Thromboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition. 2. Synthesis and Biological Activity of 8-(Benzenesulfonamido)-7-(3-pyridinyl)octanoic Acid and Related Compounds

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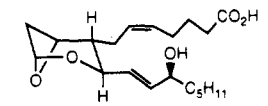
A series of arylsulfonamido alkanoic acids substituted with a 3-pyridinyl group along the aliphatic chain were synthesized and tested in vitro for their ability to antagonize thromboxane A_2 (TxA_2) receptors and inhibit thromboxane synthase. These compounds were found to potently inhibit the U 46619-induced aggregation of human platelets and to also inhibit TxA_2 biosynthesis in a human microsomal platelet preparation. However, some members of the series, notably compound **21**, were found to display *agonist* activity on the rabbit aorta TxA_2 receptor. This unwanted agonist activity appeared to be related to the presence of a substituent β to the arylsulfonamido group.

Thromboxane A_2 (TXA_2, **1**), an unstable metabolite of arachidonic acid, is one of the most potent vasoconstricting and platelet-aggregating agents known.[1-3] The potent biological activity of TxA_2 may play an important role in the pathogenesis of various circulatory and certain renal disorders.[4,5] Thromboxane synthase inhibitors (TxSIs) and thromboxane receptor antagonists (TxRAs) have been developed to treat these disorders.[6-8] A TxSI by itself has not shown efficacy in the treatment of various forms of angina and peripheral vascular disease.[8] One of the reasons cited[9] for this lack of efficacy is that the endoperoxide (PGH_2 (**2**), which accumulates due to the inhibition of biosynthesis of TxA_2, is itself a potent platelet-aggregating and vasoconstricting agent[10,11] and this accumulation of PGH_2 may negate the beneficial effects of TxS inhibition.



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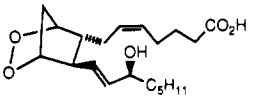

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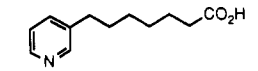

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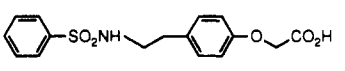

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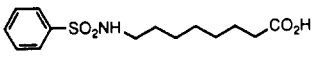

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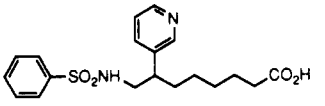

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It has been proposed that the use of a combination of TxSI and TxRA for the treatment of the clinical conditions cited above would be more beneficial than the use of either agent alone.[12-17] Use of a TxSI would prevent the biosynthesis of TxA_2 and lead to redirection of at least part of the accumulated PGH_2 to beneficial prostaglandins like PGI_2, PGD_2, and PGE_2, which would not be possible by the use of a TxRA. The TxRA, on the other hand,

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would antagonize the actions of TxA_2 and PGH_2. Studies on combination therapy in animals[12,13] and normal human volunteers[14] have demonstrated that the two agents have greater therapeutic benefit in combination than when given individually.

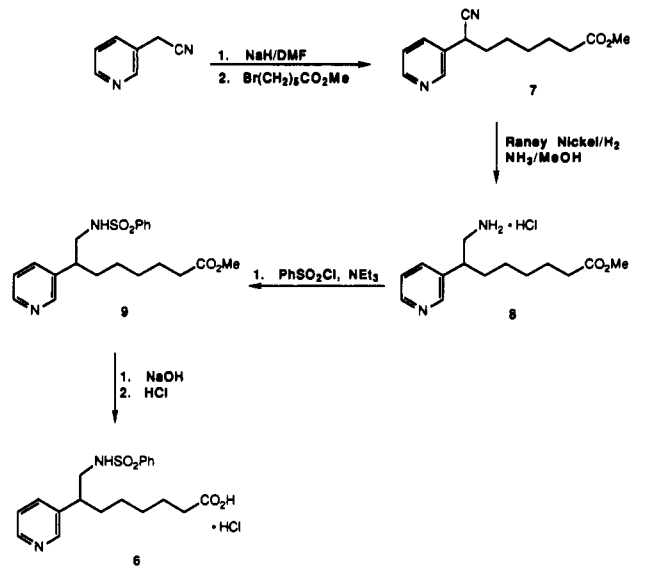
Recently, several compounds have been reported which possess both TxRA and TxSI properties in a single chemical entity.[18] In this paper we describe the design, synthesis, and in vitro pharmacology of a novel series of compounds possessing both TxRA and TxSI activities.

