Thromboxane Modulating Agents. 3. 1*H*-Imidazol-1-ylalkyl- and 3-Pyridinylalkyl-Substituted 3-[2-[(Arylsulfonyl)amino]ethyl]benzenepropanoic Acid Derivatives as Dual Thromboxane Synthase Inhibitor/Thromboxane Receptor Antagonists

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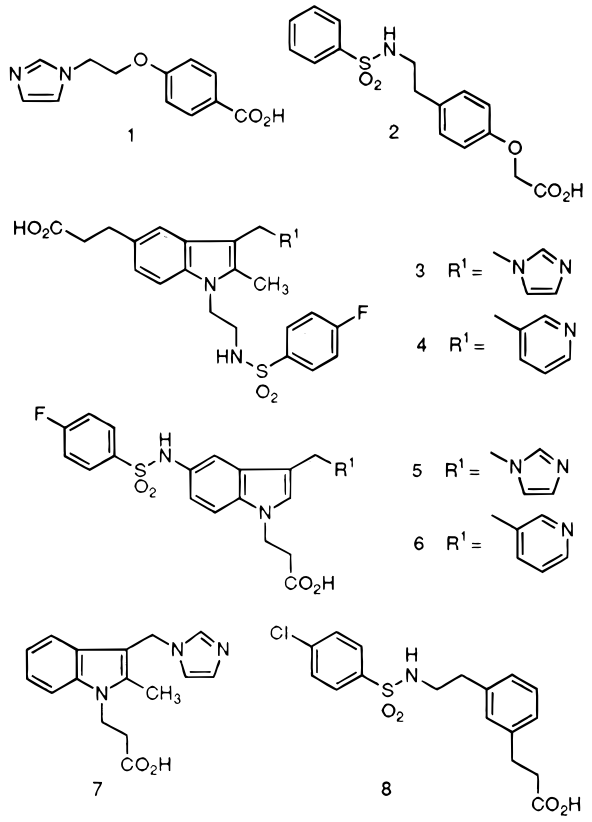
The design of a series of dual thromboxane synthase inhibitor/thromboxane receptor antagonists based on a 3-[2-[(arylsulfonyl)amino]ethyl]benzenepropanoic acid thromboxane receptor antagonist template is described. Introduction of a 5-(1*H*-imidazol-1-ylmethyl), a 5-(3-pyridinylmethyl), or a 5-(3-pyridinyloxy) substituent leads to dual agents with thromboxane synthase inhibitory activity comparable with that of dazmegrel (**7**). In addition, 3-pyridinylalkyl substituents also make a significant contribution to thromboxane receptor binding. Oral administration of compound **74** (5 mg/kg) to conscious dogs produces long-lasting thromboxane synthase inhibition and thromboxane receptor blockade as measured by inhibition of U46619-induced platelet aggregation ex vivo.

Thromboxane A_2 (TXA_2), which is formed by the action of the enzyme thromboxane synthase on the prostaglandin endoperoxide PGH_2, is a potent vasoconstrictor and platelet-aggregating agent[1] and has been implicated as a causative factor in a number of cardiovascular and renal diseases.[2−7] Considerable effort has been devoted to the design of TXA_2 synthase inhibitors which may have utility in the therapy of these diseases.[8−10] A potential advantage following from inhibition of TXA_2 synthase is that accumulated PGH_2 substrate may be utilized by PGI_2 synthase present in vascular endothelium to produce increased amounts of the potent vasodilator and platelet-inhibitory agent PGI_2.[11,12] However, despite extensive clinical evaluation, TXA_2 synthase inhibitors have failed to fulfill their promise.[10,13] Possible reasons for the disappointing clinical performance of TXA_2 synthase inhibitors have been discussed,[14] and an important factor is believed to be the buildup of substrate PGH_2 which is itself a potent agonist at the TXA_2 receptor.[15,16]

An alternative approach to preventing the action of TXA_2 which has also attracted considerable attention is to use a TXA_2 receptor antagonist.[8−10,17−24] This approach has the advantage of also being able to antagonize the action of PGH_2 at the TXA_2 receptor but does not lead to diversion of PGH_2 to produce increased PGI_2.

Combination of a TXA_2 receptor antagonist with a TXA_2 synthase inhibitor should have the beneficial effect of blocking the action of accumulated PGH_2 at the TXA_2 receptor while still allowing conversion to PGI_2. In support of this idea, a synergistic effect on collagen-induced (TXA_2-dependent) platelet aggregation has been demonstrated using a combination of the TXA_2 synthase inhibitor dazoxiben (**1**) and TXA_2 receptor antagonists (Chart 1).[25,26] Importantly, the combined administration of **1** and the TXA_2 receptor antagonist sulotroban (**2**) to human volunteers gave a stronger inhibition of platelet aggregation ex vivo than either agent alone.[27] Such observations have stimulated interest in combining the two activities in one molecule,[28,29] and several groups have reported on the effect of incorporating the (arylsulfonamido)alkyl moiety of sulotroban and related antagonists into imidazole- or pyridine-based TXA_2 synthase structures.[30] In an earlier paper in this series[31] we described the adoption of this approach to design indole-based dual TXA_2 synthase inhibitor/receptor antagonists such as **3** and **4**. Alternative arrangements of the side chains are possible, and the previous paper[32] described the design of dual agents such as **5** and **6**, based on the structure of the TXA_2 synthase inhibitor dazmegrel (**7**).[33] These compounds were potent

Chart 1



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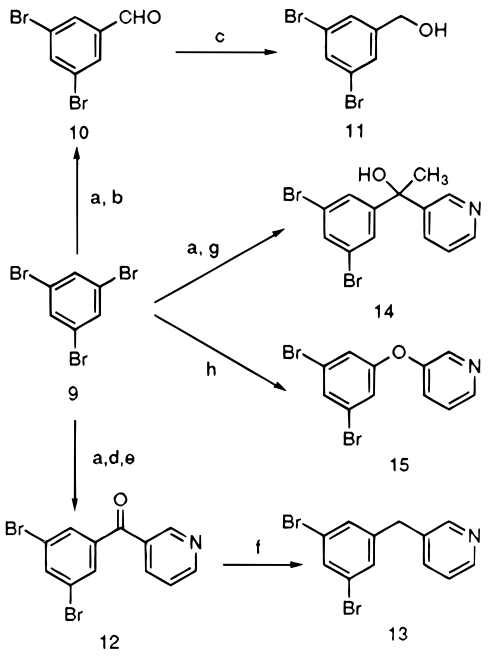
Scheme 1[a]



[a] Conditions/reagents: (a) *n*-BuLi, Et_2O, −78 °C; (b) dimethylformamide; (c) $NaBH_4$, MeOH; (d) 3-cyanopyridine; (e) H^+/H_2O; (f) N_2H_4, KOH; (g) 3-acetylpyridine; (h) NaH, CuO, 3-pyridinol, 2,4,6-trimethylpyridine.

dual agents in vitro, but several, such as **3** and **4**, showed only limited efficacy in vivo.[31] This was ascribed to the fact that they underwent rapid hepatic uptake and clearance, a commonly observed phenomenon with high molecular weight acids.[34]

In this paper, we describe our efforts to overcome this problem by replacement of the indole template with the lower molecular weight benzene ring. Since completion of this work, a related series of benzene-based dual agents has been reported.[30k]

Compound Design

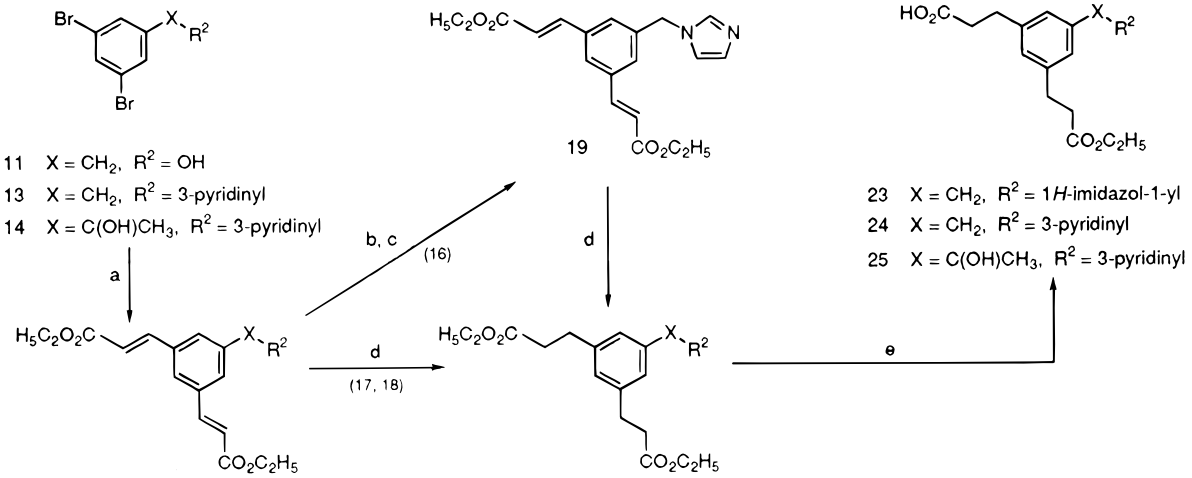
Simplification of the indole systems was based on the templates of **5** and **6** and involved excision of the 6,7 carbon atoms of the indole ring and replacement of the pyrrole ring with benzene to give a 3-[2-[(arylsulfonyl)amino]ethyl]benzenepropanoic acid with a 5-(1*H*-imidazol-1-ylalkyl) or 5-(3-pyridinylalkyl) substituent. The belief that the resulting 3-[2-[(arylsulfonyl)amino]ethyl]benzenepropanoic acid system should be compatible with good TXA_2 receptor antagonist activity is supported by a patent claim that 1,3 isomers of **2** retain antagonist activity.[35] The benzenepropanoic acid analog **8** was synthesized and found to be a more potent antagonist than **2** (see below), confirming its suitability as a template for the design of dual agents. Furthermore, the 1,3 orientation of the acid and heterocycle (imidazole or pyridine) side chains present in **5**−**7** is retained in the target systems, suggesting that good synthase inhibition may be expected.

