Synthesis and Thromboxane A_2 Antagonistic Activity of [[1-Aryl(or Benzyl)-1-(benzenesulfonamido)methyl]phenyl]alkanoic Acid Derivatives

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In order to find new antiasthmatic and antithrombotic agents, various [[1-aryl(or benzyl)-1-(benzenesulfonamido)methyl]phenyl]alkanoic acid derivatives were synthesized. Evaluation of these compounds for thromboxane A_2 (TXA_2) antagonistic activities indicated that 4-[4-[(4-chlorobenzenesulfonamido)phenylmethyl]phenyl]butyric acid (6h), 4-[4-[1-(4-chlorobenzenesulfonamido)-2-phenylethyl]phenyl]butyric acid (6y) and many other compounds have potent inhibitory effects on U-46619-induced guinea-pig platelet aggregation. No significant difference in the inhibitory effect between (+)-6h and its antipode could be detected, although (+)-6y was about 10 times more potent than (−)-6y. The pK_b values of 6h and 6y were estimated to be 8.9 and 10, respectively on U-46619-induced contraction of guinea-pig trachea as a pharmacological measure of TXA_2 antagonistic activity. These compounds also showed potent inhibitory effects on U-46619-induced bronchoconstriction in guinea-pig after oral administration *in vivo*. They were also evaluated for other related pharmacological effects involving the arachidonic acid cascade. It was found that these compounds possess TXA_2 synthase inhibitory activity together with TXA_2 antagonistic activity, and 6h also possesses weak leukotriene D_4 (LTD_4) antagonistic activity. Structure–activity relationships for TXA_2 antagonistic activity of these derivatives are discussed.

Key words thromboxane A_2; thromboxane A_2 antagonistic activity; thromboxane A_2 synthase inhibitory activity; leukotriene D_4 antagonistic activity; antithrombotic agent; structure–activity relationship

Metabolites of arachidonic acid are closely associated with human homeostasis and with the etiology of many physiological disorders.[1] Thromboxane A_2 (TXA_2), a representative metabolite of arachidonic acid, may have an etiological role in various circulatory disorders and asthma because of its strong platelet-aggregating effect and its bronchoconstricting action.[2] Thus, efforts have been made to develop TXA_2 receptor antagonists (TXRAs) as candidate antithrombotic and antiasthmatic agents, and some compounds are under clinical trial for the treatment of thrombosis and asthma.[3]

We are searching for new TXRAs as part of our studies on drugs related to the arachidonic acid cascade. TXRAs reported so far contain both benzenesulfonamido and carboxyl functionalities as a common structural feature, as in sulotroban (**1**),[4] daltroban (**2**),[5] S-1452 (**3**)[3c] and Bay U-3405 (**4**).[3d] To develop a new prototype skeleton for TXRAs, we were interested in the structure of the antiinflammatory agent ketoprofen (**5**),[6] since it has a cyclooxygenase inhibitory effect. Compound **5** possesses a carbonyl group, which is easily convertible into various functionalities, together with a carboxyl group, which can be found in many drugs related to the arachidonic acid cascade. We designed compounds with the general structure **6**, in which the carbonyl group of **5** is replaced by a benzenesulfonamido group, with the aim of generating TXA_2 antagonistic activity. The sulfonamido group of many non-prostanoid TXRAs is mainly at the β-position of the phenylethyl moiety in **1** and **2**. The structure **6** has the sulfonamido group at the α-position of the phenylalkyl skeleton. Therefore, it is of interest to test their structure–activity relationships. This paper deals with