Compound Design

In order to prepare compounds with dual TxRA and TxSI activities it was first necessary to determine the basic pharmacophore for each activity, then secondly to design hybrid structures that fulfill the structural requirement for each activity. Fortunately, in the case of TxSIs, the essential structural features for activity have already been determined, i.e. a basic nitrogen atom (of a 3-substituted pyridine or 1-substituted imidazole) and a carboxylic acid group separated by a distance of 9–10 Å.[19] The prototypical TxSI for the pyridine series can therefore be considered to be **3**. In the case of TxRAs, a wide variety of structural types have been shown to possess TxRA activity.[20] BM 13177, **4**, seemed to offer the most promise as a starting point for compound design due to its structural simplicity and the fact that it (like **3**) also contained a carboxylic acid group which might therefore serve as a common structural element between the two classes of compound. A brief SAR analysis of **4** (data not shown) showed that while both the carboxylic acid and arylsulfonamido groups were essential to the TxRA activity, the (4-ethylphenoxy)methyl moiety functioned only as a "spacer" and could be replaced by a simple methylene chain of appropriate length. As a result, the prototypical TxRA for this series was determined to be **5**.

Inspection of the two prototypical compounds, **3** and **5**, led to the development of the hybrid structure **6**, wherein the key distance of six methylene groups between the pyridine and carboxylic acid moiety (for TxSI activity) and seven methylene groups between the arylsulfonamido and carboxylic acid moieties (for TxRA activity) were fulfilled. Having constructed this hybrid target structure we then embarked upon the synthesis of this compound and related structures.

Scheme I



Chemistry

Synthesis of **6** was accomplished by alkylation of 3-pyridinylacetonitrile with methyl 6-bromohexanoate (Scheme I). The resulting branched nitrile **7** was hydrogenated in methanol saturated with ammonia at 50 psi using Raney nickel as catalyst to give the corresponding amine **8**, which was sulfonylated with phenylsulfonyl chloride. Finally, hydrolysis of the ester **9** gave the desired hybrid target structure **6**, isolated as its HCl salt. The SAR of this series of compounds was explored using the same overall reaction scheme with a wide variety of arylsulfonyl chlorides, and bromoalkanoic acids (Table I).

In Vitro Pharmacology and Discussion

The compounds described herein were initially tested for their thromboxane synthase inhibitory activity. Inhibition of TxB_2 formation from human microsomal platelet preparations, incubated with (^{14}C)arachidonic acid, was measured. The compounds were then tested for inhibition of aggregation of aspirinated, washed human platelets (WP) challenged with U 46619, a stable PGH_2/TxA_2 mimic. The platelet aggregation was measured on a Payton dual-channel aggregometer. The IC_{50} values for thromboxane synthase inhibition and thromboxane receptor antagonism are shown in Table I.

As shown in Table I, the parent compound **6** possessed the desired dual TxSI (IC_{50} = 210 nM) and TxRA (IC_{50} = 250 nM) activities. A detailed SAR analysis of the arylsulfonamido group revealed that a wide variety of substituents, such as *p*-chloro, 3,4-dichloro, *p*-nitro, *p*-Me, and *o*-Me (**10**, **11**, **12**, **13**, **14**, respectively), maintained or even enhanced the activity of the series relative to **6** while more polar substituents, such as *p*-carboxylic acid and *p*-methoxy (**15**, **16**), resulted in reduced activity. Replacement of the phenyl group by α- or β-naphthyl (**17**, **18**) produced compounds with superior activity. Varying the length of the alkanoic acid in the *p*-chlorophenyl series from five to eight methylenes (**19**, **20**, **10**, **21**) confirmed