Chemistry

Our strategy for obtaining the required 1,3,5-trisubstitution pattern depended largely on the ready functionalization of 1,3,5-tribromobenzene (**9**) via lithiation in ether (Scheme 1).[36] Thus, treatment of the lithio intermediate with DMF followed by reduction of the aldehyde product **10**[36] with $NaBH_4$ gave the alcohol **11**. Treatment with 3-cyanopyridine gave the ketone **12** which was reduced under Huang Minlon conditions to give **13**. Treatment with acetylpyridine gave the alcohol **14**. The corresponding ether analog **15** was prepared by reaction of **9** with the sodium salt of 3-pyridinol using copper catalysis.

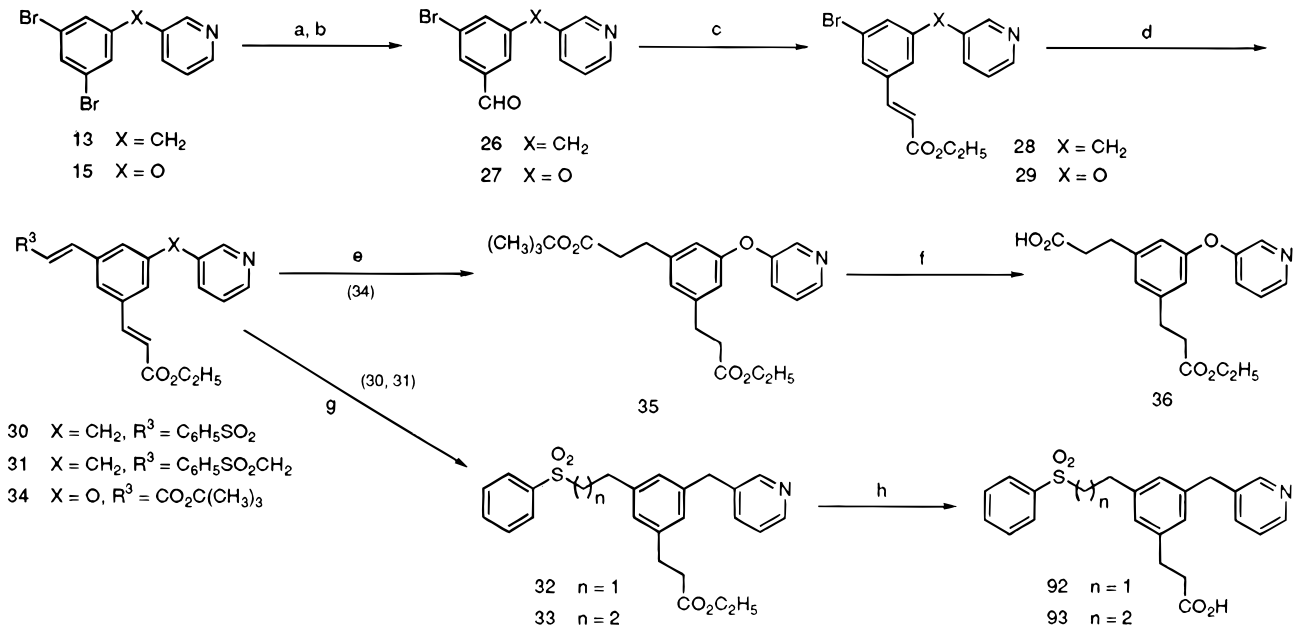
Introduction of the remaining carbon skeleton was then largely dependent on Heck methodology (Scheme 2). Treatment of **11**, **13**, and **14** with 2 equiv of ethyl propenoate in the presence of Pd^0 gave the corresponding bis-propenoic acid esters **16**−**18**, respectively. The alcohol **16** was treated successively with methanesulfonyl chloride/Et_3N followed by imidazole to give **19**. The bis-propenoic esters **17**−**19** were then hydrogenated to the corresponding bis-propanoic esters **21**, **22**, and **20**, respectively. To permit differentiation of the side chains, the bis-esters were hydrolyzed with 1 equiv of

Scheme 2[a]



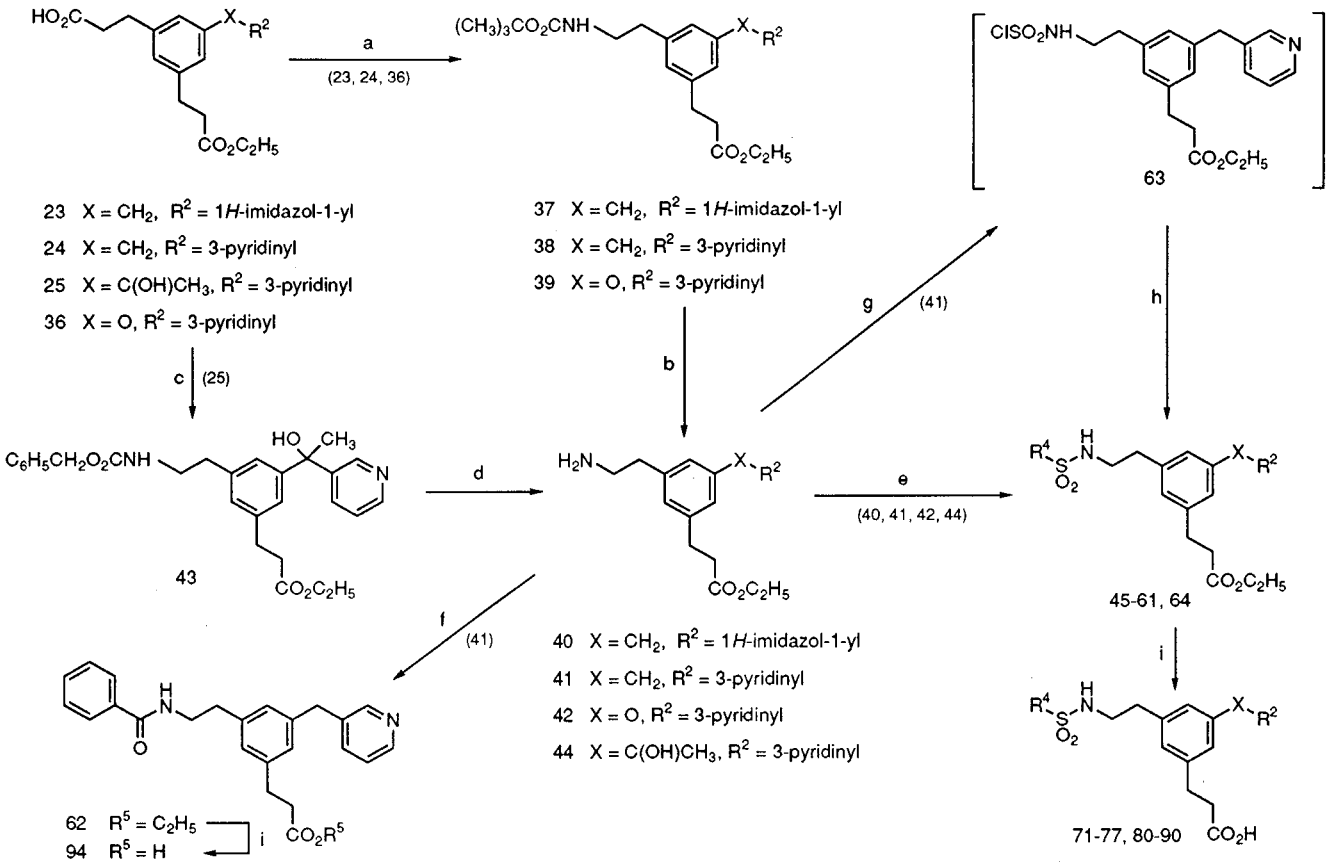
[a] Conditions/reagents: (a) $H_2C{=}CHCO_2C_2H_5$, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Et_3N, CH_3CN; (b) $MeSO_2Cl$, Et_3N; (c) imidazole; (d) HCO_2NH_4, Pd/C, EtOH, THF; (e) NaOH, H_2O.

Scheme 3[a]



[a] Conditions/reagents: (a) *s*-BuLi, Et_2O; (b) dimethylformamide; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH; (d) $H_2C{=}CHR^3$, $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, CH_3CN; (e) HCO_2NH_4, Pd/C, EtOH, THF; (f) TFA; (g) 4-$MeC_6H_4SO_2NHNH_2$, PhMe, reflux; (h) NaOH, H_2O.

Scheme 4[a]

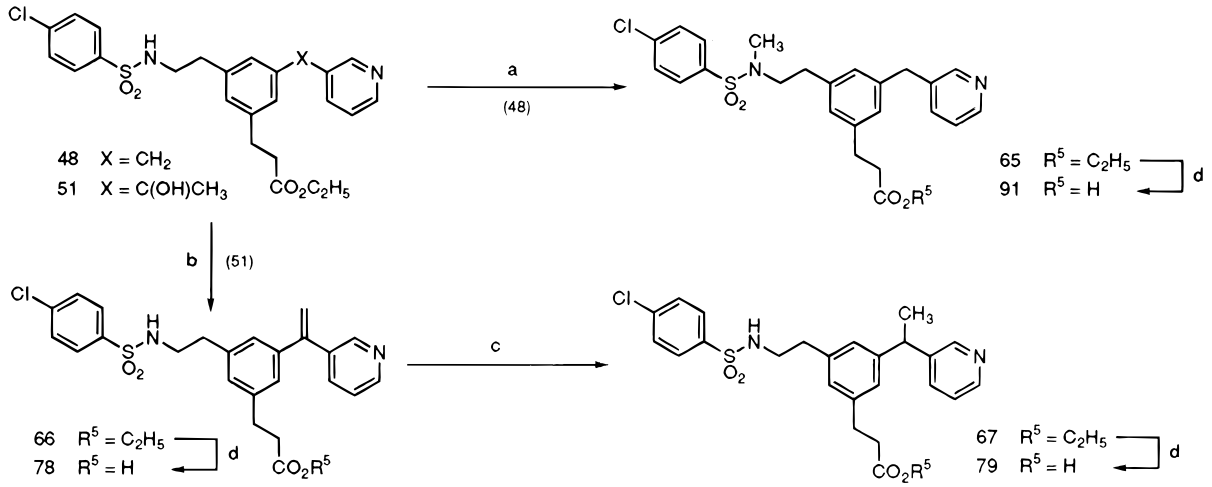


[a] Conditions/reagents: (a) diphenyl phosphorazidate, *t*-BuOH, Et_3N; (b) TFA; (c) diphenyl phosphorazidate, $PhCH_2OH$, Et_3N, dioxane; (d) HCO_2NH_4, Pd/C, EtOH; (e) R^4SO_2Cl, base; (f) PhCOCl, Et_3N; (g) SO_2Cl_2, DMAP, CH_2Cl_2; (h) 4-$ClC_6H_4NH_2$, Et_3N, CH_2Cl_2; (i) NaOH, MeOH, H_2O.

