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Development of Dual-Acting Agents for Thromboxane Receptor Antagonism and Thromboxane Synthase Inhibition—I. Synthesis, Structure–Activity Relationship, and Evaluation of Substituted ω-Phenyl-ω-(3-Pyridyl)Alkenoic Acids

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Abstract—A series of arylsulfonamido-substituted ω-phenyl-ω-(3-pyridyl)alkenoic acids were synthesized and evaluated *in vitro* for their ability to act as both a thromboxane A_2 receptor antagonist (TRA) and thromboxane synthase inhibitor (TSI). Variations of alkenoic acid chain length, olefin geometry, substituent effect on the benzenesulfonamido group, and conformational flexibility of the substituted arylsulfonamido group were examined. Among the various substituents, iodo-substitution gave the most potent compound. Conformational flexibility between the arylsulfonamido group and the phenyl ring attached to the alkenoic acid side chain significantly enhanced the dual activities. The compound (*E*)-**21c** was identified as the most potent TRA/TSI (TRA: K_d = 53 nM; TSI: IC_{50} = 23 nM) in the series studied. The compounds **9c** and **10c** have indicated that these series of compounds are orally active and are specific TSIs as exhibited by the so-called 'shunt' effect on prostacyclin synthesis *in vitro*.

Introduction

Modulation of either the synthesis or the activity of arachidonic acid metabolites continues to be an area that attracts substantial research interest in potential therapeutic agents for various circulatory disorders.[1–4] An appropriate balance between the biosynthesis of thromboxane A_2 (TXA_2, **1**) and prostacyclin (PGI_2, **2**), two extremely unstable metabolites of arachidonic acid with opposing activities, is considered an important factor for maintaining a normal hemodynamic status. In particular, TXA_2, being an extremely potent platelet-aggregating and vasoconstricting agent, plays a major role in the pathogenesis of certain vascular and renal disorders.[5] Thromboxane synthase inhibitors (TSIs) and thromboxane receptor antagonists (TRAs) have been developed to treat these disorders.[2–4] While the efficacy of TRAs has yet to be established, TSIs have performed poorly in clinical trials.[6] The lack of efficacy of TSIs has been ascribed to PGH_2 (**3**) which accumulates from inhibition of thromboxane synthase and whose agonist activity nullifies the benefits of reducing TXA_2 levels. Theoretical arguments have been made to support the potentially superior antithrombotic efficacy of using a combined TRA/TSI over either class of agent alone or aspirin.[7–10] Thromboxane synthase inhibitory action of such an agent would prevent the biosynthesis of TXA_2 while the accumulated PGH_2 would be redirected and converted to beneficial prostaglandins such as PGI_2 (prostacyclin) and PGD_2. This so-called 'shunt' effect is not possible by the use of a TRA or aspirin which inhibits prostacyclin production. The thromboxane receptor antagonism of the combined agent, at the same time, would antagonize the action of PGH_2. We and others[11–14] have undertaken a program to develop compounds which contain both TRA and TSI activities in a single chemical entity. Such compounds would minimize and overcome the limitation of aspirin or a TRA or TSI alone and would solve the impracticality of using two drugs with potentially different pharmacokinetics for therapeutic purposes.

In this paper, we describe the design, synthesis, structure and activity relationship (SAR), and *in vitro* and *in vivo* pharmacology of a series of compounds which possess TRA/TSI activity.

Compound Design

Our strategy to identify compounds which possess dual TRA and TSI was based upon a design of hybrid structures by incorporating the basic pharmacophore for each activity. The essential structural features of a TSI are a basic nitrogen atom of a 3-substituted pyridine or a 1-substituted imidazole ring and a carboxylic acid functionality separated by a distance of 8.5–10 Å.[15] The pharmacophores for TRA vary widely in structural type, of which a combination of aryl sulfonamide and carboxylic acid is well known. In the process of our program development, the compound **4** (LY280978) was identified as a potent TRA.[16] Design of the target molecule **I** which

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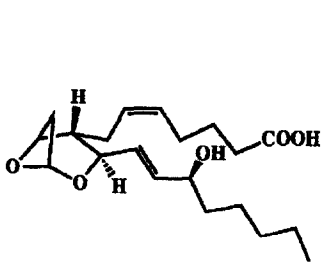
incorporates a pyridyl ring into **4** to hopefully induce a balanced combined TRA/TSI activity appeared promising. Examples such as **5** (CV-4151)[15] and **6** (R68070)[28] have been reported to possess a combined TRA/TSI activity albeit with modest TRA.[4,9]

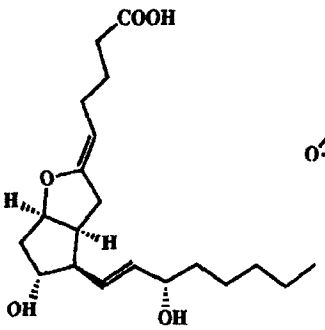
Chemistry

The initial target molecules **9** and **10** were synthesized via a Wittig reaction of the benzenesulfonamido-substituted phenyl pyridyl ketones **7** and **8**, respectively, as shown in Scheme I. The ketones **7** and **8** were prepared from commercially available 3- or 4-bromoaniline in three steps: (1) sulfonamide formation ($PhSO_2Cl$, pyridine, 0 °C, 98 %); (2) phenyl(pyridyl)carbinol formation (*n*-BuLi, THF, –78 °C; 3-pyridinecarboxaldehyde, 59–60 %); and (3) oxidation of the carbinols to the ketones by any one of the conventional oxidation methods such as Swern, Jones, or preferably MnO_2 oxidation (MnO_2, 1,4-dioxane, 70 °C overnight, 96 %). The Wittig reaction of these ketones with (ω-carboxyalkyl)triphenylphosphonium bromide[15] in the presence of NaHMDS, THF, –78 °C (34–55 %) or *t*-BuOK, THF, –10 ~ 0 °C (88–100 %) yielded mixtures of (*E*)- and (*Z*)-alkenoic acids **9** and **10**, predominantly as the (*E*)-isomers,[17] as shown in Table 1.

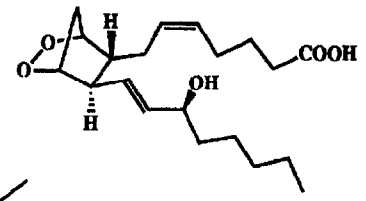
In order to assess the effect of the double bond geometry of the alkenoic acids and substituent effect on the sulfonamide phenyl ring, the chemistry was modified to separate the two geometric isomers as shown in Scheme II. The nitrophenyl pyridyl ketones **11** and **12** were obtained in two steps from 3-bromopyridine: (1) nitrophenyl-(pyridyl)carbinol formation (*n*-BuLi, Et_2O, –78 °C; nitrobenzaldehyde, 35–54 %); and (2) MnO_2 or Swern oxidation of the carbinols to the ketones (94–98 %). The ketones were then subjected to a Wittig reaction followed



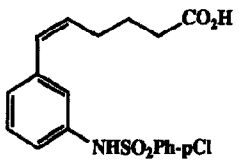
TXA_2 (1)



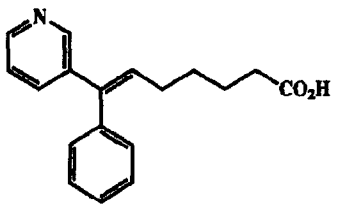
PGI_2 (2)



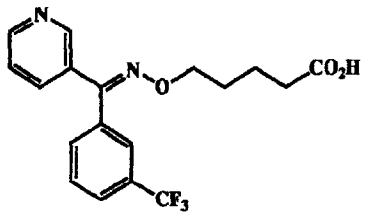
PGH_2 (3)



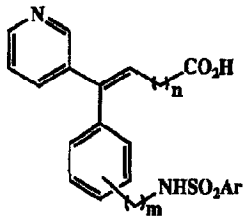
4 (LY280978)



5 (CV-4151)

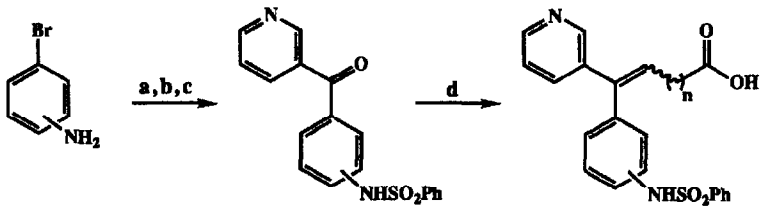


6 (R 68070)



(n = 2-7; m = 0,1)

I

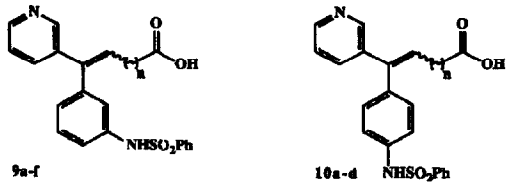


7 (*m*- 41%)
8 (*p*- 55%)

9a-f (*m*- 34-55%)
10a-d (*p*- 88-100%)

Scheme I. a) $PhSO_2Cl$, pyr.; b) *n*-BuLi, THF, –78 °C; 3-pyridinecarboxaldehyde; c) MnO_2, dioxane, 70 °C; d) $Br^-Ph_3P^+(CH_2)_{n+1}CO_2H$, *t*-BuOK, THF, –10 ~ 0 °C.

