Thromboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition. 4. 8-[[(4-Chlorophenyl)sulfonyl]amino]-4-(3-(3-pyridinyl)propyl)octanoic Acid and Analogs

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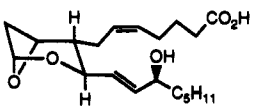
The title compound (**10a**) and its analogs were synthesized and found to possess two activities, the inhibition of the biosynthesis of thromboxane A2 and antagonism of its receptors. The in vitro and in vivo profile of these compounds as thromboxane receptor antagonists (TxRAs) and thromboxane synthase inhibitors (TxSIs) is described. **10a** and its analogs displayed very potent TxRA activity in human washed platelets ($IC_{50} \approx 10^{-7}$–10^{-9} M) and dog saphenous vein ($pA_2 \approx 9$) and also potent TxSI activity ($IC_{50} \approx 10^{-9}$ M). The good bioavailability and the long duration of action of some of these compounds was demonstrated using ex vivo measurement of the TxRA activity upon oral administration to guinea pigs. Compounds **10a**, **20**, and **33** potently inhibited arachidonic acid induced bronchoconstriction in guinea pigs.

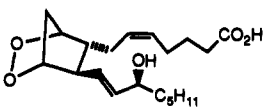
Metabolism of arachidonic acid via the cyclooxygenase pathway produces prostaglandins and thromboxanes, the autocoids having important physiological roles in the normal functioning of the body. Of these metabolites, thromboxane A_2 (TxA_2, **1**) is the most unstable compound with extremely potent vasoconstricting and platelet aggregating properties.[1-3] It has been postulated that TxA_2 plays an important role in the pathogenesis of circulatory and certain renal disorders. Evidence for this postulate comes from the measurement of higher levels of stable metabolites of **1** in patients with unstable angina[4] and renal dysfunction due to cyclosporine administration.[5]

Pharmaceutical research for the treatment of TxA_2-related disorders has addressed the inhibition of the enzyme thromboxane synthase and the antagonism of the TxA_2 receptor.[6-8] Thromboxane synthase inhibitors (TxSIs) have performed poorly in the clinic.[8] It has been hypothesized that the lack of efficacy of TxSI is due to the accumulation of PGH_2 (**2**), the endoperoxide precursor of **1** in the biosynthetic cascade.[9] PGH_2, albeit slightly less potent than **1**, itself is a platelet aggregating and vasoconstricting agent and binds to the same receptor as TxA_2.[10,11] Therefore, according to this hypothesis, a TxSI does not fully accomplish the inhibition of platelet aggregation and vasoconstriction. Thromboxane receptor antagonists (TxRAs) have been developed and some are currently undergoing clinical trials.[8] The results from these studies could establish the level of efficacy of a TxRA.

It has been postulated[12-14] and subsequently substantiated from in vivo results[15-17] that a combination of TxSI



1 (TxA_2)



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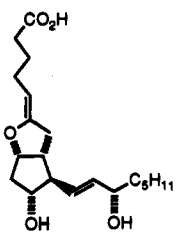
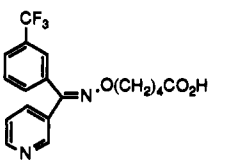


3 (PGI_2)



4 (R 68070)

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and TxRA is more beneficial than either agent alone. A plausible explanation for the beneficial effects of a physical mixture over either agent alone in these in vivo models is that the TxRA antagonizes both 2 and 1 at the receptor level and the TxSI inhibits the biosynthesis of 1 and possibly increases the levels of beneficial prostaglandins by redirection of accumulated 2 to PGI_2 (3), PGE_2, and other beneficial prostanoids. The combined action could totally block the platelet aggregation and vasoconstriction arising from 1 and 2. We and others have undertaken programs to identify and develop compounds which possess both TxRA and TxSI activities (TxRA/TxSI).[18-21] In this paper we describe the synthesis, structure–activity relationship (SAR), and in vivo results of 3-pyridinyl- or 1-imidazolyl-substituted sulfonamidoalkanoic acids.

Chemistry

The compounds described here were synthesized using one of the three strategies depending on the nature of substitution in the side chains (Schemes I–III). Alkylation of diethyl malonate with 3-(3-pyridinyl)-1-bromopropane followed by a tandem one-pot alkylation and displacement using 1-bromo-4-chlorobutane and sodium azide gave 5. Conversion of the azide to amine followed by decarboxylation in refluxing 6 N HCl and esterification gave 6. The amino group of 6 was sulfonylated using 4-chlorobenzenesulfonyl chloride to give 7b. A two-carbon homologation via a Wittig reaction of the aldehyde from 7b gave 9. Reduction of the double bond using $NaBH_4/CoCl_2$ followed by saponification gave 10a (Scheme I). Compounds 10b–h were prepared similarly using the appropriate sulfonyl chloride. The carboxylic acid 7a was converted to the primary amide ($SOCl_2$, reflux 1 h; NH_3–CH_2Cl_2 1 h; 100%) which was decarbonylated using bis(trifluoroacetoxy)-iodobenzene[22] (1.5 equiv of anhydrous CH_3CN, room temperature, 3 h, 64%) to give a primary amine. Acylation of the amine with ethyl oxalyl chloride (1 equiv, CH_2Cl_2, 1.2 equiv of Et_3N, room temperature, 18 h, 25%) followed by ester hydrolysis (3 equiv of NaOH, MeOH, 95%) gave 8. Compound 10a was converted to the primary amide 11a as described above ($SOCl_2$, reflux 1 h; NH_3–CH_2Cl_2, 3 h; 98%) and then dehydrated to give 11b (1.1 equiv of trifluoroacetic anhydride, 2 equiv of pyridine, dioxane, 0 °C–room temperature, 3 h, 100%). The nitrile 11b was converted to the tetrazole 11c by heating a THF solution of tri-*n*-butyltin azide (3 equiv) in a sealed tube for 64 h (39%). Reduction of the methyl ester of 10a gave the primary alcohol 12 (THF, 3.67 equiv of Dibal (1.5 M solution in toluene), −78 °C–room temperature, 1 h, 86%). Esterification of 10a gave 13 as a prodrug (EtOH, excess $SOCl_2$, room temperature, 18 h, 95%). Compound 10a was oxidized to give the pyridine *N*-oxide 14 (1.05 equiv of mCPBA, CH_2Cl_2, room temperature, 36 h, 100%). The imidazole analog, 15, was prepared analogously by employing 3-(1-imidazolyl)bromopropane in place of 3-(3-pyridinyl)propyl bromide in Scheme I.

Scheme II was devised for the preparation of compounds which were not easily accessible using Scheme I. Birch reduction of 16 followed by acid hydrolysis and hydrogenation gave the hydroxy ketone 17. Baeyer–Villiger oxidation provided the key intermediate 18. Conversion of the primary hydroxyl group of 18 to the azide via the mesylate, followed by reduction to the primary amine, sulfonylation of the amine, and direct alcoholysis or saponification and esterification of the lactone ring gave the hydroxy ester 19. Mitsunobu etherification using 3-hydroxypyridine and saponification gave 20. Compound 19 was mesylated (1.2 equiv of methanesulfonyl chloride, CH_2Cl_2, 1.6 equiv of Et_3N, 0 °C, 1 h, 100% crude) and the crude mesylate was heated with imidazole (3.2 equiv imidazole, DMF, 100 °C, 8 h, 60% for 19) to give an imidizolide which was saponified (2.1 equiv of 1 N NaOH, MeOH, room temperature, 18 h, 88%) to give 21 as a white powder. Swern oxidation of 19 (6.8 equiv of DMSO, 4.9 equiv of $(COCl)_2$, CH_2Cl_2, 14 equiv Et_3N, −60 °C, 15 min, 100% crude) gave an aldehyde which was reacted with the phosphorane derived from (3-pyridinylmethyl)triphenylphosphonium chloride in THF (1.2 equiv of phosphonium salt, 2.2 equiv of 1.61 M KOtBu in THF, room temperature, 1 h for phosphorane formation followed by aldehyde addition, 18 h, 27% from 19) to give 22a as a 2:1 mixture of *E*:*Z* isomers. Saponification of 22a (2.1 equiv of 1 N NaOH, dioxane, room temperature, 18 h, workup, KOtBu–tBuOH, 100%) gave 22b as the potassium salt of the carboxylic acid. Hydrogenation of 22a (H_2, 10% Pd/

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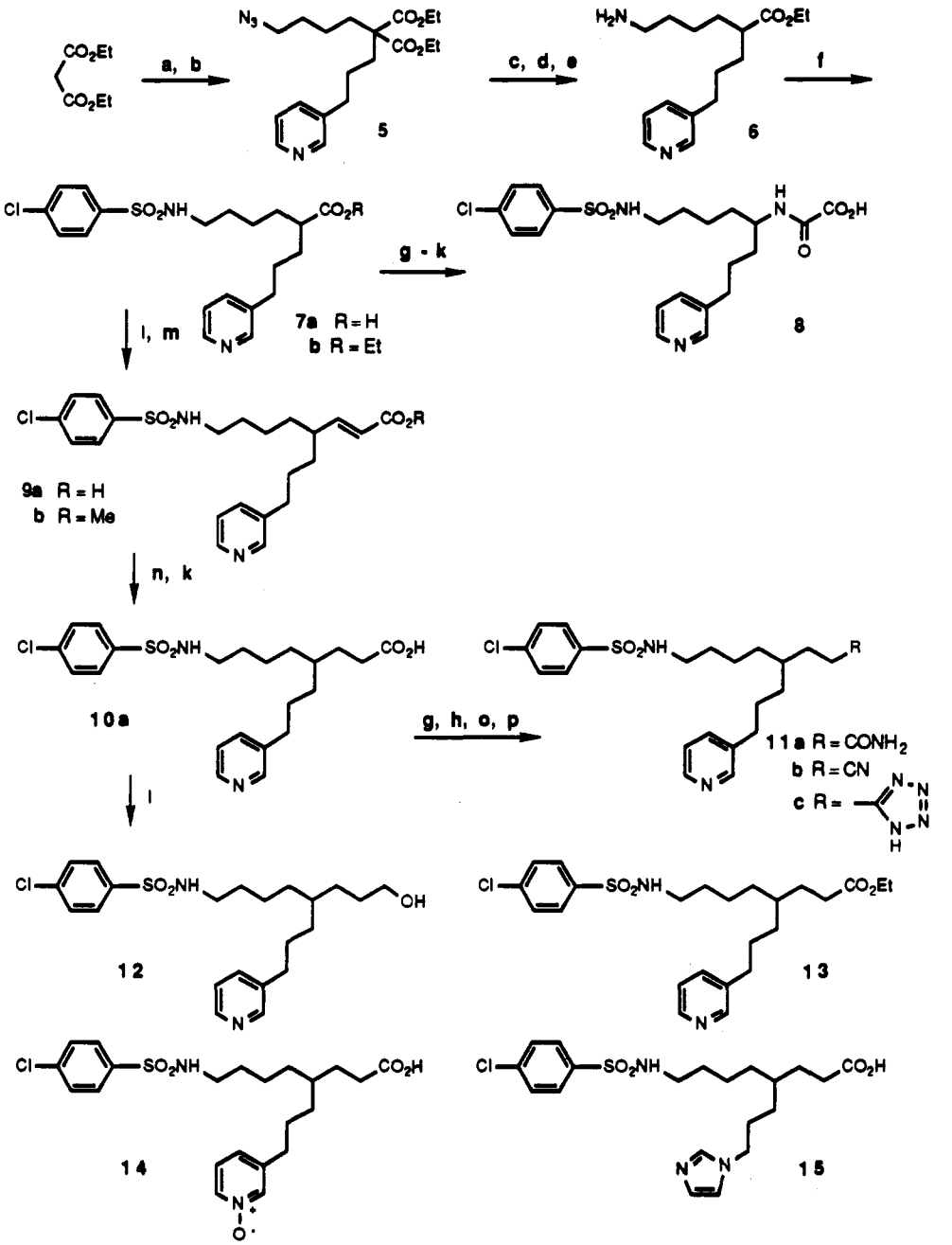
Scheme I[a]

