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THROMBOXANE MODULATING AGENTS. 4. DESIGN AND SYNTHESIS OF 3-(2-[{(4-CHLOROPHENYL)SULFONYL}-AMINO]ETHYL)BENZENEPROPANOIC ACID DERIVATIVES AS POTENT THROMBOXANE RECEPTOR ANTAGONISTS.

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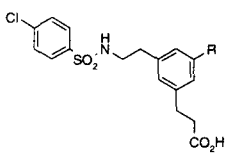
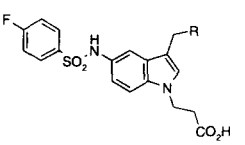
Abstract: The design of a series of thromboxane receptor antagonists based on 3-(2-[{(4-chlorophenyl)sulfonyl}amino]ethyl)benzenepropanoic acid (**1**) is described. Addition of an arylmethyl group at the 5-position of **1** gave exceptionally potent agents *in vitro* and *in vivo*, with **13a** (UK-147,535) giving complete blockade of the TxA_2 receptor for greater than 12 hours in dogs, following an oral dose of 0.1mg/kg.

Introduction:

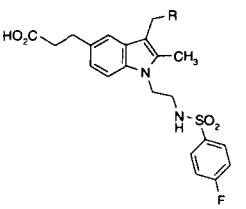
There has been considerable interest in recent years in the design of agents to prevent the vasoconstrictor and platelet aggregatory actions of thromboxane A_2 (TxA_2). [1-6] In particular, we[7-9] and others[10,11] have reported on the design of dual TxA_2 synthase inhibitors/TxA_2 receptor antagonists. Such compounds are capable not only of preventing formation of TxA_2 from its precursor PGH_2, but also of preventing activation of the TxA_2 receptor by accumulated PGH_2, which is itself a potent agonist.[12,13] Activation of the TxA_2 receptor by PGH_2 is believed to be one reason for the disappointing clinical performance of TxA_2 synthase inhibitors.[12]



1; R = H
2; R = 3-pyridinyl-CH_2



3; R = 3-pyridinyl
4; R = 4-FC_6H_4



5; R = 3-pyridinyl
6; R = 4-pyridinyl

In the previous paper[7] we described the design and synthesis of a series of potent dual TxA_2 synthase inhibitors/TxA_2 receptor antagonists based on the antagonist template **1**. It was shown that introduction of a 3-pyridinylmethyl group to confer TxA_2 synthase activity, as in **2**, led to an increase in receptor antagonist potency. A similar effect was observed in an indole based series of dual agents as exemplified by **3**, and an even more potent receptor antagonist, devoid of TxA_2 synthase inhibitory activity, resulted from replacement of the

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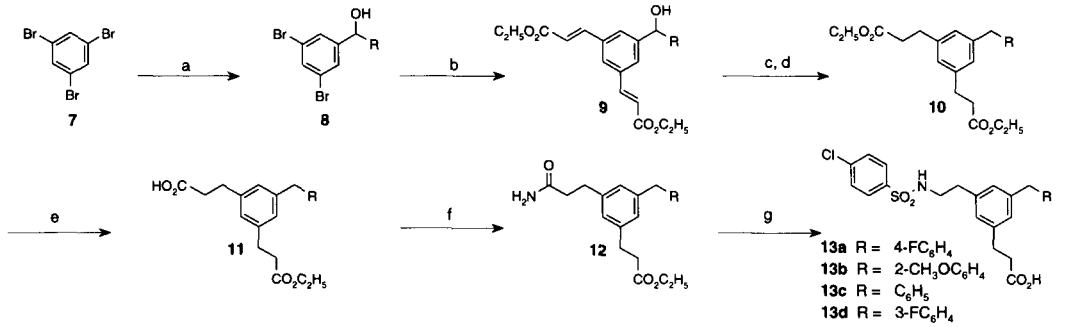
3-pyridinylmethyl group with 4-fluorobenzyl as in **4**.[8] In another indole series it was demonstrated that replacement of the 3-pyridinylmethyl substituent of **5** with 4-pyridinylmethyl to give **6** also led to an increase in antagonist potency.[9]

With the aim of further investigating structural requirements for TxA_2 receptor antagonist activity, we have studied the effect of replacement of the 3-pyridinylmethyl group in **2** with benzylic substituents and with 4-pyridinylmethyl. In this communication we report that these modifications lead to receptor antagonists with an exceptional level of potency.