NaOH to give the monoesters **23**−**25**. Yields were only modest, but it was possible to recycle unreacted diester.

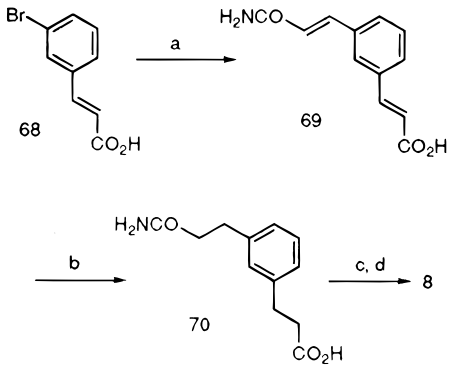
As an alternative approach to differentiation of the side chains, **13** and **15** were treated successively with *s*-BuLi in ether and then DMF to give the aldehydes **26** and **27**, respectively (Scheme 3). These were converted to the propenoate esters **28** and **29** using the Horner−Emmons modification of the Wittig reaction. Treatment of **28** with phenyl vinyl sulfone or allyl phenyl sulfone under Heck conditions gave the unstaurated sulfone esters **30** and **31** which were reduced to the propanoate esters **32** and **33** using diimide generated in situ by

Scheme 5[a]



[a] Conditions/reagents: (a) NaH, DMF, 4-$CH_3C_6H_4SO_3CH_3$; (b) TFA; (c) H_2, Pd/C, EtOH; (d) NaOH, MeOH, H_2O.

Scheme 6[a]



[a] Conditions/reagents: (a) $H_2C{=}CHCONH_2$, $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, CH_3CN; (b) HCO_2NH_4, Pd/C, EtOH, THF; (c) 14% aq NaOCl, 2 N NaOH, dioxane; (d) 4-$ClC_6H_4SO_2Cl$.

thermolysis of 4-methylbenzenesulfonic acid hydrazide. Heck reaction of **29** with *tert*-butyl acrylate gave the unsymmetrical bis-propenoate **34** which was hydrogenated to the bis-propanoate **35**. The latter was converted to the monoethyl ester **36** by treatment with TFA.

The acids **23**, **24**, and **36** were treated with diphenyl phosphorazidate in the presence of *tert*-butyl alochol to give the carbamates **37**−**39**, which were then converted to the amines **40**−**42**, respectively, by reaction with TFA (Scheme 4). In the case of the acid **25**, the Curtius reaction was carried out in the presence of benzyl alcohol, and the resulting carbamate **43** was converted to the amine **44** by hydrogenolysis.

The amines **40**−**42** and **44** were treated with a sulfonyl or sulfamoyl chloride in the presence of an organic base to give the ester products **45**−**61** (see the Experimental Section for specific conditions). The benzamide ester **62** was prepared similarly using benzoyl chloride. In an alternative approach, the amine **41** was first treated with sulfuryl chloride in the presence of 4-DMAP to give the sulfamoyl chloride **63**, which was then treated in situ with 4-chloroaniline to give the corresponding sulfamide ester **64** (R^4 = 4-ClC_6H_4NH). The *N*-methylsulfonamide ester **65** was prepared by methylation of **48** using NaH/4-methylbenzenesulfonic acid methyl ester (Scheme 5). The ester **51** was dehydrated using TFA to give the olefin **66**, which was hydrogenated to the α-methyl analog **67**. The ester intermediates were hydrolyzed under basic conditions to give the product acids listed in Tables 1 and 2 (Schemes 3−5).

The antagonist **8** was prepared from 3-(bromophenyl)-2-propenoic acid (**68**) by a Heck reaction with acrylamide to give **69**, which was reduced to **70** (Scheme 6). This was then converted to **8** in a one-pot reaction by a Hofmann rearrangement using NaOCl, followed by addition of 4-chlorobenzenesulfonyl chloride to the resulting alkaline solution of amine.

Results and Discussion

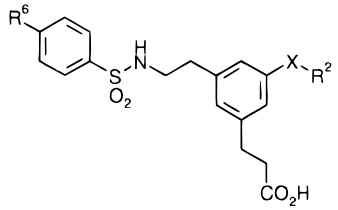
Compound **2** has only modest TXA_2 receptor antagonist activity as measured by inhibition of U46619-induced contraction of rat aorta (Table 1), but the 3-substituted benzenepropanoic acid analog **8** shows a marked increase in potency, confirming the suitability of this system as a basis for the design of dual TXA_2 synthase inhibitor/TXA_2 receptor antagonists. The effect of introducing 3-(1*H*-imidazol-1-yl) or 3-pyridinyl substituents necessary for activity against TXA_2 synthase was then examined. Introduction of 1*H*-imidazol-1-ylmethyl (**72**) has a negligible effect, but antagonist potency is increased by substituents such as 3-pyridinylmethyl (**74**) or 3-pyridinyloxy (**76**). An even greater increase in potency is shown by the methylene- and methyl-substituted analogs **78** and **79**. The antagonist activity of **72** and **74** (Table 1) and the 4-fluorobenzenesulfonyl analog **80** (Table 2) compares favorably with that of the earlier indole-based antagonists **3**−**6**.

Thus, introduction of imidazole or pyridine substituents into the thromboxane receptor antagonist molecule **8** is tolerated, and the more lipophilic pyridinyl substituents make a marked contribution to TXA_2 receptor binding. A pyridinylalkyl group was also found to have a potency-enhancing effect in the previous indole-based series.[31,32]

The effect of modification of the sulfonamide substituent was also studied (Tables 1 and 2). The 4-chlorobenzenesulfonamides **72**, **74**, and **76** and 4-bromobenzenesulfonamide **81** are more potent than the corresponding unsubstituted analogs **71**, **73**, and **75**. These results are consistent with findings with other arylsulfonamide-based TXA_2 receptor antagonists.[17−24,29,30]

Modifications designed to reduce the overall molecular weight of the system were of particular interest in view

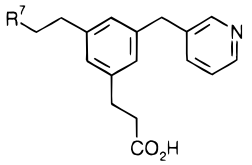
Table 1. Physical Constants and in Vitro Activity of Dual TXA_2 Synthase Inhibitor/TXA_2 Receptor Antagonists



no.	X	R^2	R^6	mp (°C)	yield (%)	formula[a]	TXA_2 receptor antagonism, pA_2	TXA_2 synthase inhibition, IC_{50} (μM)
2							7.09	
3							8.80	0.039
4							9.16	0.061
5							8.20	0.034
6							8.85	0.048
7								0.028
8		H	Cl	98−100	51	$C_{17}H_{18}ClNO_4S$	8.71	
71	CH_2	1-imid[b]	H	123−125	60	$C_{21}H_{23}N_3O_4S$	7.89	0.018
72	CH_2	1-imid	Cl	185−187	67	$C_{21}H_{22}ClN_3O_4S$	8.54	0.038
73	CH_2	3-pyr[c]	H	137−139	61	$C_{23}H_{24}N_2O_4S$	8.80	0.045
74	CH_2	3-pyr	Cl	150−152	89	$C_{23}H_{23}ClN_2O_4S$	9.39	0.039
75	O	3-pyr	H	99−101	84	$C_{22}H_{22}N_2O_5S$	9.06	0.038
76	O	3-pyr	Cl	112−115	56	$C_{22}H_{21}ClN_2O_5S$	9.40	0.037
77	$C(OH)CH_3$	3-pyr	Cl	gum	28	$C_{24}H_{25}ClN_2O_5S$[d]	9.07	0.061
78	$C{=}CH_2$	3-pyr	Cl	gum	59	$C_{24}H_{23}ClN_2O_4S$	10.01	0.053
79	$CH(CH_3)$	3-pyr	Cl	gum	56	$C_{24}H_{25}ClN_2O_4S$	10.16	0.038

[a] C, H, and N analyses were within ±0.4% of calculated values unless otherwise stated. [b] 1*H*-Imidazol-1-yl. [c] 3-Pyridinyl. [d] C: calcd, 58.94; found, 58.34.