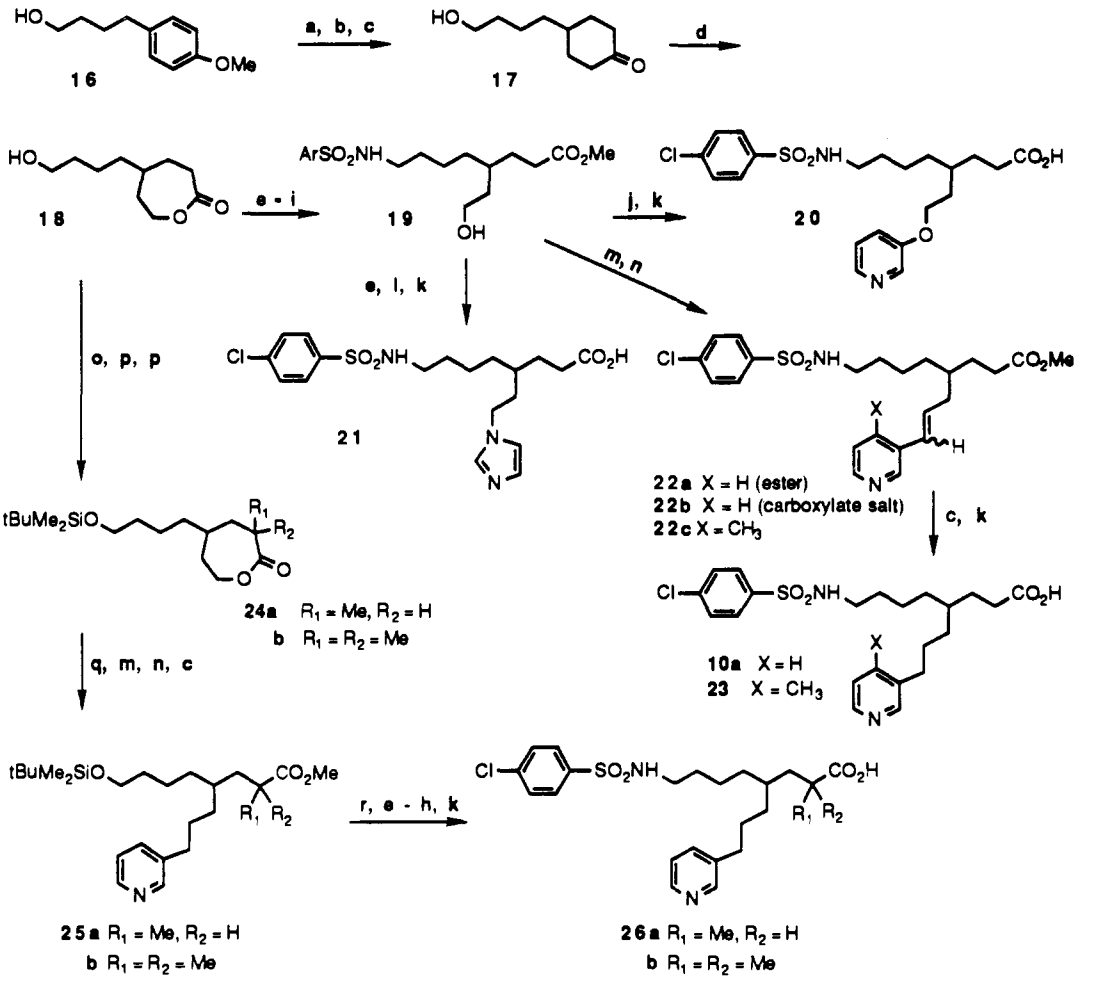


[a] (a) NaOEt, 3-py$(CH_2)_3Br$; (b) NaH, $Cl(CH_2)_4Br$, NaN_3, DMF, 60 °C; (c) Ph_3P, H_2O, THF; (d) 6 N HCl ↑↓; (e) EtOH, $SOCl_2$; (f) $ArSO_2Cl$, Et_3N; (g) $SOCl_2$ ↑↓; (h) NH_4OH; (i) $PhI(OCOCF_3)_2$, CH_3CN; (j) EtO_2CCOCl; (k) NaOH; (l) DIBAL, CH_2Cl_2, −78 °C; (m) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; (n) $NaBH_4$, $CoCl_2{\cdot}6H_2O$, MeOH; (o) $(CF_3CO)_2O$, pyridine; (p) Bu_3SnN_3, Δ.

C, EtOH, 1 atm, 18 h) followed by saponification gave **10a**. The aldehyde obtained from the Swern oxidation of **19** was condensed with the phosphorane derived from (4-methylpyridin-3-yl)methylphosphonium chloride[23] (1.1 equiv of phosphonium salt, THF, 2.1 equiv of 1.61 M KOtBu in THF, room temperature, 1 h for phosphorane formation followed by aldehyde addition, 2 h, 42% from **19**) gave **22c**. Hydrogenation (H_2, 10% Pd/C, EtOAc, 1 atm, 68 h, 82%) followed by saponification (2.1 equiv of 1 N NaOH, dioxane, room temperature, 20 h, 97%) gave **23**. Protection of the hydroxy group of **18** as its *tert*-butyldimethylsilyl ether (1.5 equiv of $tBuMe_2SiCl$, DMF, 1.9 equiv of imidazole, room temperature, 18 h, 74%) followed by alkylation of the lactone (2 equiv of LDA, THF, room temperature, 0.5 h for the enolate formation followed by 6.5 equiv of MeI, 3 h, 65%) gave **24a** as the only major product. Further methylation of **24a** under identical conditions gave **24b** (23% from **24a**) Methanolysis of the lactone rings of **24a** and **24b** (1 equiv of NaOMe, MeOH, 3 h, 99%) followed by the sequence of reactions used for the conversion of **19** to the methyl ester of **10a** gave **25a** and **25b**. Desilation of **25a** and **25b** (1.1 equiv of 1 M Bu_4NF in THF, 1 h, 94%) followed by conversion of the primary alcohol to the (arylsulfonyl)-

(23) (4-Methylpyridin-3-yl)methylphosphonium chloride required for the synthesis of **22c** was prepared as follows: The 4,4-dimethyloxazoline prepared from nicotinic acid was treated with methyllithium and the adduct was oxidized (DDQ) and hydrolyzed (6 N HCl) to give 4-methylpyridine-3-carboxylic acid. Conversion of the carboxylic acid to the corresponding alcohol-hydrochloride salt followed by treatment with $SOCl_2$ gave the hydrochloride salt of (4-methylpyridin-3-yl)methyl chloride. Treatment of this chloride with triphenylphosphine in the presence of nBu_3N gave the desired phosphonium salt.

Scheme II[a]



[a] (a) Li, NH_3, −40 °C; (b) 1 N H_2SO_4; (c) H_2, Pd/C; (d) mCPBA, CH_2Cl_2; (e) MsCl, Et_3N, CH_2Cl_2; (f) NaN_3, DMF; (g) Ph_3P, H_2O, THF; (h) $ArSO_2Cl$, Et_3N, CH_2Cl_2; (i) NaOH, MeOH; MeOH, $SOCl_2$; (j) DEAD, Ph_3P, 3-hydroxypyridine, CH_2Cl_2; (k) NaOH, dioxane, H_2O; (l) imidazole, DMF, 60 °C; (m) $(COCl)_2$, DMSO, CH_2Cl_2, −65 °C; (n) (4-X)pyCH=PPh_3; (o) tBuMe$_2$SiCl, imidazole, DMF; (p) LDA, THF, −10 °C, CH_3I, HMPA; (q) MeONa, MeOH; (r) nBu$_4$NF, THF.

amino group using the reaction conditions used for the conversion of **18** to **19** and saponification gave **26a** and **26b**.

The above schemes could not be employed for the synthesis of β-hetero analogs of **10** and their syntheses are shown in Scheme III. Epoxidation of **27** followed by ring opening with lithium acetylide gave **28**. Ullmann-type coupling of **28** with 3-bromopyridine followed by hydrogenation yielded **29**. Displacement of the tosylate formed from **29** with the potassium anion of ethyl mercaptoacetic acid gave **32**. Deprotection of the THP–ether followed by the conversion of the primary alcohol to the (arylsulfonyl)-amino group as shown in Scheme III and saponification gave the β-thia analog **33**. The anion of **29** was reacted with the sodium salt of bromoacetic acid (DMF, 2 equiv of 1.61 M KOtBu in THF, 0.5 h for anion formation, 2.2 equiv of $BrCH_2CO_2Na$, DMF, room temperature, 15 h) and the resulting crude was esterified (MeOH excess $SOCl_2$, 19%, from **29**) to give **30**. Compound **30** was converted to **31** under the conditions used for the conversion of **32** to **33**. Swern oxidation of **29** (CH_2Cl_2, 6.8 equiv of DMSO, 5 equiv of $(COCl)_2$ 14 equiv of Et_3N, −60 °C, 0.25 h, 100% crude) followed by Homer–Emmons reaction of the resulting ketone (2 equiv of ethyl (diethylphosphono)-acetate, 2 equiv of 0.58 M potassium hexamethyldisilazide in toluene, toluene solvent, reflux, 18 h, 84%) and hydrogenation (H_2, 10% Pd/C, EtOAc, 50 psi, 13 h, 92%) gave **34**. Compound **34** was converted to **35** under the conditions used for the conversion of **32** to **33**.

