Dual-Acting Thromboxane Receptor Antagonist/Synthase Inhibitors: Synthesis and Biological Properties of [2-Substituted-4-(3-pyridyl)-1,3-dioxan-5-yl]alkenoic Acids

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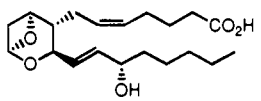
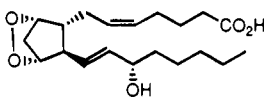
The design, synthesis, and pharmacology of a new class of compounds possessing both thromboxane receptor antagonist and thromboxane synthase inhibitory properties are described. Replacement of the phenol group of the known thromboxane antagonist series 4(*Z*)-6-[(4*RS*,5*SR*)-4-(2-hydroxyphenyl)-1,3-dioxan-5-yl]hex-4-enoic acid by a 3-pyridyl group led to a series of compounds, **5**, which were potent thromboxane synthase inhibitors and weak thromboxane antagonists. Further modifications at the dioxane C2 position led to compounds, **7**, which were potent dual-acting agents. In the case of compound **7w**, the dual activity was shown to reside almost exclusively in the (−)-enantiomer, **7x**. Following oral dosing to rats and dogs, **7x** (3 mg/kg) displayed significant dual activity over a period of at least 8 h.

Introduction

The short-lived arachidonate metabolite thromboxane A_2 (TxA_2, **1**) is an extremely potent vasoconstrictor and platelet aggregating agent.[1,2] TxA_2 is produced by the action of the enzyme thromboxane synthase (TxS) on the prostaglandin endoperoxide PGH_2, **2**, which is itself a potent agonist at the thromboxane receptor.[3,4] It has



1 (TXA_2)



2 (PGH_2)

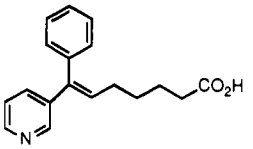
been suggested that TxA_2 (and PGH_2) may be implicated in a variety of disease conditions, for example, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, and certain renal disorders,[5–8] and accordingly, both inhibitors of TxS (TXSIs) and thromboxane receptor antagonists (TXRAs) have been developed in an attempt to treat these conditions. To date, TXSIs have proved disappointing as agents for the treatment of angina and peripheral vascular disease,[9,10] possibly owing to the accumulation of PGH_2 and/or the failure to achieve at least 95% inhibition of TxA_2 synthesis during the trials.[11] On the other hand, clinical trials of TXRA compounds have been inconclusive, possibly owing to the large local levels of TxA_2 produced at the site of platelet activation in pathogenic situations.

It has been postulated that the combination of a TXSI with a TXRA, either as a mixture of two compounds or as a dual-acting single compound, would overcome the shortcomings in the use of either agent alone;[12,13] the TXRA would attenuate the effects of any residual TxA_2 produced (or of accumulated PGH_2), while the TXSI would redirect PGH_2 metabolism so as to produce increased quantities of the vasodilator/antiplatelet aggregatory prostaglandins, for instance, PGD_2 in the platelet and in particular PGI_2, which is formed by the action of the enzyme prostacyclin synthase in the endothelium.[14,15] Prostacyclin synthase and TxS have similar substrate requirements, not surprisingly since they compete for the same substrate in the natural system. In order to maximize the benefit from redirection of PGH_2 to PGI_2, it is desirable that the TXSI should have a minimal inhibitory effect on prostacyclin synthase.

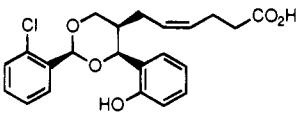
In this paper we describe the design, synthesis, and pharmacology (*in vitro* and *ex vivo*) of a series of dual-acting TXSI/TXRA compounds.

Compound Design

The key structural feature of potent TXSIs, e.g., isbogrel, **3**, is the presence of a ligand for heme iron, such as the 3-pyridyl group, and a carboxylic acid at a distance of approximately 10 Å.[16] We decided to introduce the 3-pyridyl group into appropriate positions of known carboxylic acid-containing TXRAs in the hope of introducing TXSI activity while maintaining TXRA activity. We chose as the TXRA starting point ICI 192605, **4**.[17] Examination of framework molecular mod-



3 (ISBOGREL)



4 (ICI 192605)

els suggested that replacement of the 4-(2-hydroxyphenyl) substituent with the 3-pyridyl group might indeed lead to the correct spacing of the nitrogen atom and the carboxylic acid. However, we expected that this modification would lead to a decrease in TXRA potency, since the phenol substituent had been previously shown to confer greater potency than, for example, an unsubstituted benzene ring.

Chemistry

The target dioxanes **5**–**9** were prepared either as the racemates (Scheme 1) or in homochiral form (Scheme 2). Methyl nicotinate (**10**) provided the starting point for the synthesis of the racemic dioxanes. Claisen condensation of the ester **10** with methyl acetate followed by alkylation with allyl bromide afforded the allyl

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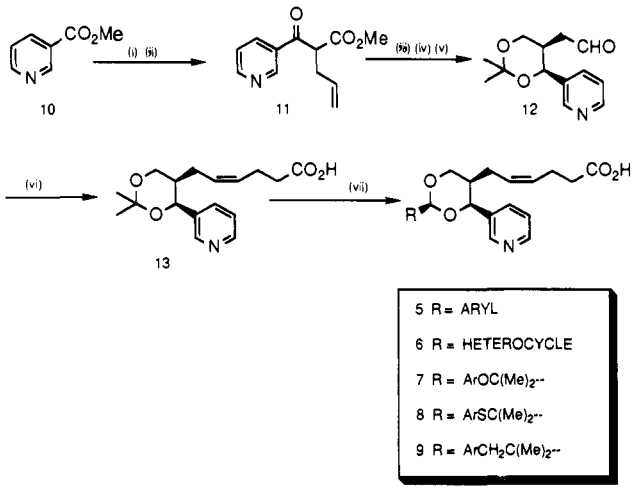
Scheme 1[a]



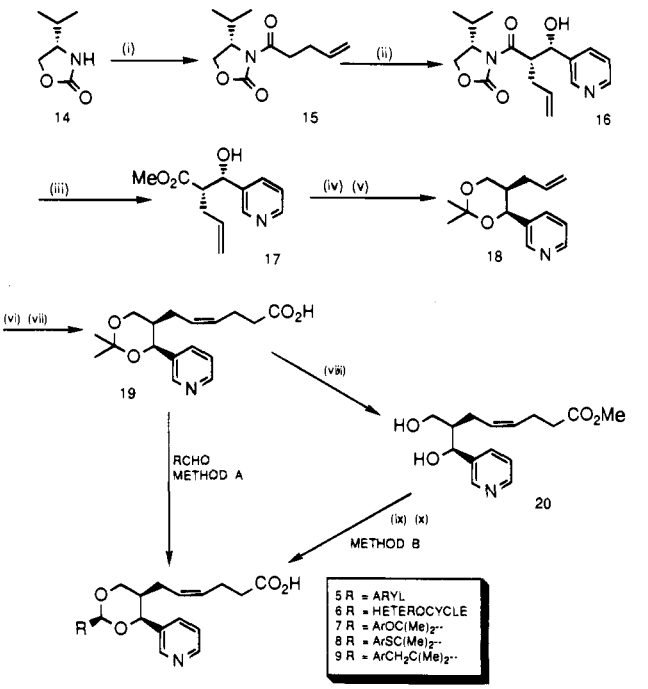
[a] (i) NaH, $CH_3CO_2CH_3$; (ii) NaOMe, $BrCH_2CH{=}CH_2$; (iii) $LiAlH_4$; (iv) $CH_3C(OCH_3)_2CH_3$; *p*-tsa; (v) O_3, DMS; separate isomers; (vi) $Ph_3P^+CH_2CH_2CH_2CO_2HBr^-$, KO^tBu; (vii) RCHO, *p*-tsa; reflux; method A.

keto ester **11**. Reduction of **11** with lithium aluminum hydride gave a 1:1 diastereomeric mixture of diols which were cyclized with 2,2-dimethoxypropane and 1.1 equiv of *p*-toluenesulfonic acid (*p*-tsa) to give the 1,3-dioxane ring system. Ozonolysis gave a 1:1 mixture of *cis*- and *trans*-1,3-dioxane aldehydes, **12**, the required *cis*-dioxane being purified by flash column chromatography. The Wittig reaction of **12** with (3-carboxypropyl)triphenylphosphonium bromide and potassium *tert*-butoxide gave the versatile intermediate **13** which could undergo acid-catalyzed transacetalization with a variety of aldehydes to give the required C2-substituted dioxanes **5-9** (method A). The appropriate aldehydes were prepared as shown in Schemes 3 and 4, and the required phenols were either commercially available or readily prepared by literature methods.