Table 2. Physical Constants and in Vitro Activity of Dual TXA_2 Synthase Inhibitor/TXA_2 Receptor Antagonists



no.	R^7	mp (°C)	yield (%)	formula[a]	TXA_2 receptor antagonism, pA_2	TXA_2 synthase inhibition, IC_{50} (μM)
80	4-$FC_6H_4SO_2NH$	132−134	47	$C_{23}H_{23}FN_2O_4S$	8.90	0.020
81	4-$BrC_6H_4SO_2NH$	136−138	85	$C_{23}H_{23}BrN_2O_4S$	9.44	0.049
82	4-$CH_3C_6H_4SO_2NH$	130−132	72	$C_{24}H_{26}N_2O_4S$	8.98	0.037
83	*n*-$C_3H_7SO_2NH$	102−103	51	$C_{20}H_{26}N_2O_4S$	7.71	0.029
84	(*t*-C_4H_9)CH_2SO_2NH	117−119	74	$C_{22}H_{30}N_2O_4S$	8.10	0.039
85	*c*-$C_6H_{11}SO_2NH$	gum	45	$C_{23}H_{30}N_2O_4S$[b]	7.81	0.043
86	$(CH_3)_2NSO_2NH$	76−78	64	$C_{19}H_{25}N_3O_4S$	7.69	0.022
87	$(C_2H_5)_2NSO_2NH$	104−106	50	$C_{21}H_{29}N_3O_4S$	7.43	0.029
88	$C_4H_8NSO_2NH$[c]	86−88	47	$C_{21}H_{27}N_3O_4S$	8.00	0.022
89	$C_5H_{10}NSO_2NH$[d]	gum	36	$C_{22}H_{29}N_3O_4S$[e]	7.81	0.043
90	4-$ClC_6H_4NHSO_2NH$	133−136	65	$C_{23}H_{24}ClN_3O_4S$	8.32	0.038
91	4-$ClC_6H_4SO_2N(CH_3)$	136−138[f]	69	$C_{24}H_{25}ClN_2O_4SNa{\cdot}2H_2O$	6.78	0.054
92	$C_6H_5SO_2$	156−158	74	$C_{23}H_{23}NO_4S$	<6[g]	0.048
93	$C_6H_5SO_2CH_2$	121−123	55	$C_{24}H_{25}NO_4S$[h]	7.80	0.027
94	C_6H_5CONH	115−117	51	$C_{24}H_{24}N_2O_3$[i]	7.96[j]	0.022

[a] C, H, and N analyses were within ±0.4% of calculated values unless otherwise stated. [b] HRMS MH^+ calcd 431.200 455, found 431.201 140. [c] Pyrrolidin-1-ylSO_2NH. [d] Piperidin-1-ylSO_2NH. [e] C: calcd, 61.22; found, 60.79. [f] Softens at 101−103 °C. [g] No significant antagonism at 10^{-6} M. [h] C: calcd, 68.06; found, 67.58. [i] C: calcd, 74.20; found, 73.79. [j] Tissue incubated with compound for 1 h prior to challenge with U46619.

of our aim of minimizing hepatic uptake and clearance in vivo. However, introduction of the smaller propanesulfonamide group (**83**) results in a reduction in potency, and compounds with larger alkyl groups show no significant improvement (**84**, **85**). The use of acyclic and cyclic sulfamides was also explored, but none of the compounds **86**−**89** is as potent as the arylsulfonamides. The arylsulfamide **90** is also less potent.

N-Methylation of the sulfonamide NH is detrimental (compare **74** and **91**) as is removal of the NH (compare **73** and **92**). The least unfavorable modification is replacement of the NH with CH_2 (compare **73** and **93**) resulting in only a 10-fold drop in potency. Comparison of **73** and the benzamide analog **94** shows that the sulfonyl linkage is preferrred to carbonyl.

Thus, for high antagonist potency, an aromatic sulfonamide, preferably substituted by 4-Cl or 4-Br and with an unsubstituted NH, is essential. It has been proposed, based on modeling studies on **2** and related antagonists, that the sulfonamide side chain acts as a mimic for the TXA_2 ω-side chain.[17,32,37−42] An alternative model has been proposed in which the sulfonyl oxygens mimic the ring oxygens of TXA_2, with the aromatic ring occupying an additional binding site on the receptor.[17] Modeling studies on the more rigid antagonist template present in **5** and **6** support this

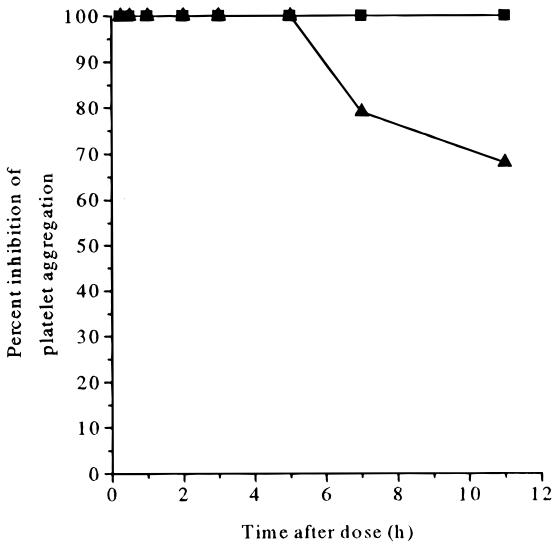


Figure 1. Inhibition of ex vivo platelet aggregation to U46619 following oral administration of compounds to conscious dogs: (■) 5 mg/kg **74** ($n = 4$); (▲) 10 mg/kg **4** ($n = 2$).

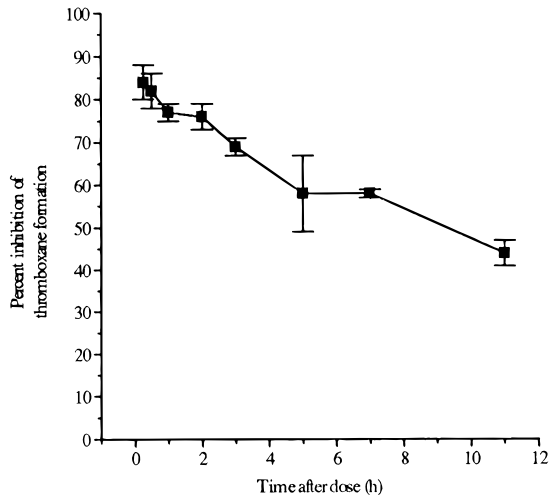


Figure 2. Inhibition of thromboxane synthase following oral administration of 5 mg/kg **74** to conscious dogs ($n = 4$).

idea, and we have proposed the existence of two distinct sites on the receptor capable of accepting a sulfonamide moiety.[32] In view of the greater conformational flexibility of the current compounds compared with **5** and **6**, neither binding mode for the sulfonamide can be excluded.

The results in Tables 1 and 2 show that activity for all compounds against TXA_2 synthase is comparable with that of the standard agent **7**. This result is not unexpected since as long as a distance of 8.5−10 Å is maintained between the imidazole or pyridine ring and the carboxylic acid group, then the enzyme is tolerant of wide structural variation.[8,10]

Based on its in vitro profile, compound **74** was selected for evaluation in vivo. Oral administration of 5 mg/kg to conscious dogs resulted in complete TXA_2 receptor blockade for 11 h as measured by inhibition of ex vivo platelet aggregation to the thromboxane agonist U46619 (Figure 1). By contrast, complete receptor blockade was only observed for 5 h following oral administration of a higher dose (10 mg/kg) of the indole **4**, which has similar activity in vitro. In a separate experiment, 100% inhibition of ex vivo platelet aggregation was observed 24 h after a 5 mg/kg oral dose of **74**, compared with only 30% inhibition of aggregation following a 10 mg/kg oral dose of **4**.

TXA_2 synthase inhibition was determined by measurement of plasma levels of TXB_2, the stable hydrolysis product of TXA_2. Greater than 50% inhibition of the enzyme was observed for at least 7 h, and significant inhibition was still detectable after 11 h (Figure 2). By contrast, no inhibition of TXA_2 synthase was observed at any time point following administration of 10 mg/kg **4** (data not shown). Presumably, inadequate intraplatelet concentrations of **4** were reached to inhibit the enzyme, even though blockade of the extracellular receptor was achievable with this dose.

Thus, we have demonstrated that replacement of the indole ring of the dual thromboxane synthase inhibitor/receptor antagonists **3** and **4** with benzene retains activity in vitro, and furthermore, this modification can result in an improved dual activity profile in vivo.

Conclusion

Incorporation of a 1*H*-imidazol-1-ylalkyl or 3-pyridinylalkyl group, key structural features for TXA_2 synthase inhibition, and a 3-(arylsulfonamido)ethyl substituent, a key feature for TXA_2 receptor antagonism, into a 3,5-disubstituted benzenepropanoic acid system leads to compounds with potent dual activity in vitro. The more lipophilic pyridinylalkyl substituents also contribute to increased TXA_2 receptor antagonist potency. An arylsulfonamido substituent, preferably substituted by chlorine or bromine, is necessary for optimal TXA_2 receptor antagonism. Modification of the SO_2NH linkage is detrimental, as is replacement of the aryl group by alkyl or dialkylamino groups.

The pyridinylmethyl analog **74** shows long-lasting dual activity following oral administration to conscious dogs. Combined TXA_2 synthase inhibitor/TXA_2 receptor antagonists such as **74** may prove to be valuable in the treatment of diseases where single agents have so far proved ineffective.

Experimental Section

Chemistry. All melting points are uncorrected and were obtained using a Büchi 510 melting point apparatus. NMR spectra were determined using a Nicolet QE 300 spectrometer, using $CDCl_3$ as solvent unless otherwise stated.

3,5-Dibromobenzenemethanol (11). $NaBH_4$ (0.75 g, 19.8 mmol) was added portionwise to a stirred suspension of 3,5-dibromobenzaldehyde (**10**)[36] (10.46 g, 39.6 mmol) in methanol (50 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, allowed to reach room temperature, and then adjusted to pH 2 with concentrated HCl. Evaporation under vacuum gave a residue that was partitioned between EtOAc and water. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give 10.0 g (95%) of **11**: mp 103−104 °C; ^{1}H NMR δ 1.79 (t, $J = 5$ Hz, 1H), 4.65 (d, $J = 5$ Hz, 2H), 7.44 (s, 2H), 7.57 (s, 1H). Anal. ($C_7H_6Br_2O$) C, H, N.