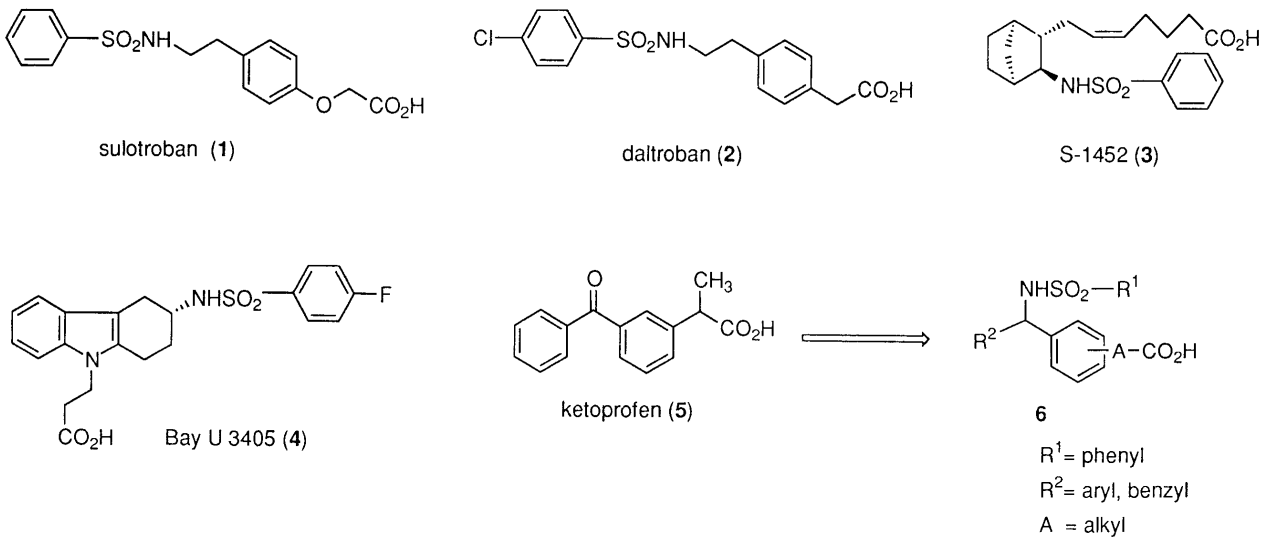

Chart 1

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the synthesis of **6a**—**af** and with their structure–activity relationships for TXA_2 antagonistic activity.

Synthesis

Compounds **6a**—**af** were synthesized as shown in Charts 2 and 3. Reduction of the ketones **7** with sodium borohydride gave the corresponding alcohols **8**. Chlorination of **8** with thionyl chloride afforded **9**, which were subsequently treated with sodium azide to yield the azides **10**. In the case of methyl 4-[4-[(2-furyl)hydroxymethyl]phenyl]butyric acid (**8p**; R^2=2-furyl, A=4-propyl), the chlorination with thionyl chloride was ineffective because of the instability of the product. Thus, **8p** was converted to the mesylate which, without purification, was exposed to sodium azide to produce **10p** (R^2=2-furyl, A=4-propyl). Hydrogenation of **10** gave the key intermediate amines **11a**—**w**, which were condensed with various benzenesulfonyl chlorides, followed by alkaline hydrolysis to afford the desired compounds **6a**—**af** (Chart 2).

The amine **20** was prepared from the bromide **13**.[7] Reaction of the Grignard reagent of **13** with benzaldehyde furnished the ketone **14** in 54% yield as a main product, along with the desired alcohol **15** in 10% yield. The ketone **14** may be produced by oxidation of the alcohol **15** under these reaction conditions. The alcohol **15**, obtained by reduction of **14** with sodium borohydride, was mesylated and then treated with sodium azide to give the azide **16**. After removal of the ketal group in **16**, the Wittig reaction