The preparation of the homochiral analogues made use of the methodology described by Evans[18] (Scheme 2). Reaction of (4*S*)-(−)-4-isopropyl-2-oxazolidinone (**14**) with *n*-butyllithium and 4-pentenoyl chloride gave the acyl oxazolidinone **15**. Treatment of **15** with Hunig's base and dibutylboron triflate in methylene chloride at 5 °C gave the *Z*-enolate. Subsequent cooling to −78 °C and addition of pyridine-3-carboxaldehyde gave **16** as a crystalline product. Treatment of **16** with sodium methoxide for approximately 5 min gave the hydroxy ester **17** without any detectable epimerization. The enantiomeric excess (ee) was measured using chiral HPLC methodology at this stage and was found to be ≥99%. Further investigation of these reaction conditions showed that performing the addition of pyridine-3-carboxaldehyde at higher temperatures (up to 5 °C) and carrying out methanolysis of the crude product **16** without purification resulted in no significant loss of ee (>99% at 5 °C; Chart 1) of the hydroxy ester **17**.

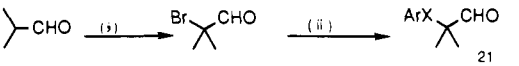
The hydroxy ester **17** was converted to the 1,3-dioxane 5-carboxylic acid **19** in a similar manner to that used for the racemate (Scheme 1), except that the separation of *cis*- and *trans*-dioxane isomers was unnecessary, since the Evans reaction produced only a single diastereomer. Direct transacetalization (method A) gave the 2-substituted-1,3-dioxanes, but poor yields and the occurrence of significant epimerization at C4 during reactions with

Scheme 2[a]



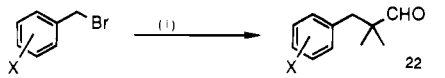
[a] (i) nBuLi, $ClCOCH_2CH_2CH{=}CH_2$; (ii) (a) $Bu_2BOTrif$, EtN^iPr_2, 5 °C, (b) 3-pyCHO, −78 °C; (iii) NaOMe, 5 min; (iv) $LiAlH_4$; (v) $CH_3C(OCH_3)_2CH_3$, *p*-tsa; (vi) O_3, DMS; (vii) $Ph_3P^+CH_2CH_2CH_2CO_2HBr^-$, KO^tBu; (viii) MeOH, *p*−tsa; (ix) RCHO, *p*-tsa, 130 °C, method B; (x) NaOH. Compounds of opposite chirality were prepared using the (4*R*)-oxazolidone.

Scheme 3[a]



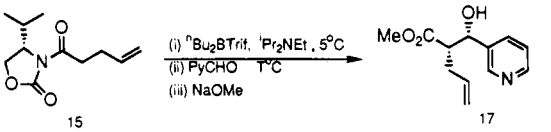
[a] (i) Br_2, K_2CO_3; (ii) ArX^-Na^+, DMPU (X = O, S).

Scheme 4[a]



[a] (i) NaOH powder, $Bu_4N^+I^-$, $(CH_3)_2CHCHO$.[19]

Chart 1



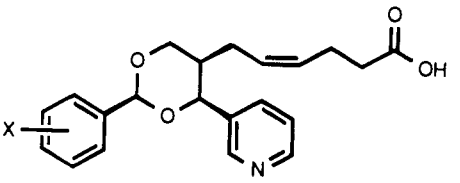
T°C	EE
-78	>99
-40	>98
+5	>99

the less reactive aldehydes warranted the development of an improved method. Accordingly, dioxane **19** was converted to the diol ester **20** using methanol and 1.1 equiv of *p*-tsa. **20** was then cyclized with the appropriate aldehyde at 130 °C using *p*-tsa catalysis, and the resulting product was saponified to give the enantiomeric 1,3-dioxanes **5−9** (method B), in improved yield and without any detectable epimerization at C4.

Results and Discussion

The compounds described herein (Tables 1−4) were initially tested *in vitro* for TXRA, TXSI, and prostacyclin

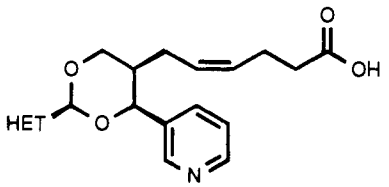
Table 1. *In Vitro* Activity of TXRA/TXSI Compounds



compound	X	(±)	mp (°C)	formula[a]	method	yield (%)	inhibition of U46619-induced aggregation of unwashed human platelets (pA_2)	inhibition IC_{50} (μM) thromboxane synthase	inhibition IC_{50} (μM) prostacyclin synthase
isbogrel (**3**)							NT	0.017	>100
192605 (**4**)							8.16	>100	NT
5a	2-Cl	(±)	75–78	$C_{21}H_{22}ClNO_4$	A	62	6.12	0.048	NT
5b	4-CN	(±)	191–198	$C_{22}H_{22}N_2O_4$	A	60	5.89	0.024	>100
5c	2-CN	(±)	151–154	$C_{22}H_{22}N_2O_4$	A	86	6.61	0.054	>100
5d	4-NO_2	(±)	131–136	$C_{21}H_{22}N_2O_6$	A	40	6.03	0.039	13
5e	2,4-Cl_2	(±)	179–181	$C_{21}H_{21}Cl_2NO_4$	A	48	6.05	0.042	2.5
5f	3,4-Cl_2	(±)	125–127	$C_{21}H_{21}Cl_2NO_4 \cdot 0.3H_2O$	A	57	6.11	0.042	9
5g	4-CF_3	(±)	138–140	$C_{22}H_{22}F_3NO_4 \cdot 0.5H_{20}$	A	33	5.75	0.044	NT

[a] C, H, and N analyses were within ±0.4% of calculated values unless otherwise stated. NT—not tested.

Table 2. *In Vitro* Activity of TXRA/TXSI Compounds



compound	HET	(±)	mp (°C)	formula	method	yield (%)	inhibition of U46619-induced aggregation of washed human platelets (pA_2)	inhibition IC_{50} (μM)[a] thromboxane synthase	inhibition IC_{50} (μM)[a] prostacyclin synthase
6a	3-pyridyl	(±)	129–133	$C_{20}H_{22}N_2O_4$	A	51	6.12	0.22	NT
6b	3-thiophenyl	(±)	146–148	$C_{19}H_{21}NO_4S$	A	47	5.8	0.5	NT
6c	2-thiophenyl	(±)	149–151	$C_{19}H_{21}NO_4S$	A	38	6.0	0.071	NT
6d	2-furyl	(±)	139–141	$C_{19}H_{21}NO_5$	A	43	5.9	0.164	NT
6e	2-naphthyl	(±)	138–142	$C_{25}H_{25}NO_4$	B	55	5.75	0.05	NT
6f	1-naphthyl	(±)	171–172	$C_{25}H_{25}NO_4$	B	40	6.2	0.04	NT

[a] NT—not tested.

synthase inhibitory activities (see the Experimental Section for methodology). Compound **5a** (the direct analogue of ICI 192605, **4**) showed potent TXSI activity (IC_{50} = 0.048 μM) but exhibited weaker TXRA activity (pA_2 = 6.12). All compounds in this series (**5a–g**) showed comparable TXSI and TXRA activities (Table 1). The most potent TXRA (**5c**; pA_2 = 6.6) was tested further in *ex vivo* models. **5c** showed similar TXSI activity to isbogrel (>80% inhibition at 24 h following an oral dose of 1 mg/kg to the dog; Table 5) but was inactive as a TXRA in rat and dog at doses of up to 25 and 10 mg/kg, respectively. **5c** was shown to be at least 1000 times less potent as an inhibitor of prostacyclin synthase (IC_{50} > 100 μM).

