2C{=}CHCO_2CH_2Ph$, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Et_3N, MeCN, reflux; (c) NaH, 1-[(4-fluorophenyl)sulfonyl]aziridine, DMF; (d) H_2, Pd/C, THF; (e) HCO_2NH_4, Pd/C, MeOH.

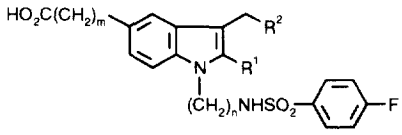
Results and Discussion:

TxA_2 receptor antagonism was measured by the ability of compounds to inhibit contraction of rat aorta induced by the stable thromboxane agonist U46619; results are expressed as a pA_2.[16] Partial agonist activity has been noted previously with several sulfonamide-based TxA_2 receptor antgonists,[4] but none of the present compounds caused contraction of rat aorta in the absence of U46619. Compounds were tested for their ability to inhibit human platelet microsomal TxA_2 synthase as described previously.[12] Results are summarised in Table 1.

Replacement of the N-methyl group of **2** with 2-[[(4-fluorophenyl)sulfonyl]amino]ethyl to give **3a** maintains TxA_2 synthase inhibition, but no TxA_2 receptor antagonist activity was observed. To explore the influence of the sulfonamide to carboxyl distance, the side chain was lengthened to give **3b** and **3c**, but without any beneficial effect on antagonist activity. Extension of the carboxyl substituent was then examined, and **12** shows antagonist activity approaching that of **1**, although at the cost of reduced TxA_2 synthase inhibition. It is known that the distance between the carboxyl and imidazole groups is important for optimal synthase activity, [1,3,12] and the distance is probably too great in **12**. In support of this, the 3-(1-imidazolylmethyl) isomer **17** in which the substituents are closer together retains good activity against TxA_2 synthase and, significantly, shows much greater potency as an antagonist. Alternatives to the imidazole were then examined. The 3-(3-pyridinylmethyl)

analogue **22** shows a small increase in antagonist activity, but the 3-(4-pyridinylmethyl) isomer **23** shows an exceptional level of antagonist activity against TxA_2 synthase, while maintaining excellent synthase activity. These results indicate that the pyridinyl substituent at the indole 3-position, necessary for synthase inhibition, can also make an important contribution to receptor binding. This is supported by the reduction in potency shown by **16**, which lacks a pyridinyl substituent, and by the fact that even when the sulfonamide side chain is removed as in **25**, a significant level of antagonist activity is retained. The 2-methyl substituent also plays an important role since removal as in **24** leads to a marked reduction in both activities. The combined effect of the 2-methyl group and the *peri*-interactions with the indole 4- and 7-hydrogens is expected to have a major influence on the direction and conformation of the 1- and 3-substituents. It appears likely that the 3-(4-pyridinylmethyl) substituent in **23** is locked into a particularly favourable conformation for both activities.

Table 1



Cpd.	R^1	R^2	m	n	mp, °C	TxA_2 Antagonism pA_2	TxA_2 Synthase IC_{50} (μM)
1	-	-	-	-	-	7.09	ND[a]
2	-	-	-	-	-	ND	0.032
3a	CH_2(1-imidazolyl)	H	0	2	155-165	<6[b]	0.020
3b	CH_2(1-imidazolyl)	H	0	3	224-225	<6	0.015
3c	CH_2(1-imidazolyl)	H	0	4	230[c]	<6	0.039
12	CH_2(1-imidazolyl)	H	2	2	143-145	6.86	0.135
16	CH_3	H	2	2	120-123	8.60	ND
17	CH_3	1-imidazolyl	2	2	191-192	8.80	0.039
22	CH_3	3-pyridinyl	2	2	195-198	9.16	0.061
23	CH_3	4-pyridinyl	2	2	189-190	10.13	0.078
24	H	4-pyridinyl	2	2	162-164	8.12	42%@ 1μM
25	CH_3	4-pyridinyl	2	-	223-223	7.22	0.022

[a] Not determined. [b] No significant antagonism at 1 μM. [c] Softening *ca.* 180-190 °C.

Thus, we have demonstrated that modification of a TxA_2 synthase inhibitor structure can lead to potent dual TxA_2 synthase inhibitor/TxA_2 receptor antagonists *in vitro*. However, only transient activity was observed following oral administration of **17**, **22** and **23** to conscious dogs.[17] Further investigations revealed that the short duration of action was a result of rapid hepatic uptake and clearance in bile.[18] Our efforts to overcome this problem to achieve compounds with potent dual activity *in vivo* will be the subject of a future publication.

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(16) Spirally cut rat aortic strips, mounted for isometric tension recording in 20 mL organ baths, were bathed in Krebs-bicarbonate solution at 37 °C and oxygenated. Following an incubation period of 2 h under 1 g resting tension, the tissues were pre-treated with the thromboxane agonist U46619 for 10 min, then washed and the tissues allowed to equilibrate for a further 1 h. Cumulative doses of U46619 over the range 1 nM to 100 nM were sequentially included in the bathing fluid and increases in the tension were noted. The test compounds were incubated with the tissue for 15 min prior to repeating the cumulative dosing of U46619, and the ability of the compound to antagonize the thromboxane receptor was determined from the dose-response curves for U46619 in the presence of varied concentrations of the test compound. Results were expressed as a pA_2. In all cases, Schild analysis gave slopes that did not differ significantly from unity. All determinations were carried out at least in duplicate.
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