

# 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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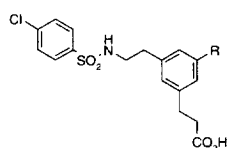
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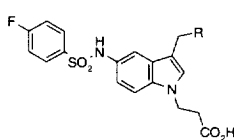
**Abstract:** The design of a series of thromboxane receptor antagonists based on 3-(2-[(4-chlorophenyl)sulfonyl]amino)ethyl)benzenepropanoic acid (**1**) is described. Addition of an arylmethyl group at the 5-position of **1** gave exceptionally potent agents *in vitro* and *in vivo*, with **13a** (UK-147,535) giving complete blockade of the TxA<sub>2</sub> receptor for greater than 12 hours in dogs, following an oral dose of 0.1mg/kg. © 1998 Elsevier Science Ltd. All rights reserved.

## Introduction:

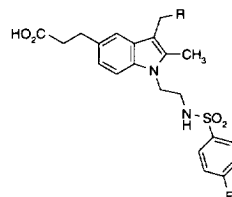
There has been considerable interest in recent years in the design of agents to prevent the vasoconstrictor and platelet aggregatory actions of thromboxane A<sub>2</sub> (TxA<sub>2</sub>).<sup>1–6</sup> In particular, we<sup>7–9</sup> and others<sup>10,11</sup> have reported on the design of dual TxA<sub>2</sub> synthase inhibitors/TxA<sub>2</sub> receptor antagonists. Such compounds are capable not only of preventing formation of TxA<sub>2</sub> from its precursor PGH<sub>2</sub>, but also of preventing activation of the TxA<sub>2</sub> receptor by accumulated PGH<sub>2</sub>, which is itself a potent agonist.<sup>12,13</sup> Activation of the TxA<sub>2</sub> receptor by PGH<sub>2</sub> is believed to be one reason for the disappointing clinical performance of TxA<sub>2</sub> synthase inhibitors.<sup>12</sup>



1: R = H  
2: R = 3-pyridinyl-CH<sub>2</sub>



3: R = 3-pyridinyl  
4: R = 4-FC<sub>6</sub>H<sub>4</sub>



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

In the previous paper<sup>7</sup> we described the design and synthesis of a series of potent dual TxA<sub>2</sub> synthase inhibitors/TxA<sub>2</sub> receptor antagonists based on the antagonist template **1**. It was shown that introduction of a 3-pyridinylmethyl group to confer TxA<sub>2</sub> 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<sub>2</sub> synthase inhibitory activity, resulted from replacement of the

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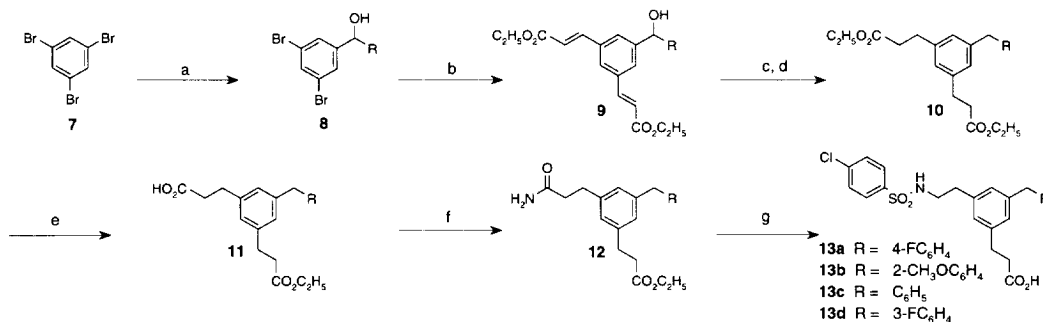
3-pyridinylmethyl group with 4-fluorobenzyl as in **4**.<sup>8</sup> In another indole series it was demonstrated that replacement of the 3-pyridinylmethyl substituent of **5** with 4-pyridinylmethyl to give **6** also led to an increase in antagonist potency.<sup>9</sup>