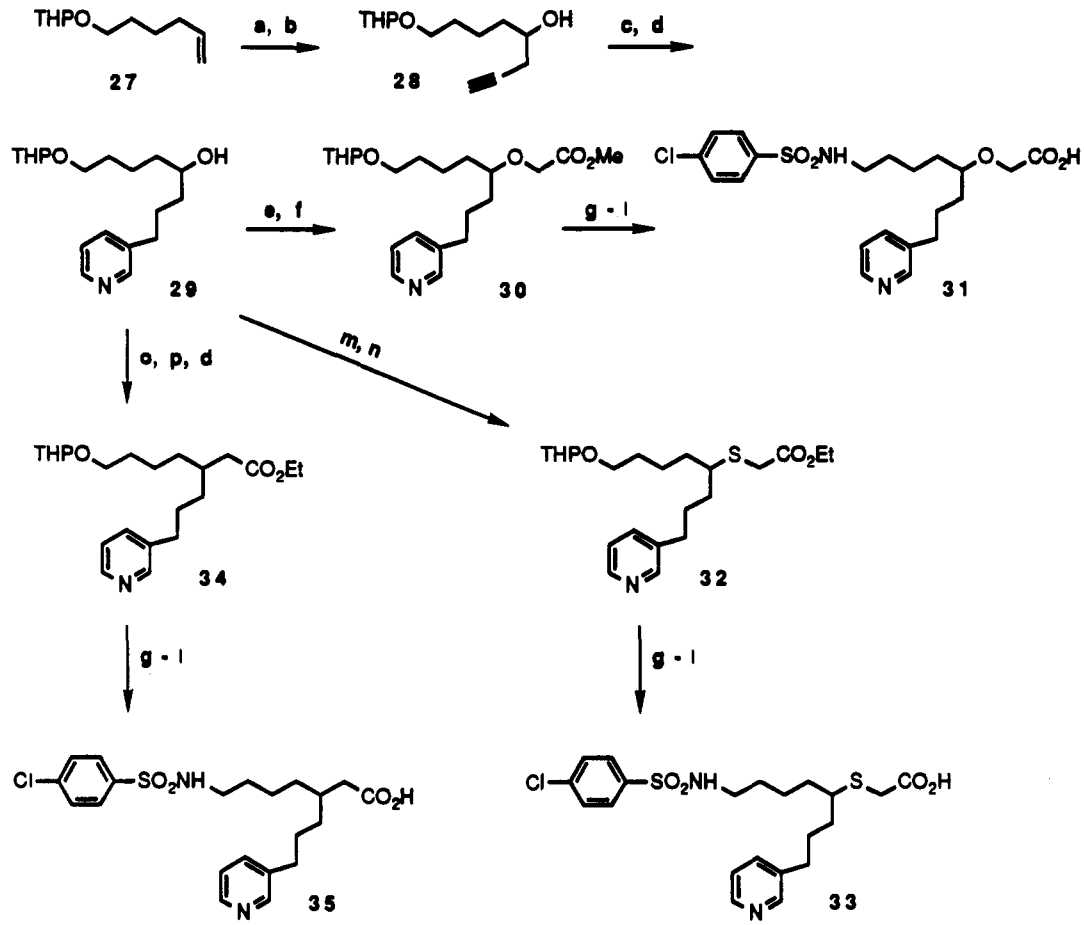
Results and Discussion

The final compounds were tested as racemates[24] for their ability to inhibit the enzyme thromboxane synthase and to antagonize the platelet and vascular receptors for **1** as per the methods described previously.[18a,b] The IC_{50} values for thromboxane synthase inhibition and antagonism of the PGH_2/TxA_2 mimetic, U 46619-induced aggregation of human washed platelets (WP) and platelet-rich plasma (PRP) and the pA_2 values for the antagonism of U 46619-induced contraction of dog saphenous vein are listed in Table I. The change in the activity of these compounds with change in the structure of the arylsulfonyl group and the pyridinylalkyl and the carboxylic acid side chain are discussed below. A reference compound (R 68070, **4**)[21a] was tested for comparison.

The para substituent on the arylsulfonyl group, while affecting the TxRA activity significantly, did not change the TxSI activity of compounds **10a–h**. It is possible that when the pyridine ring and the carboxylic acid group bind to the enzyme, the sulfonamide chain orients itself in such

(24) The enantiomers of **10a** and **20** were synthesized and found to be as active as the racemate. This work has been submitted for publication in *J. Med. Chem.*

Scheme III[a]



[a] (a) mCPBA, CH_2Cl_2; (b) HC≡CLi, DMSO; (c) 3-bromopyridine, $(Ph_3P)_2PdCl_2$ (cat.), Et_3N, 100 °C; (d) H_2, Pd/C; (e) KOtBu, DMF, $BrCH_2CO_2Na$; (f) MeOH, $SOCl_2$; (g) aq HCl, THF; (h) MsCl, Et_3N, CH_2Cl_2; (i) NaN_3, DMF; (j) Ph_3P, THF, H_2O; (k) $ArSO_2Cl$, Et_3N, CH_2Cl_2; (l) NaOH, dioxane, H_2O; (m) TsCl, pyridine, CH_2Cl_2; (n) $KSCH_2CO_2Et$, DMF; (o) $(COCl)_2$, DMSO, CH_2Cl_2, −65 °C; (p) $(EtO)_2P(O)CH_2CO_2Et$, KOtBu, toluene ↑↓.

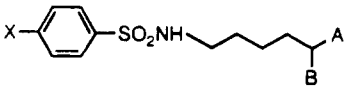
a way that both electronic and steric variations at the end of its chain have minimal effect on the enzyme inhibitory activity. Changes in the pyridinylalkyl chain, on the other hand, had significant effect on the TxRA activity (vide infra). Compounds **10a–h** were extremely potent as TxSIs with IC_{50} values of <5 nM. Some of these compounds (e.g. **10a**) were also active as TxRAs. Compounds **10a–g** potently inhibited the U 46619-induced aggregation of human WP (IC_{50} = 19–240 nM). Compound **10h** was surprisingly inactive as a TxRA. However, these compounds were less potent in PRP possibly due to plasma protein binding. The drop in TxRA activity in PRP was 10 fold or greater compared to that in WP. The platelet and vascular receptor for 1 are different to a certain extent.[25] Therefore, some of the more potent compounds were tested for their ability to antagonize the vascular receptor for 1. Compound **10a** and **10d** which were extremely potent TxRA on the platelet receptor, also exhibited antagonist activity on the vascular receptor for 1. Thus, **10a** competitively inhibited the U 46619-induced contraction of dog saphenous vein with a pA_2 value of 8.9.

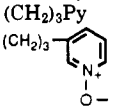
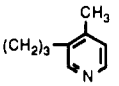
Structural variations in the pyridinylalkyl chain also had a significant effect on the TxRA activity. Oxidation of the pyridine ring of **10a** produced **14**, which was a potent TxSI (IC_{50} =3 nM) but a relatively weak TxRA. It is interesting to note that even the *N*-oxide binds to thromboxane synthase in this case. Replacing the 3-pyridinyl ring of **10a** by the 1-imidazolyl ring (**15**) retained the potent TxSI activity; however, it was detrimental to the TxRA activity (IC_{50} = 0.98 μM). Shortening the chain length of **15** by one carbon led to **21**, which was 10-fold weaker as a TxSI. Introducing a double bond next to the pyridine ring (**22b**, 2:1 mixture of *E*:*Z*) or a methyl group at the 4-position (**23**) maintained the TxSI and TxRA activities. However, **23** was much weaker as a TxRA in PRP (IC_{50} = 4.86 μM), probably because of extensive plasma protein binding. Compound **22b** was also a potent TxRA in the dog saphenous vein with pA_2 = 9.22. Replacing one methylene of **10a** by an oxygen atom gave **20**, which was found to be at least equipotent to **10a** in all of the in vitro assays. On the vascular receptor, **20** was more potent (pA_2 = 9.4) than **10a** (pA_2 = 8.89).

The TxRA and TxSI activity of these compounds varies with structural modifications in the carboxylic acid side chain. Compounds **35** and **7a**, which lack one or both methylene groups of the carboxylic acid side chain of **10a**, are less active as TxRAs. Although the one carbon lower homolog, **35**, with five carbons spanning the pyridine and carboxylic acid, maintained potent in vitro TxSI activity, the two carbon lower homolog **7a** was significantly less active as TxSI. Replacing the propionic acid side chain of **10a** by oxamic acid (**8**) led to loss of TxSI as well as platelet TxRA activity in PRP. Introducing a double bond at the α,β-position (**9a**) or one or two methyl groups α to

(25) Mais, D. E.; Halushka, P. V.; Saussy, D. L. Platelet and vacular smooth muscle thromboxane A_2/prostaglandin H_2 receptors. *Advances in Eicosanoid Research*; Halushka, P. V., Mais, D. E., Eds.; MTP Press: Lancaster, UK, 1988; pp 210–231.