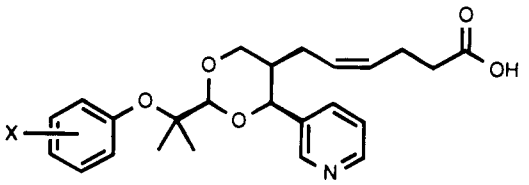
Replacement of the C2 pendant aryl ring by a range of heterocycles produced compounds of similar biological profile (Table 2). Improved TXRA activity was achieved by the insertion of a spacing group between the C2 aryl and dioxane rings (Tables 3 and 4). The unsubstituted 2-aryloxy dimethyl compound (**7a**) was 10-fold more active than **5a** as an antagonist (**7a**, pA_2 = 7.12; **5a**, pA_2 = 6.12) while retaining potent TXSI properties (IC_{50} = 0.052 μM).

A range of monosubstituted 2-aryloxy dimethyl compounds, **7b–t**, was prepared, and selected compounds were examined in more detail. While most modifications, **7b–o**, led to no improvement in the *in vitro* activity, the incorporation of small strongly electron-withdrawing groups (nitro and cyano) into the ortho position of the aryl ring led to an increase in TXRA potency (**7r**, pA_2 = 7.95; **7s**, pA_2 = 7.88). The compound containing the larger methylsulfonyl group, **7t**, did not show the same increase in potency. Further studies with **7r** revealed that dual activity was expressed following oral dosing to the rat (10 mg/kg) although the TXRA effects were of short duration (Table 6). However, **7r** showed relatively poor enzyme selectivity (IC_{50} < 1 μM versus prostacyclin synthase; Table 3).

In order to study the distribution of biological activity between the two enantiomeric forms of the aryloxy dimethyl dioxanes, the two enantiomers of the 4-bromo analogue **7b** were prepared. The (−)-enantiomer, **7q**, was shown to be a potent dual-acting agent (TXRA, pA_2 = 6.48; TXSI, IC_{50} = 0.022 μM), whereas the (+)-isomer, **7p**, showed only weak TXRA activity (pA_2 = 5.61) and no TXSI activity. However, the two enantiomers inhibited prostacyclin synthase (**7q**, IC_{50} = 4 μM; **7p**, IC_{50} < 1 μM) to an undesirable level.

Although **7r,p,q** showed little selectivity for TXS compared with prostacyclin synthase, the 4-methoxy-substituted compound **7c** was highly selective (TXSI, IC_{50} = 0.04 μM; prostacyclin synthase, IC_{50} > 100 μM).

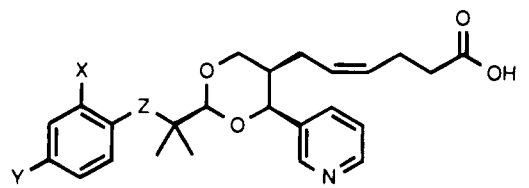
Table 3. *In Vitro* Activity of TXRA/TXSI Compounds



compound	X	(±)	mp (°C)	formula[a]	method	yield (%)	inhibition of U46619-induced aggregation of unwashed human platelets (pA_2)	inhibition IC_{50} (μM) thromboxane synthase	inhibition IC_{50} (μM) prostacyclin synthase
7a	H	(±)	131–134	$C_{24}H_{29}NO_5$	A	58	7.12	0.052	75
7b	4-Br	(±)	123–125	$C_{24}H_{28}BrNO_5$	A	47	6.42	0.051	3.4
7c	4-CH_3O	(±)	127–135	$C_{24}H_{31}NO_6$	A	51	6.52	0.041	>100
7d	4-^{t}Bu	(±)	157–159	$C_{28}H_{37}NO_5$	A	24	5.72	0.28	NT
7e	4-CN	(±)	107–110	$C_{25}H_{28}N_2O_2$	A	18	6.89	0.046	4
7f	4-SCH_3	(±)	135–138	$C_{25}H_{31}NO_5S$	A	26	6.43	0.039	32
7g	4-SO_2CH_3	(±)	114–116	$C_{25}H_{31}NO_7S$	A	21	7.04	0.034	8
7h	4-F	(±)	115–118	$C_{24}H_{28}FNO_5$	A	59	6.92	0.051	2
7i	4-CH_3	(±)	84–100	$C_{25}H_{31}NO_5$	A	27	6.2	0.36	25
7j	3-F	(±)	gum	$C_{24}H_{28}FNO_5$	A	25	6.9	0.026	40
7k	2-F	(±)	gum	$C_{24}H_{28}FNO_5$	A	40	6.78	0.045	<1
7l	2-OCH_3	(±)	122–125	$C_{24}H_{31}NO_6$	A	42	6.65	0.06	51
7m	2-SCH_3	(±)	93–97	$C_{25}H_{31}NO_5S$	A	45	7.05	0.036	>100
7n	2-OH	(±)	74–80	$C_{24}H_{29}NO_6 \cdot 0.25H_2O$	*b*		7.02	0.032	>100
7o	2-Br	(±)	gum	$C_{24}H_{28}BrNO_5 \cdot H_2O$	A	27	7.2	0.029	7
7p	4-Br	(+)	gum	$C_{24}H_{28}BrNO_5 \cdot 0.5H_2O$	A	32	5.61	>10	<1
7q	4-Br	(−)	gum	$C_{24}H_{28}BrNO_5 \cdot 0.25H_2O$	A	19	6.48	0.022	4
7r	2-NO_2	(±)	gum	$C_{24}H_{23}N_2O_7 \cdot 0.25H_2O$	A	29	7.95	<0.01	<1
7s	2-CN	(±)	gum	$C_{25}H_{28}N_2O_5$	B	50[c]	7.88	0.045	3
7t	2-SO_2CH_3	(±)	gum	$C_{25}H_{31}NO_7S \cdot 0.75H_2O$	A	29	6.23	0.045	2
7u	2-CO_2Me	(±)	87–93	$C_{26}H_{31}NO_7 \cdot 0.75H_2O$	A	22	7.19	0.066	73
7v	2-NO_2, 4-OMe	(±)	gum	$C_{25}H_{30}N_2O_8$	A	10	8.21	0.037	23
7w	2-NO_2, 4-Me	(±)	gum	$C_{25}H_{30}N_2O_7$	A	28	8.34	0.027	33
7x	2-NO_2, 4-Me	(−)	113–115	$C_{25}H_{30}N_2O_7$	B	78[c]	8.43	0.019	28
7y	2-NO_2, 4-Me	(+)	114–115	$C_{25}H_{30}N_2O_7$	B	68	<5.0	>10	NT
7z	2-NO_2, 4-F	(−)	134–135	$C_{24}H_{27}FN_2O_7$	B	50	8.6	0.02	9
7aa	2-NO_2, 4-SCH_3	(−)	99–102	$C_{25}H_{30}N_2O_7S$	B	68	8.35	0.022	5
7ab	2-NO_2, 4-CH_3CO	(−)	151–155	$C_{26}H_{30}N_2O_8$	B	84	8.82	<0.01	4
7ac	2-CN, 4-Me	(±)	137–138	$C_{26}H_{30}N_2O_5$	B	73	8.1	0.05	47
7ad	2-CN, 5-Me	(±)	108–111	$C_{26}H_{30}N_2O_5$	A	17	7.8	0.05	>100
7ae	2-CN, 6-Me	(±)	110–111	$C_{26}H_{30}N_2O_5$	B	52	7.6	0.09	60
7af	2-CN, 4-Me	(−)	99–101	$C_{26}H_{30}N_2O_5$	B	90	8.4	0.025	12
7ag	2-CN, 4-F	(−)	97–100	$C_{25}H_{27}FN_2O_5$	B	64	9.15	0.015	37

[a] As for Table 1. [b] Prepared by demethylation of **7l** (see the Experimental Section). [c] Yield of ring closure reaction: **20** → dioxane ester. NT—not tested.