With the aim of further investigating structural requirements for TxA<sub>2</sub> 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

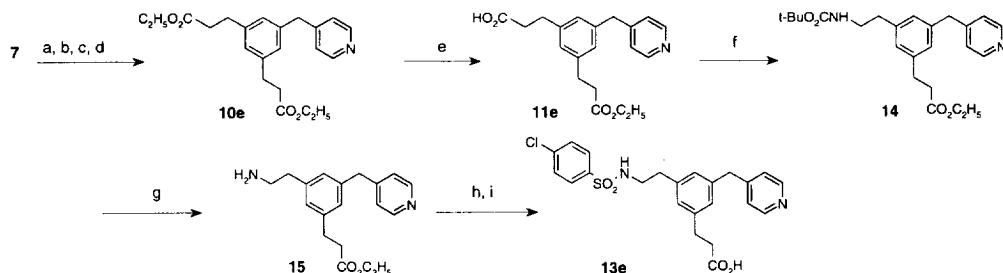


Conditions: (a) *n*-BuLi, Et<sub>2</sub>O, RCHO, 87%\*; (b) H<sub>2</sub>C=CHCO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, Pd(OAc)<sub>2</sub>, P(*o*-Tol)<sub>3</sub>, Et<sub>3</sub>N, MeCN, reflux, 89%\*; (c) Ac<sub>2</sub>O, pyridine, cat. DMAP, 96%\*; (d) H<sub>2</sub>, Pd/C, EtOAc, 99%\*; (e) NaOH (1eq.), EtOH, H<sub>2</sub>O, 52%\*; (f) (COCl)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, then excess NH<sub>4</sub>OH, 94%\*; (g) NaOCl, excess NaOH, H<sub>2</sub>O, dioxan reflux, then 4-ClC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl, 82%\*

\* typical yields given for R = 4-FC<sub>6</sub>H<sub>4</sub>.

The 4-pyridinylmethyl derivative **13e** (Scheme II) was prepared from the diester **10e**, which was synthesised following the method described previously<sup>7</sup> 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**.