Table 1. *In vitro* activities of compounds **9** and **10**



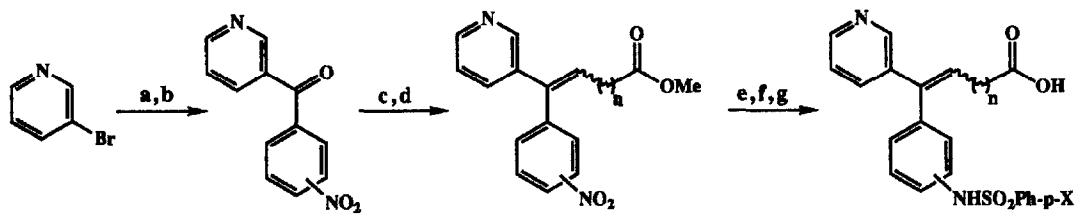
9a-f 10a-d

Compounds	n	E/Z[a]	TRA Kd (μM)[b]	TSI IC50 (nM)[b]
9a	2	90 : 10	4.0 ± 0.3	8,000
9b	3	77 : 23	3.9 ± 0.3	2,000
9c	4	84 : 16	2.8 ± 0.2	230
9d	5	100 : 0	2.7 ± 0.2	180
9e	6	96 : 4	5.8 ± 0.5	400
9f	7	73 : 27	2.7 ± 0.4	93
10a	3	98 : 2	1.2 ± 0.15	2,100
10b	4	97 : 3	1.1 ± 0.20	2,200
10c	5	93 : 7	0.324 ± 0.031	130
10d	6	96 : 4	2.3 ± 0.40	140
6			8.0 ± 0.35	14.7±4.9

[a]The (*E/Z*) ratio was determined by HPLC analysis.
[b]The thromboxane receptor antagonism (TRA) and thromboxane synthase inhibition (TSI) were determined in triplicate using a human platelet binding assay and human serum levels of TXB_2.

by esterification ((ω-carboxyalkyl)triphenylphosphonium bromide, *t*-BuOK, THF, 0 °C; CH_2N_2, Et_2O–THF, 0 °C, 45–57 %). In this case, the (*Z*)-isomers (the less polar material) were the predominant products in all cases (*E/Z* = 1/~3 for *meta*-series; *E/Z* =1/~5 for *para*-series). The (*E/Z*)-mixture of **13** and **14** were separated by chromatography at this stage. Each isomer was then subjected to the following conditions to furnish the desired products **15** and **16**: (1) amine formation ($NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 0 °C,[18] 65–88 %); (2) sulfonamide formation followed by hydrolysis (*p*-X-$PhSO_2Cl$, pyr., 0 °C to rt; 1.0 N NaOH, THF–MeOH; H^+ 40–92 %).

Scheme III describes the synthetic route to the series **21** and **22**. These compounds were synthesized in 11 steps from commercially available 1,3- or 1,4-benzenedimethanol. Benzenedimethanol was mono-protected with *t*-butyldimethylsilyl chloride (TBSCl) by a standard method (36–48 %). The mono-protected diol was oxidized with MnO_2 in THF at reflux to afford the aldehyde (83–86 %), which was then treated with 3-lithiopyridine (generated by the reaction of 3-bromopyridine with *n*-BuLi at –78 °C in Et_2O). The pyridylcarbinol thus obtained (79–89 %) was oxidized with MnO_2 to the corresponding ketones **17** and **18** (96–97 %). These ketones were then subjected to a Wittig reaction with an (ω-carboxyalkyl)-triphenylphosphonium bromide and *t*-BuOK in THF at 0 °C. The two geometrical (*E*)- and (*Z*)-isomers obtained could be separated by chromatography at this stage or in a subsequent step. In all cases the (*Z*)-isomer (less polar material) was the predominant Wittig reaction product (*E/Z* = ~ 1 / 2.5 for the *m*-substituted phenyl derivatives; *E/Z* = ~1 / 5 for the *p*-substituted). The heptenoic acids were esterified with CH_2N_2 (yields for the above two steps: *m*- 52–84 %; *p*- 41–72 %). Deprotection of TBS group (n-$Bu_4N^+F^-$, THF, 38–100 %) and one pot formation of azide[19] via a mesylate yielded in 71–91 % the desired azides **19** and **20**. Typically the (*E*)- and (*Z*)-isomers were separated at this stage. The nickel chloride catalyzed $NaBH_4$ reduction of the azide to amine (47–84 %), then sulfonamide formation (39–82 %), followed by hydrolysis of the ester (44–99 %) furnished the final products **21** and **22**.



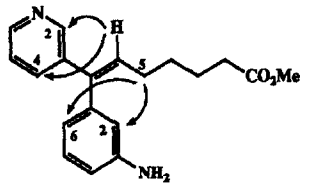
11 (*m*- 53%)
12 (*p*- 33%)

13 (*m*- 45%)
14 (*p*- 57%)

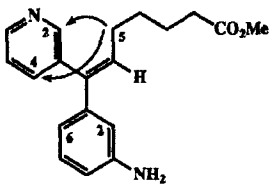
15a-h (*m*- ~32%)
16a-b (*p*- ~50%)

Scheme II. a) *n*-BuLi, Et_2O, –78 °C; nitrobenzaldehyde; b) MnO_2, THF, reflux; c) $Br^-Ph_3P^+(CH_2)_{n+1}CO_2H$, *t*-BuOK, THF, 0 °C; d) CH_2N_2, Et_2O–THF; chromatographic separation; e) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 0 °C; f) *p*-X-$PhSO_2Cl$, pyr.; g) 1 N NaOH, THF–MeOH (1:1); H^+.

Stereochemical assignments of the trisubstituted ω-alkenoic acids rested on their ^1H NMR spectra, NOE experiments (NOESY) on their key intermediates, and their mobility on silica gel. The chemical shift of the olefinic proton of *E*-isomers was shielded upfield compared to that of *Z*-isomers. The nuclear Overhauser effect (NOE) was observed between the olefinic proton of the alkenoic acid chain and the C_2 and C_4 protons of pyridyl ring as well as between the C_5 allylic protons of the alkenoic acid chain and the C_2 and C_6 protons of phenyl ring for the (*E*)-isomer. For the (*Z*)-isomer, a NOE was observed between the allylic protons of alkenoic acid chain and the C_2 and C_4 protons of pyridyl ring, whereas NOE between the olefinic proton and the C_2 and C_6 protons of phenyl ring was not observable.



(*E*)-isomer

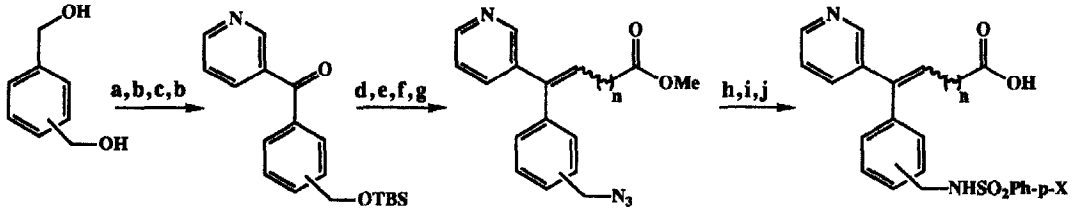


(*Z*)-isomer

Mobility of the geometrical isomers indicated that, in general, the (*E*)-isomers were more polar on silica gel than the (*Z*)-isomers. Observation of ^1H NMR spectra and mobility of our compounds was consistent with the literature precedence.[15]

Pharmacological Results and Discussion

The series of compounds synthesized and depicted by the structure **I** were evaluated for their *in vitro* potency in a receptor binding assay and inhibition of TXA_2 biosynthesis. Tables 1–3 list the K_d and IC_{50} values for *in vitro* TRA and TSI assays, respectively. Our initial structure and activity relationship study (SAR) in the series **9** and **10** indicated that alkenoic acid chain length had a profound effect on TSI and somewhat modest effect on TRA activity (Table 1). In the *meta* substituted series, compounds **9c**, **9d**, and **9f** (where $n = 4$, 5, and 7) were the best TRAs and TSIs (TRAs: $K_d = 2.8$–2.7 μM; TSIs: $IC_{50} = 230$–93 nM), whereas in the *para* series **10c** ($n = 5$) had distinctively superior dual activities than other compounds with either shorter or longer chain length. Moreover, the octenoic acid **10c** showed fairly balanced TRA and TSI activity ($K_d = 324$ nM, $IC_{50} = 130$ nM). The next step in our SAR was to examine the effects of substitution on the benzenesulfonamide ring and double bond geometry to improve and balance the combined activity. We chose **9c** in the *meta* series as the base structure for this study since the distance (~9 Å) between the pyridyl nitrogen and the carboxylic acid group of the side chain has been estimated to be optimal for TSI activity.[15,20] A profound substituent effect was seen with TRA activity (Table 2). The electron withdrawing groups (with the exception of fluoro compound) appear to be more beneficial than the electron donating groups for the TRA activity. For example, the halogenated benzenesulfonamide derivatives **15e**, **15f**, and **15g** showed far better TRA activity ($K_d = 0.80$–0.59 μM) than others. However, the substituent effect on TSI was not as clear. Among the halogenated compounds, the TRA activity increased dramatically from the fluoro- (**15d**) to the iodo-substituted compound (**15g**), whereas the order of TSI activity was completely reversed. The double bond geometry of the alkenoic acid side chain affected both the TRA and TSI activity but more profoundly the TSI. Kato *et al.* have reported[15] that (*E*)-ω-pyridylalkenoic acids were 2–10 times better TSI than the (*Z*)-isomers. This appeared to be true with our compounds. The base structure **9c** was prepared according to Scheme II to separate the (*E*/*Z*)-mixture. The *in vitro* assay showed that (*E*)-**9c** was a better TRA/TSI than (*Z*)-**9c** (Table 2). With these results, we speculated that the iodo-substituted (the best TRA) (*E*)-alkenoic acid (better TSI) should be a superior dual-acting agent than others in the series. This was indeed the case. The compound (*E*)-**15g** was the best TRA/TSI and showed a well-balanced TRA/TSI activity ($K_d = 322$ nM, $IC_{50} = 300$ nM). Notice that (*E*)-**15b** was tenfold more potent than (*Z*)-**15b** as a TSI. In the *para* series, we modified **10c** by incorporating iodine in the benzenesulfonamide ring (**16b**). This resulted in a twofold improvement in both TRA and TSI activity compared to **10c** ($K_d = 162$ nM, $IC_{50} = 68$ nM).



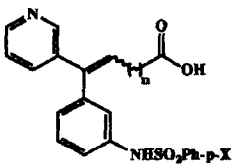
17 (*m*- 30%)
18 (*p*- 26%)

19 (*m*- 35-68%)
20 (*p*- 7-41%)

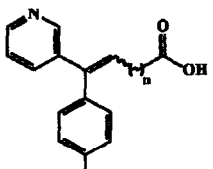
21a-d (*m*- 16-65%)
22a-d (*p*- 9-54%)

Scheme III. a) TBSCl, imidazole, CH_2Cl_2; b) MnO_2, THF, reflux; c) 3-lithiopyridine, Et_2O, –78 °C; d) $Br^-Ph_3P^+(CH_2)_{n+1}CO_2H$, *t*-BuOK, THF, 0 °C; e) CH_2N_2, Et_2O–THF; f) *n*-$Bu_4N^+F^-$, THF; g) $MeSO_2Cl$, Et_3N, $PhCH_3$, 0 °C; aq. NaN_3/*n*-$Bu_4N^+F^-$, 60 °C; chromatographic separation; h) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 0 °C; i) *p*-X-$PhSO_2Cl$, pyr.; j) 1 N NaOH, THF–MeOH (1:1); H^+.

