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THROMBOXANE MODULATING AGENTS. 2. THROMBOXANE RECEPTOR ANTAGONISTS DERIVED FROM THE THROMBOXANE SYNTHASE INHIBITOR DAZMEGREL.

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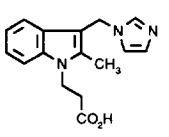
Abstract: The design of dual thromboxane synthase inhibitor/thromboxane receptor antagonists (e.g. **15**) based on the structure of the thromboxane synthase inhibitor dazmegrel is described. More potent receptor antagonists (e.g. **16c**) result from replacement of the pyridinyl subsituent with 4-fluorophenyl. Modelling suggests the existence of more than one site capable of interacting with the aryl sulfonamide of TxA_2 receptor antagonists.

Introduction:

Thromboxane (TxA_2) synthase inhibitors have attracted considerable interest in recent years because of their ability to prevent formation of the potent vasoconstrictor and platelet aggregating agent TxA_2.[1-3] In addition, TxA_2 synthase inhibition has the potential advantage of allowing conversion of accumulated substrate PGH_2 to the vasodilator and antiaggregatory PGI_2 by the enzyme PGI_2 synthase.[4,5] We have reported previously that dazmegrel **1** is a potent and selective TxA_2 synthase inhibitor,[6] and the compound has undergone clinical evaluation.[7,8] However, in general, clinical studies with TxA_2 synthase inhibitors in conditions where vasospasm and/or platelet activation are believed to be important have been disappointing,[3] possibly due in part to the fact that accumulated substrate PGH_2 is also a potent TxA_2 agonist.[9] As a means of overcoming this problem, several groups have shown interest in the design of dual TxA_2 synthase inhibitor/TxA_2 receptor antagonists which are able not only to inhibit TxA_2 synthesis but also to block the TxA_2 receptor, thereby preventing activation by PGH_2.[3,10-12]



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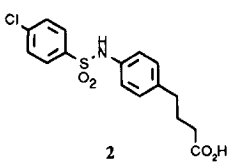

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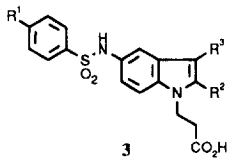

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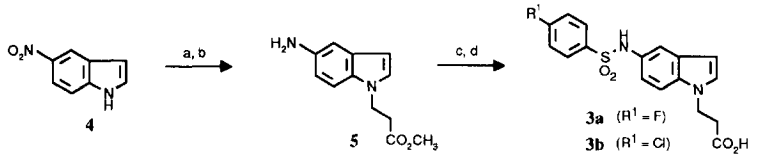
The previous paper[13] described the design of dual TxA_2 synthase inhibitor/TxA_2 receptor antagonists by introduction of an arylsulfonamide unit, a common feature of many TxA_2 receptor antagonists,[3,10-12] into an indole TxA_2 synthase inhibitor system. Following on from this, we were interested in the possibility of designing dual agents based on the structure of **1**. A patent[14] claims that **2** is a TxA_2 receptor antagonist and superposition of the skeleton of **2** on the indole-1-propanoic acid template of **1** suggests that structures of type **3** may be TxA_2 receptor antagonists. This communication describes the synthesis and TxA_2 modulating activity of compounds of type **3**.

Chemistry:

Compounds of type **3** (R^2 = R^3 = H) were prepared by alkylation of 5-nitroindole **4** with methyl acrylate, followed by hydrogenation to give the amine **5** (Scheme I). Sulfonylation followed by base hydrolysis gave the acids **3a** and **3b**.

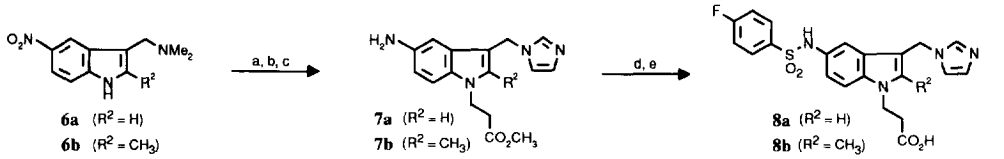
Scheme I



Conditions: (a) H_2C=$CHCO_2CH_3$, $PhCH_2NMe_3^+OH^-$, dioxan; (b) H_2, Pd/C, MeOH; (c) 4-$R^1C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2; (d) NaOH, MeOH, H_2O.

3-(1-Imidazolylmethyl) analogues of **3a** were prepared as shown in Scheme II. The nitrogramine derivatives **6a**[15] and **6b**[16] were heated with imidazole, and the products were successively N-alkylated with methyl acrylate and reduced to give **7a** and **7b**. The amines were converted to the products **8a** and **8b** as described above.