Chemistry:

The desired analogues of **2** were all prepared from 1,3,5-tribromobenzene **7** as shown in Scheme I. Reaction with *n*-butyllithium in diethyl ether, followed by addition of an arylaldehyde, furnished the alcohols **8**. Treatment of these derivatives with ethyl acrylate under Heck conditions to give the bis-propenoates **9**, followed by acylation of the alcohol prior to hydrogenation, gave the bis-propanoate esters **10**. Careful hydrolysis using one equivalent of base gave the mono acids **11** which were converted to the carboxamides **12**. A Hofmann reaction of the latter to give the aminoethyl derivatives (with concomitant ester hydrolysis), and then *in situ* sulfonylation delivered the target compounds **13a-13d**.

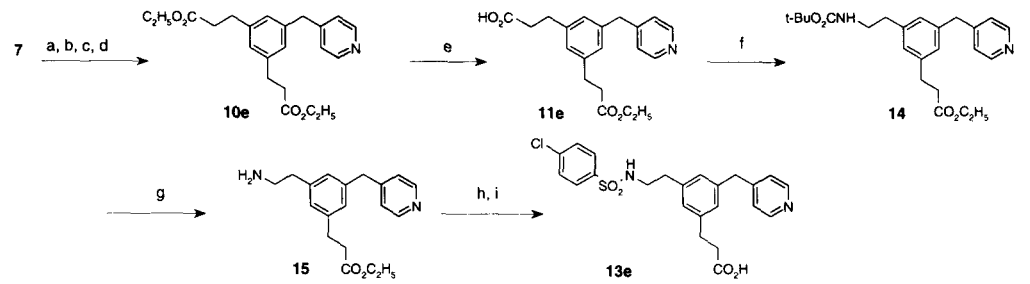
Scheme I



Conditions: (a) n-BuLi, Et_2O, RCHO, 87%*; (b) $H_2C{=}CHCO_2C_2H_5$, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Et_3N, MeCN, reflux, 89%*; (c) Ac_2O, pyridine, cat. DMAP, 96%*; (d) H_2 , Pd/C, EtOAc, 99%*; (e) NaOH (1eq.), EtOH, H_2O, 52%*; (f) $(COCl)_2$, CH_2Cl_2, then excess NH_4OH, 94%*; (g) NaOCl, excess NaOH, H_2O, dioxan reflux, then 4-$ClC_6H_4SO_2Cl$, 82%*
* typical yields given for R = 4-FC_6H_4.

The 4-pyridinylmethyl derivative **13e** (Scheme II) was prepared from the diester **10e**, which was synthesised following the method described previously[7] for the preparation of 3-pyridinylmethyl analogue **2**. Partial hydrolysis to the mono acid **11e** followed by treatment with diphenylphosphoryl azide in the presence of *t*-butanol gave the carbamate **14**, which was converted to the amine **15** by treatment with TFA. The amine was sulfonylated with chlorobenzenesulfonyl chloride, and then the ester was hydrolysed to give the target **13e**.

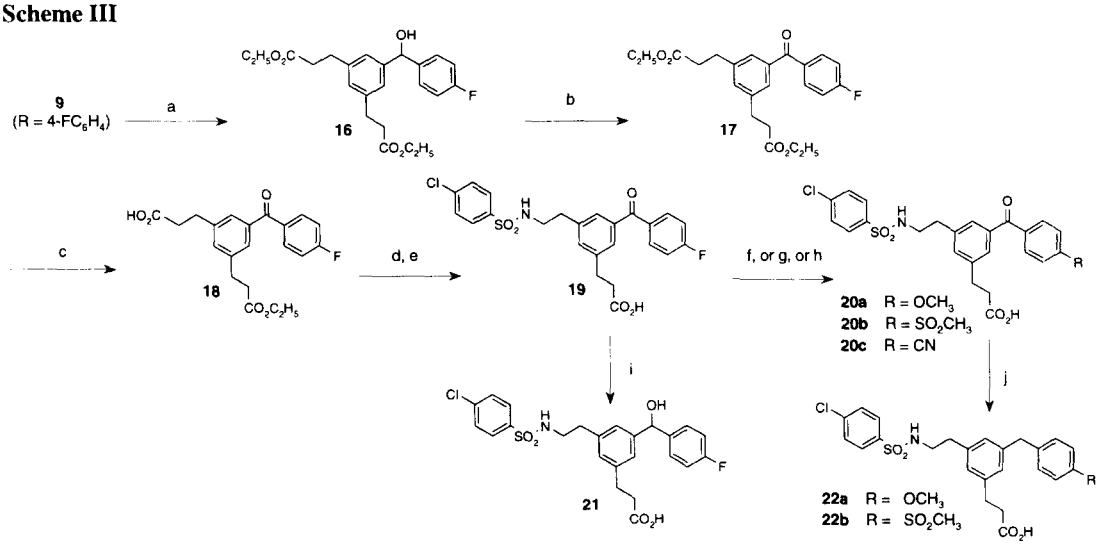
Scheme II



Conditions: (a) *n*-BuLi, Et_2O, -78°C, 4-cyanopyridine, then H^+/H_2O, 67%; (b) N_2H_4, KOH, ethylene glycol, 67%; (c) $H_2C{=}CHCO_2C_2H_5$, $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, MeCN, reflux, 74%; (d) $HCO_2^-NH_4^+$, Pd/C, EtOH, THF, 99%; (e) NaOH (1eq.), EtOH, H_2O, 41%; (f) diphenylphosphoryl azide, *t*-BuOH, Et_3N, 76%; (g) TFA, CH_2Cl_2, 75%; (h) 4-$ClC_6H_4SO_2Cl$, Et_3N, CH_2Cl_2, 86%; (i) NaOH, H_2O, MeOH, 88%.