Table 2. *In vitro* activities of compounds **15** and **16**



15a-h

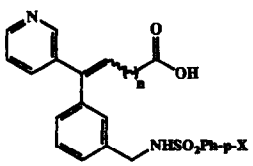


16a-b

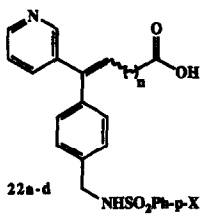
Compounds	n	X	E/Z	TRA Kd (μM)[b]	TSI IC50 (nM)[b]
9c	4	H	Z	5.8 ± 0.6	498 ± 180
15a	4	Me	Z	2.3 ± 0.2	840
15b	4	OMe	Z	5.4 ± 0.5	3,100
15c	4	CF_3	Z	1.1 ± 0.2	470 ± 110
15d	4	F	Z	3.0 ± 0.3	300
15e	4	Cl	Z	0.80 ± 0.06	900
15f	4	Br	Z	0.72 ± 0.09	1,030 ± 270
15g	4	I	Z	0.59 ± 0.04	4,000
15h	4	Ph	Z	2.01 ± 0.35	1,000 ± 50
16a	4	I	Z	0.162±0.025	4,300
9c	4	H	E	2.6 ± 0.3	300
15g	4	I	E	0.322 ± 0.021	300
16b	5	I	>96%E[a]	0.162±0.015	68 ± 21

[a]The (*E*/*Z*) ratio was determined by HPLC analysis.
[b]The thromboxane receptor antagonism (TRA) and thromboxane synthase inhibition (TSI) were determined in triplicate using a human platelet binding assay and human serum levels of TXB_2.

Table 3. *In vitro* activities of compounds **21** and **22**



21a-d



22a-d

Compounds	n	X	E/Z[a]	TRA Kd (μM)	TSI IC50 (nM)
21a	3	H	>97.6%E	0.310 ± 0.038	32 ± 15
			>95.5%Z	0.265 ± 0.040	205 ± 40
21b	4	H	76 : 24	0.280 ± 0.051	30 ± 10
			9 : 91	0.700 ± 0.110	67 ± 15
21c	4	I	86 : 14	0.053 ± 0.008	23 ± 4
			21 : 79	0.131 ± 0.026	53 ± 9
21d	5	H	50 : 50	0.312 ± 0.047	38 ± 18
			94%Z	0.708 ± 0.080	336 ± 124
22a	3	H	91%E	0.380 ± 0.020	44 ± 7
			>99%Z	2.100 ± 0.260	550 ± 200
22b	4	H	>81%E	0.410 ± 0.050	49 ± 7
			>98%Z	2.660 ± 0.850	290 ± 160
22c	4	I	97%Z	0.220 ± 0.010	390 ± 10
22d	5	H	≥69%E	0.580 ± 0.030	28 ± 6
			>91%Z	1.260 ± 0.090	750 ± 160

[a]The (*E*/*Z*) ratio was determined by HPLC analysis.
[b]The thromboxane receptor antagonism (TRA) and thromboxane synthase inhibition (TSI) were determined in triplicate using a human platelet binding assay and human serum levels of TXB_2.

The third step of our SAR study was to give more conformational flexibility to the arylsulfonamido group. This was done by incorporating a methylene chain between the sulfonamide nitrogen and the phenyl ring attached to the alkenoic acid chain, as in the series **21** and **22** (Scheme III). Such flexibility in the molecule may optimize the fit of the inhibitor in the enzyme active site as well as at the receptor site. Our results show that this goal was apparently realized (Table 3). A dramatic improvement in both TRA and TSI was seen in *meta* series: for example, **9b** to **21a**, **9c** to **21b**, **9d** to **21d**, and **15g** to **21c**. The effects of changing double bond geometry and chain length of the alkenoic acids in the *meta* series **21** were significantly diminished, though the (*E*)-isomers were still preferred and $n = 4$ was optimal chain length. The effect of iodo-substitution for TRA resulted in about five-fold improvement (**21b** to **21c**), significant but not as much as in the series lacking the methylene chain; i.e. **9c** to **15g** (8~10-fold). Compound (*E*)-**21c** was identified as the most potent TRA/TSI ($K_d = 53$ nM, $IC_{50} = 23$ nM) in this series. The dramatic improvement by incorporating a methylene chain was also observed in the *para* series except where $n = 5$; for example, **10a** to (*E*)-**22a** and **10b** to (*E*)-**22b**. Interestingly, the effect of double bond geometry of the alkenoic acid side chain for both TRA and TSI was more pronounced in the *para* series **22** than in the *meta* series **21**. However, length of the alkenoic chain had little effect and the little effect observed was inconsistent in the *para* series **22**. The beneficial effect of iodo-substitution for TRA was observed in this series also ((*Z*)-**22b** to **22c**). Of these homologated series, the (*E*)-isomers were more potent than the (*Z*)-isomers and the *meta* series **21** was more potent than the *para* series **22** for both TRA and TSI activity in all cases. The iodo-substituent on the benzenesulfonamide, while affecting the TRA significantly, did not influence the TSI activity appreciably even in the case of (*Z*)-isomer (**21b** vs **21c**, (*Z*)-**22b** vs **22c**) in these homologated series. It is possible that when the pyridine ring and the carboxylic acid group bind to the enzyme,[15] the sulfonamide chain with its conformational flexibility orientates itself in such a way that both electronic and steric variations at the end of its chain have minimal effect on the enzyme inhibitory activity. Neither the series **9** and **10** where the changes in the alkenoic acid side chain length became an important factor, nor the series **15** and **16** where the (*E*)-geometry of the double bond became significant, had this flexibility. Indeed, such inflexibility in these compounds most likely limited their TRA/TSI activity.

One of the advantages of TSI agents is the so-called 'shunt' effect whereby accumulated PGH_2, resulting from inhibition of TXA_2 biosynthesis by the agent, is redirected to PGI_2 synthesis. We have examined whether such an effect is indeed manifested by our dual-acting compounds. The result is shown in Figure 1. The compound **9c** significantly increased the production of serum PGI_2 *in vitro* as measured by the amount of 6-keto-$PGF_{1\alpha}$, a stable metabolite of PGI_2, produced. In contrast, aspirin abolished PGI_2 formation via its action against cyclooxygenase.

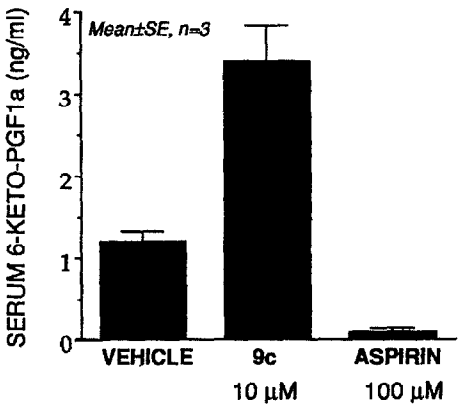


Figure 1. Effect of **9c** and aspirin on human serum prostacyclin levels.

Another important aspect in the development of TRA/TSI agents is that the compound should be orally active. We felt that the oral activity of the agent ought to be examined in the early stage of drug development. Therefore the *ex vivo* activity of compounds **9c** and **10c** via the oral route was determined in rats. ED_{50}s for TSI after 1 h dosing were ~1.0 mg/kg for **9c** and ~1.2 mg/kg for **10c**.

Conclusion

The series of compounds described in this paper, designed by 'hybridizing' two prototypical representatives of the TRA and TSI pharmacophores were found to exhibit dual TRA/TSI activities. Changes in the chain length as well as the trisubstituted olefin geometry of ω-pyridylalkenoic acid side chain had significant effects on both TXA_2 biosynthesis[21] and TXA_2 receptor blockade. The substitution pattern of the arylsulfonamido group profoundly affected the TXA_2 receptor blockade.[22] Among the various substituents, iodo-substitution gave the most potent compound. The flexibility between the arylsulfonamido group and the phenyl ring attached to the alkenoic acid side chain significantly enhanced both activities. The compound (*E*)-**21c** was identified as the most potent TRA/TSI (K_d = 53 nM, IC_{50} = 23 nM) in the series studied. The compounds **9c** and **10c** have indicated that members of this series of compounds also exhibit the so-called 'shunt' effect by showing a lack of cyclooxygenase inhibition while promoting PGI_2 production *in vitro*. In addition, they have demonstrated activity following oral administration.

These results indicate that type **I** compounds have therapeutic potential as orally active, dual-acting TRA/TSI agents for cardiovascular and renal diseases.[23]

Experimental Section

General procedure

All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Triethylamine and pyridine were distilled from CaH_2 and stored over 4 Å molecular sieves. Benzene and toluene were dried over sodium metal. All reactions were performed under a positive pressure of dry nitrogen. The 'preparative HPLC' was performed on a Waters PrepLC System 500A with the solvent indicated. Analytical HPLC was carried out on a Waters Model 510 using Nova C_{18} column with CH_3CN–MeOH–H_2O solvent system which contained 0.5 % NH_4OAc or Chiralcel OD-R column with CH_3CN–H_2O solvent system which contained 0.1 % $NaClO_4$. Flash chromatography was carried out on E. Merck Kieselgel 60 (230–400 mesh). ^1H NMR spectra were recorded on a GE Q(E)-300 (routine) and on Bruker AM-500 (NOE) spectrometer. The chemical shifts are given in δ values relative to residual proton resonances of the deuterated solvents used ($CDCl_3$ 7.26, DMSO-d_6 2.49, acetone-d_6 2.05). Analysis of the (*E*/*Z*) isomeric ratio of alkenoic acids was accomplished either by analytical HPLC or ^1H NMR. In the latter method, the ratio was obtained from integration of the olefinic proton of the product acids or their esters. The chemical purity of isomeric product mixtures was determined by analytical HPLC where the hygroscopic nature of these compounds made correct elemental analysis difficult. Field desorption (FDMS) and fast atom bombardment mass spectra (FABMS) were obtained on a VG ZAB-3F or VG 70-SE instrument.