Table I. In Vitro Pharmacology of 10a and Analogs[a]



no.	X	A	B	formula[b]	mp, °C	thromboxane synthase inhibition IC_{50},[e] μM	inhibition of U 46619 induced aggregation of WP,[c] IC_{50},[f] μM	inhibition of U 46619 induced aggregation of PRP,[d] IC_{50},[f] μM	contraction of dog saphenous vein, pA_2[g] (slope ± 95% confidence limits)
10a	Cl	$(CH_2)_2CO_2H$	$(CH_2)_3Py$[h]	$C_{22}H_{29}ClN_2O_4S$	114–115	0.002	0.019[i]	0.39[i]	8.9 (−1.29 ± 0.29)
10b	F	$(CH_2)_2CO_2H$	$(CH_2)_3Py$	$C_{22}H_{29}FN_2O_4S$	88–90	0.001	0.108	>30	
10c	CF_3	$(CH_2)_2CO_2H$	$(CH_2)_3Py$	$C_{23}H_{29}F_3N_2O_4S$	138–140	0.002	0.23	0.61	
10d	CH_3	$(CH_2)_2CO_2H$	$(CH_2)_3Py$	$C_{23}H_{32}N_2O_4S$	92–94	0.001	0.058	15.2	8.81 (−0.95 ± 0.20)
10e	*n*	$(CH_2)_2CO_2H$	$(CH_2)_3Py$	$C_{26}H_{32}N_2O_4S$	103–104	0.0015	0.24	2.8	
10f	OCH_3	$(CH_2)_2CO_2H$	$(CH_2)_3Py$	$C_{23}H_{32}N_2O_5S \cdot H_2O$	116–118	0.003	0.22	1.34	
10g	N_3	$(CH_2)_2CO_2H$	$(CH_2)_3Py$	$C_{22}H_{29}N_5O_4S$	120–122	0.004	0.035	2.0	
10h	SO_2CH_3	$(CH_2)_2CO_2H$	$(CH_2)_3Py$	$C_{23}H_{32}N_2O_6S_2$	109–112	0.004	>10		
14	Cl	$(CH_2)_2CO_2H$		$C_{22}H_{29}ClN_2O_5S$	55–57	0.003	0.5	8.7	8.13 (−0.69 ± 0.20)
15	Cl	$(CH_2)_2CO_2H$	$(CH_2)_3$-Im[k]	$C_{20}H_{28}ClN_3O_4S$	136–138	0.003	0.98	3.7	8.26 (−0.87 ± 0.11)
21	Cl	$(CH_2)_2CO_2H$	$(CH_2)_2Im$	$C_{19}H_{26}ClN_3O_4S \cdot 0.93HCl$	66–72	0.040	1.52		7.46 (−1.05 ± 0.32)
22b	Cl	$(CH_2)_2CO_2K$	$CH_2CH{=}CH$-Py	$C_{22}H_{26}ClN_2O_4SK \cdot H_2O$	75–78	0.007	0.027	1.19	9.22 (−1.0 ± 0.59)
23	Cl	$(CH_2)_2CO_2H$		$C_{23}H_{31}ClN_2O_4S$	61–71	0.001	0.006	4.54	
20	Cl	$(CH_2)_2CO_2H$	$(CH_2)_2O$-Py	$C_{21}H_{27}ClN_2O_5S$	87–89	0.003	0.013[l]	0.28[m]	9.4 (−0.98 ± 0.29)
7a	Cl	CO_2H	$(CH_2)_3Py$	$C_{20}H_{25}ClN_2O_4S$	139–141	0.09	9.3		
35	Cl	CH_2CO_2H	$(CH_2)_3Py$	$C_{21}H_{27}ClN_2O_4S$	95–97	0.007	0.2		8.43 (−0.86 ± 0.15)
8	Cl	$NHCOCO_2H$	$(CH_2)_3Py$	$C_{21}H_{26}ClN_3O_5S$	95–98	0.15	0.59	11.3	8.73 (−0.99 ± 0.24)
9a	Cl	$CH{=}CHCO_2H$	$(CH_2)_3Py$	$C_{22}H_{27}ClN_2O_4S$	72–75	0.01	0.07	0.77	
11a	Cl	$(CH_2)_2CONH_2$	$(CH_2)_3Py$	$C_{22}H_{30}ClN_3O_3S$	100–102	0.06	>10		
11c	Cl	$(CH_2)_2CHN_4$	$(CH_2)_3Py$	$C_{22}H_{29}ClN_6O_2S \cdot 0.5H_2O$	56–81	0.005	0.022	0.91	9.33 (−1.35 ± 0.18)
12	Cl	$(CH_2)_3OH$	$(CH_2)_3Py$	$C_{22}H_{31}ClN_2O_3S$	oil	0.07	2.36		
26a	Cl	$CH_2CH(CH_3)CO_2H$	$(CH_2)_3Py$	$C_{23}H_{31}ClN_2O_4SNa \cdot 0.5H_2O$	foam	0.003	0.053	2.9	8.83 (−1.19 ± 0.30)
26b	Cl	$CH_2C(CH_3)_2CO_2H$	$(CH_2)_3Py$	$C_{24}H_{33}ClN_2O_4S$	114–115	0.02	0.018	3.7	9.0 (−1.37 ± 0.34)
31	Cl	OCH_2CO_2H	$(CH_2)_3Py$	$C_{21}H_{27}ClN_2O_5S$	101–104	0.018	0.015	1.6	
33	Cl	SCH_2CO_2H	$(CH_2)_3Py$	$C_{21}H_{27}ClN_2O_4S_2$	85–88	0.002	0.006	0.4	9.57 (−1.11 ± 0.25)
4						0.003	1.28	2.83	6.35 (−1.27 ± 0.33)

[a] See ref 18 for description of methods. [b] C, H, and N analyses were within ±0.4% of calculated values unless otherwise indicated. All the compounds had ^1H NMR, IR, and MS consistent with their structure. [c] WP = washed platelets. [d] PRP = platelet-rich plasma. [e] Values represent one or two determinations. [f] Values represent a single determination unless otherwise indicated. [g] Number of determinations = 1; number of rings in each determination >12; a single concentration of drug was used on each ring. [h] Py = 3-substituted pyridine ring. [i] $n = 10$, SEM = ±0.003. [j] $n = 7$, SEM = ±0.023. [k] Im = 1-substituted imidazole ring. [l] $n = 3$, SEM = ±0.001. [m] $n = 4$, SEM = ±0.10. [n] A β-naphthyl ring replacing the aromatic ring of the arylsulfonamido group.

the carboxylic acid (**26a** and **26b**) did not affect the TxSI and TxRA activities significantly. However, their TxRA activity in PRP was reduced quite significantly. Compounds **26a** and **26b** were potent TxRA on the vascular receptor with pA_2 values of 8.83 and 9.1, respectively. The β-hetero analogs, **31** and **33**, were very active as a TxRA and a TxSI. The β-oxa analog, **31**, showed higher protein binding and was therefore less potent in PRP. The β-thia analog, **33**, on the other hand, was as active as **10a** in the in vitro assays. Compound **33** was the most potent TxRA on the vascular receptor in this series of compounds. Changing the carboxylic acid into primary amide (**11a**) and primary alcohol (**12**) led to >100-fold loss of TxRA activity and ~10-fold loss of TxSI activity. Interestingly though, conversion of **10a** into its tetrazole, **11c**, retained its TxSI and TxRA activities. Although **11c** was less active than **10a** in PRP, it was more potent than **10a** as a TxRA in the dog saphenous vein (pA_2 = 9.33).

Compounds **10a**, **11c**, **20**, and **33** were very potent TxRA/TxSI with highly desirable in vitro activity profiles. In comparison to **4**, these compounds were >100-fold more active as a TxRA in WP and equipotent as TxSIs. On the vascular receptor, **20** was more active than **4** by 3 orders of magnitude. Several of the compounds listed in Table

Table II. Ex Vivo Inhibition of U46619-Induced Aggregation of Guinea Pig Platelets[a]

compd	dose, mg/kg, po	n	time,[b] h	concn ratio[c]
vehicle	-	22		1.0
10a	10	8	1	27.3 ± 4.9
	10	8	6	11.8 ± 2.8
11c	10	3	1	10.0 ± 3.0
13	3	3	3	3.0 ± 1.0
20	3	4	1	>100
	3	3	6	>100
26a	10	7	1	9.0 ± 2.5
26b	10	4	1	8.7 ± 3.8
31	10	4	1	2.6 ± 0.8
33	10	3	1	33.0 ± 8.5
4	10	4	1	5.6 ± 1.6

[a] See Experimental Section for methodology. [b] Time at which blood samples were taken out to measure platelet aggregability. [c] Concentration ratio = EC_{50} for drug/EC_{50} for control.

I showing a desirable in vitro activity profile were tested further in ex vivo and in vivo models.

The compounds shown in Table II were administered orally to guinea pigs. After 1 h, the plasma samples from these drug-treated animals were tested with the TxA_2/PGH_2 mimetic, U 46619 to measure the ability of the drugs to inhibit the U 46619-induced platelet aggregation. The aggregation ratio, the ratio of EC_{50} for the sample from drug-treated animals over the control, was used as a measure of efficacy of the drug to inhibit platelet aggregation. Compounds **10a**, **20**, and **33** exhibited good platelet inhibition, indicating that the drugs are orally bioavailable in guinea pigs. These compounds inhibited the platelet aggregation for 6 h after drug administration, indicating a good duration of action in these animals. It was not possible to elicit a response to U 46619, even at 6 h after drug administration, in animals treated with **20** (3 mg/kg po). In this model **20** is the most potent compound of this series with a >6 h duration of action. Compound **4** produced much weaker platelet inhibition in this assay. The other compounds in Table II, **11c**, **26a**, **26b**, and **31**, were less active than **10a**, **20**, and **33**. Since these compounds display good in vitro activity, it is possible that the weaker in vivo activity is a reflection of lower bioavailability. The activity of the prodrug, **13**, is similar to that of **10a** at the same dose. It is not clear why the β-oxa analog, **31**, is less active than the β-thia analog **33**. The ex vivo TxSI activity could not be measured reliably in guinea pigs because significant levels of 1 are produced from sources other then platelets. However ex vivo studies[26] in cynomolgus monkeys, have indicated that both **10a** and **20** produce a long lasting high degree of antagonism of the receptor for 1 and inhibition of the enzyme for its biosynthesis in this species.

Inhibition of arachidonic acid (AA) induced bronchoconstriction in anesthetized guinea pigs was used to test the in vivo efficacy of the compounds in a disease model. The test compounds were administered intravenously upon administration of a priming dose (0.25 mg/kg iv) and a subsequent dose (0.5 mg/kg iv) of AA. The test compound was administered (iv bolus) and the animals were challenged with AA (0.5 mg/kg iv bolus). Bronchoconstriction was measured as peak insufflation pressure and expressed as a percentage of the control. Table III lists the ED_{50} values for **10a**, **20**, and **33**. These compounds potently inhibited AA-induced bronchoconstriction in guinea pigs

(26) These studies were done by Mr. David S. Cohen and will be published elsewhere.