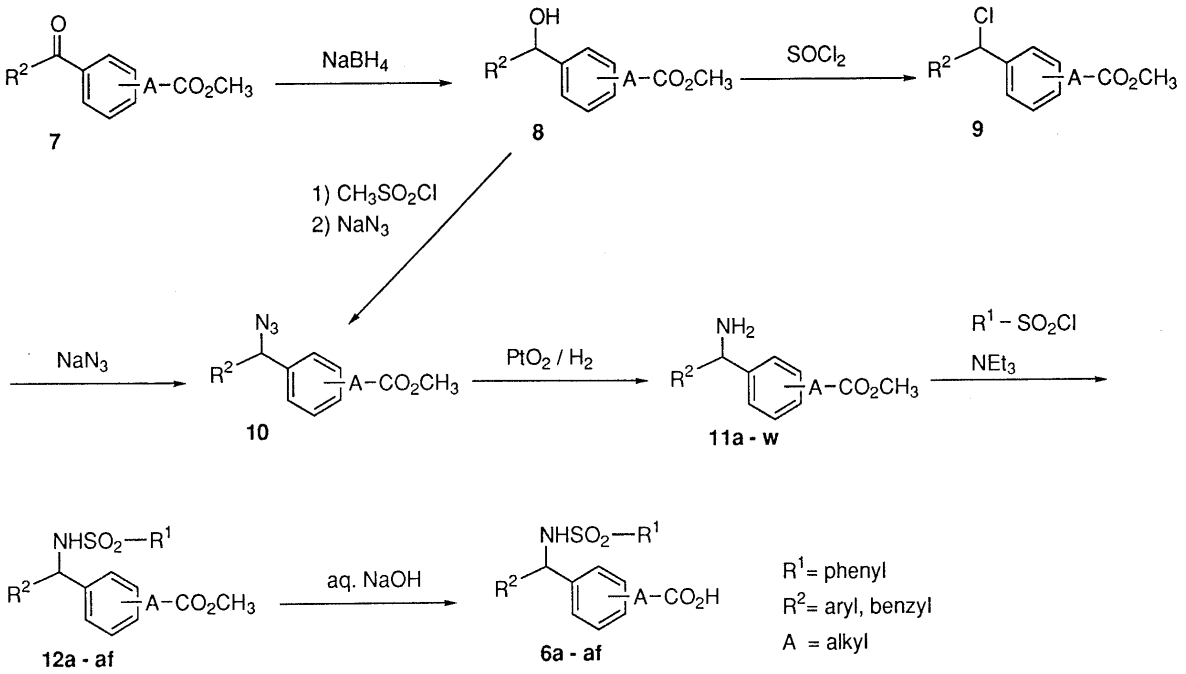


Chart 2

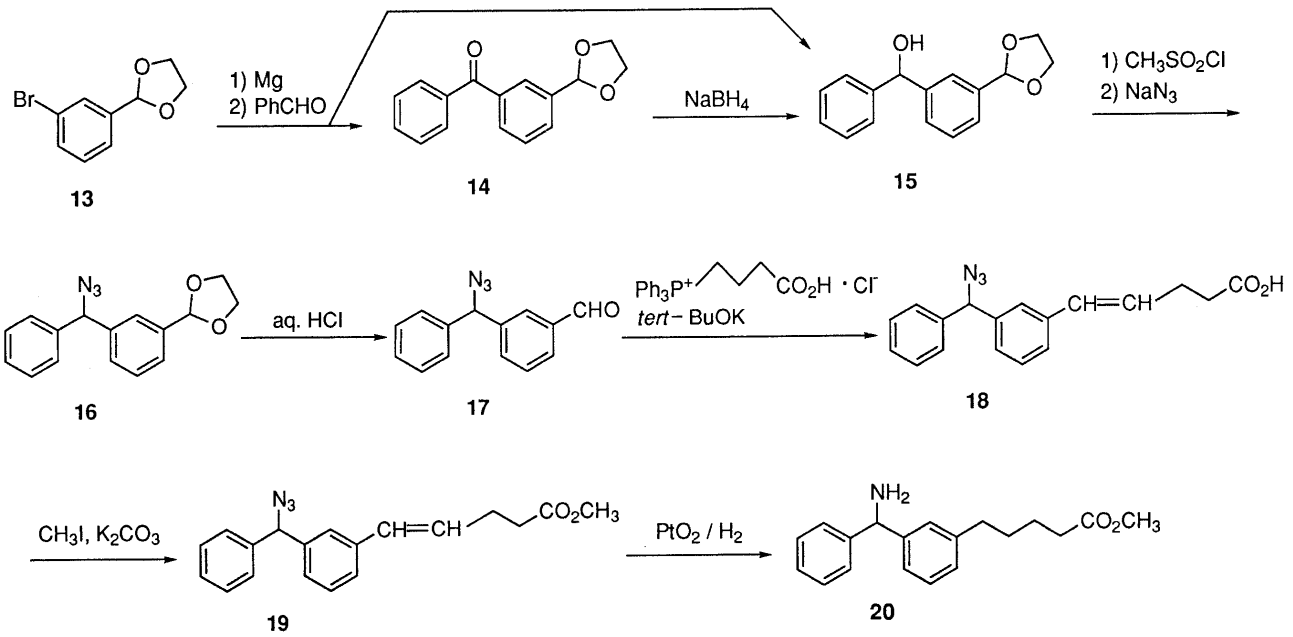


Chart 3

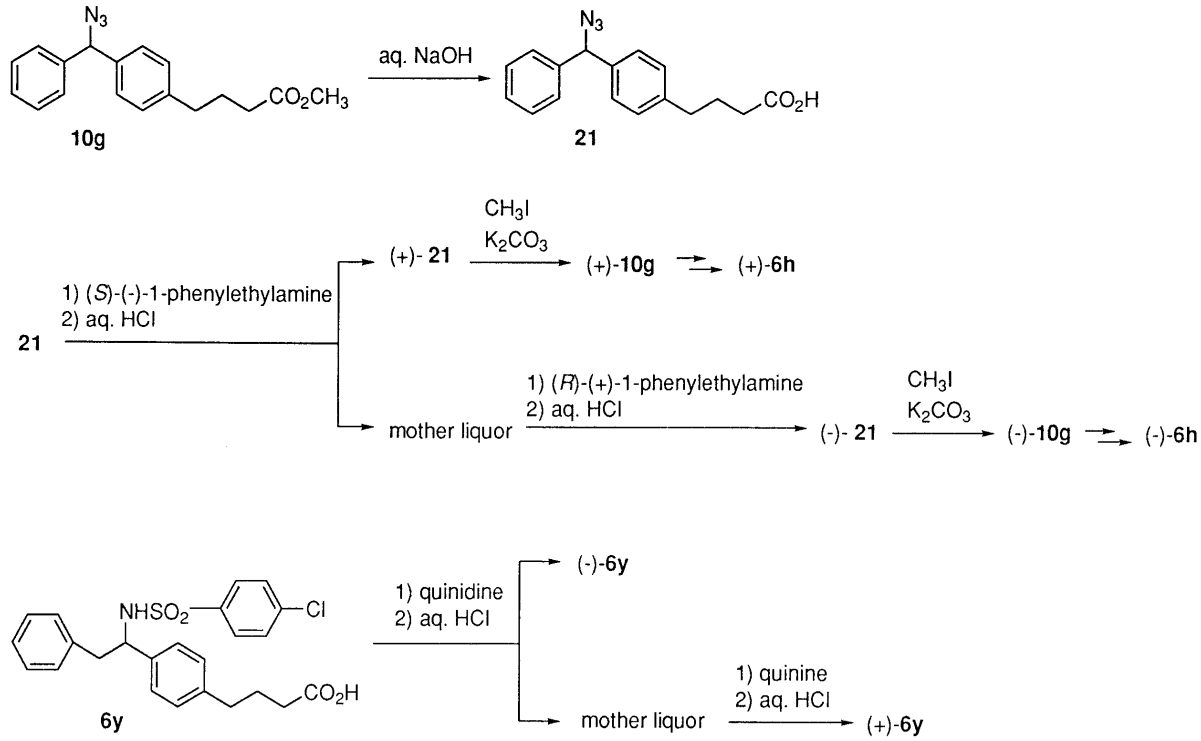
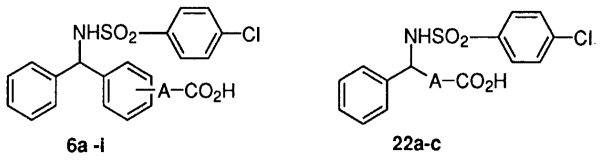


Chart 4

Table 1. Physicochemical and Pharmacological Data for Sulfonamides **6a**—**i** and **22a**—**c**



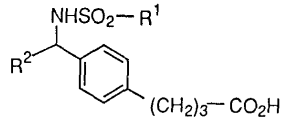
Compound No.	A	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula[b]	Platelet aggreg.[c] IC_{50} (μM)
6a	3-$CH(CH_3)$	97	58—63[d]	$C_{22}H_{20}ClNO_4S$	63
6b	3-CH_2	82	124.5—126 (EA–IE)	$C_{21}H_{18}ClNO_4S$	32
6c	3-$(CH_2)_2$	95	153—155 (aq. M)	$C_{22}H_{20}ClNO_4S$	3.2
6d	3-$(CH_2)_3$	79	137.5—138.5 (aq. M)	$C_{23}H_{22}ClNO_4S$	0.79
6e	3-$(CH_2)_4$	75	118—120 (aq. M)	$C_{24}H_{24}ClNO_4S$	0.40
6f	4-CH_2	83	217—219 (D–WA)	$C_{21}H_{18}ClNO_4S$	>100
6g	4-$(CH_2)_2$	71	157—158.5 (EA–IE)	$C_{22}H_{20}ClNO_4S$	3.2
6h	4-$(CH_2)_3$	80	153—155.5 (EA–IE)	$C_{23}H_{22}ClNO_4S$	0.20
6i	4-$(CH_2)_4$	80	138.5—140 (EA–IE)	$C_{24}H_{24}ClNO_4S$	0.63
22a	$(CH_2)_5$	79	128—130 (EA)	$C_{19}H_{22}ClNO_4S$	20
22b	$(CH_2)_6$	88	101—102 (EA–IE)	$C_{20}H_{24}ClNO_4S$	3.2
22c	$(CH_2)_7$	79	94—95.5 (IE)	$C_{21}H_{26}ClNO_4S$	2.0
2					2.0

a) The symbols are as follows: EA, ethyl acetate; D, *N*, *N*-dimethylformamide; IE, isopropyl ether; M, methanol; WA, water. *b*) All elemental analyses for C, H and N were within ±0.3% of the calculated values. *c*) Concentration needed to inhibit U-46619 (2 μg/ml)-induced platelet aggregation in guinea-pig platelet-rich plasma (PRP) by 50%. *d*) Amorphous.

of the resulting aldehyde **17** with (3-carboxypropyl)triphenylphosphonium chloride in the presence of potassium *tert*-butoxide provided the carboxylic acid **18**. The amine **20** was then obtained by esterification and subsequent hydrogenation under the standard conditions (Chart 3).