3-[(Benzenesulfonyl)amino]phenyl 3-pyridyl ketone (7)

To a solution of 2.5 g (8.0 mmol) of 3-[(benzenesulfonyl)amino]bromobenzene in 80 mL of THF was added dropwise 10.0 mL (16.0 mmol) of 1.6 M *n*-BuLi at –78 °C. After stirring for 75 min, 1.8 mL (19.2 mmol) of 3-pyridinecarboxaldehyde was added and the mixture was stirred at –78 °C for 2.5 h. The reaction was quenched with 80 mL of saturated aqueous NH_4Cl and extracted with 3 × 110 mL of EtOAc. The extract was dried over $MgSO_4$, concentrated, and purified by flash chromatography using 3 % MeOH–CH_2Cl_2 to yield 1.62 g (60 %) of 3-(benzenesulfonylamino)phenyl(3-pyridyl)-carbinol. The carbinol (1.60 g) was oxidized by Swern's method[24] to furnish 0.67 g (42 %) of the desired ketone **7**: ^1H NMR (DMSO) δ 10.55 (s, 1H), 8.79 (br d, *J* = 4.3 Hz, 1H), 8.73 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.60–7.39 (m, 8H); FDMS 338 (M^+).

4-[(Benzenesulfonyl)amino]phenyl 3-pyridyl ketone (8)

4-[(Benzenesulfonyl)amino]phenyl(3-pyridyl)carbinol was prepared as above from 2.5 g (8.0 mmol) of 4-[(benzenesulfonyl)amino]bromobenzene in 59 % yield. The carbinol, 1.36 g (4.0 mmol), was oxidized with 5.44 g (4 × by weight) of MnO_2 in 50 mL of 1,4-dioxane at 70 °C (bath temperature) for 9 h. The removal of the oxidant by filtration through a silica gel–Celite pad and of the solvent under reduced pressure yielded 1.30 g (96 %) of the clean crude ketone **8** which was used without further purification: ^{1}H NMR (DMSO) δ 10.96 (s, 1H), 8.75 (br s, 1H), 8.74 (s, 1H), 7.98 (dt, J = 7.9, 1.8 Hz, 1H), 7.81 (d, J = 6.9 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 7.56 (m, 4H), 7.24 (d, J = 8.6 Hz, 2H); FDMS 338 (M^+). Anal. ($C_{18}H_{14}N_2O_3S$) C, H, N.

General procedure for Wittig reactions (A)

*5-[3-[(Benzenesulfonyl)amino]phenyl]-5-(3-pyridyl)-pent-4-enoic acid (**9a**).* A suspension of 2.93 g (6.82 mmol) of (3-carboxypropyl)triphenylphosphonium bromide in 7.5 mL of THF was treated with 13.7 mL (13.7 mmol) of 1.0 M sodium hexamethyldisilazide (NaHMDS) in THF at –78 °C for 2 h 45 min. To this ylide solution was then added 1.0 g (3.10 mmol) of 3-[(benzenesulfonyl)amino]phenyl 3-pyridyl ketone (**7**) in 8 mL of THF and the mixture was stirred at –78 °C for 22 h, warmed to room temperature and stirred for an additional 2 h. The reaction was then quenched with 30 mL of brine. The mixture was concentrated to dryness, suspended in MeOH, and filtered. The filtrate was concentrated and purified by flash chromatography using MeOH–Acetone–CH_2Cl_2 (5:5:90) to give 0.605 g (48 %) of the Wittig product **9a** in that (*E*)-isomer predominated: FDMS 409 (M+1). Anal. ($C_{22}H_{20}N_2O_4S$) C, H, N: calcd, 6.86; found, 5.03. 98.5 % Pure by analytical HPLC.

*6-[3-[(Benzenesulfonyl)amino]phenyl]-6-(3-pyridyl)-hex-5-enoic acid (**9b**).* Prepared as above from 975.3 mg (2.2 mmol) of (4-carboxybutyl)triphenylphosphonium bromide, 4.4 mL (4.4 mmol) of 1.0 M NaHMDS in THF and 340 mg (1.0 mmol) of the ketone **7** in 55 % yield: FDMS 423 (M+1). 97.6 % Pure by analytical HPLC.

*7-[3-[(Benzenesulfonyl)amino]phenyl]-7-(3-pyridyl)-hept-7-enoic acid (**9c**).* Prepared as above from 3.41 g (7.46 mmol) of (5-carboxypentyl)triphenylphosphonium bromide, 15.0 mL (15.0 mmol) of 1.0 M NaHMDS in THF and 1.14 g (3.37 mmol) of the ketone **7** in 54 % yield: FDMS 437 (M+1). Anal. ($C_{24}H_{24}N_2O_4S$) C, H, N. 100 % Pure by analytical HPLC.

*8-[3-[(Benzenesulfonyl)amino]phenyl]-8-(3-pyridyl)-oct-7-enoic acid (**9d**).* Prepared as above from 623 mg (1.32 mmol) of (6-carboxyhexyl)triphenylphosphonium bromide, 2.64 mL (2.64 mmol) of 1.0 M NaHMDS in THF and 203 mg (0.6 mmol) of the ketone **7** in 9 % yield: FDMS 451 (M+1). 99.0 % Pure by analytical HPLC.

*9-[3-[(Benzenesulfonyl)amino]phenyl]-9-(3-pyridyl)-non-8-enoic acid (**9e**).* Prepared as above from 880 mg (1.8 mmol) of (7-carboxyheptyl)triphenylphosphonium bromide, 3.6 mL (3.6 mmol) of 1.0 M NaHMDS in THF and 205 mg (0.6 mmol) of the ketone **7** in 34 % yield: FDMS 465 (M+1). 97.4 % Pure by analytical HPLC.

*10-[3-[(Benzenesulfonyl)amino]pheny]-10-(3-pyridyl)-dec-9-enoic acid (**9f**).* Prepared as above from 2.25 g (3.75 mmol) of [9-(*t*-butyldimethylsiloxy)nonyl]triphenylphosphonium bromide, 7.5 mL (7.5 mmol) of 1.0 M NaHMDS in THF and 573 mg (1.7 mmol) of the ketone **7** to yield 10-[3-[(benzenesulfonyl)amino]phenyl]-10-(3-pyridyl)-dec-9-enyl *t*-butyldimethylsilyl ether which was oxidized with Jones reagent (2 equiv.) in acetone at 0 °C for 2 h and purified by flash chromatography using EtOH–*i*-PrOH–CH_2Cl_2 (5:5:90) to provide the decenoic acid **9f** (2 %): FDMS 479 (M+1). 91.0 % Pure by analytical HPLC.

General procedure for Wittig reactions (B).

*6-[4-[(Benzenesulfonyl)amino]phenyl]-6-(3-pyridyl)-hex-5-enoic acid (**10a**).* To a suspension of 203 mg (0.6 mmol) of 4-[(benzenesulfonyl)amino]phenyl 3-pyridyl ketone (**8**) and 586 mg (1.32 mmol) of (4-carboxybutyl)-triphenylphosphonium bromide in 3.0 mL of THF was added dropwise 2.6 mL (2.60 mmol) of 1.0 M *t*-BuOK in THF at –10 °C. The mixture was stirred at –9 to 14 °C overnight and then allowed to warm to room temperature and stirred for another 20 h. The reaction mixture was then quenched with 1.0 N HCl while adjusting pH to ~7, concentrated, and purified by flash chromatography using MeOH–AcOH–CH_2Cl_2 (5:0.5:94.5) to afford 233.3 mg (92 %) of the hexenoic acid **10a**: ^{1}H NMR ($CDCl_3$) δ 8.42 (br d, J = 4.5 Hz, 1H), 8.39 (br s, 1H), 7.78 (br d, J = 7.5 Hz, 2H), 7.44 (m, 5H), 7.20 (dd, J = 7.9, 5.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.3 Hz, 2H), 6.06 (t, J = 7.4 Hz, 1H), 2.30 (dd, J = 7.4, 7.3 Hz, 2H), 2.12 (ddd, J = 7.5, 7.3, 7.2 Hz, 2H), 1.70 (m, 2H); FDMS 423 (M+1). Anal. ($C_{23}H_{22}N_2O_4S$) C, H, N: calcd, 6.63; found, 5.25. 98.4 % Pure by analytical HPLC.

*7-[4-[(Benzenesulfonyl)amino]phenyl]-7-(3-pyridyl)-hept-6-enoic acid (**10b**).* Prepared as above from 205 mg (0.61 mmol) of the ketone **8**, 605 mg (1.32 mmol) of (5-carboxypentyl)triphenylphosphonium bromide, and 2.65 mL (2.65 mmol) of 1.0 M *t*-BuOK in THF in 88 % yield: FDMS 437 (M+1). 91.9 % Pure by analytical HPLC.

*8-[4-[(Benzenesulfonyl)amino]phenyl]-8-(3-pyridyl)-oct-7-enoic acid (**10c**).* Prepared as above from 205 mg (0.61 mmol) of the ketone **8**, 627 mg (1.33 mmol) of (6-carboxyhexyl)triphenylphosphonium bromide, and 2.65 mL (2.65 mmol) of 1.0 M *t*-BuOK in THF in quantitative yield: FDMS 451 (M+1). 98.0 % Pure by analytical HPLC.

*9-[4-[(Benzenesulfonyl)amino]phenyl]-9-(3-pyridyl)-non-8-enoic acid (**10d**).* Prepared as above from 340 mg (1.0 mmol) of the ketone **8**, 1.46 g (3.0 mmol) of (7-carboxyheptyl)triphenylphosphonium bromide, and 6.0 mL (6.0 mmol) of 1.0 M *t*-BuOK in THF in quantitative yield: FDMS 465 (M+1). 95.3 % Pure by analytical HPLC.