Table III. Inhibition of Bronchoconstriction in Guinea Pigs[a]

compd	ED_{50},[b] μg/kg	compd	ED_{50},[b] μg/kg
10a	5.75	**33**	7.42
20	5.20	**4**	48.32

[a] See Experimental Section for methodology. [b] Inhibition of bronchoconstriction performed at *five* different doses (0.1–1000 μg/kg) of the compounds using six to eight guinea pigs for each dose.

(ED_{50} = 5–7 μg/kg) and are more potent than **4** in this model. At all the doses tested in this model these drugs did not show any agonistic activity which manifests as pressor effect or airway hyper-reactivity. This model thus serves to demonstrate the pharmacological efficacy of **10a**, **20**, and **33**.

Conclusion

The 8-[(arylsulfonyl)amino]octanoic acids with a pyridinylalkyl substituent at the 4-position display very potent TxRA and TxSI activities. The TxRA activity of these compounds was quite sensitive to the structural variations in any of the three side chains. The TxSI activity, however, was not seriously affected by these changes. A number of the compounds displaying potent in vitro activity were tested further in animal models. The U 46619-induced ex vivo platelet aggregation in guinea pigs was inhibited for >6 h upon oral administration. This and other studies have demonstrated a desirable bioavailability and duration of action for some of the compounds including **10a** in this paper. Compounds **10a**, **20**, and **33** were very efficacious in inhibiting the arachidonic acid induced bronchoconstriction in guinea pigs. The attractive pharmacological and toxicological profile of **10a** has led to its selection as a candidate for clinical trials.

Experimental Section

Infrared (IR) spectra were recorded on a Nicolet 5SXFT spectrometer. Proton NMR spectra were recorded on a Varian EM-390, Varian XL-300, or Varian XL-400 spectrometer. Chemical shifts are reported in ppm (δ) using tetramethylsilane, $CDCl_3$, or CD_3OD as internal standard. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Methylene chloride (CH_2Cl_2) was dried over 4-Å molecular sieves for 72 h before use. Organic solutions during workup were dried using anhydrous $MgSO_4$ or Na_2SO_4. Flash chromatography[27] was performed using silica gel 60 (0.04–0.06 mm) (Merck).

Diethyl (4-Azidobutyl)[3-(3-pyridinyl)propyl]malonate (5). To a solution of diethyl malonate (48 mL, 0.32 mol) in EtOH (960 mL) were added pieces of Na (14 g, 0.61 mol) and the reaction mixture was allowed to stir until all the metal was dissolved. The solution was heated to reflux and a solution of 3-(3-pyridinyl)-propyl bromide hydrobromide salt (80 g, 0.28 mol) in EtOH (960 mL) was added rapidly. The reaction mixture was refluxed for 10 h and the solvent was evaporated in vacuo. The residue was taken up in hexane (400 mL) and extracted with 1 N HCl (400 mL). The organic phase was discarded and the aqueous phase was adjusted to pH = 8 by addition of solid $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (2 × 300 mL) and the combined organic extract was dried, filtered, and evaporated in vacuo to give 54.8 g (70%) of an amber oil which was used as is for the next step.

To a solution of crude product obtained above (54.8 g) in DMF (950 mL) was added NaH (8.58 g, 0.21 mol, 60% dispersion in oil) in small portions. The mixture was allowed to stir for 30 min and 1-bromo-4-chlorobutane (24.2 mL, 0.2 mol) was added. The

(27) Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.

reaction mixture was heated at 60 °C for 10 h and NaN_3 (59.1 g, 0.4 mol) was added followed by NaI (38.5 g, 0.59 mol) and 18-crown-6 (7.8 g, 29.5 mmol). The mixture was heated at 60 °C for 18 h and then cooled and poured on to a ice/H_2O mixture and extracted with Et_2O (4 × 500 mL). Combined organic extract was dried, filtered and evaporated in vacuo to give 42.3 g (40% overall) of **5** as an amber oil which was used as is for further elaboration: IR (CH_2Cl_2) 2934, 2100, 1726, 1179 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.53 (br, 2 H), 7.68 (m, 1 H), 7.3 (m, 1 H), 4.21 (q, J = 7 Hz, 4 H), 3.3 (t, J = 7 Hz, 2 H), 2.67 (t, J = 7 Hz, 2 H), 1.4–2.1 (m, 10 H), 1.3 (t, J = 7 Hz, 6 H).

Ethyl 6-Amino-2-[(3-pyridinyl)propyl]hexanoate (6). To a solution of **5** (42.3 g, 0.11 mol) in THF (270 mL) were added four boiling stones followed by triphenylphosphine (31.5 g, 0.12 mol) and H_2O (4.4 mL, 0.24 mol). The solution was allowed to stir for 62 h at room temperature and the solvent was evaporated in vacuo. The residue was purified by flash chromatography first using EtOAc to remove triphenylphosphine oxide and then changing the eluent to 9:1 MeOH/Et_3N to obtain 24.8 g (25% from the pyridinylpropyl bromide) of diethyl (4-aminobutyl)-(3-(3-pyridinyl)propyl)malonate as an amber oil: IR (CH_2Cl_2) 3524, 3381, 2935, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.54 (br, 2 H), 7.6 (m, 1 H), 7.3 (m, 1 H), 4.21 (q, J = 7 Hz, 4 H), 2.5–2.8 (m, 4 H), 1.4–2.1 (m, 10 H), 1.26 (t, J = 7 Hz, 6 H).

The compound prepared above (24.8 g, 70.7 mmol) was dissolved in HOAc (200 mL), and 6 N HCl (200 mL) was added. The mixture was heated at reflux for 18 h, and the volatiles were removed in vacuo. The residue was taken up in EtOH (500 mL) and evaporated in vacuo. The residue was dissolved in EtOH (200 mL) and toluene (300 mL). The solvent was evaporated and the residue (24.4 g) used as is for further elaboration.

The crude acid (24.4 g) prepared above was dissolved in EtOH (300 mL) and $SOCl_2$ (30 mL) was added dropwise, the temperature being kept below 50 °C. The solution was allowed to stir at room temperature for 18 h and then the solvent was evaporated in vacuo. The residue was poured on ice and the pH was adjusted to 8.0 using solid $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 300 mL) and combined organic extract was dried, filtered, and evaporated to give 81.8 g of an amber oil. Purification by flash chromatography on silica gel first using EtOAc as eluent to remove impurities and then changing the solvent to 9:1 MeOH/Et_3N gave 12.2 g (40% from **5**) of **6** as an amber oil: ^1H NMR ($CDCl_3$) δ 8.56 (br s, 2 H), 7.57 (m, 1 H), 7.27 (m, 1 H), 5.92 (br, 2 H), 4.18 (q, J = 7 Hz, 2 H), 2.2–3 (m, 5 H), 1.1–1.9 (m, 13 H).

Ethyl 6-[[(4-Chlorophenyl)sulfonyl]amino]-2-[3-(3-pyridinyl)propyl]hexanoate (7b). To a solution of **6** (12.15 g, 44 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (11 mL, 79 mmol) followed by 4-chlorobenzenesulfonyl chloride (8.75 g, 41 mmol). The solution was stirred for 18 h, diluted with CH_2Cl_2 (100 mL), and washed with saturated aqueous $NaHCO_3$. The organic phase was dried, filtered, and concentrated in vacuo to give a dark residue which upon purification by flash chromatography using 3:2 EtOAc/hexane as eluent gave 14.3 g (75%) of **7b** as a light yellow oil: IR (CH_2Cl_2) 3373, 2944, 2864, 1724, 1478, 1338, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (br s, 2 H), 7.79 (d, J = 8 Hz, 2 H), 7.48 (m, 1 H), 7.47 (d, J = 8 Hz, 2 H), 7.23 (dd, J = 8, 4.5 Hz, 1 H), 5.0 (t, J = 6 Hz, 1 H), 4.1 (q, J = 7 Hz, 2 H), 2.92 (q, J = 7 Hz, 2 H), 2.61 (t, J = 7 Hz, 2 H), 2.29 (m, 1 H), 1.3–1.65 (m, 8 H), 1.22 (t, J = 7 Hz, 3 H).

Methyl 8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[3-(3-pyridinyl)propyl]oct-2-enoate (9b). A solution of **7b** (5.07 g, 12 mmol) in CH_2Cl_2 (150 mL) was cooled to −78 °C and a solution of diisobutylaluminum hydride in toluene (22.2 mL of 1.53 M solution, 34 mmol) was added slowly. The reaction mixture was allowed to stir at −78 °C for 5 min and MeOH (16 mL) was added followed by Et_2O (500 mL). The cold bath was removed and brine (16 mL) was added followed by finely powdered Na_2SO_4 (11.5 g). The suspension was allowed to stir vigorously for 2 h and then filtered off. The filter cake was washed with CH_2Cl_2 (4 × 50 mL) and the combined filtrate was evaporated to give 4.65 g (100%) of the desired aldehyde as a yellow oil which was used as it was for further elaboration: IR (CH_2Cl_2) 3373, 2940, 2862, 2702, 1722, 1479, 1338, 1165 cm^{-1}.

To a solution of the aldehyde prepared above (4.65 g, 11.4 mmol) in $CHCl_3$ (61 mL) was added methyl(triphenylphosphoranylidene)acetate (4.35 g, 12.7 mmol) and the reaction mixture was allowed to stir for 18 h. The solvent was evaporated in vacuo and the residue taken up in Et_2O and extracted with 0.5 N HCl (3 × 25 mL). The combined aqueous phase was adjusted to pH = 8 and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was dried, filtered, and evaporated in vacuo and the residue purified by flash chromatography using 3:2 EtOAc/hexane as eluent to give 4.66 g (89% from **7b**) of **9b** as a clear oil: IR (CH_2Cl_2) 3373, 2939, 2865, 1719, 1657, 1337, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (br s, 2 H), 7.2–7.9 (m, 6 H), 6.69 (dd, J = 15, 9 Hz, 1 H), 6.28 (br t, J = 6 Hz, 1 H), 5.72 (d, J = 15 Hz, 1 H), 3.74 (s, 3 H), 2.9 (q, J = 7 Hz, 2 H), 2.55 (t, J = 7 Hz, 2 H), 2.07 (m, 1 H), 1.15–1.6 (m, 10 H).