(3,5-Dibromophenyl)-3-pyridinylmethanone (12). A 2.5 M solution of *n*-BuLi in hexane (40.0 mL, 100 mmol) was added dropwise to a stirred mixture of 1,3,5-tribromobenzene (**10**) (31.5 g, 100 mmol) in dry ether (1 L) at −78 °C under dry N_2. The resulting solution was stirred at −78 °C for 30 min, and then 3-cyanopyridine (10.4 g, 100 mmol) in dry ether (100 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, and then the temperature was allowed to rise to 0 °C; 2 N hydrochloric acid (200 mL) was added with stirring, and the ether layer was decanted off and extracted several times with 2 N hydrochloric acid. The combined acid extracts were warmed on a steam bath for 20 min, then cooled, and basified with 2 N KOH solution. The solid was filtered off, washed

with water, dried, and combined with the solid obtained by evaporation of the ether solution. The mixture was chromatographed on silica gel using CH_2Cl_2 as eluent to give 23.33 g (68%) of **12**: mp 124−126 °C; ^{1}H NMR δ 7.47−7.52 (m, 1H), 7.84 (s, 2H), 8.02 (s, 1H), 8.08−8.12 (m, 1H), 8.82−8.85 (m, 1H), 8.96−8.98 (m, 1H). Anal. ($C_{12}H_7Br_2NO$) C, H, N.

3-[(3,5-Dibromophenyl)methyl]pyridine (13). A solution of **12** (19.0 g, 55.7 mmol) and hydrazine hydrate (13.9 mL, 446 mmol) in ethylene glycol (140 mL) was heated under reflux for 45 min. Volatile material was distilled off until the internal temperature reached 180 °C, and then the mixture was cooled to 80 °C. KOH (7.80 g, 140 mmol) was added, and the solution was heated under reflux for 30 min, cooled, and poured into water. The mixture was extracted several times with EtOAc, and the combined extracts were washed with water, dried ($MgSO_4$), and evaporated to give 16.38 g (90%) of **13**: mp 70−72 °C (from EtOAc/hexane); ^{1}H NMR δ 3.91 (s, 2H), 7.21−7.25 (3H + $CHCl_3$), 7.42−7.45 (m, 1H), 7.53 (s, 1H), 8.47−8.52 (m, 2H). Anal. ($C_{12}H_9Br_2N$) C, H, N.

α-(3,5-Dibromophenyl)-α-methyl-3-pyridinemethanol (14). 1,3,5-Tribromobenzene (**9**) (15.74 g, 50 mmol) in dry ether (550 mL) was treated with 2.5 M *n*-BuLi in hexane (20.0 mL, 50 mmol) as described for the preparation of **12**. 3-Acetylpyridine (6.06 g, 50 mmol) in dry ether (50 mL) was added, and the mixture was stirred at about −55 °C for 30 min and then allowed to warm to room temperature. Brine was added, and the organic layer was separated, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent and trituration of the residue with hexane gave 13.22 g (74%) of **14**: mp 152−155 °C; ^{1}H NMR δ 1.95 (s, 3H), 2.39 (s, 1H), 7.49 (s, 2H), 7.55 (s, 1H), 7.69−7.72 (m, 1H), 8.50 (m, 1H), 8.66 (m, 1H). Anal. ($C_{13}H_{11}Br_2NO$) C, H, N.

3-(3,5-Dibromophenoxy)pyridine (15). Sodium hydride (3.24 g, 81 mmol of 60% dispersion in mineral oil) was added portionwise to a stirred mixture of **9** (76.4 g, 242 mmol), 3-pyridinol (15.4 g, 162 mmol), cuprous oxide (11.6 g, 81 mmol), and 2,4,6-trimethylpyridine (400 mL). After cessation of hydrogen evolution, the mixture was heated at 200 °C for 8 h and then cooled, diluted with water and EtOAc, basified with concentrated aqueous NH_3, and filtered. The residue was washed with EtOAc, and the organic layer of the filtrate and washings were combined, washed with brine, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel. Elution with Et_2O/hexane (1:4) gave 18.55 g (35% based on 3-pyridinol) of **15** as an oil: ^{1}H NMR δ 7.07 (s, 2H), 7.32−7.36 (m, 2H), 7.42 (s, 1H), 8.42 (s, 1H), 8.47 (m, 1H). Anal. ($C_{11}H_7Br_2NO$) C, H, N.

3-Bromo-5-(3-pyridinylmethyl)benzaldehyde (26). A 1.3 M solution of *s*-BuLi in hexane (27.7 mL, 36 mmol) was added dropwise to a stirred suspension of **13** (9.81 g, 30 mmol) in dry ether (300 mL) at −78 °C under dry N_2, and the mixture was stirred at this temperature for 15 min. DMF (6.60 g, 90 mmol) was added, the mixture was stirred at −78 °C for 30 min and allowed to warm up to room temperature, and AcOH (12 mL) was added. After 10 min, water (150 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc, and the organic layers were combined, washed with saturated $NaHCO_3$ solution, and dried ($MgSO_4$). The solvent was evaporated, and the residue was crystallized from Et_2O/hexane to give 5.25 g (63%) of **26**: mp 97−98 °C; ^{1}H NMR δ 4.03 (s, 2H), 7.22−7.26 (m, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.57 (s, 1H), 7.61 (s, 1H), 7.86 (s, 1H), 8.50−8.51 (m, 2H), 9.50 (s, 1H). Anal. ($C_{13}H_{10}BrNO$) C, H, N.

Compound **27** (65%, oil) was prepared in a similar manner, using chromatography (silica gel/CH_2Cl_2) for purification: ^{1}H NMR δ 7.36−7.43 (m, 4H), 7.76 (s, 1H), 8.45 (d, J = 1.7 Hz, 1H), 8.48−8.50 (m, 1H), 9.90 (s, 1H). Anal. ($C_{12}H_8BrNO_2$) C, H, N.

3-[3-Bromo-5-(3-pyridinylmethyl)phenyl]-2-propenoic Acid Ethyl Ester (28). Triethyl phosphonoacetate (607 mg, 2.71 mmol) was added dropwise to a stirred suspension of sodium hydride (108 mg of 40% suspension in mineral oil, 2.71 mmol) in dry THF. The mixture was stirred for 30 min at room temperature, and then **26** (680 mg, 2.46 mmol) was added. Stirring was continued for 1 h, and the mixture was partitioned between ether and water. The organic layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was chromatographed on silica gel using a hexane/EtOAc elution gradient (30−70% EtOAc) to give 754 mg (89%) of **28**: mp 81−83 °C (from Et_2O); ^{1}H NMR δ 1.32 (t, J = 7.15 Hz, 3H), 3.96 (s, 2H), 4.25 (q, J = 7.15 Hz, 2H), 6.39 (d, J = 16 Hz, 1H), 7.22 (s, 1H), 7.22−7.26 (m, 1H), 7.32 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.53 (s, 1H), 7.54 (d, J = 16 Hz, 1H), 8.49−8.51 (m, 2H). Anal. ($C_{17}H_{16}BrNO_2$) C, H, N.

Compound **29** (84%, oil) was prepared similarly from **27** and triethyl phosphonoacetate: ^{1}H NMR δ 1.31 (t, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 6.37 (d, J = 16 Hz, 1H), 7.05 (s, 1H), 7.14 (s, 1H), 7.32−7.33 (m, 2H), 7.42 (s, 1H), 7.52 (d, J = 16 Hz, 1H), 8.42−8.45 (m, 2H). Anal. ($C_{16}H_{14}BrNO_3$) C, H, N.

3,3′-[5-(Hydroxymethyl)-1,3-phenylene]bis(2-propenoic acid) Diethyl Ester (16). A stirred mixture of **11** (9.80 g, 36.9 mmol), ethyl propenoate (11.1 g, 110.6 mmol), palladium(II) acetate (0.45 g, 1.84 mmol), tri-*o*-tolylphosphine (1.12 g, 3.69 mmol), Et_3N (11.2 g, 110.6 mmol), and CH_3CN (15 mL) was heated under reflux under N_2 for 1 h and then cooled and partitioned between CH_2Cl_2 and water. The aqueous layer was separated and washed with CH_2Cl_2, and the combined organic layers were washed with water and dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue on silica gel (CH_2Cl_2/MeOH, 99:1) gave 10.61 g (94%) of **16**: mp 68−69.5 °C (from Et_2O/hexane); ^{1}H NMR δ 1.33 (t, J = 7 Hz, 6H), 2.00 (t, J = 4.5 Hz, 1H), 4.26 (q, J = 7 Hz, 4H), 4.74 (d, J = 4.5 Hz, 2H), 6.47 (d, J = 16 Hz, 2H), 7.54 (s, 3H), 7.65 (d, J = 16 Hz, 2H). Anal. ($C_{17}H_{20}O_5$) C, H.

The following compounds were prepared similarly.

Compound **17** (83%, mp 94−96 °C) from **13** and ethyl propenoate: ^{1}H NMR δ 1.33 (t, J = 7 Hz, 6H), 4.00 (s, 2H), 4.26 (q, J = 7 Hz, 4H), 6.43 (d, J = 16 Hz, 2H), 7.21−7.26 (m, 1H), 7.33 (s, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.62 (d, J = 16 Hz, 2H), 8.49−8.51 (m, 2H). Anal. ($C_{22}H_{23}NO_4$) C, H, N.

Compound **18** (98%, oil) from **14** and ethyl propenate: ^{1}H NMR δ 1.32 (t, J = 7.1 Hz, 6H), 2.00 (s, 3H), 2.66 (s, 1H), 4.26 (q, J = 7.1 Hz, 4H), 6.44 (d, J = 16 Hz, 2H), 7.23−7.28 (m, 1H), 7.53 (s, 1H), 7.58 (s, 2H), 7.63 (d, J = 16 Hz, 2H), 7.72−7.76 (m, 1H), 8.49 (m, 1H), 8.68 (m, 1H).

Compound **30** (54%, mp 118−120 °C) from **28** and phenyl vinyl sulfone: ^{1}H NMR δ 1.32 (d, J = 7.1 Hz, 3H), 3.99 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 6.41 (d, J = 16 Hz, 1H), 6.86 (d, J = 16.4 Hz, 1H), 7.21−7.25 (m, 1H), 7.28 (s, 1H), 7.36 (s, 1H), 7.43−7.46 (m, 2H), 7.48 (s, 1H), 7.54−7.65 (m, 5H), 7.93−7.96 (m, 2H), 8.48−8.50 (m, 2H). Anal. ($C_{25}H_{23}NO_4S$) C, H, N.