*3-Nitrophenyl 3-pyridyl ketone (**11**)*

To a solution of 5.13 g (32.5 mmol) of 3-bromopyridine in 100 mL of anhydrous Et_2O was added dropwise 20.0 mL (32.5 mmol) of 1.6 M *n*-BuLi in hexanes at –78 °C over a 20 min period. After stirring for 30 min, 4.91 g (32.5 mmol) of 3-nitrobenzaldehyde in 90 mL of anhydrous Et_2O was cannulated into the yellow slurry solution. The mixture was stirred at –78 °C for 2.5 h. The cold bath was removed and the reaction was quenched with 100 mL of brine after 10 min. The mixture was extracted with 250–500 mL of CH_2Cl_2 (4 ×) which was washed once with 100 mL of brine. The extracts were dried over $MgSO_4$, concentrated and purified by preparative HPLC with 50 % EtOAc–CH_2Cl_2 to afford 4.05 g (54 %) of the 3-nitrophenyl(3-pyridyl)carbinol. The carbinol was oxidized by Swern's method to the ketone **11** in 98 % yield: ^{1}H NMR ($CDCl_3$) δ 8.98 (s, 1H), 8.86 (d, *J* = 4.0 Hz, 1H), 8.62 (dd, *J* = 1.8, 1.5 Hz, 1H), 8.48 (m, 1H), 8.13 (m, 2H), 7.74 (t, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 7.8, 4.8 Hz, 1H).

*4-Nitrophenyl 3-pyridyl ketone (**12**)*

4-Nitrophenyl(3-pyridyl)carbinol was prepared similarly to the above from 5.59 g (35.4 mmol) of 3-bromopyridine treated with 24.5 mL (39.2 mmol) of 1.6 M *n*-BuLi and 5.88 g (38.9 mmol) of 4-nitrobenzaldehyde in 35 % yield. The carbinol, 2.86 g (12.4 mmol) was oxidized with 11.44 g of MnO_2 in 100 mL of THF at reflux for 2 h. Removal of the oxidant by filtration through a silica gel–Celite pad and of the solvent under reduced pressure yielded 2.70 g (95 %) of the clean crude ketone **12** which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 8.99 (d, *J* = 1.8 Hz, 1H), 8.87 (dd, *J* = 4.6, 1.4 Hz, 1H), 8.38 (d, *J* = 8.6 Hz, 2H), 8.15 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 2H), 7.52 (m, 1H).

*Methyl (E)- and (Z)-7-(3-nitrophenyl)-7-(3-pyridyl)-hept-6-enoates (**13c**)*

7-(3-Nitrophenyl)-7-(3-pyridyl)-hept-6-enoic acid was prepared from 1.1544 g (5.06 mmol) of 3-nitrophenyl 3-pyridyl ketone (**11**), 4.6274 g (10.1 mmol) of (5-carboxypentyl)triphenylphosphonium bromide and 10.5 mL (10.5 mmol) of 1.0 M *t*-BuOK in THF according to the Wittig reaction method (B). Flash chromatography with MeOH–Et_2O–CH_2Cl_2 (5:15:80) gave *ca* 880 mg of the acid which was esterified with CH_2N_2 by a standard method and purified by flash chromatography with Et_2O–Hex–CH_2Cl_2 (1:1:1) to yield 601.3 mg of the (*Z*)-heptenoate (less polar material) and 206.5 mg of (*E*)-heptenoate (45 % in total for two steps). *(E)-isomer:* ^{1}H NMR ($CDCl_3$) δ 8.46 (m, 2H), 8.19 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.02 (br s, 1H), 7.57 (dd, *J* = 8.0, 7.8 Hz, 1H), 7.48 (br d, *J* = 7.3 Hz, 1H), 7.41 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.19 (dd, *J* = 5.0, 3.0 Hz, 1H), 6.19 (t, *J* = 7.5 Hz, 1H), 3.63 (s, 3H), 2.26 (dd, *J* = 7.3, 7.1 Hz, 2H), 2.14 (ddd, *J* = 7.4, 7.3, 7.3 Hz, 2H), 1.64 (m, 2H), 1.49 (m, 2H); FDMS 340 (M^+). *(Z)-isomer:* ^{1}H NMR ($CDCl_3$) δ 8.59 (dd, *J* = 4.9, 1.3 Hz, 1H), 8.44 (br d, *J* = 1.7 Hz, 1H), 8.06 (m, 2H), 7.43 (m, 3H), 7.34 (dd, *J* = 7.9, 4.6 Hz, 1H), 6.27 (t, *J* = 7.5 Hz, 1H), 3.64 (s, 3H), 2.26 (dd, *J* = 7.0, 6.4 Hz, 2H), 2.15 (ddd, *J* = 7.4, 7.3, 7.3 Hz, 2H), 1.62 (m, 2H), 1.51 (m, 2H); FDMS 340 (M^+).

*Methyl (E)- and (Z)-7-(4-nitrophenyl)-7-(3-pyridyl)-hept-6-enoates (**14b**)*

7-(4-Nitrophenyl)-7-(3-pyridyl)-hept-6-enoic acid was prepared similarly to the above from 518.2 mg (2.27 mmol) of 4-nitrophenyl 3-pyridyl ketone (**12**), 2.077 g (4.54 mmol) of (5-carboxypentyl)triphenylphosphonium bromide and 4.5 mL (4.5 mmol) of 1.0 M *t*-BuOK in THF. The esterification of the (*E*/*Z*)-mixture of acids yielded 368.4 mg of (*Z*)-heptenoate and 69.3 mg of (*E*)-heptenoate (57 % in total for two steps). *(E)-isomer:* ^{1}H NMR ($CDCl_3$) δ 8.46 (br s, 2H), 8.24 (d, *J* = 8.6 Hz, 2H), 7.39 (br d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.20 (m, 1H), 6.19 (t, *J* = 7.5 Hz, 1H), 3.64 (s, 3H), 2.26 (dd, *J* = 7.4, 7.1 Hz, 2H), 2.14 (ddd, *J* = 7.4, 7.3, 7.3 Hz, 2H), 1.60 (m, 2H), 1.50 (m, 2H). *(Z)-isomer:* ^{1}H NMR ($CDCl_3$) δ 8.59 (br d, *J* = 1.9 Hz, 1H), 8.42 (br s, 1H), 8.10 (d, *J* = 8.7 Hz, 2H), 7.44 (br dd, *J* = 7.8, 1.5 Hz, 1H), 7.34 (m, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 6.32 (t, *J* = 7.5 Hz, 1H), 3.62 (s, 3H), 2.25 (dd, *J* = 7.4, 7.0 Hz, 2H), 2.14 (ddd, *J* = 7.4, 7.3, 7.2 Hz, 2H), 1.59 (m, 2H), 1.49 (m, 2H).

General procedure for the alkenoic acids

*(Z)-7-[3-[4-(Toluenesulfonyl)amino]phenyl]-7-(3-pyridyl)-hept-6-enoic acid (**15a**).* To a pale green, clear solution of 525.1 mg (1.54 mmol) of methyl (*Z*)-7-(3-nitrophenyl)-7-(3-pyridyl)-hept-6-enoate ((*Z*)-**13c**) and 366.5 mg (1.54 mmol) of $NiCl_2 \cdot 6H_2O$ in 14 mL of MeOH at 0 °C was added 292 mg (7.11 mmol) of $NaBH_4$ in small portions over a 30 min period. After stirring for 30 min, the solvent was removed under reduced pressure and the residue was treated with *ca* 5 mL of 5 N HCl and then basified with *ca* 30 mL of 28 % NH_4OH at 0 °C. The clear purple solution was then extracted with 3 × 50 mL of CH_2Cl_2 which was washed with *ca* 30 mL of brine. The extract was dried over $MgSO_4$, concentrated, and purified by flash chromatography using 75 % EtOAc–hexanes to afford 420.5 mg (88 %) of methyl (*Z*)-7-(3-aminophenyl)-7-(3-pyridyl)-hept-6-enoate: ^{1}H NMR ($CDCl_3$) δ 8.53 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 7.45 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.27 (m, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.56 (m, 2H), 6.45 (dd, *J* = 1.9, 1.7 Hz, 1H), 6.11 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.61 (br s, 2H), 2.25 (dd, *J* = 7.5, 7.2 Hz, 2H), 2.08 (ddd, *J* = 7.4, 7.3, 7.3 Hz, 2H), 1.60 (m, 2H), 1.46 (m, 2H); FDMS 310 (M^+).

A solution of 34.4 mg (0.11 mmol) of the above amine and 42.3 mg (0.22 mmol) of 4-toluenesulfonyl chloride in 0.5 mL of pyridine was stirred at 0–10 °C for 4 h. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography with 30 % EtOAc–CH_2Cl_2 to afford 45.5 mg (0.098 mmol) of the corresponding sulfonamide ester which was dissolved in 0.5 mL of THF and hydrolyzed with 200 μL of 1.0 N NaOH (0.20 mmol) at room temperature overnight. After the solution was neutralized with 200 μL of 1.0 N HCl at 0

°C and concentrated to dryness, the crude product was suspended in CH_2Cl_2 and filtered through a filter paper to remove the NaCl salt formed. The filtrate was concentrated *in vacuo* to yield 41.8 mg (84 % for 2 steps) of the desired acid **15a**: ^{1}H NMR ($CDCl_3$) δ ~10.1 (very br s, 1H), 8.51 (br s, 1H), 8.33 (br s, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.44 (distorted br d, J = 7.3 Hz, 1H), 7.31 (br s, 1H), 7.15 (d, J = 7.9 Hz, 2H), 7.07 (br dd, J = 7.9, 7.9 Hz, 1H), 6.99 (distorted br d, J = 7.7 Hz, 1H), 6.83 (br s, 2H), 6.06 (t, J = 7.3 Hz, 1H), 2.31 (s, 3H), 2.27 (buried, 2H), 2.03 (m, 2H), 1.59–1.45 (m, 4H); FDMS 451 (M+1). Anal. ($C_{25}H_{26}N_2O_4S$) C, H, N.

*(Z)-7-[3-[4-(Methoxybenzenesulfonyl)amino]phenyl]-7-(3-pyridyl)-hept-6-enoic acid (**15b**).* Prepared as above in 3 steps from (*Z*)-**13c** and 4-methoxybenzenesulfonyl chloride (79 %): ^{1}H NMR ($CDCl_3$) δ ~9.50 (very br s, 1H), 8.50 (br s, 1H), 8.34 (br s, 1H), 7.63 (d, J = 8.9 Hz, 2H), 7.43 (distorted d, J = 7.7 Hz, 1H), 7.33 (br s, 1H), 7.08 (dd, J = 7.8, 7.7 Hz, 1H), 7.00 (distorted d, J = 8.1 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.83 (buried, 2H), 6.07 (t, J = 7.4 Hz, 1H), 3.77 (s, 3H), 2.28 (dd, J = 7.1, 6.9 Hz, 2H), 2.05 (ddd, J = 7.2, 7.2, 6.9 Hz, 2H), 1.62–1.41 (m, 4H); FDMS 466 (M^+). Anal. ($C_{25}H_{26}N_2O_5S$) C, H, N.