8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[3-(3-pyridinyl)-propyl]octanoic Acid (10a). To a solution of **9b** (4.66 g, 10 mmol) in MeOH (45 mL) was added $CoCl_2 \cdot 6H_2O$ (0.66 g, 2.8 mmol). The solution was cooled to 0 °C and $NaBH_4$ (0.85 g, 0.22 mmol) was added in small portions. The black suspension was allowed to stir for 1 h at room temperature and then filtered through Florisil and washed with MeOH (20 × 50 mL). The combined filtrate was evaporated in vacuo to give 4.26 g (91%) of the methyl ester of **10a** as a white solid: mp 80–82 °C; IR ($CDCl_3$) 3395, 2939, 2864, 1731, 1332, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.46 (br, 2 H), 7.79 (d, J = 8 Hz, 2 H), 7.47 (d, J = 8 Hz, 2 H), 7.48 (m, 1 H), 7.22 (dd, J = 8, 4.5 Hz, 1 H), 5.07 (t, J = 6 Hz, 1 H), 3.63 (s, 3 H), 2.92 (q, J = 7 Hz, 2 H), 2.57 (t, J = 7 Hz, 2 H), 2.22 (t, J = 7 Hz, 2 H), 1.1–1.62 (m, 13 H).

The methyl ester obtained above (1.26 g, 2.7 mmol) was dissolved in MeOH (10 mL), 1 N NaOH (5.5 mL, 5.5 mmol) was added, and the reaction mixture was allowed to stir for 18 h. The solvent was evaporated in vacuo and the residue taken up in H_2O and adjusted to pH = 5 and then extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extract was dried, filtered, and evaporated in vacuo to give 1.29 g of a clear oil. Trituration with Et_2O gave 1.19 g (97%) of **10a** as a white solid: mp 114–115 °C; IR (KBr) 3620–2200 (br), 3277, 2941, 1706, 1584, 1476, 1334, 1162, 752 cm^{-1}; ^1H NMR (CD_3OD) δ 8.37 (d, J = 1 Hz, 1 H), 8.32 (dd, J = 4.5, 1 Hz, 1 H), 7.81 (d, J = 8 Hz, 2 H), 7.7 (td, J = 8, 1 Hz, 1 H), 7.56 (d, J = 8 Hz, 2 H), 7.35 (dd, J = 8, 4.5 Hz, 1 H), 2.86 (t, J = 7 Hz, 2 H), 2.62 (t, J = 7 Hz, 2 H), 2.2 (t, J = 7 Hz, 2 H), 1.15–1.7 (m, 13 H). Anal. ($C_{22}H_{29}ClN_2O_4S$) C, H, N.

4-(4-Hydroxybutyl)cyclohexanone (17). A solution of **16** (15 g, 83 mmol) in EtOH (70 mL) was added to liquid NH_3 (225 mL) at −78 °C and the solution was warmed to −40 °C. Sodium metal (8.28 g, 0.36 mol) was added in small portions over a 1-h period. The deep blue solution was allowed to stir at −40 °C for 10 min. The reaction mixture was quenched by adding NH_4Cl (17.6 g) followed by water (75 mL), and the volatiles were removed with a stream of nitrogen gas. The residue was poured onto brine and extracted with Et_2O (4 × 100 mL). The combined organic extract was dried, filtered, and evaporated in vacuo to give 17.8 g (100%) of clear oil identified as 4-(4-hydroxybutyl)-1-methoxycyclohexa-1,4-diene, which was used as it was for the next step: ^1H NMR ($CDCl_3$) δ 5.46 (br s, 1 H), 4.68 (br s, 1 H), 3.67 (t, J = 7 Hz, 2 H), 3.6 (s, 3 H), 2.75 (br s, 4 H), 1.4–2.3 (m, 7 H).

The compound prepared above (17.8 g, 83 mmol) was suspended in 1 N H_2SO_4 (280 mL) and allowed to stir for 1 h at room temperature. The mixture was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic extract was dried, filtered, and evaporated in vacuo to give 17.5 g (100%) of 4-(4-hydroxybutyl)-cyclohex-3-en-1-one as a clear oil which was used as it was for the next step: ^1H NMR ($CDCl_3$) δ 5.45 (m, 1 H), 3.67 (t, J = 7 Hz, 2 H), 2.86 (br s, 2 H), 2.3–2.5 (m, 4 H), 1.4–2.1 (m, 7 H).

The cyclohexenone prepared above (16.9 g, 83 mmol) was dissolved in acetone (200 mL), and 10% Pd on C (1.69 g) was added. The mixture was hydrogenated in a Parr apparatus at 50 psi until the theoretical amount of H_2 was consumed. The catalyst was filtered off and washed with acetone (4 × 30 mL). The solvent was evaporated in vacuo and the residue purified by flash chromatography using 2:3 EtOAc/hexane as eluent to give 1.2 g (86% from **16**) of **17** as a clear colorless oil: IR (CH_2Cl_2) 3616, 2935, 2862, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (t, J = 7 Hz, 2 H), 2.35 (m, 4 H), 2.03 (m, 2 H), 1.3–1.8 (m, 10 H).

4-(4-Hydroxybutyl)-ε-caprolactone (18). To a solution of **17** (12.2 g, 72 mmol) in CH_2Cl_2 (225 mL) was added mCPBA (23.5 g, 65% pure, 88 mmol). After 3 h, the reaction mixture was

quenched by the addition of saturated aqueous Na_2SO_3 (50 mL) and dilute $NaHCO_3$ (50 mL). The organic layer was dried, filtered, and evaporated in vacuo to give 12.67 g (94%) of 18 which was used as it was for the next step: IR (CH_2Cl_2) 3679, 3604, 2927, 1726, 1415, 1275 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (ddd, J = 12.5, 8, 1 Hz, 1 H), 4.15 (dd, J = 12.5, 8 Hz, 1 H), 3.61 (t, J = 6 Hz, 2 H), 2.62 (m, 2 H), 1.93 (m, 2 H), 1.25–1.65 (m, 10 H).

Methyl 8-[[(4-Chlorophenyl)sulfonyl]amino]-4-(2-hydroxyethyl)octanoate (19). To a solution of 18 (12.64 g, 68 mmol) in CH_2Cl_2 (360 mL) at 0 °C was added Et_3N (15.4 mL, 108 mmol) followed by slow addition of methanesulfonyl chloride (6.5 mL, 85 mmol). After 1 h, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was dried, filtered, and evaporated in vacuo to give 20.4 g (100%) of the desired mesylate which was used without purification: ^1H NMR ($CDCl_3$) δ 4.1–4.4 (m, 4 H), 3.02 (s, 3 H), 2.52–2.75 (m, 2 H), 1.3–2.05 (m, 11 H).

The mesylate prepared above (18.67 g, 71 mmol) was dissolved in DMF (100 mL), NaN_3 (5.5 g, 85 mmol) was added, and the reaction mixture was allowed to stir for 18 h. It was then poured on H_2O (300 mL) and extracted with EtOAc (1 × 400 mL). The organic phase was washed with H_2O (3 × 100 mL) and brine (50 mL), dried, filtered, and evaporated in vacuo to give 13.8 g (92%) of the azide which was used as it was for the next reaction: IR (CH_2Cl_2) 2937, 2100, 1731, 1290, 1081 cm^{-1}.

To a solution of the azide prepared above (13.8 g, 65.3 mmol) in THF (160 mL) was added triphenylphosphine (18.35 g, 70 mmol) followed by H_2O (2.2 mL) and few boiling stones. The solution was allowed to stir at room temperature for 18 h and then the solvent was evaporated and the residue was taken in toluene (100 mL) and evaporated in vacuo to remove water. The residue (31 g, 100%) was used as it was for the next step: IR (CH_2Cl_2) 3350 (br), 2931, 1730, 1653 cm^{-1}.

To a solution of the amine (31 g, 65 mmol) dissolved in CH_2Cl_2 (340 mL) was added 4-(dimethylamino)pyridine (0.01 g) followed by Et_3N (13 mL, 93 mmol) and 4-chlorobenzenesulfonyl chloride (15.62 g, 72 mmol). The reaction mixture was allowed to stir for 18 h and then washed with saturated $NaHCO_3$ solution. The organic phase was dried, filtered, and evaporated in vacuo to give 46.5 g (100%) of an amber solid which was used as it was for the next step: ^1H NMR ($CDCl_3$) δ 7.8 (d, J = 8 Hz, 2 H), 2.5 (d, J = 8 Hz, 2 H), 4.7 (t, J = 6 Hz, 1 H), 4.28 (ddd, J = 9, 6, 1 Hz, 1 H), 4.13 (dd, J = 9, 8 Hz, 1 H), 2.95 (q, J = 6 Hz, 2 H), 2.5–2.7 (m, 2 H), 1.8–1.95 (m, 2 H), 1.15–1.55 (m, 9 H).

The crude reaction product (46.5 g, 65 mmol) obtained above was dissolved in MeOH (500 mL), 1 N NaOH (250 mL, 0.25 mol) was added, and the reaction mixture was allowed to stir for 18 h. The solvent was evaporated in vacuo and the residue taken up in H_2O (100 mL) and filtered to remove triphenylphosphine oxide. The filtrate was washed with 1:1 EtOAc/Et_2O (1 × 50 mL) and the aqueous phase was made strongly acidic and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extract was dried, filtered, and evaporated to give 10.7 g (43%) of an amber oil which was esterified immediately.

The crude product (10.7 g, 28 mmol) from above was dissolved in MeOH (430 mL), and $SOCl_2$ (8.1 mL, 0.11 mol) was added dropwise to keep the reaction temperature below 40 °C. The reaction mixture was allowed to stir for 2.5 h and then adjusted to pH = 5–6 by addition of saturated $NaHCO_3$ solution. The solvent was evaporated and the residue poured into H_2O (100 mL) and then extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extract was dried, filtered, and evaporated in vacuo to give 18.1 g of an amber oil which was purified by flash chromatography using 3:2 EtOAc/hexane as eluent to give 7.3 (26% from 17) of 19 as a pale yellow oil: IR (CH_2Cl_2) 3686, 3604, 3373, 2940, 1733, 1337, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (d, J = 8 Hz, 2 H), 7.48 (d, J = 8 Hz, 2 H), 5.03 (t, J = 6 Hz, 1 H), 3.67 (overlapping s and t, 5 H), 2.93 (q, J = 6 Hz, 2 H), 2.39 (t, J = 8 Hz, 2 H), 1.2–1.65 (m, 12 H).