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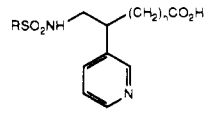
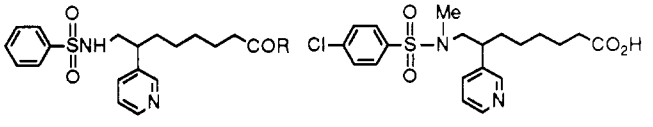
Table I. Physical Constants and in Vitro Activity of TxSI/TxRA



compd	R	n	mp, °C	formula[a]	IC_{50}, μM: thromboxane synthase inhibn[b]	IC_{50}, μM: inhibn of U46619-Induced aggregation of washed human platelets[c]
6	C_6H_5	5	158–161	$C_{19}H_{25}ClN_2O_4S$	0.21	0.25
10	4-ClC_6H_4	5	107–110	$C_{19}H_{24}Cl_2N_2O_4S \cdot H_2O$	0.22	0.02
11	3,4-$Cl_2C_6H_3$	5	152–154	$C_{19}H_{23}Cl_3N_2O_4S$	0.04	0.08
12	4-$NO_2C_6H_4$	5	155–158	$C_{19}H_{24}ClN_3O_6S$	0.12	0.07
13	4-$CH_3C_6H_4$	5	112–115	$C_{20}H_{17}ClN_2O_4S$	0.05	0.2
14	2-$CH_3C_6H_4$	5	135–139	$C_{20}H_{17}ClN_2O_4S$	0.2	0.38
15	4-$CO_2HC_6H_4$	5	154–156	$C_{20}H_{24}N_2O_6S$	>10	>10
16	4-$MeOC_6H_4$	5	144–146	$C_{20}H_{27}ClN_2O_5S$	0.94	0.3
17	α-naphthyl	5	186–189	$C_{23}H_{27}ClN_2O_4S$	0.09	0.08
18	β-naphthyl	5	157–160	$C_{23}H_{27}ClN_2O_4S$	0.065	0.004
19	4-ClC_6H_4	3	100–103	$C_{17}H_{20}Cl_2N_2O_4S \cdot 0.5H_2O$	2	>10
20	4-ClC_6H_4	4	169–172	$C_{18}H_{22}Cl_2N_2O_4S$	0.077	0.08
21	4-ClC_6H_4	6	98–102	$C_{20}H_{26}Cl_2N_2O_4S$	0.24	0.01
22	amide[d]		106–108	$C_{19}H_{25}N_3O_3S$	>10	>10
23	ester[d]		110–112	$C_{20}H_{27}ClN_2O_4S$	>10	>10
24	N-methyl[d]		186–189	$C_{20}H_{26}Cl_2N_2O_4S$	>10	>10
25	Ph[d]		89–92	$C_{20}H_{24}ClNO_4S$	>10	0.004

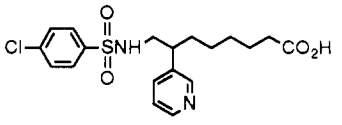
[a] C, H, and N analyses were within ±0.4% of the calculated values. [b] Values represent an average of two determinations. [c] Values represent a single determination. [d] For structures, see below.

the previous SAR for TxSI and TxRA activity in that the optimal chain length for TxSI activity occurred with five or six methylenes and for TXRA activity with seven or eight methylenes.



22 R = NH_2
23 R = OMe

24



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The presence of a free carboxylic acid group was essential to both activities as shown by the complete loss of activity with the primary amide **22** and ester **23** analogs. Similarly, a secondary sulfonamido group is also critical to the SAR as the *N*-methyl analog **24** was completely inactive in both TxSI and TxRA assays. The compounds with the best dual activity in this series (**6, 10, 11, 17, 18, 21**) were then tested further for their receptor antagonist properties in human platelet-rich plasma (PRP) and on rabbit aortic strips (Table II). The activity in PRP represents the functional antagonist property in a physiologically more relevant media and the activity in the rabbit aorta represents antagonism on the vascular receptor for TxA_2. These two additional tests were important as we desired to identify compounds that could function as dual antagonists in vivo, where both protein binding and non-platelet TxA_2 receptors may play a crucial role.

The PRP data (Table II) showed that this dually active series was more protein bound (PRP:WP ratios of 8–36

Table II. Thromboxane Antagonist Activity on Platelet and Vascular Receptors

compd	IC_{50},[a] μM: inhibn of U 46619-induced aggregation of washed platelets (WP)	IC_{50},[a] μM: inhibn of U 46619-induced aggregation of platelet rich plasma (PRP)	ratio PRP:WP	IC_{50},[a] μM: contraction of rabbit aortic strips
4	1.5	4.0	2.6	0.3
6	0.25	2.1	8.2	0.4
10	0.02	0.6	30	agonist[b]
11	0.08	2.5	32	1.0
17	0.08	2.9	36	1.0
18	0.004	>10	>2500	1.0
21	0.01	0.2	20	agonist[b]
25	0.004	ND	ND[c]	agonist[b]

[a] Values represent a single determination. [b] Marked agonist activity was observed at 10^{-5}–10^{-7} M. [c] ND, not determined.

for compounds **6, 10, 11, 17,** and **21**) than the corresponding parent TxRA, BM 13177, **4** (PRP:WP ratio of 2.6). Compound **18** containing a β-naphthyl sulfonamide group displayed the largest protein binding effect with a PRP:WP ratio in excess of 2500.