*(Z) -7- [3- [[4- (Trifluoromethyl) benzenesulfonyl] amino] -phenyl]-7-(3-pyridyl)-hept-6-enoic acid (**15c**).* Prepared as above in 3 steps from (*Z*)-**13c** and 4-(trifluoromethyl)benzenesulfonyl chloride (80 %): ^{1}H NMR ($CDCl_3$) δ 8.49 (br d, J = 1.3 Hz, 1H), 8.41 (buried, 1H), 8.33 (br s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.42 (br d, J = 7.6 Hz, 2H), 7.31 (m, 1H), 7.09 (m, 2H), 6.89 (br d, J = 7.3 Hz, 1H), 6.79 (s, 1H), 6.09 (t, J = 7.3 Hz, 1H), 2.24 (br t, 2H), 2.02 (br d, 2H), 1.58–1.42 (m, 4H); FDMS 505 (M+1).

*(Z)-7- [3- [(4-Fluorobenzenesulfonyl)amino] phenyl]-7-(3-pyridyl)-hept-6-enoic acid (**15d**).* Prepared as above in 3 steps from (*Z*)-**13c** and 4-fluorobenzenesulfonyl chloride (73 %): ^{1}H NMR ($CDCl_3$) δ 8.49 (br s, 1H), 8.31 (s, 1H), 7.69 (dd, J = 8.7, 5.0 Hz, 2H), 7.43 (br d, J = 7.7 Hz, 1H), 7.31 (m, 1H), 7.13–6.99 (m, 4H), 6.88 (d, J = 7.6 Hz, 1H), 6.77 (s, 1H), 6.07 (t, J = 7.4 Hz, 1H), 2.27 (distorted dd, J = 6.7, 6.5 Hz, 2H), 2.04 (distorted ddd, J = 7.2, 7.1, 6.8 Hz, 2H), 1.61–1.41 (m, 2H); FDMS 455 (M^+). Anal. ($C_{24}H_{23}FN_2O_4S$) C, H, N.

*(Z)-7-[3-[(4-Chlorobenzenesulfonyl)amino]phenyl]-7- (3-pyridyl)-hept-6-enoic acid (**15e**).* Prepared as above in 3 steps from (*Z*)-**13c** and 4-chlorobenzenesulfonyl chloride (61 %): ^{1}H NMR ($CDCl_3$) δ ~9.5 (very br s, 1H), 8.49 (br d, J = 3.4 Hz, 1H), 8.32 (s, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.42 (br d, J = 7.7 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.32 (buried, 1H), 7.11 (dd, J = 7.8, 7.8 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 6.07 (t, J = 7.4 Hz, 1H), 2.27 (dd, J = 6.8, 6.4 Hz, 2H), 2.04 (ddd, J = 7.1, 6.9, 6.8 Hz, 2H), 1.61–1.41 (m, 4H); FDMS 471 (M+1). Anal. ($C_{24}H_{23}ClN_2O_4S$) C, H, N.

*(Z)-7-[3- [(4-Bromobenzenesulfonyl) amino] phenyl] -7- (3-pyridyl)-hept-6-enoic acid (**15f**).* Prepared as above in 3 steps from (*Z*)-**13c** and 4-bromobenzenesulfonyl chloride (59 %): ^{1}H NMR ($CDCl_3$) δ 8.52 (br d, J = 3.5 Hz, 1H), 8.34 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.33 (m, 1H), 7.13 (dd, J = 7.9, 7.8 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.76 (s, 1H), 6.07 (t, J = 7.5 Hz, 1H), 2.27 (dd, J = 7.0, 6.9 Hz, 2H), 2.05 (br q, J = ~7.1 Hz, 2H), 1.61–1.43 (m, 4H); FDMS 515 (M^+).

*(Z)-7- [3- [(4-Iodobenzenesulfonyl) amino] phenyl] -7- (3-pyridyl)-hept-6-enoic acid (**15g**).* Prepared as above in 3 steps from (*Z*)-**13c** and 4-iodobenzenesulfonyl chloride (50 %): ^{1}H NMR ($CDCl_3$) δ 8.60 (very br s, 1H), 8.53 (br d, J = 1.9 Hz, 1H), 8.36 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.46–7.34 (m, 3H), 7.40 (d, J = 8.4 Hz, 2H), 7.15 (dd, J = 7.9, 7.8 Hz, 1H), 7.06 (distorted d, J = 8.3 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.78 (s, 1H), 6.10 (t, J = 7.5 Hz, 1H), 2.32 (distorted dd, J = 6.9, 6.5 Hz, 2H), 2.08 (distorted ddd, J = 7.2, 7.1, 7.0 Hz, 2H), 1.65–1.44 (m, 4H); FDMS 563 (M+1). Anal. ($C_{24}H_{23}IN_2O_4S$) H, N, C: calcd, 51.25; found, 52.05.

*(Z) -7- [3- [(4-Biphenylylsulfonyl) amino] phenyl] -7- (3-pyridyl)-hept-6-enoic acid (**15h**).* Prepared as above in 3 steps from (*Z*)-**13c** and 4-biphenylylsulfonyl chloride (61 %): ^{1}H NMR ($CDCl_3$) δ ~9.45 (very br s, 1H), 8.47 (d, J = 4.1 Hz, 1H), 8.34 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 6.9 Hz, 2H), 7.41 (m, 4H), 7.25 (m, 1H), 7.09 (m, 2H), 6.85 (br s, 2H), 6.06 (t, J = 7.5 Hz, 1H), 2.25 (dd, J = 7.1, 6.8 Hz, 2H), 2.03 (ddd, J = 7.4, 7.1, 7.1 Hz, 2H), 1.59–1.42 (m, 4H); FDMS 513 (M^+). Anal. ($C_{30}H_{28}N_2O_4S \cdot 0.6CH_2Cl_2$) C, H, N.

*(Z)-7-[3-[(Benzenesulfonyl)amino] phenyl] -7- (3- pyridyl)-hept-6-enoic acid ((Z)-**9c**).* Prepared as above in 3 steps from (*Z*)-**13c**) and benzenesulfonyl chloride (35 %): ^{1}H NMR ($CDCl_3$) δ 8.51 (dd, J = 4.6, 1.3 Hz, 1H), 8.32 (br d, J = 1.5 Hz, 1H), 7.69 (dd, J = 7.6, 1.2 Hz, 2H), 7.49–7.25 (m, 5H), 7.10 (dd, J = 7.9, 7.7 Hz, 2H), 7.02 (br d, J = 8.4 Hz, 1H), 6.85 (br d, J = 7.6 Hz, 1H), 6.79 (br d, J = 1.3 Hz, 1H), 6.05 (t, J = 7.5 Hz, 1H), 2.27 (dd, J = 7.1, 6.8 Hz, 2H), 2.04 (distorted dt, J = 7.1, 7.1 Hz, 2H), 1.60–1.42 (m, 4H); FDMS 437 (M+1).

*(E)-7-[3-[(Benzenesulfonyl) amino] phenyl]-7-(3- pyridyl)-hept-6-enoic acid ((E)-**9c**).* Prepared as above in 3 steps from methyl (*E*)-7-(3-nitrophenyl)-7-(3-pyridyl)-hept-6-enoate [(*E*)-**13c**] and benzenesulfonyl chloride (11 %): ^{1}H NMR ($CDCl_3$) δ 8.43 (dd, J = 4.8, 1.0 Hz, 1H), 8.39 (s, 1H), 7.74 (dd, J = 8.1, 1.1 Hz, 2H), 7.52–7.17 (m, 8H), 6.81 (br d, J = 1.4 Hz, 2H), 6.06 (t, J = 7.6 Hz, 1H), 2.28 (dd, J = 7.0, 6.8 Hz, 2H), 2.00 (dt, J = 7.2, 7.2 Hz, 2H), 1.62–1.43 (m, 4H); FDMS 437 (M+1).

*(E)-7- [3- [(4-Iodobenzenesulfonyl) amino] phenyl] -7- (3-pyridyl)-hept-6-enoic acid ((E)-**15g**).* Prepared as above in 3 steps from (*E*)-**13c** and 4-iodobenzenesulfonyl chloride (24 %): ^{1}H NMR ($CDCl_3$) δ 8.44 (br s, 2H), 7.93 (very br s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.22 (m, 4H), 6.83 (buried d, 1H), 6.81 (s, 1H), 6.07 (t, J = 7.5 Hz, 1H), 2.28 (dd, J = 6.9, 6.5 Hz, 2H), 2.00 (ddd, J = 7.1, 7.1, 6.9 Hz, 2H), 1.59–1.46

(m, 4H); FDMS 563 (M+1). Anal. ($C_{24}H_{23}IN_2O_4S$) C, H, N.

*(Z)-7- [4- [(4-Iodobenzenesulfonyl) amino] phenyl] -7- (3-pyridyl)-hept-6-enoic acid (**16a**).* Prepared as above in 3 steps from methyl (*Z*)-7-(4-nitrophenyl)-7-(3-pyridyl)-hept-6-enoate ((*Z*)-**14b**) (50 %): ^{1}H NMR (DMSO) δ ~10.4 (very br s, 1H), 8.48 (dd, *J* = 3.0, 1.1 Hz, 1H), 8.23 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.38 (m, 2H), 6.96 (m, 4H), 6.09 (t, *J* = 7.4 Hz, 1H), 2.07 (dd, *J* = 6.9, 6.5 Hz, 2H), 1.91 (ddd, *J* = 7.1, 6.9, 6.7 Hz, 2H), 1.37 (m, 4H); FDMS 563 (M+1). Anal. ($C_{24}H_{23}IN_2O_4S$) H; C: calcd, 51.25; found, 51.86; N: calcd, 4.98; found, 4.27.

*(E) -8- [4- [(4-Iodobenzenesulfonyl) amino] phenyl]-8- (3-pyridyl)-oct-7-enoic acid (**16b**).* Prepared as above in 5 steps from the ketone **12** (10 %): ^{1}H NMR (acetone-d_6) δ 8.39 (br s, 2H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (br d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H), 7.24 (buried, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.16 (t, *J* = 7.4 Hz, 1H), 2.24 (dd, *J* = 7.3, 7.2 Hz, 2H), 2.05 (m, 2H), 1.55–1.26 (m, 6H); FDMS 577 (M+1). 96 % Pure by analytical HPLC.