Optically active **6h** and **6y** were obtained as shown in Chart 4. Optical resolution of racemic **21**, derived from **10g** (R^2 = phenyl, A = 4-propyl) by alkaline hydrolysis, was achieved by fractional crystallization with the aid of each optically active 1-phenylethylamine. After separate esterification of (+)- and (−)-**21**, the resulting (+)- and (−)-**10g** were converted to (+)- and (−)-**6h**, respectively, in a similar manner to that shown in Chart 2. On the other hand, optically active **6y** was easily obtained by fractional recrystallization of the quinidine or quinine salts of racemic **6y**. The optical purity of each enantiomer ((+)- and (−)-**6h**, (+)- and (−)-**6y**) was determined to be over 98% ee by HPLC analysis.

Table 2. Physicochemical and Pharmacological Data for Sulfonamides **6j**—**af**, optically active **6h** and **6y**



6j—**af**

Compound No.	$R^{1a)}$	$R^{2a)}$	Yield (%)	mp (°C) (Recryst. solv.)[b]	Formula[c]	Platelet aggreg.[d] IC_{50} (μM)
6j	Ph	Ph	77	131.5—132.5 (EA–IE)	$C_{23}H_{23}NO_4S$	0.79
6k	4-F-Ph	Ph	80	122—123 (EA–IE)	$C_{23}H_{22}FNO_4S$	2.0
6l	4-Br-Ph	Ph	97	137—139.5 (EA–IE)	$C_{23}H_{22}BrNO_4S$	0.40
6m	4-CH_3-Ph	Ph	84	130.5—131.5 (EA–IE)	$C_{24}H_{25}NO_4S$	0.32
6n	4-CH_3O-Ph	Ph	83	118—118.5 (EA–IE)	$C_{24}H_{25}NO_5S$	2.0
6o	Bn	Ph	88	Oil	—	32
6p	CH_3	Ph	58	127—128 (aq. E)	$C_{18}H_{21}NO_4S$	3.2
6q	4-Cl-Ph	2-F-Ph	82	128—129 (EA–IE)	$C_{23}H_{21}ClFNO_4S$	2.5
6r	4-Cl-Ph	3-F-Ph	93	129—130 (EA–IE)	$C_{23}H_{21}ClFNO_4S$	0.25
6s	4-Cl-Ph	4-F-Ph	95	169.5—170.5 (EA–IE)	$C_{23}H_{21}ClFNO_4S$	6.3
6t	4-Cl-Ph	4-Cl-Ph	94	152—153 (EA–IE)	$C_{23}H_{21}Cl_2NO_4S$	4.0
6u	4-Cl-Ph	4-CH_3-Ph	89	132.5—133.5 (EA–IE)	$C_{24}H_{24}ClNO_4S$	13
6v	4-Cl-Ph	4-CF_3-Ph	94	157—159 (EA–IE)	$C_{24}H_{21}ClF_3NO_4S$	25
6w	4-Cl-Ph	2-Thi	77	128—129.5 (EA–IE)	$C_{21}H_{20}ClNO_4S_2$	0.16
6x	4-Cl-Ph	2-Fur	84	141.5—142.5 (EA–IE)	$C_{21}H_{20}ClNO_5S$	0.25
6y	4-Cl-Ph	Bn	96	152—153 (EA–IE)	$C_{24}H_{24}ClNO_4S$	0.050
6z	4-Cl-Ph	2-F-Bn	98	149.5—150.5 (aq. M)	$C_{24}H_{23}ClFNO_4S$	0.32
6aa	4-Cl-Ph	3-F-Bn	97	157—159 (aq. M)	$C_{24}H_{23}ClFNO_4S$	0.063
6ab	4-Cl-Ph	4-F-Bn	90	166—167.5 (aq. M)	$C_{24}H_{23}ClFNO_4S$	0.16
6ac	4-Cl-Ph	4-Cl-Bn	99	169.5—171 (M)	$C_{24}H_{23}Cl_2NO_4S$	0.63
6ad	4-Cl-Ph	4-CH_3-BN	98	148—148.5 (EA–IE)	$C_{25}H_{26}ClNO_4S$	0.32
6ae	4-Cl-Ph	CH_3	87	98—98.5 (EA–IE)	$C_{18}H_{20}ClNO_4S$	1.3
6af	4-Cl-Ph	H	82	169—171 (aq. M)	$C_{17}H_{18}ClNO_4S$	3.2
(+)-**6h**	4-Cl-Ph	Ph	—	135—137.5 (aq. M)	$C_{23}H_{22}ClNO_4S$	0.32
(−)-**6h**	4-Cl-Ph	Ph	—	135.5—137.5 (aq. M)	$C_{23}H_{22}ClNO_4S$	0.25
(+)-**6y**	4-Cl-Ph	Bn	—	173—174 (aq. E)	$C_{24}H_{24}ClNO_4S$	0.032
(−)-**6y**	4-Cl-Ph	Bn	—	173.5—174 (aq. E)	$C_{24}H_{24}ClNO_4S$	0.20
2						2.0