Table 4. *In Vitro* Activity of TXRA/TXSI Compounds



compound	X	Y	Z	(±)	mp (°C)	formula	method	yield (%)	inhibition of U46619-induced aggregation of unwashed human platelets (pA_2)	inhibition IC_{50} (μM)[a] thromboxane synthase	inhibition IC_{50} (μM)[a] prostacyclin synthase
8a	H	H	S	(±)	118–120	$C_{24}H_{29}NO_4S$	A	63	6.7	0.04	NT
8b	NO_2	Me	S	(±)	112–114	$C_{25}H_{30}N_2O_6S$	B	50	6.8	0.03	NT
8c	NO_2	OCH_3	S	(±)	102–106	$C_{25}H_{30}N_2O_7S$	A	79	6.8	0.04	NT
8d	CN	H	S	(±)	45–46	$C_{25}H_{28}N_2O_4S$	B	63	6.5	0.04	NT
8e	H	H	SO_2	(±)	156–160	$C_{23}H_{29}NO_6S$	A	6	5.5	0.04	NT
9a	H	H	CH_2	(±)	102–105	$C_{25}H_{31}NO_4$	A	38	6.29	0.012	13
9b	H	F	CH_2	(±)	gum	$C_{25}H_{30}FNO_4$	A	37	7.05	0.045	2
9c	CN	H	CH_2	(±)	176–178	$C_{26}H_{30}N_2O_4$	B	81	7.56	0.037	14
9d	CN	F	CH_2	(−)	102–104	$C_{26}H_{29}FN_2O_4$	B	81	8.66	<0.01	7

[a] NT—not tested.

We therefore decided to incorporate para substituents into **7r** in the hope of increasing the enzyme selectivity. It was also hoped that such a modification might increase the duration of activity in the *ex vivo* models

Table 5. *Ex Vivo* TXSI Activity Following Oral Dosing in the Dog: Comparison of Isbogrel and **5c**

			TXA_2 synthase activity, % inhibition (± SEM), hours after dosing					
compound	dose (mg/kg)	*n*	1	2	3	5	8	24
isbogrel (**3**)	1	6	92.7 ± 1.2		82.8 ± 5.1	81.6 ± 3.5	77.6 ± 4.2	57.4 + 14.9
5c	1	4		84.0 ± 10.1		91.0 ± 2.4	84.0 ± 1.5	82.6 ± 1.9

Table 6. *Ex Vivo* TXRA/TXSI Activities Following Oral Dosing in the Rat

			TXA_2 antagonist activity, U46619-induced aggregation (dose ratio), hours after dosing			TXA_2 synthase inhibition, % inhibition (±SEM), hours after dosing		
compound	dose (mg/kg)	*n*	1	3	5	1	3	5
7h	10	6	6	4	4	93.2 ± 1.9	80.0 ± 2.6	83.0 ± 2.1
7r	10	6	>57[a]	9	3	85.5 ± 4.4	75.8 ± 6.5	63.2 ± 5.2
7x	10	6	>113	>71	>92	95.6 ± 0.2	93.9 ± 0.5	89.0 ± 1.1
7x	5	6	>60	>59	>47	92.9 ± 0.9	89.2 ± 1.0	79.3 ± 3.6
7x	3	6	>34	>23	>21	90.8 ± 0.7	82.5 ± 1.8	68.3 ± 5.3
7x	1	6	>21	>27	>9	61.8 ± 6.9	38.8 ± 10	NA

[a] Symbols indicate at least one animal in the group exhibited insurmountable blockade. NA—not active.

Table 7. *Ex Vivo* TXRA/TXSI Activities of **7x** after Oral Dosing in the Dog

		TXA_2 antagonist activity against U46619-induced aggregation, hours after dosing (dose ratio)				TXA_2 synthase inhibition, % inhibition (±SEM), hours after dosing			
dose (mg/kg)	*n*	2	5	8	24	2	5	8	24
10	4	>522[a]	>522	>522	>522	93.5 ± 2.1	84.1 ± 4.4	74.0 ± 11.6	57.1 ± 16.4
3	4	>321	>321	>321	>281	92.2 ± 2.3	89.2 ± 2.8	73.6 ± 3.9	46.0 ± 12.6
1	4	>506	>506	>506	>1.4 ± 0.74	72.2 ± 1.8	53.5 ± 13.0	49.1 ± 10.7	41.1 ± 5.7

[a] Symbols indicate at least one animal in the group exhibited insurmountable blockade.

by blocking a potential site of metabolism, although it should be emphasized that there was no evidence to suggest that the short duration of action of **7r** in the rat was due to rapid metabolism.

Compounds **7v,w** not only proved to be more enzyme selective (TXSI, IC_{50} = 0.037 and 0.027 μM; prostacyclin synthase, IC_{50} = 23 and 33 μM, respectively) but also showed increased TXRA potency (pA_2 = 8.21 and 8.34, respectively). Furthermore, all of the dual activity of the racemic **7w** could be attributed to the (−)-enantiomer, **7x** (Table 3). Other 2,4-disubstituted homochiral compounds also show enhanced TXRA potency (**7z,aa,af,ag**). When the methyl substituent was moved from the 4 position to other positions, then decreased activity was observed (**7ac−ae**).

On *ex vivo* testing in the rat and dog, **7x** showed significant dual activity over a duration of at least 8 h following an oral dose of 3 mg/kg (Tables 6 and 7). A more detailed account of the pharmacology has been given elsewhere.[20]

The X-ray crystallographic structure determination of **7x** shows the distance between the pyridyl nitrogen atom and the carboxylic acid carbon atom to be 9.74 Å (Figure 1), in agreement with the proposed optimal distance for TXSI activity.[16]

Replacement of the oxygen atom in the spacing oxy dimethyl group by sulfur resulted in retention of TXSI activity but a decrease in TXRA potency (Table 4; **8a−e**). Replacement by a methylene unit, however, led to compounds which retained both TXSI and TXRA activity (compare **9b,d** with **7h,ag**, respectively).

Conclusion

Compounds from the series of 4(*Z*)-6-[(2*S*,4*S*,5*R*)-2-[1-(aryloxy)-1-methylethyl]-4-(3-pyridyl)-1,3-dioxan-5-yl]-hexenoic acids described above were found to exhibit potent TXRA and TXSI properties. Compound **7x** was furthermore shown to exhibit long-lived dual activity in the rat and dog following an oral dose of 3 mg/kg and to be selective for TXS versus prostacyclin synthase.