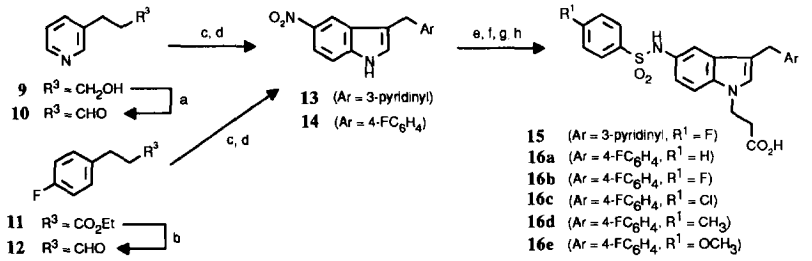
Scheme II



Conditions: (a) Imidazole, xylene, reflux; (b) H_2C=$CHCO_2CH_3$, $PhCH_2NMe_3^+OH^-$, dioxan; (c) H_2, Pd/C, MeOH; (d) 4-$FC_6H_4SO_2Cl$, Et_3N, CH_2Cl_2; (e) NaOH, MeOH, H_2O.

Intermediates for the 3-(3-pyridinyl) and 3-(4-fluorobenzyl) analogues were obtained by the Fischer indole synthesis (Scheme III). Thus, Swern oxidation of 3-(3-pyridinyl)propanol **9** gave the aldehyde **10** which was subjected to a Fischer cyclisation with 4-nitrophenylhydrazine to give the indole **13**. The ester **11** was reduced to the aldehyde **12** which was converted similarly to the indole **14**. The indoles **13** and **14** were converted to the products **15** and **16a -16e** as before.

Scheme III

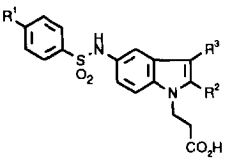


Conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -70 °C; (b) DIBAL, PhMe, -70 °C; (c) $4\text{-}NO_2C_6H_4NHNH_2$, Et_2O; (d) PPA, PhMe, 110 °C; (e) $H_2C{=}CHCO_2CH_3$, $PhCH_2NMe_3^+OH^-$, dioxan; (f) H_2, Pd/C, MeOH; (g) $4\text{-}R^1C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2; (h) NaOH, MeOH, H_2O.

Results and Discussion:

TxA_2 receptor antagonism was measured by the ability of compounds to inhibit contraction of rat aorta induced by the stable TxA_2 agonist U46619 as described in the previous paper.[13] Activity against human platelet microsomal TxA_2 synthase was measured as described previously.[17] The results are summarised in Table 1.

Table 1



Cpd.	R^1	R^2	R^3	mp, °C	TxA_2 Antagonism pA_2[a]	TxA_2 Synthase IC_{50} (μM)
1	-	-	-	-	<6[b]	0.028
2	-	-	-	-	7.00	ND[c]
3a	F	H	H	140-141	8.43	ND
3b	Cl	H	H	174-176	8.56	ND
8a	F	H	CH_2(1-imidazolyl)	185-186	8.20	0.034
8b	F	CH_3	CH_2(1-imidazolyl)	foam	5.42	0.019
15	F	H	CH_2(3-pyridinyl)	154-156	8.85	0.048
16a	H	H	4-fluorobenzyl	178-181	9.17	ND
16b	F	H	4-fluorobenzyl	185-186	9.32	ND
16c	Cl	H	4-fluorobenzyl	144-147	9.63	ND
16d	CH_3	H	4-fluorobenzyl	203-206	9.57	ND
16e	OCH_3	H	4-fluorobenzyl	166-168	9.76	ND

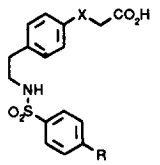
[a] Schild analysis gave slopes that did not differ significantly from unity. [b] No significant antagonism at 1μM. [c] Not determined.

Compound **2** has modest TxA_2 receptor antagonist activity, but the indoles **3a** and **3b** are more potent, confirming their suitability as templates for dual TxA_2 synthase inhibitor/TxA_2 antagonists. Introduction of a 3-(1-imidazolylmethyl) substituent as in **8a** is tolerated, and the compound has the same level of TxA_2 synthase activity as dazmegrel **1**. The 2-methyl analogue **8b** has similar TxA_2 synthase activity, but shows a dramatic

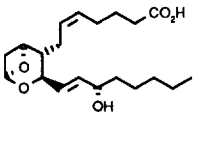
loss of TxA_2 antagonist activity, presumably because the 2-methyl substituent has an unfavourable effect on the conformation of the 1- and/or 3-substituents.

Replacement of imidazole with 3-pyridinyl results in an increase in antagonist activity in line with previous findings,[13] and **15** is a potent dual TxA_2 synthase inhibitor/TxA_2 antagonist. The increase in antagonist activity may be due to an increase in lipophilicity of the 3-substituent, and raises the possibility that even more potent TxA_2 receptor antagonists may result from replacement of the imidazole or pyridine required for TxA_2 synthase activity by a phenyl substituent. This expectation was realised, and the 3-(4-fluorobenzyl) analogue **16b** shows a further increase in potency. The beneficial effect of the benzylic substituent is clearly demonstrated by the tenfold greater potencies of **16b** and **16c** compared with the corresponding unsubstituted analogues **3a** and **3b**. Other 4-substituents in the benzenesulfonamide give a similar level of activity (**16d**, **16e**), but the unsubstituted sulfonamide **16a** is slightly weaker.