The rabbit aorta data (Table II) were more surprising as some of the key compounds (**6, 11, 17, 18**) were much less active (IC_{50}'s in the 1 μM range) than anticipated from the platelet receptor data, suggesting partial agonist activity. Indeed, two of the compounds, **10** and **21**, showed potent *agonist* activity in this receptor preparation. The origin of this agonist activity does not appear to be related to the dual activity of these compounds, as the corresponding analog was prepared where the pyridine group was replaced by a phenyl group. This compound (**25**) as expected was devoid of TxSI activity but showed extremely potent Tx receptor agonist activity on the vascular receptor. Thus, the agonist activity appeared to be related to the presence of an aromatic substituent positioned β to the arylsulfonamido group.

Conclusion

The compounds described in this paper, designed by "hybridizing" two prototypical representatives of the TxSI

and TxRA classes of compounds were found to exhibit dual activities. Compounds **6**, **10**, **11**, **17**, and **21** inhibited TxA_2 biosynthesis in human platelets with IC_{50}'s in the 10^{-8} M range. In addition, these compounds were also potent antagonists of the TxA_2 receptor on human platelets with IC_{50}'s again in the 10^{-8}–10^{-9} M range. Unfortunately, these compounds were weak antagonists of the rabbit aorta TxA_2 receptor, and two members of the series, compounds **10** and **21**, were found to exhibit pronounced Tx receptor *agonism*. This agonist activity appeared to be related to the presence of substituents β to the arylsulfonamido group. In the following paper, we describe our efforts to eliminate this unwanted agonist activity.

Experimental Section

Infrared (IR) spectra were recorded on a Nicolet 5SXFT spectrometer. Proton NMR spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are reported in ppm (δ) using tetramethylsilane as internal standard. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Methylene chloride (CH_2Cl_2) was dried over 4-Å molecular series for 72 h before use. Organic solutions during workup were dried with anhydrous $MgSO_4$ or Na_2SO_4. Flash chromatography[21] was performed with silica gel 60 (0.04–0.06 mm) (Merck).

Methyl 7-Cyano-7-(3-pyridinyl)heptanoate (7). To a suspension of NaH (1.1 g of 50% dispersion in oil) in DMF (50 mL) was added a solution of 3-pyridylacetonitrile (3.0 g, 25.4 mmol) in DMF (5 mL) over a period of 0.5 h. The reaction mixture was stirred at room temperature for 0.5 h and then cooled to −20 °C before adding methyl 6-bromohexanoate (6.2 g, 29.7 mmol). The mixture was then allowed to warm up to room temperature and stirred for a further 18 h. The reaction mixture was then poured into water (100 mL) and extracted with EtOAc (3 × 100 mL). The organic phase was dried, filtered, and evaporated to give crude product which was further purified by flash chromatography over silica gel using EtOAc to elute the product as a colorless oil (2.37 g, 38%): IR (CH_2Cl_2) 2983, 2840, 2664, 2238, 1729, 1426, 1374 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.5 (m, 2 H), 7.65 (m, 1 H), 7.25 (m, 1 H), 3.75 (t, J = 8 Hz, 1 H), 3.65 (s, 3 H), 2.25 (t, J = 7 Hz, 2 H), 1.8 (m, 2 H), 1.6–1.2 (m, 6 H).

Methyl 8-Amino-7-(3-pyridyl)octanoate (8). To a solution of the above nitrile (1.45 g, 5.9 mmol) in MeOH (100 mL) saturated with ammonia gas was added Raney nickel (2.5 mL). The mixture was hydrogenated at 50 psi of hydrogen at room temperature for 4 h. The catalyst was then filtered off, and the solvents were removed under reduced pressure to yield crude amine (1.47 g, 100%): IR (CH_2Cl_2) 3030, 2934, 2859, 1730, 1671, 1203 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.6 (m, 2 H), 7.6 (m, 1 H), 7.3 (m, 1 H), 3.65 (s, 3 H), 3.1 (m, 2 H), 2.7 (m, 1 H), 2.15 (t, J = 7 Hz, 2 H), 1.6–1.2 (m, 8 H).