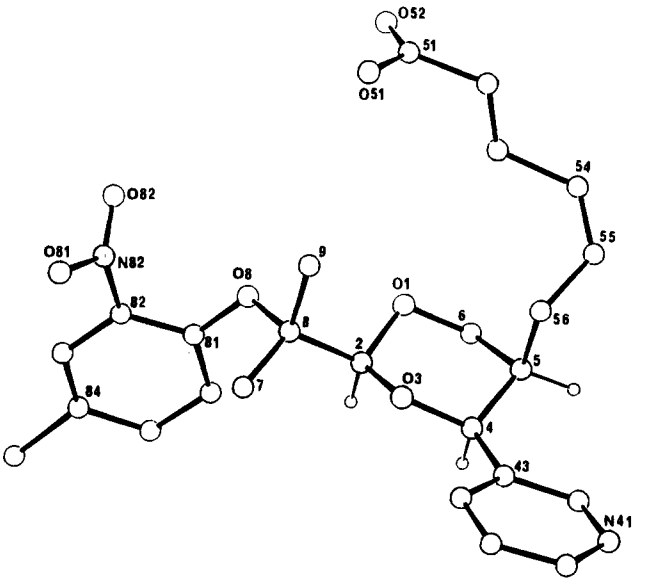


Figure 1. X-ray crystal structure of **7x** showing the N^{41}−C^{51} distance.

Experimental Section

Melting points (uncorrected) were determined in open capillary tubes using a Muchi-Totoli apparatus. Optical rotations were determined in a Perkin-Elmer 241 polarimeter at the sodium D line. NMR spectra were obtained with a Bruker AK 200 spectrometer in $CDCl_3$, DMSO-d_6, or DMSO-d_6/AcOH-d_4. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si. Mass spectral data were determined on VG-12-12, VG 70-250, and VG ZAB HF instruments, giving anticipated molecular ions and fragmentation patterns. Analytical TLC was performed on 0.25 mm silica gel plates (Merck Kieselgel 60, 230−400 mesh). Flash column chromatography was carried out on silica gel (Merck Kieselgel 60, 230−400 mesh). Enantiomeric excesses were measured using HPLC methodology utilizing a mobile phase (phosphate buffer

(pH 7) and isopropyl alcohol) containing bovine serum albumen on a 10 cm × 0.46 cm Spherisorb S5CN column. Elemental analyses were performed by B. Crooks and associates, ZENECA Pharmaceuticals. X-ray analysis was performed by M. McPartlin, School of Chemistry, University of North London, and the data is available as supplementary material.

Methyl 2-Nicotinyl-4-pentenoate (11). To methyl acetate (500 mL) was added, with cooling, sodium hydride (140 g, 2.40 mol, 55% dispersion in oil) keeping the temperature below 25 °C. Methyl nicotinate (219.03 g, 1.599 mol) was then added. The mixture was allowed to warm to room temperature until an exotherm commenced. The reaction mixture was allowed to reflux gently and then was stirred at room temperature for 18 h. The reaction was quenched with iced H_2O (500 mL) and the mixture extracted with Et_2O (1 L). The aqueous layer was adjusted to pH 7.7 with concentrated HCl, extracted with CH_2Cl_2 (2 L), dried ($MgSO_4$), and evaporated to give methyl (2-nicotinyl)acetate (256.65 g) as an oil. Without further purification, this was added under argon to a solution of sodium metal (32.98 g, 1.434 mol) in MeOH (1.4 L), and the resulting mixture was stirred at 25 °C for 1 h. Allyl bromide (136.5 mL, 1.577 mol) was added dropwise, and the mixture was allowed to stir at room temperature for 18 h and then concentrated. The residual oil was partitioned between H_2O (500 mL) and Et_2O (1 L), and the aqueous layer was extracted three times with Et_2O (500 mL). The combined organic extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated. The resulting oil was distilled to give **11** (142.3 g, 50%): bp 138–140 °C/1.0 mmHg; NMR ($CDCl_3$) δ 2.6–2.9 (m, 2H, CH_2), 3.7 (s, 3H, OCH_3), 4.4 (m, 1H, $COCHCO_2$), 4.9–5.2 (m, 2H, $CH{=}CH_2$), 5.5–6.0 (m, 1H, $-CH{=}CH_2$), 7.2–7.5 (m, 1H, 4-py), 8.1–8.3 (m, 1H, 5-py), 8.7–8.8 (m, 1H, 6-py), 9.1–9.2 (m, 1H, 2-py); MS *m/e* 220 $(M + H)^+$. This material was used without further characterization.

***cis*-[2,2-Dimethyl-4-(3-pyridyl)-1,3-dioxan-5-yl]acetaldehyde (12).** A solution of **11** (139.8 g, 0.638 mol) in THF (150 mL) was added to a suspension of $LiAlH_4$ in THF (750 mL) at such a rate that the temperature did not exceed 10 °C. After stirring at room temperature for 3 h, the mixture was cooled to 5 °C, and EtOAc (100 mL) was then added to destroy excess reagent followed by saturated NH_4Cl (500 mL). The precipitate was removed by filtration and washed with EtOAc. The aqueous phase was separated and extracted with EtOAc (3 × 500 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to give 2-allyl-1-(3-pyridyl)-1,3-propanediol as an oil (102.3 g). Without further purification, this was dissolved in $(CH_3)_2C(OMe)_2$ (500 mL), treated with *p*-toluenesulfonic acid (110 g, 0.58 mol), and stirred at room temperature for 18 h. The pH was adjusted to 8–10 by addition of NEt_3. The resulting mixture was partitioned between H_2O (500 mL) and Et_2O (500 mL). The aqueous layer was extracted with Et_2O (2 × 500 mL), and the combined organics were dried ($MgSO_4$) and evaporated to give an oil. Distillation gave a mixture of *cis/trans*-5-allyl-2,2-dimethyl-4-(3-pyridyl)-1,3-dioxane (67.88 g, 46%): bp 126–129 °C/1.0 mmHg); NMR ($CDCl_3$) δ 1.53 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.6–2.1 (m, 2H, $CH_2CH{=}CH_2$), 2.3–2.5 (m, 1H, CH-allyl), 3.7–4.2 (m, 2H, OCH_2, cis + trans), 4.55 (d, J = 10 Hz, 0.5H, OCH, trans), 4.85–5.0 (m, 2H, $CH{=}CH_2$), 5.25 (d, J = 3 Hz, 0.5H, OCH, cis), 5.4–5.7 (m, 1H, $CH{=}CH_2$), 7.25–7.35 (m, 1H, 4-py), 7.6–7.8 (m, 1H, 5-py), 8.5–8.65 (m, 2H, 2+6-py); MS *m/e* 234 $(M + H)^+$. This material was used without further characterization.

Ozone in oxygen was bubbled through a solution of 5-allyl-2,2-dimethyl-4-(3-pyridyl)-1,3-dioxane (50.1 g, 0.21 mol) in MeOH (1.2 L) at −70 °C until a blue color persisted throughout. Argon was passed through the solution to discharge the excess ozone, and dimethyl sulfide (75 mL) was added. The mixture was allowed to warm to room temperature and then stirred for 18 h. The solution was concentrated and then partitioned between H_2O (500 mL) and Et_2O (500 mL). The aqueous layer was extracted with further amounts of Et_2O (3 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated to give an oil. The *cis*-dioxane acetaldehyde **12** was separated by flash column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (99:1 increasing to 97:3) to give **12** (19.48 g, 40%) as an oil: NMR ($CDCl_3$) δ 1.53 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.1–2.45 (m, 2H, $CHCH_2$), 2.85–3.0 (m, 1H, $CHCH_2$), 3.8–3.85 (m, 1H, CH_2O), 4.25–4.35 (m, 1H, OCH_2), 5.25 (d, J = 3 Hz, 1H, OCHpy), 7.3–7.45 (m, 1H, 4-py), 7.6–7.7 (m, 1H, 5-py), 8.5–8.6 (m, 2H, 2+6-py), 9.6 (s, 1H, CHO); MS *m/e* 236 $(M + H)^+$. This material was used without further characterization.