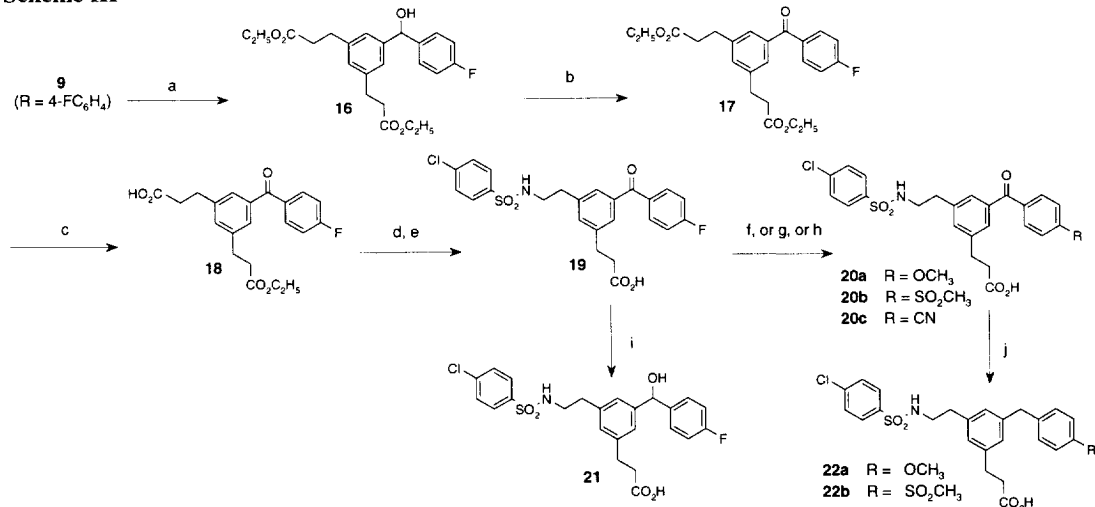
## Scheme II



Conditions: (a) *n*-BuLi, Et<sub>2</sub>O, -78°C, 4-cyanopyridine, then H<sup>+</sup>/H<sub>2</sub>O, 67%; (b) N<sub>2</sub>H<sub>4</sub>, KOH, ethylene glycol, 67%; (c) H<sub>2</sub>C=CHCO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, Pd(OAc)<sub>2</sub>, P(*o*-Tol)<sub>3</sub>, Et<sub>3</sub>N, MeCN, reflux, 74%; (d) HCO<sub>2</sub><sup>-</sup>NH<sub>4</sub><sup>+</sup>, Pd/C, EtOH, THF, 99%; (e) NaOH (1eq.), EtOH, H<sub>2</sub>O, 41%; (f) diphenylphosphoryl azide, *t*-BuOH, Et<sub>3</sub>N, 76%; (g) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 75%; (h) 4-ClC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 86%; (i) NaOH, H<sub>2</sub>O, MeOH, 88%.

The 4-fluorobenzoyl analogue **19** (Scheme III) was prepared from the intermediate alcohol **9** (R = 4-FC<sub>6</sub>H<sub>4</sub>) 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, methanesulfonate, 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**.

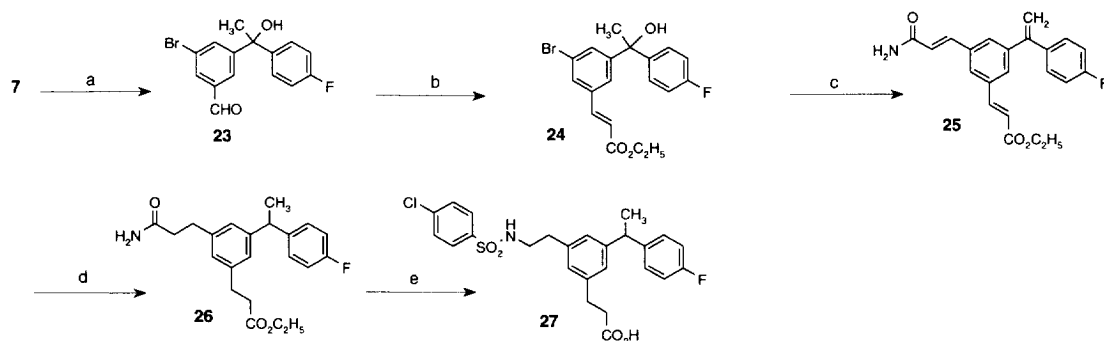
## Scheme III



Conditions: (a) HCO<sub>2</sub><sup>-</sup>NH<sub>4</sub><sup>+</sup>, Pd/C, EtOH, THF, 99%; (b) (COCl)<sub>2</sub>, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, 95%; (c) NaOH (1eq.), EtOH, H<sub>2</sub>O, 50%; (d) (COCl)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, then excess NH<sub>4</sub>OH, 90%; (e) NaOCl, excess NaOH, H<sub>2</sub>O, dioxan reflux, then 4-ClC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl, 41%; (f) K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>OH, reflux to give **20a**, 89%; (g) MeSO<sub>2</sub>Na, DMSO, 130°C to give **20b**, 63%; (h) KCN, DMF, 125°C, to give **20c**, 25%; (i) NaBH<sub>4</sub>, EtOH, 72%; (j) Et<sub>3</sub>SiH, TFA, CH<sub>2</sub>Cl<sub>2</sub>, **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  $\alpha$ -methyl derivative **27**.

Scheme IV



Conditions: (a) *n*-BuLi, Et<sub>2</sub>O, 4-FC<sub>6</sub>H<sub>4</sub>COCH<sub>3</sub>, then *n*-BuLi, DMF, 48%; (b) NaH, (EtO)<sub>2</sub>POCH<sub>2</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, THF, 41%; (c) H<sub>2</sub>C=CHCONH<sub>2</sub>, Pd(OAc)<sub>2</sub>, P(*o*-Tol)<sub>3</sub>, Et<sub>3</sub>N, MeCN, reflux, 45%; (d) H<sub>2</sub>, Pd/C, AcOH, 99%; (e) NaOCl, excess NaOH, H<sub>2</sub>O, dioxan reflux, then 4-ClC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl, 36%.