Methyl 8-[(Phenylsulfonyl)amino]-7-(3-pyridinyl)octanoate (9). To a solution of the amine prepared above (1.4 g, 5.6 mmol) in EtOAc (20 mL) was added Et_3N (0.62 g, 6.1 mmol) followed by a solution of phenylsulfonyl chloride (1.08 g, 6.1 mmol) in EtOAc (5 mL) over a period of 0.5 h. The reaction mixture was stirred for 2 h and then poured into 1 N NaOH solution and extracted with EtOAc. The organic phase was then dried, filtered, and concentrated to give crude product which was further purified by flash chromatography over silica gel using $MeOH/CH_2Cl_2$ (5:95) to elute the product as a colorless oil (1.8 g, 82%): IR (CH_2Cl_2) 2937, 2860, 1731, 1332, 1164, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.4 (br d, 1 H), 8.2 (s, 1 H), 7.8–7.1 (m, 7 H), 3.65 (s, 3 H), 3.25 (m, 1 H), 3.0 (m, 1 H), 2.7 (m, 1 H), 2.15 (t, J = 7 Hz, 2 H), 1.7–1.1 (m, 8 H).

8-[(Phenylsulfonyl)amino]-7-(3-pyridinyl)octanoic Acid (6). A solution of the above ester (1.6 g, 4 mmol) in MeOH (20 mL) and 1 N aqueous NaOH (5 mL) was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure to remove the MeOH and the aqueous solution acidified to pH 6 with 1 N aqueous HCl. The mixture was then extracted with EtOAc and the organic phase dried, filtered, and concentrated to give the crude product which was redissolved in EtOAc and treated with hydrogen chloride gas. Removal of the solvent under reduced pressure and recrystallization from CH_2Cl_2 gave the pure product (0.8 g, 48%) as a crystalline solid: mp 156–161 °C; IR (KBr) 3336, 3241, 2938, 2857, 1713, 1331, 1161, 752, 625 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.8 (s, 1 H), 8.4 (d, J = 7 Hz, 1 H), 8.0–7.5 (m, 7 H), 3.1 (m, 2 H), 3.0 (m, 1 H), 2.15 (t, J = 7 Hz, 2 H), 1.8–1.0 (m, 8 H).

Biological Assays. The in vitro measurement of thromboxane synthase inhibition and inhibition of U 46619-induced aggregation of human washed platelets and plasma rich plasma was done as described previously.[18i,j]

Inhibition of U 46619-Induced Contraction of Rabbit Aortic Vein. Sections of the thorasic aorta (approximately 3 cm long) were excised from anesthetized male New Zealand rabbits (1.4–2.4 kg, Hare/Marland, Marland Farms, Hewitt, NJ) and cleaned of excess fat and tissue. Rings of approximately 3 mm were cut from the aorta and then the individual rings were cut open to yield strips of tissue 3 mm wide and 1 cm long. The strips were mounted vertically in smooth muscle chambers of 20 mL in modified Krebs solution at 35 °C, aerated with 95% O_2/5% CO_2 mixture and maintained at pH 7.4. The physiological solution also contained indomethacin (1 μM) in order to prevent the formation of endogenous prostaglandins. The tissues were attached to a FT .03 isometric force transducer (Grass Instruments, Quincy, MA) and the Buxco T 120B automated in vitro bath system (Sharon, CT) was used in all experiments. The preload tension was 2.0 g, and the tissues were allowed to equilibrate for 1 h.

The tissues were made to contract by the introduction of U 46619 (3×10^{-9} M) into the baths. After plateau responses were obtained (20 min), the strips were washed with physiological solution to obtain vascular relaxation to baseline tensions. Contraction of the tissues by the agonist followed by vasorelaxation was repeated until two consistent consecutive responses were obtained. The test compound was then added to the baths and, 10 min later, another agonist contractile response was obtained. The inhibitory effect produced by the contraction of the test compound was expressed as percent inhibition of the pretest compound control agonist-induced response.

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