4(*Z*)-6-*cis*-[2,2-Dimethyl-4-(3-pyridyl)-1,3-dioxan-5-yl]-hexenoic Acid (13). A solution of **12** (19.47 g, 0.083 mol) in dry THF (100 mL) was added under argon to a stirred, ice-cooled solution of the ylide prepared from (3-carboxypropyl)-triphenylphosphonium bromide (88.9 g, 0.207 mol) and KO^{t}Bu (46.5 g, 0.414 mol) in dry THF (1.1 L). The mixture was stirred at room temperature for 18 h and then treated with ice-cooled H_2O (500 mL) and extracted with EtOAc (500 mL). The organic extract was extracted with 1 N NaOH (2 × 200 mL). The aqueous layers were combined and acidified to pH 4–5 with HOAc. The mixture was extracted with EtOAc (3 × 500 mL), dried ($MgSO_4$), and concentrated to an oil. Trituration with ether, filtration of the precipitated Ph_3PO, and evaporation gave an oil which was purified by flash chromatography on silica gel, eluting with CH_2Cl_2–MeOH (95:5) to give **13** (19.42 g, 77%) as an oil: NMR ($CDCl_3$) δ 1.55 (s, 6H, CH_3), 1.55–1.75 (m, 2H, $CH_2CH{=}CH_2$), 2.2–2.6 (m, 5H, $CH_2CH_2CO_2H$ + CH-allyl), 3.8–3.9 and 4.1–4.2 (m, 2H, OCH_2), 5.15–5.5 (d + m, 3H, CHpy + $CH{=}CH$), 7.3–7.4 (m, 1H, 4-py), 7.7–7.8 (m, 1H, 5-py), 8.5–8.6 (m, 2H, 2+6-py), 8.8 (vb, 1H, CO_2H); MS *m/e* 306 $(M + H)^+$. Anal. ($C_{17}H_{23}NO_4$) C, H, N.

Method A—General Method for the Preparation of the Dioxanes 5–9. To a solution of **13** (2.21 g, 7.25 mmol) in CH_3CN (40 mL) was added 2-cyanobenzaldehyde (2.85 g, 21.75 mmol) followed by *p*-tsa (1.65 g, 8.69 mmol). The resulting mixture was refluxed for 5 h, before cooling and partitioning between EtOAc (50 mL) and 1 N NaOH 20 mL. The organic layer was re-extracted with 1 N NaOH (20 mL). The aqueous extracts were combined, adjusted to pH 5–6 with HOAc, and extracted with EtOAc (4 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated to give a gum which was purified by flash column chromatography on silica gel, eluting with MeOH–CH_2Cl_2 (5:95) to give a solid. This was triturated with Et_2O and collected by filtration to give **5c** (2.08 g, 86%) as a white solid: mp 151–154 °C; NMR (DMSO-d_6) δ 1.5–2.4 (m, 7H, $CHCH_2$), 4.1–4.3 (m, 2H, OCH_2), 5.15–5.5 (m, 2H, $CH{=}CH$), 5.45 (d, J = 3 Hz, 1H, CHpy), 5.9 (s, 1H, ArCH), 7.35–7.9 (m, 6H, ArH + 3+4-py), 8.45–8.6 (m, 2H, 2+6-py); MS *m/e* 379 $(M + H)^+$. Anal. ($C_{22}H_{22}N_2O_4$) C, H, N.

In a similar manner were prepared compounds **5a–g**, **6a–d**, **7a–w**, **8a,e**, and **9a,b**.

(4*S*)-4-Isopropyl-3-(4-pentenoyl)oxazolidin-2-one (15). A 1.53 M solution of nBuLi in hexane (117.7 mL) was added to a solution of (4*S*)-(−)-isopropyl-2-oxazolidinone (23.22 g, 0.181 mol) in dry THF (450 mL), cooled to −78 °C under argon. The mixture was allowed to warm to −50 °C and then stirred for 30 min. The mixture was then recooled to −78 °C, and a solution of 4-pentenoyl chloride (21.29 g, 0.181 mol) in dry THF (20 mL) was added dropwise. After the addition, the mixture was stirred at −78 °C for 30 min and then allowed to warm to −20 °C. Saturated NH_4Cl solution (80 mL) was added and the mixture extracted with EtOAc (3 × 400 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc–hexane (20:80) to give **15** (33.68 g, 88%) as an oil: NMR ($CDCl_3$) δ 0.9 (t, 6H, CH_3), 2.3–2.5 (m, 3H, $CHCH_2$ + $CHMe_2$), 2.9–3.2 (m, 2H, $CH_2CH{=}CH_2$), 4.15–4.33 (m, 2H, OCH_2), 4.4–4.47 (m, 1H, CHN), 4.95–5.15 (m, 2H, $CH{=}CH_2$), 5.75–5.95 (m, 1H, $CH{=}CH_2$); MS *m/e* 212 $(M + H)^+$.

(4*S*)-3-[(2*S*)-2-[(1*S*)-1-Hydroxy-1-(3-pyridyl)methyl]pent-4-enoyl]-4-isopropyloxazolidin-2-one (16). A 1 M solution of dibutylboron triflate in CH_2Cl_2 (48.45 mL, 0.048 mol) was added to a solution of **15** (9.31 g, 0.0438 mol) in CH_2Cl_2 (200 mL), cooled to 5 °C under argon, followed by EtN^iPr_2 (9.25 mL, 0.053 mol). The reaction mixture was stirred for 30 min and then cooled to −78 °C. 3-Pyridinecarboxaldehyde (4.5 g, 0.0482 mol) was added dropwise. The mixture was stirred for 30 min at −78 °C and then allowed to warm to −50 °C over 30 min.

The cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The mixture was then cooled to 5 °C and the reaction quenched with pH 7 phosphate buffer (50 mL) followed by H_2O_2 (14 mL, 30% (w/v) aqueous solution). The mixture was stirred for 30 min and then poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc–hexane (1:1) increasing gradually to 100% EtOAc to give a solid, which was recrystallized from toluene to give **16** (9.42 g, 68%): mp 112–113 °C; $[\alpha]^{25}_D$ = +135.8° (EtOH, *c* = 0.67); NMR ($CDCl_3$) δ 0.84 (d, 3H, *J* = 7 Hz, CH_3), 0.89 (d, 3H, *J* = 7 Hz, CH_3), 2.23–2.63 (m, 4H, CH_2 allyl, CHCO, + $CHMe_2$), 4.03–4.18 (m, 2H, CHN, OH), 4.31–4.55 (m, 2H, CH_2O), 4.96–5.10 (m, 3H, CH=CH_2 + pyCHOH), 5.67–5.84 (m, 1H, CH=CH_2), 7.26–7.33 (m, 1H, 4-py), 7.77–7.81 (m, 1H, 5-py), 8.52–8.60 (m, 2H, 2 + 6-py); MS *m/e* 319 $(M + H)^+$. Anal. ($C_{17}H_{22}N_2O_4$) C, H, N.

Methyl (2*S*)-2-[(1*S*)-1-Hydroxy-1-(3-pyridyl)methyl]-pent-4-enoate (17). A solution of NaOMe in methanol (7.0 mL, 30% (w/w), 0.325 mol) was added to a solution of **16** (9.38 g, 0.0294 mol) in MeOH (50 mL) cooled to 5 °C. The mixture was stirred for 15 min, and then saturated NH_4Cl (20 mL) and ether (100 mL) were added. Sufficient water was added to dissolve any precipitated inorganics, and the mixture was extracted with Et_2O (4 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc to give **17** (4.30 g, 66%) as an oil which soldified on standing: mp 63–65 °C; $[\alpha]^{25}_D$ = +20.5° (EtOH, *c* = 1.5); NMR ($CDCl_3$), δ 2.34–2.58 (m, 2H, CH_2), 2.80–2.87 (m, 1H, COCH), 3.58 (s, 3H, CH_3), 4.97–5.08 (m, 3H, CH=CH_2 + CHOH), 5.64–5.82 (m, 1H, CH=CH_2), 7.24–7.30 (m, 1H, 4-py), 7.70–7.75 (m, 1H, 5-py), 8.43–8.55 (m, 2H, 2+6-py); MS *m/e* 222 $(M + H)^+$. Anal. ($C_{12}H_{15}NO_3$) C, H, N.