Compound **31** (29%, oil) from **28** and allyl phenyl sulfone: ^{1}H NMR δ 1.35 (t, J = 7.1 Hz, 3H), 3.93−3.98 (s + m, 4H), 4.15 (q, J = 7.1 Hz, 2H), 6.07−6.17 (m, 1H), 6.32−6.41 (m, 2H), 7.09 (m, 3H), 7.22−7.28 (m, 3H), 7.43−7.68 (m, 4H), 7.87−7.89 (m, 2H), 8.50 (m, 2H).

Compound **34** (85%, mp 116−118 °C) from **29** and *tert*-butyl propenoate: ^{1}H NMR δ 1.32 (t, J = 7 Hz, 3H), 1.51 (s, 9H), 4.25 (q, J = 7 Hz, 2H), 6.33 (d, J = 16 Hz, 1H), 6.39 (d, J = 16 Hz, 1H), 7.14 (s, 2H), 7.30−7.31 (m, 2H), 7.39 (s, 1H), 7.49 (d, J = 16 Hz, 1H), 7.59 (d, J = 16 Hz, 1H), 8.42−8.43 (m, 2H). Anal. ($C_{23}H_{25}NO_5$) C, H, N.

Compound **69** (91%, mp >250 °C) from 3-(bromophenyl)-2-propenoic acid (**68**) and acrylamide: ^{1}H NMR (DMSO-d_6) δ 6.57 (d, J = 15.7 Hz, 1H), 6.66 (d, J = 15.8 Hz, 1H), 7.09 (s, 1H), 7.41 (d, J = 15.8 Hz), 7.40−7.46 (m, 1H), 7.48 (s, br, 1H), 7.55−7.67 (m, 3H), 7.85 (s, 1H), 12.40 (s, 1H). Anal. ($C_{12}H_{11}NO_3$) H, N; C: calcd, 66.35; found, 65.92.

3,3′-[5-(1*H*-Imidazol-1-ylmethyl)-1,3-phenylene]bis(2-propenoic acid) Diethyl Ester (19). Methanesulfonyl chloride (4.33 g, 37.8 mmol) was added dropwise to a stirred solution of **16** (10.46 g, 34.4 mmol) and Et_3N (3.83 g, 37.8 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C, and the mixture was allowed to stand for 1 h, washed with water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was dissolved in acetone (100 mL). This solution was added over 20 min to a stirred mixture of imidazole (23.0 g, 344 mmol), anhydrous Na_2CO_3 (7.29 g, 68.8 mmol), and NaI (100 mg) in acetone (100 mL) at room temperature, and the mixture was heated under reflux for 10 h, then cooled, and filtered. The

solid was washed with acetone, and the combined filtrate and washings were evaporated. The residue was chromatographed on silica gel using CH_2Cl_2/MeOH (95:5) to give 10.8 g (89% from **16**) of **19**: mp 116−117.5 °C; ^{1}H NMR δ 1.33 (t, J = 7.1 Hz, 6H), 4.26 (q, J = 7.1 Hz, 4H), 5.16 (s, 2H), 6.43 (d, J = 16 Hz, 2H), 6.91 (s, 1H), 7.14 (s, 1H), 7.26 (s, 1H), 7.58 (s, 1H), 7.59 (s, 1H), 7.62 (d, J = 16 Hz, 2H). Anal. ($C_{20}H_{22}N_2O_4$) C, H, N.

5-(1*H*-Imidazol-1-ylmethyl)-1,3-benzenedipropanoic Acid Diethyl Ester (20). Pd on carbon (10%) (1.0 g) was added portionwise to a stirred mixture of **19** (10.55 g, 29.8 mmol), HCO_2NH_4 (18.75 g, 298 mmol), EtOH (60 mL), and THF (60 mL) at room temperature under N_2. The mixture was heated at 60 °C for 1 h, then cooled, and filtered. The filtrate was evaporated, and the residue was partitioned between EtOAc and water. The EtOAc layer was separated, washed with water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel using CH_2Cl_2 as eluent to give 8.62 g (81%) of **20** as an oil: ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 6H), 2.55 (t, J = 7.7 Hz, 4H), 2.88 (t, J = 7.7 Hz, 4H), 4.10 (q, J = 7.1 Hz, 4H), 5.04 (s, 2H), 6.82 (s, 2H), 6.87 (s, 1H), 6.99 (s, 1H), 7.07 (s, 1H), 7.52 (s, 1H). Anal. ($C_{20}H_{26}N_2O_4$) H, N; C: calcd, 67.01; found, 66.29.

The following compounds were prepared similarly.

Compound **21** (95%, oil) from **17**: ^{1}H NMR δ 1.20 (t, J = 7.1 Hz, 6H), 2.55 (t, J = 7.8 Hz, 4H), 2.86 (t, J = 7.8 Hz, 4H), 3.89 (s, 2H), 4.09 (q, J = 7.1 Hz, 4H), 6.84 (s, 2H), 6.89 (s, 1H), 7.16−7.20 (m, 1H), 7.41−7.45 (m, 1H), 8.43−8.47 (m, 1H).

Compound **22** (95%, oil) from **18**: ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 6H), 1.95 (s, 3H), 2.56 (t, J = 7.8 Hz, 4H), 2.88 (t, J = 7.8 Hz, 4H), 4.08 (q, J = 7.1 Hz, 4H), 6.95 (s, 1H), 7.08 (s, 2H), 7.19−7.22 (m, 1H), 7.68−7.71 (m, 1H), 8.45−8.47 (m, 1H), 8.62−8.63 (m, 1H).

Compound **35** (98%, oil) from **34**: ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 2.52 (t, J = 7.7 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.93 (t, J = 7.7 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 6.73 (s, 2H), 6.86 (s, 1H), 7.28−7.30 (m, 2H), 8.38−8.41 (m, 2H). Anal. ($C_{23}H_{29}NO_5$) C, H, N.

Compound **70** (52%, mp 140−142 °C) from **69** using MeOH/THF (1:1) as solvent and 8 h reflux: ^{1}H NMR (DMSO-d_6) δ 2.31 (t, J = 7.9 Hz, 2H), ca. 2.48 (t, 2H + DMSO), 2.71−2.78 (m, 4H), 6.70 (s, br, 1H), 6.99−7.04 (m, 3H), 7.12−7.17 (m, 1H), 7.23 (s, br, 1H), 12.03 (s, br, 1H). Anal. ($C_{12}H_{15}NO_3$) C, H; N: calcd, 6.33; found, 5.60.

5-(3-Pyridinylmethyl)-1,3-benzenedipropanoic Acid Monoethyl Ester (24). A solution of NaOH (1.66 g, 41.5 mmol) in water (3 mL) was added to a solution of **21** (15.27 g, 41.6 mmol) in EtOH (25 mL), and the mixture was heated under reflux for 45 min. The solution was evaporated, and the residue was partitioned between EtOAc and water. The aqueous layer was washed with EtOAc and the organic layers were combined, dried ($MgSO_4$), and evaporated to give 4.18 g (27%) of recovered **21**. The aqueous phase was acidified with AcOH, and the mixture was extracted several times with EtOAc. The combined extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent gave an oil that was chromatographed on silica gel using CH_2Cl_2/MeOH/Et_2NH (90:5:5) as eluent. The early product fractions were evaporated to give 6.13 g (43%) of **24**: mp 62−64 °C; ^{1}H NMR δ 1.20 (t, J = 7.1 Hz, 3H), 2.54−2.64 (m, 4H), 2.85−2.93 (m, 4H), 3.92 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 6.85 (s, 1H), 6.89 (s, 1H), 6.93 (s, 1H), 7.23−7.27 (m, 1H), 7.53 (d, J = 7.8 Hz), 8.42−8.48 (m, 2H).

The following compounds were prepared similarly.

Compound **23** (41%, mp 103−104.5 °C) from **20**: ^{1}H NMR (DMSO-d_6) δ 1.09 (t, J = 7.1 Hz, 3H), 2.42−2.55 (m, 4H), 2.69−2.75 (m, 4H), 3.29 (br, 1H), 3.98 (q, J = 7.1 Hz, 2H), 5.06 (s, 2H), 6.84 (s, 1H), 6.89 (s, 1H), 6.93 (s, 1H), 6.98 (s, 1H), 7.11 (s, 1H), 7.67 (s, 1H). Anal. ($C_{18}H_{22}N_2O_4$) C, H, N.

Compound **25** (33%, oil) from **22**: ^{1}H NMR δ 1.20 (t, J = 7.1 Hz, 3H), 1.90 (s, 3H), 2.50−2.60 (m, 4H), 2.83−2.90 (m, 4H), 4.07 (q, J = 7.1 Hz, 2H), 6.93 (s, 1H), 7.08 (s, 2H), 7.21−7.23 (m, 1H), 7.78−7.81 (m, 1H), 8.32−8.34 (m, 1H), 8.51−8.52 (m, 1H).

5-(3-Pyridinyloxy)-1,3-benzenedipropanoic Acid Monoethyl Ester (36). A solution of **35** (7.80 g, 19.5 mmol) in TFA (20 mL) and CH_2Cl_2 was stirred at room temperature for 20 h and then evaporated. The residue was azeotroped with PhMe and then dissolved in Et_2O (100 mL) and pyridine (10 mL). The mixture was washed with water, and the combined aqueous washings were extracted with EtOAc. The organic solutions were combined, washed with water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was triturated with Et_2O and hexane to give 6.56 g (98%) of **36**: mp 85−87 °C; ^{1}H NMR (DMSO-d_6) δ 1.08 (t, J = 7 Hz, 3H), 2.45−2.56 (m, 4H), 2.70−2.75 (m, 4H), 3.98 (q, J = 7 Hz, 2H), 6.71 (s, 1H), 6.74 (s, 1H), 6.88 (s, 1H), 7.36−7.37 (m, 2H), 8.30 (s, 2H). Anal. ($C_{19}H_{21}NO_5$) C, H, N.