8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[2-(3-pyridinyloxy)ethyl]octanoic Acid (20). To a solution of 19 (3.35 g, 8.5 mmol) in CH_2Cl_2 (33 mL) was added triphenylphosphine (3.2 g, 12 mmol) and 3-hydroxypyridine (0.94 g, 9.9 mmol) followed 5 min later by diethyl azodicarboxylate (1.6 mL, 9.6 mmol). The reaction mixture was allowed to stir for 2 h, the solvent was evaporated in vacuo and the residue purified by flash chromatography using 7:3 EtOAc/hexane as eluent to give 2.03 g (51%) of methyl 8-[[(4-chlorophenyl)sulfonyl]amino]-4-[2-(3-pyridinyloxy)ethyl]octanoate: IR (CH_2Cl_2) 3370, 2942, 2867, 1733, 1580, 1337, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.3 (br s, 1 H), 8.21 (br s, 1 H), 7.8 (d, J = 8 Hz, 2 H), 7.48 (d, J = 8 H, 2 H), 7.25 (m, 2 H), 5.08 (t, J = 6 Hz, 1 H), 4.01 (t, J = 8 Hz, 2 H), 3.67 (s, 3 H), 2.94 (q, J = 6 Hz, 2 H), 2.31 (t, J = 8 Hz, 2 H), 1.25–1.8 (m, 11 H).

The methyl ester prepared above (1.82 g, 3.9 mmol) was dissolved in dioxane (10 mL) and 1 N NaOH (7.8 mL, 7.8 mmol) was added. The reaction mixture was allowed to stir for 18 h and the solvent was evaporated in vacuo. The residue was taken up in H_2O (50 mL) and adjusted to pH = 6 and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was dried, filtered, and evaporated in vacuo to give 1.99 g of a clear oil which was triturated with ether to give 1.59 g (90%) of 20 as a colorless solid: mp 87–89 °C; IR (KBr) 3600–2200 (br), 3277, 2943, 1712, 1588, 1425, 1332, 1275, 1162, 1093, 754 cm^{-1}; ^1H NMR (CD_3OD) δ 8.21 (d, J = 3 Hz, 1 H), 8.1 (dd, J = 5, 1.5 Hz, 1 H), 7.81 (d, J = 8 Hz, 2 H), 7.56 (d, J = 8 Hz, 2 H), 7.38 (m, 2 H), 4.08 (t, J = 7 Hz, 2 H), 2.87 (t, J = 7 Hz, 2 H), 2.3 (t, J = 7 Hz, 2 H), 1.74 (q, J = 7 Hz, 2 H), 1.61 (m, 3 H), 1.25–1.5 (m, 6 H). Anal. ($C_{21}H_{27}ClN_2O_5S$) C, H, N.

1-[(Tetrahydropyran-1-yl)oxy]-5-hydroxyoct-7-yne (28). A mixture of mCPBA (42.5 g, 65% slurry in H_2O, 160 mmol) and CH_2Cl_2 (350 mL) was allowed to stir well and the aqueous layer was separated. To the organic layer was added 1-[(tetrahydropyran-2-yl)oxy]hex-5-ene (26.6 g, 145 mmol) and the reaction mixture was allowed to stir for 18 h. A solution of saturated $NaHCO_3$ was added until pH = 8.0, followed by a solution of saturated Na_2SO_3 (20 mL) so that the test for peroxides (KI paper) was negative. The organic layer was separated and washed with brine and dried, filtered, and evaporated in vacuo to give 29.5 g (100%) of 1,2-epoxy-6-[(tetrahydropyran-2-yl)oxy]hexane as a clear oil which was used without purification: IR (CH_2Cl_2) 2945, 2869, 1450, 1344, 1077, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.61 (br s, 1 H), 3.3–4.0 (m, 4 H), 2.94 (m, 1 H), 2.75 (t, J = 5 Hz, 1 H), 2.47 (dd, J = 5, 3 Hz, 1 H), 1.35–1.9 (m, 12 H).

To a solution of the epoxide prepared above (29.5 g, 14.5 mmol) in DMSO (150 mL) was added lithium acetylide–ethylene diamine complex (16.4 g, 169 mmol). The resulting dark brown solution was allowed to stir at room temperature for 48 h and then quenched by the addition of saturated NH_4Cl (200 mL). The mixture was extracted with EtOAc (400 mL, 2 × 200 mL). To the combined organic layer was added solid NaCl (100 g) and the mixture filtered. The organic phase was dried, filtered, and evaporated in vacuo to give 41.6 g of a dark brown oil. Purification by flash chromatography using 3:7 EtOAc/hexane as eluent gave 28.1 g (86% for two steps) of 28 as a pale yellow oil: IR (CH_2Cl_2) 3588, 3304, 2944, 1455, 1353, 1120, 1077, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (br s, 1 H), 3.3–4.05 (m, 5 H), 2.41 (dd, J = 6, 2 Hz, 2 H), 2.1 (t, J = 2 Hz, 1 H), 1.4–2.0 (m, 12 H).

5-Hydroxy-1-[(tetrahydropyran-2-yl)oxy]-8-(3-pyridinyl)octane (29). To a solution of 28 (28.1 g, 124 mmol) in Et_2NH (300 mL) under nitrogen was added 3-bromopyridine (78.7 g, 500 mmol) followed by CuI (0.154 g, 0.81 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.9 g, 1.3 mmol). The reaction mixture was allowed to stir for 18 h and then taken up in Et_2O (1.2 L) and washed with saturated $NaHCO_3$ (250 mL) followed by H_2O (2 × 250 mL) and brine (250 mL). The organic layer was dried, filtered, and evaporated in vacuo to give 85.5 g of a brown oil which upon flash chromatography using 8:2 Et_2O/hexane as eluent gave 33 g (88%) of 5-hydroxy-1-[(tetrahydropyran-2-yl)oxy]-8-(3-pyridinyl)oct-7-yne as an orange oil: IR (CH_2Cl_2) 3611, 2944, 2870, 1476, 1408, 1077, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.8 (m, 1 H), 8.65 (m, 1 H), 7.83 (dt, J = 8, 1.5 Hz, 1 H), 7.33 (dd, J = 8, 5 Hz, 1 H), 4.61 (br s, 1 H), 3.3–4.05 (m, 5 H), 2.75 (s, 1 H, OH), 2.63 (d, J = 6 Hz, 2 H), 1.35–1.9 (m, 12 H).

The alkyne prepared above (33 g, 109 mmol) was dissolved in EtOH (200 mL) and 10% Pd/C (3.3 g) was added and the mixture was hydrogenated in a Parr shaker at 50 psi. The hydrogenation was stopped when the theoretical amount of H_2 was consumed (3 h) and the mixture was filtered through Celite and washed with EtOH. The filtrate was evaporated in vacuo and the residue passed through a plug of silica gel using EtOAc as eluent. Evaporation of the solvent in vacuo gave 32 g (96%) of 29 as a

apale yellow oil: IR (CH_2Cl_2) 3613, 2944, 2866m, 1574, 1415, 1077, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.53 (m, 2 H), 7.6 (br d, J = 8 Hz, 1 H), 7.27 (dd, J = 8, 5 Hz, 1 H), 4.6 (br s, 1 H), 4.05 (m, 5 H), 2.8 (br, 1 H, OH), 2.64 (t, J = 8 Hz, 2 H), 1.3–1.85 (m, 12 H).

Ethyl 8-[(Tetrahydropyran-2-yl)oxy]-4-[3-(3-pyridinyl)-propyl]-3-thiaoctanoate (32). To a solution of **29** (10 g, 33 mmol) in CH_2Cl_2 (160 mL) was added 4-(dimethylamino)pyridine (0.11 g) followed by Et_3N (14 mL, 100 mmol) and *p*-toluenesulfonyl chloride (12.6 g, 66 mmol) and the reaction mixture was allowed to stir for 18 h. The reaction mixture was washed with saturated $NaHCO_3$ (150 mL) and the organic layer was dried, filtered, and evaporated in vacuo to give an amber oil which was purified by flash chromatography to obtain 7.65 g (51%) of the tosylate of **29**: ^1H NMR ($CDCl_3$) 8.44 (d, J = 5 Hz, 1 H), 8.36 (s, 1 H), 7.76 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz), 7.29 (d, J = 8 Hz, 2 H), 7.22 (dd, J = 8, 5 Hz, 1 H), 4.58 (qn, J = 6 Hz, 1 H), 4.51 (br s, 1 H), 3.81 (m, 1 H), 3.63 (m, 1 H), 3.48 (m, 1 H), 3.38 (m, 1 H), 2.53 (t, J = 8 Hz, 2 H), 2.41 (s, 2 H), 1.2–1.85 (m, 16 H).

To a solution of ethyl 2-mercaptoacetate (2.3 mL, 21 mmol) in DMF (10 mL) was added dropwise a 1.61 M solution of KOtBu in THF (13.0 mL, 21 mmol) and the mixture was allowed to stir for 30 min. A solution of the tosylate prepared above (7.65 g, 16.7 mmol) in DMF (10 mL) was added dropwise. The reaction mixture was allowed to stir for 48 h and then diluted with EtOAc (100 mL) and washed with H_2O (2 × 25 mL). The aqueous layer was extracted with EtOAc (50 mL) and the combined organic extract was washed with brine, dried, filtered, and evaporated to give 7.1 g of an oil. Purification by flash chromatography using Et_2O as eluent gave 4.9 g (72%) of **32** as a pale yellow oil: IR (CH_2Cl_2) 2943, 2865, 1730, 1285, 1135, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.46 (br s, 2 H), 7.57 (d, J = 8 Hz, 1 H), 7.26 (t, J = 8 Hz, 1 H), 4.56 (br s, 1 H), 4.15 (q, J = 7 Hz, 2 H), 3.85 (m, 1 H), 3.72 (m, 1 H), 3.49 (m, 1 H), 3.37 (m, 1 H), 3.17 (s, 2 H), 2.78 (qn, J = 6 Hz, 1 H), 2.63 (t, J = 8 Hz, 2 H), 1.45–1.9 (m, 16 H), 1.26 (t, J = 7 Hz, 3 H).