It is believed that the minimum pharmacophore requirements for high affinity interaction with the receptor for sulfonamide-based TxA_2 receptor antagonists are the carboxyl and sulfonamide moieties.[18] Modelling studies on sulotroban **17**[19] and daltroban **18**[20, 21] have highlighted low energy hairpin-like conformations of the antagonists in which it is possible to overlap the carboxyl group and sulfonamide aryl group with the carboxyl group and omega side chain respectively of low energy hairpin conformations of TxA_2 **19**. It has also been suggested that there is a hydrogen bond donor on the receptor which interacts with the agonist 15-OH group and a sulfonyl oxygen of the antagonists.[20] Jin and Hopfinger[21] have reported a detailed modelling study in which possible low energy conformations of several antagonists including **18**, SQ 29,548 **20** and analogues were compared in order to define the optimal distance between the key recognition sites. A distance of 4.6-5.6Å between a carboxyl oxygen and hydrogen bond acceptor (CO or SO_2) oxygen was calculated.[21] A hydrophobic binding site to accommodate the terminal aryl groups in **18** and **20** was also proposed.[21]



17 (R = H, X = O)
18 (R = Cl, X = direct link)



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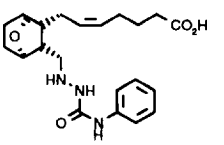

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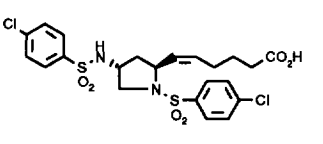

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In view of the greater rigidity of the current series of antagonists compared with **17** and **18**, it was interesting to examine whether a similar hairpin-like conformation is feasible. In the X-ray crystal structure of **3b**[22] (Fig.1), the arylsulfonamido indole system exists in a folded arrangement, with the propanoic acid in an extended conformation. This basic structure was used as a template to model low energy conformations of **3b**. Since the

arylsulfonamido indole is already in a partial hairpin conformation, this was held fixed, and possible low energy conformations of the carboxyl side chain were explored.[23] The hairpin conformation of **3b** with the closest carbonyl O to sulfonyl O distance (Fig. 2) is also the global minimum energy conformation. The possible carboxyl O to sulfonyl O distances are in the range 6.76-8.13Å, which is appreciably greater than the postulated range of 4.6-5.6Å,[21] suggesting that other binding modes should be considered.

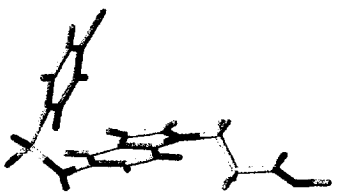

Fig. 1. X-Ray crystal structure of **3b**

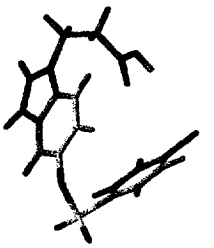

Fig. 2. Energy minimised conformation of **3b**

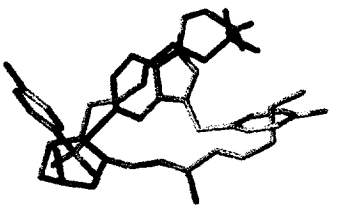

Fig. 3. Overlap of low energy conformations of **16c** and TxA_2

Hall[10] has suggested an alternative binding mode for sulfonamide based antagonists in which the sulfonyl oxygens interact with the same binding site as the bicyclic ring oxygens of TxA_2. To test the possibility that the current series of compounds bind in this way, the more potent antagonist **16c** was modelled by building on the indole 3-substituent and minimisation as for **3b**, and the best alignments of low energy conformations of **16c** and the low energy conformations of TxA_2 calculated by Ezumi *et al.*[19] were determined. Fig. 3 shows that a good overlap can be obtained for **16c** and the low energy TxA_2 conformer T3 of Ezumi *et al.*[19] In the conformation shown, there is a good overlap of the sulfonyl O atoms with the TxA_2 ring oxygens, and the benzylic substituent occupies the same region of space as the terminus of the TxA_2 omega side chain. It has been proposed that the binding of TxA_2 to its receptor involves a hydrogen bond to the oxetane ring oxygen,[24] and it is possible that one of the sulfonyl oxygens of the antagonist may also act as a hydrogen bond acceptor.

Although modelling of **16c** supports the binding mode postulated by Hall, compounds such as **17** and **18** probably have sufficient flexibility to adopt either required conformation, and it is possible that there are two distinct sites on the receptor that can accept a sulfonamide moiety. The high potency (pA_2 9.94 in our hands) of FR106,881[25] **21** which incorporates two arylsulfonamide moieties supports this concept.

In summary, we have shown that dual TxA_2 synthase inhibitor/TxA_2 receptor antagonists may be designed based on the structure of dazmegrel, and potent receptor antagonism results from removal of the 2-methyl group and replacement of the 3-heterocyclic substituent with 4-(fluorobenzyl). Modelling has suggested the

existence of more than one site capable of interacting with the arylsulfonamide of TxA_2 receptor antagonists. The information obtained should prove valuable in the design of more potent antagonists.

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