3-[2-[[(1,1-Dimethylethoxy)carbonyl]amino]ethyl]-5-(1*H*-imidazol-1-ylmethyl)benzenepropanoic Acid Ethyl Ester (37). A solution of **23** (3.0 g, 9.08 mmol), diphenyl phosphorazidate (2.75 g, 9.99 mmol), and Et_3N (1.01 g, 9.99 mmol) in 1,1-dimethylethanol (30 mL) was heated under reflux for 18 h and then evaporated. The residue was dissolved in EtOAc, and the solution was washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel using CH_2Cl_2/MeOH (97:3) as eluent to give 1.45 g (40%) of **37** as an oil: ^{1}H NMR δ 1.21 (t, J = 7.15 Hz, 3H), 1.43 (s, 9H), 2.56 (t, J = 7.7 Hz, 2H), 2,73 (t, J = 7.1 Hz, 2H), 2.88 (t, J = 7.7 Hz, 2H), 3.28−3.34 (m, 2H), 4.10 (q, J = 7.15 Hz, 2H), 4.53 (br, 1H), 5.05 (s, 2H), 6.83 (s, 2H), 6.88 (s, 1H), 7.11 (s, 1H), 7.52 (s, 1H). Anal. ($C_{22}H_{31}N_3O_4$) C, H, N.

Compounds **38** and **39** were prepared similarly as oils from **24** and **36**, respectively, and used directly in the next stage. Spectral data are summarized in the Supporting Information.

3-(2-Aminoethyl)-5-(1*H*-imidazol-1ylmethyl)benzenepropanoic Acid Ethyl Ester (40). A solution of **37** (2.00 g, 4.98 mmol) and TFA (4 mL) in CH_2Cl_2 (20 mL) was stirred at room temperature for 4 h and then evaporated. The residue was partitioned between CH_2Cl_2 and dilute aqueous NH_3 solution. The aqueous layer was separated and extracted with CH_2Cl_2, and the organic extracts were combined, washed with water, and evaporated. The residue was partitioned between EtOAc and water containing sufficient AcOH to extract out the product. The aqueous layer was washed with EtOAc, basified with NH_3 solution, and extracted three times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated to give 1.30 g (87%) of **40** as an oil which was used directly in the next stage: ^{1}H NMR δ 1.20 (t, J = 7.1 Hz, 3H), 2.57 (t, J = 7.7 Hz), 2.67 (t, J = 6.8 Hz, 2H), 2.85−2.95 (m, 4H), 4.08 (q, J = 7.1 Hz, 2H), 5.06 (s, 2H), 6.82 (s, 1H), 6.83 (s, 1H), 6.90 (s, 1H), 6.99 (s, 1H), 7.08 (s, 1H), 7.53 (s, 1H).

Compounds **41** and **42** were prepared similarly as oils from **38** and **39**, respectively, and used directly in the next stage. Spectral data are summarized in the Supporting Information.

3-[1-Hydroxy-1-(3-pyridinyl)ethyl]-5-[2-[[(phenylmethoxy)carbonyl]amino]ethyl]benzenepropanoic Acid Ethyl Ester (43). A solution of **25** (1.68 g, 4.5 mmol), diphenyl phosphorazidate (1.40 g, 5.1 mmol), and Et_3N (0.50 g, 5.0 mmol) in dry dioxane (20 mL) was heated at 100 °C for 1 h. Benzyl alcohol (1.08 g, 10.0 mmol) was added, and the solution was heated under reflux for 18 h and then evaporated. The residue was partitioned between EtOAc and water, and the aqueous layer was separated and extracted with EtOAc. The organic layers were combined, washed with brine, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel using CH_2Cl_2/MeOH (95:5) as eluent to give 1.02 g (46%) of **43** as an oil which was used directly in the next stage: ^{1}H NMR δ 1.11 (t, J = 7.1 Hz, 3H), 1.92 (s, 3H), 2.56 (t, J = 7.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.88 (t, J = 7.8 Hz, 3H), 3.37−3.43 (m, 2H), 3.70 (s, 1H), 4.08 (q, J = 7.1 Hz, 2H), 5.07 (s, 2H), 6.91 (s, 1H), 7.09 (s, 1H), 7.11 (s, 1H), 7.20−7.36 (m, 6H), 7.70−7.73 (m, 1H), 8.41−8.43 (m, 1H), 8.61−8.62 (m, 1H).

3-(2-Aminoethyl)-5-[1-hydroxy-1-(3-pyridinyl)ethyl]benzenepropanoic Acid Ethyl Ester (44). A stirred mixture of **43** (1.0 g, 2.1 mmol), HCO_2NH_4 (1.32 g, 21.0 mmol), and 10% Pd on carbon (0.10 g) in EtOH (20 mL) was heated under reflux for 16 h, allowed to cool slightly, and then filtered. The residue was washed with EtOH, and the combined filtrate and washings were evaporated. The residue was chromatographed on silica gel using CH_2Cl_2/MeOH/NH_3 solution (SG 0.880),

initially in a ratio of 95:5:0.5 followed by 90:10:1, to give 0.50 g (70%) of **44** as an oil which was used directly in the next stage: ^{1}H NMR δ 1.20 (t, J = 7.1 Hz, 3H), 1.91 (s, 3H), 2.07 (br, 2H), 2.57 (t, J = 7.7 Hz, 2H), 2.66 (t, J = 6.7 Hz, 2H), 2.81−2.90 (m, 4H), 4.08 (q, J = 7.1 Hz, 2H), 6.90 (s, 1H), 7.07 (s, 2H), 7.18−7.22 (m, 1H), 7.68−7.72 (m, 1H), 8.40−8.42 (m, 1H), 8.60−8.61 (m, 1H).

3-[2-[[(4-Chlorophenyl)sulfonyl]amino]ethyl]-5-(1*H*-imidazol-1-ylmethyl)benzenepropanoic Acid Ethyl Ester (46). 4-Chlorobenzenesulfonyl chloride (358 mg, 1.82 mmol) was added to a stirred solution of **40** (500 mg, 1.66 mmol) and 4-(dimethylamino)pyridine (223 mg, 1.82 mmol) in CH_2Cl_2 (5 mL) at room temperature, and the mixture was stirred for 2.5 h, then washed with water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel using CH_2Cl_2/MeOH (elution gradient 100:0 to 95:5) as eluent to give 489 mg (62%) of **46** as an oil: ^{1}H NMR δ 1.21 (t, J = 7 Hz, 2H), 2.55 (t, J = 7.5 Hz, 2H), 2.72 (t, J = 6.8 Hz, 2H), 2.86 (t, J = 7.5 Hz, 2H), 3.18 (m, 2H), 4.10 (q, J = 7 Hz, 2H), 4.74−4.77 (m, 1H), 5.03 (s, 2H), 6.69 (s, 1H), 6.84 (s, 1H), 6.87 (s, 1H), 6.89 (s, 1H), 7.07 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.51 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H). Anal. ($C_{23}H_{26}ClN_3O_4S$) C, H, N.

The amine **40** was converted similarly to **45** (R^4 = C_6H_5). Et_3N was used as base in the conversion of **41** to **47** (R^4 = C_6H_5), **48** (R^4 = 4-ClC_6H_4), **52** (R^4 = 4-FC_6H_4), **53** (R^4 = 4-BrC_6H_4), **54** (R^4 = 4-$CH_3C_6H_4$), **55** (R^4 = n-C_3H_7), **58** (R^4 = $(CH_3)_2N$), and **62** (R^6 = C_6H_5CO), in the conversion of **42** to **49** (R^4 = C_6H_5) and **50** (R^4 = 4-ClC_6H_4), and in the conversion of **44** to **51** (R^4 = 4-ClC_6H_4). A 1:1 mixture of Et_3N and 4-DMAP was used as base in the conversion of **41** to **56** (R^4 = *t*-$(C_4H_9)CH_2$), **57** (R^4 = *c*-C_6H_{11}), **59** (R^4 = $(C_2H_5)_2N$), **60** (R^4 = pyrrolidin-1-yl), and **61** (R^4 = piperidin-1-yl). All products were isolated as oils. Spectral data are summarized in the Supporting Information.

3-[2-[[[(4-Chlorophenyl)amino]sulfonyl]amino]ethyl]-5-(3-pyridinylmethyl)benzenepropanoic Acid Ethyl Ester (64). A solution of **41** (500 mg, 1.60 mmol) and 4-(dimethylamino)pyridine (195 mg, 1.60 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 305 min to a stirred solution of sulfuryl chloride (252 mg, 1.87 mmol) in dry CH_2Cl_2 (1 mL) at −75 °C. The mixture was stirred at −75 °C for 15 min and at room temperature for 1 h and then cooled again to −75 °C, and 4-chloroaniline (408 mg, 3.2 mmol) and Et_3N (320 mg, 3.2 mmol) were added. The resulting mixture was stirred at room temperature for 5 h, then washed with water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel using CH_2Cl_2/MeOH (99:1) as eluent to give 480 mg (60%) of **64** as a gum: ^{1}H NMR δ 1.20 (t, J = 7.15 Hz, 3H), 2.54 (t, J = 7.7 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H), 2.84 (t, J = 7.7 Hz, 2H), 3.24−3.30 (m, 2H), 3.87 (s, 2H), 4.09 (q, J = 7.15 Hz, 2H), 4.69 (t, J = 6.1 Hz, 1H), 6.72 (s, 1H), 6.78 (s, 1H), 6.87 (s, 1H), 7.04 (d, J = 8.7 Hz, 2H), 7.18−7.22 (m, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 7.9 Hz, 1H), 8.44 (m, 2H). Anal. ($C_{25}H_{28}ClN_3O_4S$) C, H, N.