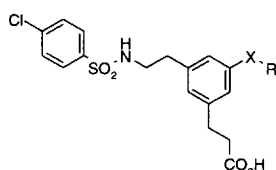
## Results and Discussion:

*In vitro* TxA<sub>2</sub> 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.<sup>9</sup> Results are expressed as a pA<sub>2</sub>. Partial agonist activity has been noted previously with several sulfonamide-based TxA<sub>2</sub> receptor antagonists,<sup>4</sup> 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  $\alpha$ -methyl is favourable (**27**), and mirrors the situation observed in the 3-pyridinyl (**2**) series.<sup>7</sup> 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<sub>2</sub> omega side chain.<sup>8</sup> The greater preference for an  $\alpha$ -methyl substituent compared with an  $\alpha$ -hydroxyl may be a consequence of more optimal binding to this lipophilic site.

Table 1



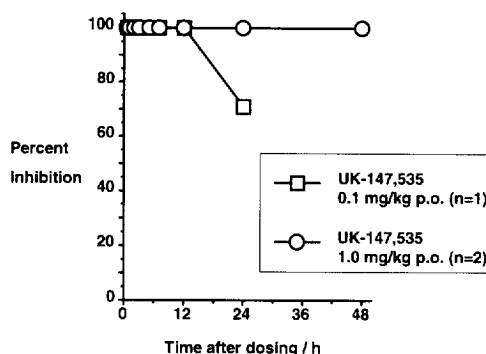
Cpd	X	R	mp, °C (uncorrected)	TxA <sub>2</sub> Antagonism pA <sub>2</sub> <sup>a</sup>
<b>1</b>	bond	H	98-100	8.7
<b>2</b>	CH <sub>2</sub>	3-pyridinyl	150-152	9.4
<b>13e</b>	CH <sub>2</sub>	4-pyridinyl <sup>b</sup>	159-160	11.6 <sup>c</sup>
<b>13a</b>	CH <sub>2</sub>	4-FC <sub>6</sub> H <sub>4</sub>	108-110	10.6
<b>13b</b>	CH <sub>2</sub>	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	98-102	10.2
<b>13c</b>	CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	80-81	10.8
<b>13d</b>	CH <sub>2</sub>	3-FC <sub>6</sub> H <sub>4</sub>	128-129	10.1
<b>22a</b>	CH <sub>2</sub>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	106-108	11.4 <sup>c</sup>
<b>22b</b>	CH <sub>2</sub>	4-CH <sub>3</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	105-107	10.2
<b>19</b>	CO	4-FC <sub>6</sub> H <sub>4</sub>	127-129	10.0
<b>20a</b>	CO	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	glass	10.6
<b>20b</b>	CO	4-CH <sub>3</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	137-139	9.5
<b>20c</b>	CO	4-cyano-C <sub>6</sub> H <sub>4</sub>	glass	10.4
<b>21</b>	CH(OH)	4-FC <sub>6</sub> H <sub>4</sub>	glass	9.7
<b>27</b>	CHCH <sub>3</sub>	4-FC <sub>6</sub> H <sub>4</sub>	glass	11.4 <sup>c</sup>

a) Schild analysis gave slopes that did not differ significantly from unity. b) TxA<sub>2</sub> synthase IC<sub>50</sub> 0.047  $\mu$ M (human platelet microsomes).<sup>14</sup> 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 (1  $\mu$ M) for 48 hours (as measured<sup>7</sup> 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 (1 $\mu$ M) 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<sub>2</sub> synthase inhibitor, in the therapy of diseases where TxA<sub>2</sub> plays an important role. An alternative large-scale synthesis<sup>15</sup> of **13a** has been developed to prepare bulk quantities for use in toxicological and clinical trials.

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