a) The symbols are as follows: Ph, phenyl; Bn, benzyl; Thi, thienyl; Fur, furyl. *b*) See footnote *a* in Table 1. E, ethanol. *c*) See footnote *b* in Table 1. *d*) See footnote *c* in Table 1.

Physicochemical data of the desired compounds **6a**—**af** are listed in Tables 1, 2 and 4, and those of the intermediates **11a**—**w** and **12a**—**af** are listed in Tables 5—7 in the experimental section.

Pharmacological Results and Discussion

TXA_2 antagonistic activity of the synthetic compounds was evaluated in terms of the inhibitory effects on U-46619[8]-induced guinea-pig platelet aggregation and the results are shown in Tables 1 and 2.

Firstly, we investigated the effects of alkyl chain length and the position of the side chain attached to the carboxyl group of phenylalkanoic acids. Compound **6a**, which has the same side chain as **5**, was less potent. But the length of the alkyl chain greatly affected the activity. The activity was enhanced as the alkyl chain become longer in both *meta*- and *para*-substituted derivatives. Compound **6e**, which has a butyl chain, among *meta*-substituted derivatives and compound **6h**, which has a propyl chain, among *para*-substituted derivatives were the most potent. In particular, **6h** showed about 10 times stronger activity than the reference compound **2**. The chain length of **6h** from the sulfonamido group to the carboxyl group is similar to the optimal chain length for the activity in previously reported compounds,[9] *i.e.*, seven or eight carbons. Simple alkanoic acids (**22a**—**c**) without a phenyl group in the molecule were synthesized for comparison. Again, the activity was enhanced as the alkyl chain become longer but these compounds were about 10 times less potent than phenylalkanoic acids with the corresponding chain length. This suggests that the benzene ring of the phenylalkanoic acid moiety is important to enhance the activity.

Next, we examined the effect of substituents (R^1) in the sulfonamido moiety. Among the *para*-substituted phenyl compounds (**6k**—**n**), the *p*-chlorophenyl compound (**6h**) showed the strongest activity, and the *p*-bromophenyl compound (**6l**) and *p*-tolyl compound (**6m**) were more active than the others except **6h**. This tendency is similar to that of TXRAs possessing a benzenesulfonamido group.[10] The benzyl compound (**6o**), for comparison, showed weak activity, and the methyl compound (**6p**) was less potent than the substituted phenyl compounds but as potent as **2**.

Finally, we investigated the influence of the substituent (R^2) at the benzyl position. Substituted phenyl groups, heteroaromatic rings, and substituted benzyl groups were selected for this purpose. Among the phenyl compounds