3-[2-[[(4-Chlorophenyl)sulfonyl]methylamino]ethyl]-5-(3-pyridinylmethyl)benzenepropanoic Acid Ethyl Ester (65). Sodium hydride (41 mg of 60% dispersion in mineral oil, 1.03 mmol) was added portionwise to a stirred, ice-cooled solution of **48** (500 mg, 1.03 mmol) in dry DMF (5 mL). The mixture was stirred with cooling for 30 min, then 4-methylbenzenesulfonic acid methyl ester (191 mg, 1.03 mmol) was added, and stirring was continued for a further 4.5 h. The mixture was partitioned between Et_2O and water, and the aqueous layer was separated and extracted with Et_2O. The organic layers were combined, washed with water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel using CH_2Cl_2 followed by CH_2Cl_2/MeOH (24:1) as eluent to give 425 mg (82%) of **65** as an oil: ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 3H), 2.56 (t, J = 7.7 Hz, 2H), 2.72 (s, 3H), 2.78 (t, J = 7.6 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 3.22 (t, J = 7.6 Hz, 2H), 3.90 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 6.83 (s, 1H), 6.88 (s, 2H), 7.29−7.33 (m, 1H), ca. 7.45 (m, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 8.46−8.48 (m, 2H). Anal. ($C_{26}H_{29}ClN_2O_4S$) C, H, N.

3-[2-[[(4-Chlorophenyl)sulfonyl]amino]ethyl]-5-[1-(3-pyridinyl)ethenyl]benzenepropanoic Acid Ethyl Ester (66). A solution of **51** (765 mg, 1.5 mmol) in TFA (10 mL) was stirred at 50 °C for 2 h and then evaporated. The residue was partitioned between EtOAc and aqueous $NaHCO_3$ solution, and the aqueous layer was washed with EtOAc. The organic layers were combined, washed with brine, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel using a CH_2Cl_2/MeOH elution gradient (0−5% MeOH) to give 736 mg (99%) of **66** as an oil: ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 3H), 2.57 (t, J = 7.7 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 2.89 (t, J = 7.7 Hz, 2H), 3.19−3.25 (m, 2H), 4.10 (q, J = 7.1 Hz, 2H), 4.25−4.30 (m, 1H), 5.49 (s, 1H), 5.50 (s, 1H), 6.83 (s, 1H), 6.92 (s, 1H), 7.01 (s, 1H), 7.23−7.30 (m, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.53−7.58 (m, 1H), 7.72 (d, J = 8.5 Hz, 2H), 8.54−8.56 (m, 2H).

3-[2-[[(4-Chlorophenyl)sulfonyl]amino]ethyl]-5-[1-(3-pyridinyl)ethyl]benzenepropanoic Acid Ethyl Ester (67). A solution of **66** (190 mg, 0.38 mmol) in EtOH (96 mL) was hydrogenated at 20 °C and 3.5 atm for 2 h in the presence of 10% Pd on C. The mixture was filtered, the residue was washed with EtOH, and the combined filtrate and washings were evaporated to give 190 mg (99%) of **67** as a gum: ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 3H), 1.61 (d, J = 7.0 Hz, 3H), 2.56 (t, J = 7.7 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H), 2.85 (t, J = 7.7 Hz, 2H), 3.15−3.22 (m, 2H), 3.70 (q, J = 7.0 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 4.51−4.56 (m, 1H), 6.77 (s, 2H), 6.90 (s, 1H), 7.22−7.26 (m, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.47−7.52 (m, 1H), 7.73 (d, J = 8.5 Hz, 2H), 8.43−8.50 (m, 2H).

3-[2-(Phenylsulfonyl)ethyl]-5-(3-pyridinylmethyl)benzenepropanoic Acid Ethyl Ester (32). A mixture of **30** (485 mg, mmol) and 4-methylbenzenesulfonic acid hydrazide (2.08 g, 11.2 mmol) in toluene (25 mL) was heated under reflux for 3 h and then evaporated. The residue was chromatographed on silica gel using an EtOAc in hexane elution gradient (50−100% EtOAc) initially followed by EtOAc/Et_2NH (19:1). The product fractions were combined and evaporated to give 384 mg (78%) of **32** as an oil: ^{1}H NMR δ 1.23 (t, J = 7.1 Hz, 3H), 2.57 (t, J = 7.7 Hz, 2H), 2.86 (t, J = 7.7 Hz, 2H), 2.97−3.03 (m, 2H), 3.30−3.36 (m, 2H), 3.91 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 6.82 (s, 1H), 6.87 (s, 1H), 6.91 (s, 1H), 7.22−7.25 (m, 1H), 7.43−7.47 (m, 1H), 7.57−7.72 (m, 3H), 7.94−7.98 (m, 2H), 8.48−8.51 (m, 2H).

Compound **33** (69%, oil) was prepared similarly from **31**: ^{1}H NMR δ 1.21 (t, 3H), 1.97−2.03 (m, 2H), 2.53−2.65 (m, 4H), 2.87 (t, 2H), 3.04 (t, 2H), 3.90 (s, 2H), 4.10 (q, 2H), 6.77 (s, 1H), 6.82 (s, 1H), 6.87 (s, 1H), 7.18−7.22 (m, 1H), 7.41−7.45 (m, 1H), 7.54−7.68 (m, 3H), 8.88 (d, 2H), 8.47 (m, 2H).

3-[2-[[(4-Chlorophenyl)sulfonyl]amino]ethyl]-5-(1*H*-imidazol-1-ylmethyl)benzenepropanoic Acid (72). A solution of **46** (489 mg, 1.03 mmol) in a mixture of 2 N NaOH solution (1.5 mL, 3.08 mmol) and MeOH (5 mL) was heated under reflux for 2 h and then evaporated. The residue was dissolved in water, and the solution was washed with EtOAc and then acidified with AcOH. The solid was filtered off, washed with water, and dried to give 307 mg (67%) of **72**: mp 185−187 °C; ^{1}H NMR (DMSO-d_6) δ ca. 2.43 (t, 2H + DMSO), 2.56 (t, J = 7.41 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.89−2.95 (m, 2H), 5.04 (s, 2H), 6.81 (s, 1H), 6.85 (s, 1H), 6.89 (s, 1H), 6.91 (s, 1H), 7.11 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.81 (t, J = Hz, 1H). Anal. ($C_{21}H_{22}ClN_3O_4S$) C, H, N.

Compounds **71**, **73**−**79** (Table 1), and **80**−**94** (Table 2) were prepared similarly.

3-[2-[[(4-Chlorophenyl)sulfonyl]amino]ethyl]benzenepropanoic Acid (8). Sodium hypochlorite (3.6 mL of 14% aqueous solution, 6.7 mmol) was added to a stirred, ice-cooled solution of **70** (1.35 g, 6.1 mmol) and 2 N NaOH solution (15.3 mL, 30.5 mmol) in dioxane (10 mL), and stirring with cooling was continued for 2 h. The temperature was raised to 100 °C and held for 30 min, and then the mixture was cooled in ice. 4-Chlorobenzenesulfonyl chloride (2.58 g, 12.2 mmol) was added, and the mixture was stirred for 3 h and then washed with ether. The aqueous layer was acidified with 10 N HCl solution and extracted several times with ether. The combined extracts were washed with water, dried ($MgSO_4$),

and evaporated, and the residue was chromatographed on silica gel. Elution with CH_2Cl_2/MeOH (99:1) gave 1.15 g (51%) of **8**: mp 98−100 °C; ^{1}H NMR (DMSO-d_6) δ ca. 2.48 (t, 2H + DMSO), 2.61 (t, J = 7.5 Hz, 2H), 2.74 (t, J = 7.6 Hz, 2H), 2.93−2.99 (m, 2H), 6.94 (d, J = 7.7 Hz, 1H), 6.97 (s, 1H), 7.01 (d, J = 7.7 Hz, 1H), 7.13 (dd, J = 7.7, 7.7 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.78 (t, J = 6.0 Hz, 1H), 12.05 (s, 1H). Anal. ($C_{17}H_{18}ClNO_4S$) C, H, N.

Biological Evaluation. A. Thromboxane Receptor Antagonism. Spirally cut rat aorta 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 pretreated with the thromboxane agonist U46619 for 10 min, then washed, and 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 are 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. Partial agonist activity has been noted previously with several sulfonamide-based TXA_2 receptor antagonists,[17] but none of the present compounds was observed to cause contraction in the absence of U46619.

B. Thromboxane Synthase Inhibition. Activity of compounds against human platelet microsome thromboxane synthase was determined as described previously.[43]

C. Oral Efficacy in Conscious Dogs. For determination of TXA_2 synthase activity ex vivo, blood samples were obtained from an external hind leg vein of conscious male beagles immediately before administration of compound to establish control serum levels of TXB_2. The test compound, ground with excipient (starch/lactose) in a ratio of 1:3, was administered either in loosely filled gelatin capsules or by oral gavage in solution. Further blood samples were then taken from each dog at intervals. The blood samples (1 mL) were allowed to clot in glass tubes for 2 h at 37 °C, and the serum was obtained by centrifugation at 2000g for 10 min at room temperature. The protein in 100 μL samples was precipitated by addition of 500 μL of EtOH, and after thorough mixing, the precipitate was centrifuged at 10000g for 2 min. Aliquots (5−10 μL) of the EtOH supernatant were added to Isogel Tris buffer (1 mL), and the TXB_2 content was determined by a specific radioimmunoassay as described previously.[43] Results were calculated as the percentage reduction in serum TXB_2 levels following compound administration, relative to control levels prior to dosing.

For determination of TXA_2 receptor antagonism, blood samples from the same dogs were drawn into 0.1 vol of 3.18% (w/v) sodium citrate and aggregated by the addition of U46619 to a final concentration of 3 μM. The aggregation was monitored by changes in electrical impedance in the blood. Results were calculated as the percent change in impedance at time points after dosing, compared with that obtained immediately before dosing.

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Supporting Information Available: Additional NMR data on final compounds and intermediates (8 pages). Ordering information is given on any current masthead page.

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