The 4-fluorobenzoyl analogue **19** (Scheme III) was prepared from the intermediate alcohol **9** (R = 4-FC_6H_4) by selective catalytic transfer hydrogenation of the propenoate esters to give the alcohol **16**. Swern oxidation to the benzophenone **17** was followed by mono ester hydrolysis as before, conversion to the carboxamide, and then Hofmann reaction and sulfonylation to give **19**. Reduction of **19** gave the alcohol **21**, whilst displacement of the 4-fluoro substituent with nucleophiles such as methoxide, methanesulfinate, or cyanide gave **20a-20c** respectively. Reduction of the ketones **20a** and **20b** using triethylsilane in TFA gave the corresponding methylene compounds **22a** and **22b**.

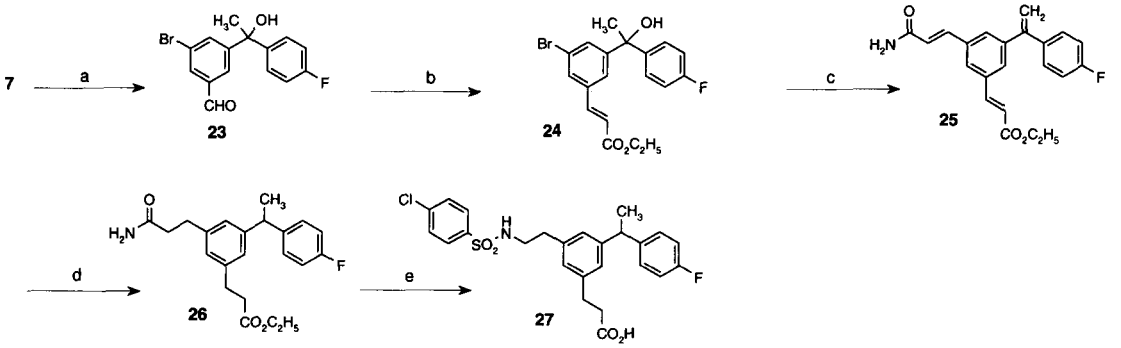
Scheme III



Conditions: (a) $HCO_2^-NH_4^+$, Pd/C, EtOH, THF, 99%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, 95%; (c) NaOH (1eq.), EtOH, H_2O, 50%; (d) $(COCl)_2$, CH_2Cl_2, then excess NH_4OH, 90%; (e) NaOCl, excess NaOH, H_2O, dioxan reflux, then 4-$ClC_6H_4SO_2Cl$, 41%; (f) K_2CO_3, CH_3OH, reflux to give **20a**, 89%; (g) $MeSO_2Na$, DMSO, 130°C to give **20b**, 63%; (h) KCN, DMF, 125°C, to give **20c**, 25%; (i) $NaBH_4$ EtOH, 72%; (j) Et_3SiH, TFA, CH_2Cl_2, **22a** 88%, **22b** 63%.

An improved, shorter synthesis of sulfonamide analogues from **7**, utilised a sequence of bromine/lithium exchange with *n*-butyllithium, and addition to 4-fluoroacetophenone then, without isolation, a second bromine/lithium exchange, followed by addition to DMF to give the benzaldehyde **23** (Scheme IV). A Wittig-Horner reaction to give **24**, followed by a Heck reaction with acrylamide, and concomitant dehydration of the tertiary alcohol, gave **25**, which was hydrogenated over Pd/C in acetic acid to **26**. Our standard conditions of Hofmann reaction, and *in situ* sulfonylation furnished the α-methyl derivative **27**.

Scheme IV



Conditions: (a) *n*-BuLi, Et_2O, 4-$FC_6H_4COCH_3$, then *n*-BuLi, DMF, 48%; (b) NaH, $(EtO)_2POCH_2CO_2C_2H_5$, THF, 41%; (c) H_2C=CHCONH$_2$, Pd(OAc)$_2$, P(*o*-Tol)$_3$, Et_3N, MeCN, reflux, 45%; (d) H_2 , Pd/C, AcOH, 99%; (e) NaOCl, excess NaOH, H_2O, dioxan reflux, then 4-$ClC_6H_4SO_2Cl$, 36%.