The THP group of **32** was hydrolyzed using aqueous acid and the resulting alcohol was converted to the corresponding amine via the mesylate and azide as per the procedure described above for the conversion of **18** to **19**. Formation of the 4-chlorobenzenesulfonamide followed by saponification of the ester using the standard conditions described above gave **33** as a white solid: mp 84–86 °C; IR (KBr) 3500–2300 (br), 3270, 2942, 1709, 1476, 1424, 1331, 1161, 1092, 754 cm^{-1}; ^1H NMR (CD_3OD) δ 8.4 (s, 1 H), 8.37 (br s, 1 H), 7.81 (d, J = 8 Hz, 2 H), 7.74 (d, J = 8 Hz, 1 H), 7.58 (d, J = 8 Hz, 2 H), 7.39 (t, J = 8 Hz, 1 H), 3.14 (s, 2 H), 2.85 (t, J = 7 Hz, 2 H), 2.74 (qn, J = 6 Hz, 1 H), 2.68 (m, 2 H), 1.78 (m, 2 H), 1.32–1.63 (m, 8 H). Anal. ($C_{21}H_{27}ClN_2O_4S_2$) C, H, N.

8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[3-(1*H*-imidazolyl)-propyl]octanoic acid (15) was prepared using Scheme I: mp 136–138 °C; IR (KBr) 3600–2200 (br), 3277, 2918, 1704, 1585, 1330, 1161, 1091 cm^{-1}; ^1H NMR (CD_3OD) δ 7.82 (d, J = 8 Hz, 2 H), 7.8 (br, 1 H), 7.57 (d, J = 8 Hz, 2 H), 7.19 (br, 1 H), 7.03 (br, 1 H), 4.02 (t, J = 7 Hz, 2 H), 2.85 (t, J = 7 Hz, 2 H), 2.21 (br t, J = 8 Hz, 2 H), 1.68 (m, 2 H), 1.18–1.6 (m, 11 H). Anal. ($C_{20}H_{28}ClN_3O_4S$) C, H, N.

7-[[(4-Chlorophenyl)sulfonyl]amino]-3-[3-(3-pyridinyl)-propyl]heptanoic acid (35) was prepared as shown in Scheme III: mp 95–97 °C; IR (KBr) 3600–2200 (br), 3251, 2928, 2861, 1707, 1587, 1424, 1321, 1158, 1092 cm^{-1}; ^1H NMR (CD_3OD) δ 8.37 (br s, 1 H), 8.33 (d, J = 4 Hz, 1 H), 7.81 (d, J = 8 Hz, 2 H), 7.67 (d, J = 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 2 H), 7.33 (dd, J = 8, 4 Hz, 1 H), 2.85 (t, J = 7 Hz, 2 H), 2.63 (t, J = 7 Hz, 2 H), 2.17 (d, J = 7 Hz, 2 H), 1.81 (m, 1 H), 1.63 (qn, J = 7 Hz, 2 H), 1.2–1.5 (m, 8 H). Anal. ($C_{21}H_{27}ClN_2O_4S$) C, H, N.

8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[3-(4-methyl-3-pyridinyl)propyl]octanoic acid (23) was prepared using Scheme II: mp 61–71 °C; IR (KBr) 3600–2100 (br), 3276, 2938, 1711, 1604, 1476, 1333, 1162, 1093, 753 cm^{-1}; ^1H NMR (CD_3OD) δ 8.37 (s, 1 H), 8.31 (d, J = 4 Hz, 1 H), 7.81 (d, J = 8 Hz, 2 H), 7.58 (d, J = 8 Hz, 2 H), 7.42 (d, J = 4 Hz, 1 H), 2.84 (t, J = 7 Hz, 2 H), 2.71 (t, J = 7 Hz, 2 H), 2.46 (s, 3 H), 2.24 (t, J = 7 Hz, 2 H), 1.2–1.7 (m, 13 H). Anal. ($C_{23}H_{31}ClN_2O_4S$) C, H, N.

8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[3-(3-pyridinyl)-propyl]oct-2-enoic acid (9a) was prepared as shown in Scheme I: mp 72–75 °C; IR ($CDCl_3$) 3700–2300 (br), 2939, 2862, 1697, 1655, 1589, 1478, 1333, 1164, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.47 (br, 2 H), 8.0 (br, 1 H, COOH), 7.79 (d, J = 8 Hz, 2 H), 7.57 (d, J = 7 Hz, 1 H), 7.44 (d, J = 8 Hz, 2 H), 7.3 (br, 1 H), 6.66 (dd, J = 15, 9 Hz, 1 H), 5.77 (d, J = 15 Hz, 1 H), 2.88 (t, J = 7 Hz, 2 H), 2.6 (m, 2 H), 2.1 (m, 1 H), 1.1–1.65 (m, 10 H). Anal. ($C_{22}H_{27}ClN_2O_4S$) C, H, N.

***N*-[1-[[(4-Chlorophenyl)sulfonyl]amino]-8-(3-pyridinyl)-oct-5-yl]oxamic acid (8)** was prepared as shown in Scheme I: mp 95=98 °C; IR ($CDCl_3$) 3500–2300 (br), 2930, 1778, 1731, 1695, 1329, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 8.7 (d, J = 4 Hz, 1 H), 8.2 (d, J = 8 Hz, 1 H), 7.89 (d, J = 8 Hz, 2 H), 7.83 (m, 1 H), 7.66 (m, 1 H), 7.46 (d, J = 8 Hz, 2 H), 3.95 (m, 1 H), 2.9 (m, 4 H), 1.2–2.4 (m, 10 H). Anal. ($C_{21}H_{26}ClN_3O_5S$) C, H, N.

1-[[(4-Chlorophenyl)sulfonyl]amino]-5-[2-(tetrazol-5-yl)-ethyl]-8-(3-pyridinyl)octane (11c) was prepared as shown in Scheme I: mp 56–81 °C; IR ($CDCl_3$) 3460–2300 (br), 2936, 2862, 1583, 1478, 1331, 1163, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.55 (br, 2 H), 8.25 (br, 1 H, CN_4H), 7.8 (d, J = 8 Hz, 2 H), 7.75 (m, 1 H), 7.45 (d, J = 8 Hz, 2 H), 7.43 (m, 1 H), 6.0 (br, 1 H), 2.93 (m, 4 H), 2.61 (m, 1 H), 1.2–1.83 (m, 13 H). Anal. ($C_{22}H_{29}ClN_6O_2S \cdot 0.5H_2O$) C, H, N.

8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[3-(3-pyridinyl)-propyl]-2,2-dimethyloctanoic acid (26b) was prepared as shown in Scheme II: mp 114–115 °C; IR (CH_2Cl_2) 3400–2200 (br), 2937, 2862, 1726 (sh), 1698, 1587, 1477, 1335, 1164, 1095 cm^{-1}; ^1H NMR (CD_3OD) δ 8.38 (s, 1 H), 8.35 (d, J = 4 Hz, 1 H), 7.82 (d, J = 8 Hz, 2 H), 7.7 (br d, J = 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 2 H), 7.35 (dd, J = 8, 4 Hz, 1 H), 3.83 (t, J = 7 Hz, 2 H), 2.6 (t, J = 7 Hz, 2 H), 1.14–2.15 (m, 13 H), 1.1 (s, 6 H). Anal. ($C_{24}H_{33}ClN_2O_4S$) C, H, N.

Biological Assay. The in vitro measurement of thromboxane synthase inhibition, inhibition of U 46619-induced aggregation of human washed platelet and PRP, and inhibition of U 46619-induced contraction of dog saphenous vein were done as per the procedure described previously.[18a,b]

Inhibition of U 46619-Induced ex Vivo Platelet Aggregation in Guinea Pigs. Male Hartley guinea pigs (350–400 g) were fasted 12–16 h prior to dosing. Groups of animals (three to six) were treated orally with the vehicle (3% fortified cornstarch suspension) alone or with compound dispersed in it. One hour (or 6 h) following administration, the animals were anesthetized by methoxyflurane inhalation, the heart exposed, and a sample of anticoagulated (0.0129 M sodium citrate, final concentration) blood was withdrawn by cardiac puncture using butterfly infusion sets attached to syringes. The blood was centrifuged at 500*g* for 7 min to obtain platelet-rich plasma. The infranatant was centrifuged at 13000*g* for 3–5 min to yield platelet-poor plasma.

Platelet aggregations were performed on Payton dual-channel aggregometers attached to a Compaq Deskpro personal computer. Aliquots (0.5 mL) of platelet-rich plasma were incubated for 1 min stirring at 900 rpm at 37 °C. At the conclusion of the incubation, the thromboxane A_2 mimetic U 46619 was then added to induce aggregation. Values were computed for both the vehicle-treated and compound treated groups as aggregation ratios which are determined by the following computation: EC_{50} drug-treated group/EC_{50} vehicle-treated group.

Inhibition of Arachidonic Acid Induced Bronchoconstriction in Guinea Pigs. Male Hartley (Elm Hill Breeding Labs, Chelmsford, MA) guinea pigs (300–500 g) were anesthetized with urethane (1.5 mg/kg) and a carotid artery and jugular vein cannulated for the measurement of blood pressure and the intravenous delivery of compounds, respectively. The trachea was cannulated and the animals placed on a small animal respirator (Harvard Rodent Ventilator, South Natick, MA) at 40 strokes/min at a stroke volume of 4.0 mL/min. Succinylcholine was administered (1.0 mg/kg) to inhibit spontaneous breathing. Resting control values were continuously recorded for 30 min when the animals were stabilized.

Arachidonic acid (Nu Chek Prep. Inc.) was administered as an initial priming dose of 0.25 mg/kg (iv bolus), increases in insufflation pressure (bronchial resistance) were recorded, and the animals were allowed to stabilize for 20–30 min or until

bronchial resistance and blood pressure returned to control values. At that time the animals were challenged with a second iv dose (0.5 mg/kg) of AA. Once the insufflation and blood pressures returned to normal the test compound was administered by a bolus iv injection while the values of the monitored parameters were recorded. At exactly 5 min postadministration of the test compound, the animals were challenged once more with a third dose of AA (0.5 mg/kg iv bolus) and responses were similarly recorded. Bronchoconstriction was measured as peak insufflation pressure and expressed as a percentage of the control (initial response).

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