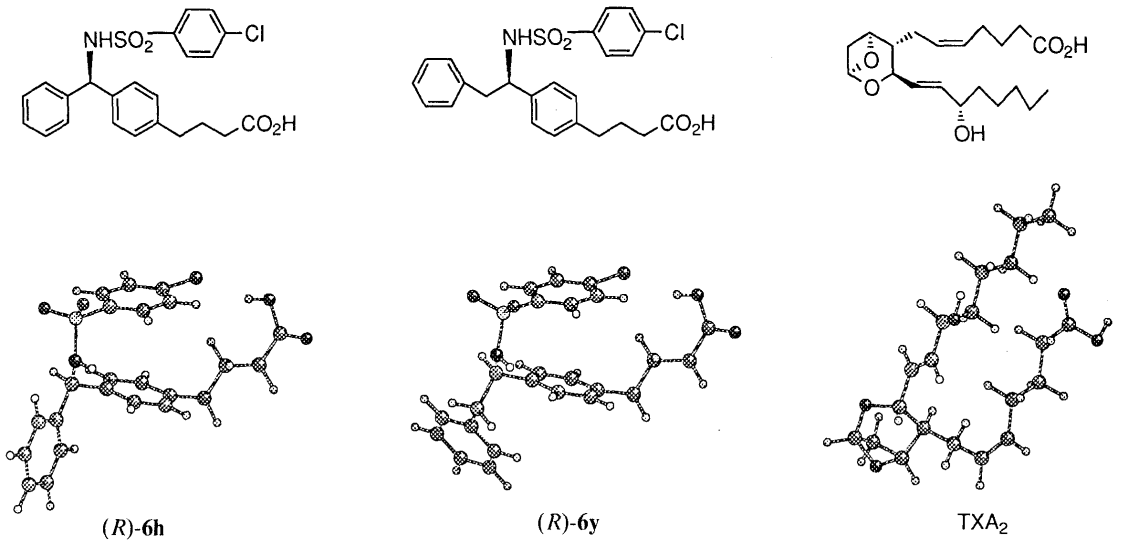


Fig. 1. The Stable Conformations for (*R*)-**6h**, (*R*)-**6y** and TXA_2

All calculations for these compounds were performed on a Fujitsu FMV-499D2 personal computer using Nemesis (version 2.0, Oxford Molecular Ltd.). Initial conformations for (*R*)-**6h** and (*R*)-**6y** were selected with a conformational search around single bonds rotated 360° in 30° increments. The stable conformations were determined by energy minimization for initial conformations. For TXA_2, the stable conformation was determined in a similar manner using torsion angles described in the literature.[11a)]

(**6h**, **6q**—**v**), the non-substituted phenyl compound (**6h**) was the most potent and the introduction of substituents on the benzene ring decreased the activity. Introduction of a *m*-fluoro group (**6r**) decreased the activity moderately while a *p*-methyl group (**6u**) and *p*-trifluoromethyl group (**6v**) were more than 50 times less potent. 2-Thienyl and 2-furyl compounds (**6w**, **6x**) as heteroaromatic derivatives showed similar activities to **6h**. Generally the benzyl compounds (**6y**—**ad**) were several times more potent than the corresponding phenyl compounds (**6h**, **6q**—**u**). The non-substituted benzyl compound (**6y**) showed the most potent activity among all of the synthesized compounds (its IC_{50} value was 0.05 μM), being about 40 times more potent than **2**. Introduction of substituents on the benzyl group decreased the activity, as was the case with the phenyl group. Introduction of small substituents such as a methyl group (**6ae**) or hydrogen atom (**6af**) as R^2, for comparison, afforded weaker activities than a phenyl group, heteroaromatic rings, and a benzyl group as R^2. These results indicated that R^2 significantly influences the activities.

In the cases of **6h** and **6y**, which have strong activities, we examined the TXA_2 antagonistic activities of their optical isomers. The activity of (+)-**6h** was similar to that of (−)-**6h**, while (+)-**6y** showed 10 times stronger activity than (−)-**6y**.

Ezumi *et al.*[11a)] and Cozzi *et al.*[11b)] reported the superimposition of the stable conformations of **1**, **2**, and TXA_2. They showed that each of the stable conformations of **1** and **2** was either a "hairpin form" in which the two benzene rings in the molecule were arranged nearly in parallel, or a "hairpin like form" in which the distance between the two benzene rings was longer than in the "hairpin form." We estimated the most stable conformations of **6h** and **6y** by molecular mechanics calculation using computer molecular modeling and compared them with the stable conformation of TXA_2 (in Fig. 1, the conformations of (*R*)-**6h** and (*R*)-**6y** of the enantiomeric

Table 3. Pharmacological Data for Compounds **6h** and **6y**

Compd. No.	TXA_2 antagonism		TXA_2 synthase inhibition[c)]	LTD_4 antagonism[d)]
	pK_b[a)]	Inhibition (%)[b)]	IC_{50} (μM)	Inhibition (%)
6h	8.9	32	2.0	44
6y	10	86[e)]	4.0	10
2	7.6	18	40	−1.4[f)]

a) The pK_b values show the inhibitory effects on U-46619-induced contraction of guinea-pig trachea. *b*) Inhibition of U-46619-induced bronchoconstriction in guinea-pig (0.3 mg/kg, *p.o.*). *c*) Concentration needed to inhibit by 50% TXB_2 production in human platelets. *d*) Inhibition of LTD_4-induced contraction of guinea-pig ileum (concentration: 3×10^{-7} M). *e*) Dose: 0.03 mg/kg, *p.o.* *f*) Concentration: 3×10^{-6} M.