General procedure for the pyridyl ketones

*4-[(*tert*-Butyldimethylsiloxy)methyl]phenyl 3-pyridyl ketone (**18**).* To a mixture of 28.0 g (0.20 mol) of 1,4-benzenedimethanol and 41.0 g (0.41 mol) of imidazole in *ca* 850 mL of anhydrous CH_2Cl_2 at 0 °C was cannulated 30.5 g (0.20 mol) of TBSCl in 150 mL of anhydrous CH_2Cl_2 over a 10–15 min period. The pale yellow solution was then stirred for 3 days. The reaction was quenched with 250 mL of cold 1.0 N HCl. The organic layer was separated and washed with 250 mL of 1.0 N HCl and saturated aqueous $NaHCO_3$ each. The aqueous layers were back-extracted with 2 × 500 mL of Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by preparative HPLC using 20 % Et_2O–hexanes as eluent to afford 18.60 g (36.4 %) of 4-(*tert*-butyldimethylsiloxy)benzyl alcohol: ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 4H), 4.74 (s, 2H), 4.67 (s, 2H), 1.69 (s, 1H), 0.95 (s, 9H), 0.095 (s, 6H); MS(EI) 195 (M–*t*-Bu). Anal. ($C_{14}H_{24}O_2$) C, H.

A mixture of 18.60 g (0.074 mol) of the above benzylic alcohol and 74.4 g of MnO_2 in 500 mL of anhydrous THF was heated at 65–70 °C (bath temperature) for 4 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated to yield 15.33 g (83.1 %) of clean crude 4-(*tert*-butyldimethylsiloxy)benzaldehyde which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 4.80 (s, 2H), 0.94 (s, 9H), 0.10 (s, 6H); FDMS 250 (M^+). Anal. ($C_{14}H_{22}O_2$) C, H.

To a solution of 10.64 g (67.3 mmol) of 3-bromopyridine in *ca* 500 mL of anhydrous Et_2O at –78 °C was added 42 mL (67.3 mmol) of 1.6 M *n*-BuLi in hexanes over a 35 min period. After stirring 30 min, 15.33 g (61.2 mmol) of the above crude benzaldehyde in 100 mL of anhydrous Et_2O was cannulated to the turbid lithiopyridine solution at –78 °C. After the addition, the yellow mixture was stirred for 2 h at this temperature, and then the cold bath was removed and the mixture was stirred for another 30 min. The reaction was quenched with *ca* 250 mL of brine and the organic layer was separated. The aqueous layer was extracted with 2 × 400 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by preparative HPLC using 2 % MeOH–CH_2Cl_2 to afford 17.99 g (89.2 %) of the desired [4-[(*tert*-butyldimethylsiloxy) methyl] phenyl] (3-pyridyl) carbinol: ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.46 (d, *J* = 3.9 Hz, 1H), 7.74 (br d, *J* = 7.8 Hz, 1H), 7.31 (s, 4H), 7.28 (m, 1H), 5.87 (s, 1H), 4.72 (s, 2H), 3.06 (br s, 1H), 0.93 (s, 9H), 0.087 (s, 6H); FDMS 329 (M^+).

A mixture of 17.99 g (54.6 mmol) of the carbinol and 72 g of MnO_2 in 400 mL of THF was heated at ~65 °C (bath temperature) overnight (15 h). The oxidant was removed by filtration through a Celite pad and washed with THF and EtOAc. The combined filtrate and washing were concentrated to give 17.29 g (96.7 %) of the clean crude ketone **18** which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.79 (m, 1H), 8.09 (br d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.45 (buried 1H), 4.82 (s, 2H), 0.94 (s, 9H), 0.11 (s, 6H); FDMS 328 (M+1). Anal. ($C_{19}H_{25}NO_2Si$) H; C: calcd, 69.68; found, 69.02; N: calcd, 4.28; found, 4.79.

*3-[(*tert*-Butyldimethylsiloxy)methyl]phenyl 3-pyridyl ketone (**17**).* Prepared as above from 1,3-benzenedimethanol in 4 steps (30 %): ^{1}H NMR ($CDCl_3$) δ 8.97 (d, *J* = 1.7 Hz, 1H), 8.78 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.08 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.74 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.45 (m, 2H), 4.78 (s, 2H), 0.90 (s, 9H), 0.08 (s, 6H); FDMS 327 (M^+). Anal. ($C_{19}H_{25}NO_2Si$) C, H, N.

General procedure for the azide intermediates

*Methyl 6-(4-azidomethylphenyl)-6-(3-pyridyl)-hex-5-enoates (**20a**).* To a suspension of 3.95g (12.0 mmol) of the ketone **18** and 16.0 g (36.0 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in 120 mL of THF at –10 °C was added dropwise 72.0 mL (72.0 mmol) of 1.0 M *t*-BuOK in THF. The orange colored suspension was stirred at this temperature for 4.5 h, and the reaction was quenched with 1.0 N HCl at 0 °C while adjusting pH to ~7. The reaction mixture was concentrated to dryness, and the residue was suspended in a small amount of MeOH and filtered to remove the salt (twice). The methanolic solution was concentrated and purified by preparative HPLC using 0.5–5.0 % MeOH–CH_2Cl_2 as eluent. The Wittig product obtained was then dissolved in 200 mL of THF and esterified with CH_2N_2 which was generated from 1-methyl-3-nitro-1-nitrosoguanidine (5.55 g) and 5.0 N NaOH (28 mL) in 140 mL of Et_2O at 0 °C. The crude reaction mixture was dried over $MgSO_4$, concentrated, and purified by preparative HPLC with 5–10 % EtOAc–CH_2Cl_2 to afford 2.66 g (52 %) of methyl 6-[4-

[(*tert*-butyldimethylsiloxy) methyl] phenyl]-6-(3-pyridyl)-hex-5-enoates (*E/Z* = ~1/5): ^{1}H NMR ($CDCl_3$, (*Z*)-isomer only) δ 8.56 (br s, 1H), 8.44 (br s, 1H), 7.49 (br d, *J* = 7.8 Hz, 1H), 7.32 (m, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.14 (t, *J* = 7.5 Hz, 1H), 4.71 (s, 2H), 3.61 (s, 3H), 2.15 (dd, *J* = 7.4, 7.4 Hz, 2H), 2.13 (ddd, *J* = 7.6, 7.4, 7.4 Hz, 2H), 1.77 (m, 2H), 0.92 (s, 9H), 0.075 (s, 6H); FDMS 425 (M^+). Anal. ($C_{25}H_{35}NO_3Si \cdot 0.4C_4H_8O_2$) C, H, N.

A solution of 1.13 g (2.65 mmol) of the above (*E/Z*)-mixture (2/3) in 27 mL of THF was treated with 8.0 mL (8.0 mmol) of 1.0 M *n*-$Bu_4N^+F^-$ in THF at 0 °C for 1 h. The solvent was removed and the residue was purified by flash chromatography with 4 % MeOH–CH_2Cl_2 as eluent to afford 718.2 mg (87.0 %) of the corresponding benzylic alcohols. To a mixture of 670 mg (2.15 mmol) of the benzylic alcohols and 0.36 mL (2.58 mmol) of Et_3N in 10.75 mL of dry toluene at 0 °C was added 183 μL (2.36 mmol) of methanesulfonyl chloride, and the solution was stirred for 30 min. To this was then cannulated a solution of 1.18 g (17.2 mmol) of NaN_3 and 68 mg (0.21 mmol) of *n*-$Bu_4N^+Br^-$ in 5.5 mL of H_2O. The mixture was heated at 60 °C (bath temperature) for 2 h. The reaction mixture was cooled to room temperature and extracted with 3 × 30 mL of EtOAc. The extract was dried over $MgSO_4$, concentrated, and purified by flash chromatography using 2 % MeOH–CH_2Cl_2 to afford 608.0 mg of a separable (*E/Z*)-mixture of azides **20a** (84.1 %): ^{1}H NMR ($CDCl_3$, (*Z*)-isomer only) δ 8.61 (dd, *J* = 4.1, 1.1 Hz, 1H), 8.48 (s, 1H), 7.70 (br d, *J* = 7.5 Hz, 1H), 7.51 (m, 1H), 7.24 (d, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.22 (t, *J* = 7.6 Hz, 1H), 4.32 (s, 2H), 3.62 (s, 3H), 2.30 (dd, *J* = 7.4, 7.3 Hz, 2H), 2.15 (m, 2H), 1.81 (m, 2H); FDMS 336 (M^+). Anal. ($C_{19}H_{20}N_4O_2 \cdot 0.2C_4H_8O_2$) C, H, N.

*Methyl 6-(3-azidomethylphenyl)-6-(3-pyridyl)-hex-5-enoates (**19a**).* Prepared as above in 4 steps from the ketone **17** (58 %): ^{1}H NMR ($CDCl_3$, (*Z*)-isomer only) δ 8.57 (br d, *J* = 4.2 Hz, 1H), 8.44 (s, 1H), 7.46 (br d, *J* = 7.8 Hz, 1H), 7.33–7.10 (m, 5H), 6.16 (t, *J* = 7.5 Hz, 1H), 4.28 (s, 2H), 3.61 (s, 3H), 2.29 (dd, *J* = 7.4, 7.4 Hz, 2H), 2.15 (ddd, *J* = 7.6, 7.4, 7.3 Hz, 2H), 1.81 (m, 2H); FDMS 336 (M^+).