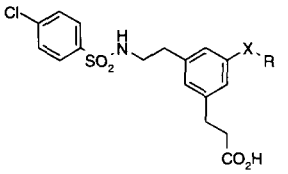
Results and Discussion:

In vitro TxA_2 receptor antagonism was measured by the ability of compounds to inhibit the contraction of rat aorta induced by the stable thromboxane agonist U46619, as described previously.[9] Results are expressed as a pA_2. 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. Results are summarised in Table 1.

Introduction of a 5-(4-fluorobenzyl) substituent into **1** to give **13a** results in an almost 100-fold increase in antagonist potency. The increase in potency is significantly greater than that observed on introduction of a (3-pyridinylmethyl) substituent to give **2**. A range of substituents are tolerated in the benzyl group, with 4-methoxy (**22a**) being particularly favourable. A dramatic increase in potency over **2** is seen with the 4-pyridinyl isomer **13e**.

Replacement of the methylene linkage by a carbonyl leads to a slight decrease in potency (cf. **13a** with **19**, and **22a** with **20a**), and substitution of the methylene linkage with hydroxyl is also slightly detrimental (**21**). However, substitution with an α-methyl is favourable (**27**), and mirrors the situation observed in the 3-pyridinyl (**2**) series.[7] Modelling studies on a close analogue of **3** suggested that the benzylic substituent may occupy the same lipophilic binding site as the terminus of the TxA_2 omega side chain.[8] The greater preference for an α-methyl substituent compared with an α-hydroxyl may be a consequence of more optimal binding to this lipophilic site.

Table 1



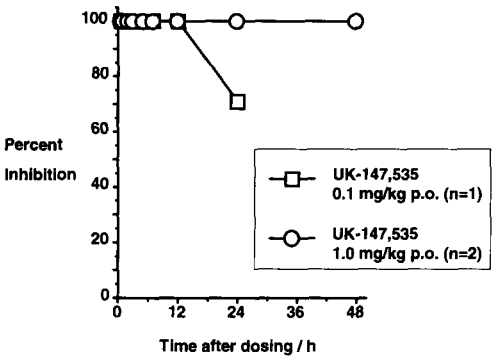
Cpd	X	R	mp, °C (uncorrected)	TxA_2 Antagonism pA_2 [a]
1	bond	H	98-100	8.7
2	CH_2	3-pyridinyl	150-152	9.4
13e	CH_2	4-pyridinyl [b]	159-160	11.6 [c]
13a	CH_2	4-FC_6H_4	108-110	10.6
13b	CH_2	2-$CH_3OC_6H_4$	98-102	10.2
13c	CH_2	C_6H_5	80-81	10.8
13d	CH_2	3-FC_6H_4	128-129	10.1
22a	CH_2	4-$CH_3OC_6H_4$	106-108	11.4 [c]
22b	CH_2	4-$CH_3SO_2C_6H_4$	105-107	10.2
19	CO	4-FC_6H_4	127-129	10.0
20a	CO	4-$CH_3OC_6H_4$	glass	10.6
20b	CO	4-$CH_3SO_2C_6H_4$	137-139	9.5
20c	CO	4-cyano-C_6H_4	glass	10.4
21	CH(OH)	4-FC_6H_4	glass	9.7
27	$CHCH_3$	4-FC_6H_4	glass	11.4 [c]

a) Schild analysis gave slopes that did not differ significantly from unity. b) TxA_2 synthase IC_{50} 0.047μM (human platelet microsomes).[14] c) Compounds pre-incubated with tissue for 60 minutes: incubation for standard 15 minutes resulted in Schild slopes significantly greater than unity.

13a (UK-147,535) was selected for further evaluation *in vivo* (see Figure 1) . At a dose of 1mg/kg p.o. in a conscious dog, **13a** caused complete blockade of the response to the thromboxane receptor agonist U46619 (1uM) for 48 hours (as measured[7] by *ex vivo* U46619-induced aggregation of blood samples). A lower dose of 0.1mg/kg p.o. maintained complete antagonism for >12 hours.

Figure 1.

Prevention of *ex vivo* platelet aggregation to U46619 (1μM) in dog, following oral administration of **13a**, (UK-147,535) at 0.1 or 1 mg/kg.



Thus, we have demonstrated that thromboxane receptor antagonists such as **13a** (UK-147,535) exhibit exceptional potency both *in vitro* and *in vivo*. Such compounds may be of use, either alone or in combination with a TxA_2 synthase inhibitor, in the therapy of diseases where TxA_2 plays an important role. An alternative large-scale synthesis[15] of **13a** has been developed to prepare bulk quantities for use in toxicological and clinical trials.

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