(4*S*,5*R*)-5-Allyl-2,2-dimethyl-4-(3-pyridyl)-1,3-dioxane (18). A solution of **17** (4.85 g, 0.0219 mol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.95 g, 0.025 mol) in THF (50 mL) cooled to 5 °C at such a rate to maintain the temperature below 10 °C. After the addition was complete, the mixture was stirred at 5 °C for 4 h. EtOAc (20 mL) was added, followed by saturated NH_4Cl solution (10 mL) and H_2O (10 mL). The mixture was extracted with EtOAc (5 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc followed by MeOH–EtOAc (10:90) to give the diol (3.17 g, 75%) as an oil: $[\alpha]^{25}_D$ = −39° (EtOH, *c* = 1.1); NMR (DMSO-d_6) δ 1.65–2.18 (m, 1H, CHCH$_2$), 1.93–2.18 (m, 2H, CH_2 allyl), 3.16–3.45 (m, 2H, CH_2OH), 4.41–4.47 (m, 1H, CHOH), 4.75–4.81 (m, 1H, CHOH), 4.90–5.01 (m, 2H, CH=CH_2), 5.25 (d, 1H, *J* = 5 Hz, CHOH), 5.62–5.82 (m, 1H, CH=CH_2), 7.30–7.47 (m, 1H, 4-py), 7.65–7.72 (m, 1H, 5-py), 8.40–8.50 (m, 2H, 2+6-py); MS *m/e* 194 $(M + H)^+$. Anal. ($C_{12}H_{15}NO_2$) C, H, N.

To a solution of the diol (2.45 g, 0.0127 mol) in 2,2-dimethoxypropane (20 mL) was added *p*-tsa (2.65 g, 0.0139 mol), and the resulting mixture was stirred at room temperature for 18 h. NEt_3 (10 mL) was added, and the mixture was partitioned between ether (50 mL) and H_2O (20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The resulting oil was distilled to give **18** (2.19 g, 74%): bp 110–111 °C/0.5 mmHg; $[\alpha]^{25}_D$ = −93.3° (EtOH, *c* = 2.4); NMR ($CDCl_3$) δ 1.52 (s, 3H, CH_3), 1.55 (s, 3H, CH_3) 1.51–1.74 (m, 2H, CH_2-CH=CH_2), 2.32–2.45 (m, 1H, CH allyl), 3.90 and 4.15 (dd + m, 2H, OCH_2), 4.93–5.02 (m, 2H, CH=CH_2), 5.27 (d, *J* = 3 Hz, 1H), 5.48–5.66 (m, 1H, CH=CH_2), 7.23–7.32 (m, 1H, 4-py), 7.62–7.68 (m, 1H, 5-py), 8.50–8.55 (m, 2H, 2+6-py); MS *m/e* 234 $(M + H)^+$. Anal. ($C_{14}H_{19}NO_2$) C, H, N.

4(*Z*)-6-[(4*S*,5*R*)-2,2-Dimethyl-4-(3-pyridyl)-1,3-dioxan-5-yl]hexenoic acid (19) was prepared using an analogous procedure to that described above. The intermediate dioxane acetaldehyde was purified by flash column chromatography eluting with EtOAc affording an oil (84%): $[\alpha]^{25}_D$ = −60.2° (EtOH, *c* = 1.62); NMR ($CDCl_3$) δ 1.52 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.15–2.42 and 2.83–2.95 (m, 3H, CHCH$_2$CHO), 3.82 and 4.3 (dd + m, 2H, OCH_2), 5.26 (d, *J* = 2 Hz, 1H, CHpy), 7.23–7.31 (m, 1H, 4-py), 7.59–7.70 (m, 1H, 5-py), 8.46–8.55 (m, 2H, 2+6-py), 9.61 (s, 1H, CHO); MS *m/e* 236 $(M + H)^+$. Anal. ($C_{13}H_{17}NO_3$) C, H, N.

This was reacted with the Wittig reagent as described for **13** to give the hexenoic acid. Recrystallization from EtOAc–hexane (2:3) gave **19** (60%) as a white solid: mp 112–114 °C; $[\alpha]^{25}_D$ = −113° (EtOH, *c* = 0.465); NMR ($CDCl_3$) δ 1.54 (s, 6H, $(CH_3)_2$), 1.63–1.68 (m, 2H, CH_2CH=CH_2), 2.24–2.58 (m, 5H, CH allyl + CH_2CO + CH_2CH=CH_2), 5.15–5.47 (m, 3H, CH=CH_2), 5.27 (d, 1H, *J* = 2 Hz, CHpy), 7.28–7.37 (m, 1H, 4-py), 7.73–7.76 (m, 1H, 5-py), 8.50–8.57 (m, 2H, 2+6-py); MS *m/e* 306 $(M + H)^+$. Anal. ($C_{17}H_{23}NO_4$) C, H, N.

Method B—General Method for Preparing Enantiomeric Dioxanes 5–9 (where racemic material was prepared, compound 13 was used instead of 19). 4(*Z*)-6-[(2*S*,4*S*,5*R*)-2-[1-Methyl-1-(2-nitro-4-methylphenoxy)ethyl]-4-(3-pyridyl)-1,3-dioxan-5-yl]hexanoic Acid (7x). *p*-Toluenesulfonic acid (16.96 g, 0.089 mol) was added to a solution of **19** (24.75 g, 0.0811 mol) in MeOH (150 mL), and the mixture was stirred at room temperature for 4 h. NEt_3 (15 mL, 0.108 mol) was added, and the mixture was partitioned between EtOAc (500 mL) and H_2O (100 mL). The organic layer was dried ($MgSO_4$) and evaporated to an oil that was purified by flash column chromatography on silica gel, eluting with MeOH–CH_2Cl_2 (6:94 rising to 12:88) to give the diol ester **20** (96%) as an oil: NMR ($CDCl_3$) 1.82–1.95 (m, 2H, CH_2-CH=CH), 2.1–2.55 (m, 5H, COCH$_2$ + CH allyl, CH_2CH=CH_2), 3.68 (s, 2H, CH_3), 3.75–3.82 (m, 2H, OCH_2), 5.15–5.42 (m, 3H, CH=CH, CHpy), 7.35–7.43 (m, 1H, 4-py), 7.73–7.78 (m, 1H, 5-py), 8.45–8.6 (m, 2H, 2+6-py); MS *m/e* 280 $(M + H)^+$. Anal. ($C_{15}H_{21}NO_4$) C, H, N.

A solution of **20** (22.05 g, 0.079 mol) and 2-methyl-2-(2-nitro-4-methylphenoxy)propanal (26.44 g, 0.118 mol) in CH_3CN (140 mL) was treated with $CH(OMe)_3$ (18.15 mL, 0.166 mol) followed by *p*-tsa monohydrate (16.52 g, 0.0869 mol), and the mixture was refluxed for 1 h. The solvent was distilled off, the temperature raised to 130 °C, and the mixture maintained at this temperature for 3 h. The mixture was cooled and partitioned between EtOAc (200 mL) and $NaHCO_3$ solution (80 mL). The organic layer was dried ($MgSO_4$) and evaporated to an oil that was purified by flash column chromatography, eluting with EtOAc–hexane (20:80) and then with EtOAc to give the dioxane ester (29.94 g, 78%) as an oil: NMR ($CDCl_3$) δ 1.44 (s, 6H, $(CH_3)_2$), 1.50–1.75 (m, 2H, CH_2CH=CH_2), 2.15–2.50 (m, 5H, CH allyl, CH_2CH_2CO), 2.34 (s, 3H, ArCH_3), 3.62 (s, 3H, OCH_3), 3.92–4.15 (m, 2H, OCH_2), 4.81 (s, 1H, OCHO), 5.10 (d, *J* = 3 Hz, 1H, OCHpy), 5.13–5.45 (m, 2H, CH=CH), 7.15–7.55 (m, 5H, Ar and 4+5-py), 8.45–8.55 (m, 2H, 2+6-py); MS *m/e* 485 $(M + H)^+$.