General procedure for the sulfonamidomethyl-incorporated alkenoic acids

*(Z)-6-[4-[[(Benzenesulfonyl)amino]methyl]phenyl]-6-(3-pyridyl)-hex-5-enoic acid ((Z)-**22a**).* To a clear green solution of 158.4 mg (0.47 mmol) of the azide **20a** (*E/Z* = ~1/8) and 112.0 mg (0.47 mmol) of $NiCl_2 \cdot 6H_2O$ at 0 °C was added 90 mg (2.4 mmol) of $NaBH_4$ in small portions over a 20 min period. After stirring for 30 min, the mixture was concentrated and treated with 5.0 mL of cold 5.0 N HCl for 10 min. This was then basified with cold conc. NH_4OH to pH 9 and extracted with 3 × 25 mL of CH_2Cl_2. The extract was dried over $MgSO_4$, concentrated, and purified by flash chromatography using 5–7 % MeOH + 0.1 % conc. NH_4OH in CH_2Cl_2 to afford 83.2 mg (56.9 %) of methyl (*Z*)-6-(4-aminomethylphenyl)-6-(3-pyridyl)-hex-5-enoate: ^{1}H NMR ($CDCl_3$) δ 8.55 (dd, *J* = 4.2 Hz, 1H), 8.42 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.29 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.13 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 2H), 3.61 (s, 3H), 2.29 (dd, *J* = 7.4, 7.4 Hz, 2H), 2.21 (br s, 2H), 2.13 (ddd, *J* = 7.5, 7.4, 7.4 Hz, 2H), 1.77 (m, 2H).

A mixture of 80.7 mg (0.26 mmol) of the above amine and 67 μL (0.52 mmol) of benzenesulfonyl chloride in 2.5 mL of pyridine was stirred at 0 °C for 4.5 h. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography using EtOAc–CH_2Cl_2 (0–1:7) to yield 76.7 mg (65.5 %) of the corresponding sulfonamide ester which was hydrolyzed with 1.0 N NaOH in THF to give, after flash chromatography with MeOH–AcOH–CH_2Cl_2 (5:0.5:94.5), 70.7 % of the (*Z*)-hexenoic acid (*Z*)-**22a**: ^{1}H NMR ($CDCl_3$) δ 8.49 (br s, 1H), ~8.45 (buried, 1H), 8.34 (br s, 1H), 7.85 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.0 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.35 (br s, 1H), 7.20–7.02 (m, 4H), 6.12 (distorted t, *J* = ~7.1 Hz, 1H), ~5.28 (br s, 1H), 4.10 (s, 2H), 2.32 (br s, 2H), 2.14 (m, 2H), 1.78 (br s, 2H); FDMS 436 (M^+). Anal. ($C_{24}H_{24}N_2O_4S \cdot 0.7C_2H_4O_2$) C, H, N.

*(E)-6-[4-[[(Benzenesulfonyl) amino] methyl] phenyl]-6-(3-pyridyl)-hex-5-enoic acid ((E)-**22a**).* Prepared as above from the azide **20a** (*E/Z* = ~8/1) in 3 steps (31 %): ^{1}H NMR ($CDCl_3$) δ 8.40 (br s, 3H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.55–7.39 (m, 2H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.16 (m, 3H), 7.01 (m, 2H), 6.06 (br s, 1H), 5.62 (very br s, 1H), 4.14 (s, 2H), 2.27 (br s, 2H), 2.11 (br s, 2H), 1.74 (br s, 2H); FDMS 437 (M+1). Anal. ($C_{24}H_{24}N_2O_4S$) C, H, N.

*(E)- and (Z)-7-[4-[[(Benzenesulfonyl)amino]methyl]-phenyl]-7-(3-pyridyl)-hept-6-enoic acids (**22b**).* Prepared as above from the ketone **18** in 7 steps: FDMS 451 (M+1). Anal. ((*E*)-isomer, $C_{25}H_{26}N_2O_4S \cdot 0.7CH_2Cl_2$) C, H, N. 98.2 % Pure by analytical HPLC ((*Z*)-isomer).

*(Z)-7-[4-[[(4-Iodobenzenesulfonyl)amino]methyl]phenyl]-7-(3-pyridyl)-hept-6-enoic acid (**22c**).* Prepared as above from the ketone **18** in 7 steps: FDMS 577 (M+1). Anal. ($C_{25}H_{25}IN_2O_4S \cdot 0.6C_2H_4O_2$) C, H, N.

*(E)- and (Z)-8-[4-[[(Benzenesulfonyl)amino]methyl]-phenyl]-8-(3-pyridyl)-oct-7-enoic acids (**22d**).* Prepared as above from the ketone **18** in 7 steps: FDMS 465 (M+1). Anal. ((Z)-isomer, $C_{26}H_{28}N_2O_4S \cdot 0.4CH_4O$) C, H, N.

*(E)- and (Z)-6-[3-[[(Benzenesulfonyl)amino]methyl]-phenyl]-6-(3-pyridyl)-hex-5-enoic acids (**21a**).* Prepared as above from the ketone **17** in 7 steps. *(E)-isomer*: ^{1}H NMR ($CDCl_3$) δ 8.40 (br s, 1H), 8.38 (br s, 1H), 7.84 (d, *J* = 7.1 Hz, 2H), 7.45 (m, 4H), 7.22 (m, 2H), 7.12 (br d, *J* = 7.8 Hz, 1H), 7.02 (s, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.09 (t, *J* = 7.6 Hz, 1H), 4.12 (s, 2H), 2.33 (dd, *J* = 6.7, 6.6 Hz, 2H), 2.13 (dt, *J* = 7.6, 7.5 Hz, 2H), 1.77 (m, 2H); FDMS 437 (M+1). Anal. ($C_{24}H_{24}N_2O_4S$) C, H, N. *(Z)-isomer:* ^{1}H NMR ($CDCl_3$) δ 8.44 (br s, 1H), 8.38 (buried, 1H), 8.32 (br s, 1H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.56–7.42 (m, 4H), 7.33 (m, 1H), 7.11 (m, 2H), 6.99 (d, *J* = 0.9 Hz, 1H),

6.98 (buried, 1H), 6.08 (t, J = 7.6 Hz, 1H), 4.08 (s, 2H), 2.30 (dd, J = 7.0, 6.9 Hz, 2H), 2.13 (ddd, J = 7.5, 7.3, 7.3 Hz, 2H), 1.77 (m, 2H); FDMS 437 (M+1). Anal. ($C_{24}H_{24}N_2O_4S \cdot 0.3C_2H_4O_2$) C, H, N.

*(E)- and (Z)-7-[3-[[(Benzenesulfonyl)amino]methyl]-phenyl]-7-(3-pyridyl)-hept-6-enoic acids (**21b**).* Prepared as above from the ketone **17** in 7 steps: FDMS 451 (M+1). Anal. ($C_{25}H_{26}N_2O_4S$) C, H, N.

*(E)- and (Z)-7-[3-[[(4-Iodobenzenesulfonyl)amino]-methyl]phenyl]-7-(3-pyridyl)-hept-6-enoic acids (**21c**).* Prepared as above from the ketone **17** in 7 steps. *(E)-isomer:* ^{1}H NMR ($CDCl_3$) δ 8.43 (br s, 2H), 7.78 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.48 (br d, J = 8.0 Hz, 1H), 7.38–6.98 (m, 6H), 6.14 (t, J = 7.6 Hz, 1H), 4.11 (s, 2H), 2.26 (dd, J = 6.9, 6.8 Hz, 2H), 2.07 (ddd, J = 7.6, 7.5, 7.3 Hz, 2H), 1.62–1.44 (m, 4H); FDMS 577 (M+1). Anal. ($C_{25}H_{25}IN_2O_4S \cdot 0.3H_2O$) C, H, N. *(Z)-isomer:* ^{1}H NMR ($CDCl_3$) δ 8.53 (br s, 1H), 8.36 (br s, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.47 (buried, 1H), 7.35–6.98 (m, 5H), 6.08 (t, J = 7.5 Hz, 1H), 4.09 (s, 2H), 2.30 (dd, J = 7.4, 7.0 Hz, 2H), 2.10 (ddd, J = 7.3, 7.3, 7.1 Hz, 2H), 1.65–1.47 (m, 4H); FDMS 577 (M+1). Anal. ($C_{25}H_{25}IN_2O_4S \cdot 0.6H_2O$) C, H, N.

*(E)- and (Z)-8-[3-[[(Benzenesulfonyl)amino]methyl]-phenyl]-8-(3-pyridyl)-oct-7-enoic acids (**21d**).* Prepared as above from the ketone **17** in 7 steps: FDMS 465 (M+1). Anal. (*(E/Z)*-mixture: $C_{26}H_{28}N_2O_4S \cdot 0.3C_2H_4O_2$; (Z)-isomer: $C_{26}H_{28}N_2O_4S \cdot 0.6C_2H_4O_2$) C, H, N.

Measurement of thromboxane receptor antagonism: receptor binding assay

Membranes from outdated human platelets were prepared as previously described.[25] Incubations (220 μL) containing 10 μg of platelet membranes were performed in silanized glass tubes (12 × 75 mm) at 30 °C for 30 min. The incubation media consisted of 10 mM Hepes, 2 mM CHAPS, 10 μM indomethacin (pH = 7.4), ~0.05 nM (~25000 cpm) of [^{125}I]IBOP per tube, and varying concentrations of competing ligands ranging from 10^{-10} to 10^{-5} M. The reaction was terminated by addition of 4 mL of ice cold buffer (25 mM Tris) at pH 7.4, followed by rapid filtration through Whatman GF/C glass filters pre-soaked in 0.3 % polyethyleneamine (Whatman, Inc., Clifton, NJ) using a Brandel M-24 cell harvester (Gaithersburg, MD). Non-specific binding was defined as that amount of radioactivity bound in the presence of a large molar excess (10 μM) of SQ29548, a potent TXA_2/PGH_2 receptor antagonist.

Measurement of thromboxane synthase inhibition and prostacyclin formation

Compound or vehicle were incubated with whole human blood for 30 min at 37 °C prior to the preparation of serum as previously described.[26] Serum TXB_2 and 6-keto-$PGF_{1\alpha}$, the stable metabolites of TXA_2 and prostacyclin, respectively, were measured by radioimmunoassay as described.[27]

Ex vivo *experiments*

Sprague Dawley rats (300 g males) were dosed by oral gavage with either vehicle (5 % acacia) or 1–10 mg/kg compound. Blood samples were collected 1 h after dosing. Animals were anesthetized (sodium pentobarbital, 87 mg/kg ip) 15 min before sample collection. Blood samples were obtained by cardiac puncture via a butterfly catheter and the first mL of blood was discarded. Blood samples were divided into duplicates and incubated at 37 °C for 1 h in 13 × 100 mm glass tubes. Serum was separated by centrifugation at 2000 *g* for 15 min at 25 °C, transferred to polypropylene tubes, and stored at –20 °C for subsequent radioimmunoassay of TXB_2 produced during incubation.

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