A solution of the dioxane ester (29.92 g, 0.062 mol) in MeOH (300 mL) was treated with 1 N NaOH solution (250 mL), and the resulting mixture was stirred at room temperature for 3 h. The mixture was acidified to pH 5 with HOAc and extracted with EtOAc (3 × 500 mL). The organic layers were combined, washed with H_2O (400 mL), dried ($MgSO_4$), and evaporated to give a gum. Trituration with Et_2O (130 mL) gave a solid which was recrystallized from EtOAc–hexane (2:1) to give **7x** (25.75 g, 88%, ee ≥99%) as a white solid: mp 114–115 °C; $[\alpha]^{25}_D$ = −117.6° (EtOH, *c* = 0.635); NMR ($CDCl_3$) δ 1.50 (s, 6H, $(CH_3)_2$), 1.57–1.87 (m, 2H, CH_2CH=CH_2), 2.30–2.54 (m, 5H, CH allyl + CH_2CH_2CO), 2.35 (s, 3H, ArCH_3), 3.98–4.22 (m, 2H, OCH_2), 4.87 (s, 1H, OCHO), 5.15–5.54 (m, 3H, CH=CH + CHpy), 7.20–7.67 (m, 5H, Ar and 4+5-py), 8.53–8.59 (m, 2H, 2+6-py), 11.35 (b, 1H, CO_2H); MS *m/e* 471 $(M + H)^+$. Anal. ($C_{25}H_{30}N_2O_7$) C, H, N.

In a similar way were prepared compounds **7s,x–ag, 8b,d**, and **9c,d**.

4(*Z*)-6-[(2*S*,4*S*,5*R*)-2-[1-Methyl-1-(2-hydroxyphenoxy)-ethyl]-4-(3-pyridyl)-1,3-dioxan-5-yl]hexenoic Acid (7n). To a solution of **7l** (331 mg, 0.825 mmol) in DMPU (6 mL) cooled to 5 °C was added NaH (216 mg, 4.95 mmol, 60% dispersion in oil) followed by ethanethiol (0.3 mL, 4.13 mmol). The resulting mixture was heated to 130 °C for 3 h. The mixture was cooled and partitioned between EtOAc (25 mL) and 1 N NaOH (10 mL). The aqueous layer was adjusted to

pH 5 with HOAc and extracted with EtOAc (3 × 25 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated to a gum that was purified by flash column chromatography, eluting with MeOH–CH_2Cl_2 (5:95) to give **7n** (253 mg, 65%) as a solid; mp 74–80 °C; NMR ($CDCl_3$) δ 1.35 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.66–1.80 (m, 2H, $CH_2CH{=}CH_2$), 2.23–2.51 (m, 5H, CH allyl + CH_2CH_2CO), 4.05–4.32 (m, 2H, OCH_2), 4.82 (s, 1H, OCHO), 5.17–5.51 (m, 3H, $CH{=}CH$ + CHpy), 6.73–7.03 (m, 4H, Ar), 7.32–7.40 (m, 1H, 4-py), 7.65–7.72 (m, 1H, 5-py), 8.52–8.62 (m, 2H, 2+6-py); MS *m/e* 426 $(M - H)^-$. Anal. ($C_{24}H_{29}NO_6$) C, H, N.

General Method for the Preparation of the 2-Methyl-2-(aryloxy)propanals. To a solution of the appropriate phenol (0.031 mol) in DMPU (20 mL) cooled to 5 °C was added NaH (0.034 mol, 55% dispersion in oil). The resulting solution was stirred for 1 h before the addition of a solution of 2-bromo-2-methylpropanal (0.047 mol) in DMPU (5 mL). The mixture was allowed to stir at room temperature for 18 h and then partitioned between EtOAc (200 mL) and H_2O (50 mL), dried ($MgSO_4$), and evaporated to give an oil which was purified by flash column chromatography, eluting with EtOAc–hexane (5:95).

Pharmacology. Test compounds were evaluated in previously reported tests, which are referenced. The *in vitro* antagonist potencies of compounds in the tables were measured[21] at human platelet TXA_2 receptor sites ($n = 2$). Venous blood from volunteers was taken into 3.2% (w/v) trisodium citrate and centrifuged at 200*g* for 10 min. The platelet rich plasma was aggregated with 15(*S*)-hydroxy-11$_\alpha$-9$_\alpha$-(epoxymethano)prosta-5(*Z*),13(*E*)-dienoic acid (U46619) in the presence and absence of different concentrations of putative antagonists to give EC_{50} agonist values from which apparent pA_2 values were derived.

The *in vitro* TXA_2 synthase inhibition was determined[22] with human blood platelet microsomes ($n = 2$). The microsomes were incubated with [1-^{14}C]arachidonic acid in the presence and absence of putative enzyme inhibitors, and the extent of conversion to labeled thromboxane B_2 was determined by a quantitative radiochromatographic method.

The *in vitro* PGI_2 synthase inhibition was determined with cultured human endothelial cells ($n = 2$). Cultured human endothelial cells (first to fourth passage) from umbilical vein were seeded (5 e^4 cells/well) into multiwell plates and allowed to grow (37 °C, O_2/CO_2 (95/5%)) to 70–80% confluence. Growth medium was aspirated from the wells, and the endothelial cell monolayers were washed twice with aliquots of medium (1 mL, Gibco 199) containing vehicle or compound. Monolayers were preincubated with medium containing vehicle or compound (30 min, 37 °C). Arachidonic acid (10 μM) was added to the medium, and the monolayers were incubated, in presence/absence of inhibitor, for a further 120 min with a fresh aliquot of medium. Incubations were terminated by aspiration of the medium into indomethacin (1 mM). Samples were stored (−20 °C), and radioimmunoassay for 6-oxo $PGF_{1\alpha}$ was performed. The effect of compounds on the capacity of endothelial cells to synthesize prostacyclin, as assessed by the measurement of the stable metabolite 6-oxo$PGF_{1\alpha}$, is expressed as percentage inhibition of control.

Antagonist and inhibitory properties of test compounds dosed to rats and dogs were found by *ex vivo* methods. Groups of conscious rats ($n = 6$) were gavaged with test compound and anesthetized, and blood was withdrawn from the abdominal aorta at 1, 3, and 5 h after compound dosing. Platelet rich plasma was prepared from an aliquot of this blood and blood platelet aggregation with U46619 compared before and after dosing to give a dose ratio of U46619. A second aliquot was treated with collagen and the TXB_2 produced determined by radioimmunoassay. The dog test was identical except that the aliquot used in platelet aggregation studies was treated with a predetermined threshold concentration of the platelet aggregation agent adenosine diphosphate (about 0.4–1.2 × 10^{-6} M) in addition to U46619. The > symbols reflect the maximum achievable dose ratio on the day of the experiment using a maximal concentration of U46619 (1 × 10^{-4} M).

Supplementary Material Available: X-ray single-crystal structure analysis of 6-[2-[2-methyl-2-(2-nitro-4-methylphenoxy)ethyl-4-(3-pyridyl)dioxan-5-yl]hex-4-enoic acid (22 pages). Ordering information is given on any current masthead page.

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