6h and **6y** are indicated as a matter of convenience). Each stable conformation of **6h** and **6y** was in a "hairpin form." An oxygen atom in the sulfonamido group approximately matched the C15-hydroxyl group of the ω-chain of TXA_2 when the carboxylic acids of **6h** and **6y** were superimposed on that of TXA_2. This result is consistent with that reported for **1** or **2**.[11)] In addition, the phenyl group of **6h** and the benzyl group of **6y** were located close to the oxane moiety of TXA_2, and the benzyl group of (*R*)-**6y** fitted particularly well. We considered that the potent activity of **6y** would be related to this orientation. Further, within the stable conformation of (*R*)-**6h**, the three benzene rings and a carboxyl group are located nearly on a plane, and a similar result was obtained for (*S*)-**6h**, so the stable conformation of (*S*)-**6h** is approximately superimposable on that of TXA_2, similarly to the case of (*R*)-**6h**. This may be the reason why there is no significant difference between (+)- and (−)-**6h** in TXA_2 antagonistic activity.

Further pharmacological evaluations of **6h** and **6y** were carried out to explore their potential as antithrombotic or antiasthmatic agents (Table 3).

As a measure of TXA_2 antagonistic activity in the

Table 4. Spectral Data for Sulfonamides **6a**—**af** and **22a**—**c**

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
6a	3280, 1712	1.41—1.46 (3H, m), 3.60—3.70 (1H, m), 5.41—5.47 (1H, m), 5.58—5.64 (1H, m), 6.92—7.26 (11H, m), 7.52 (2H, d, J=8.5 Hz)
6b	3268, 1714, 1704	3.54 (2H, s), 5.51 (1H, d, J=7.5 Hz), 5.60 (1H, d, J=7.5 Hz), 6.95—7.23 (9H, m), 7.23 (2H, d, J=8.5 Hz), 7.52 (2H, d, J=8.5 Hz)
6c	3256, 1710	2.60 (2H, t, J=7.5 Hz), 2.84 (2H, t, J=7.5 Hz), 5.46 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.90—6.98 (2H, m), 7.03—7.28 (7H, m), 7.25 (2H, d, J=8.5 Hz), 7.54 (2H, d, J=8.5 Hz)
6d	3308, 1710	1.86 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 5.43 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.89—6.94 (2H, m), 7.00—7.24 (7H, m), 7.26 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=8.5 Hz)
6e	3328, 1704	1.57—1.62 (4H, m), 2.37 (2H, t, J=7 Hz), 2.54 (2H, t, J=7 Hz), 5.37 (1H, d, J=7.5 Hz), 5.60 (1H, d, J=7.5 Hz), 6.84—7.27 (9H, m), 7.26 (2H, d, J=8.5 Hz), 7.54 (2H, d, J=8.5 Hz)
6f	3316, 1708	3.48 (2H, s), 5.54 (1H, d, J=9 Hz), 7.11 (5H, s), 7.18 (4H, s), 7.39 (2H, d, J=9 Hz), 7.58 (2H, d, J=9 Hz), 8.75 (1H, d, J=9 Hz)[a]
6g	3256, 1712	2.63 (2H, t, J=7.5 Hz), 2.89 (2H, t, J=7.5 Hz), 5.49 (1H, d, J=7.5 Hz), 5.58 (1H, d, J=7.5 Hz), 6.95—7.40 (9H, m), 7.25 (2H, d, J=9 Hz), 7.54 (2H, d, J=9 Hz)
6h	3284, 1706	1.91 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 5.40 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.82—7.40 (11H, m), 7.54 (2H, d, J=8.5 Hz)
6i	3328, 1706	1.55—1.73 (4H, m), 2.38 (2H, t, J=7 Hz), 2.56 (2H, t, J=7 Hz), 5.35 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.98 (2H, d, J=8.5 Hz), 7.01 (2H, d, J=8.5 Hz), 7.09—7.13 (2H, m), 7.19—7.23 (3H, m), 7.24 (2H, d, J=9 Hz), 7.54 (2H, d, J=9 Hz)
6j	3320, 1712	1.90 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 5.22 (1H, d, J=7.5 Hz), 5.58 (1H, d, J=7.5 Hz), 7.06—7.49 (12H, m), 7.67 (2H, dd, J=8, 1 Hz)
6k	3280, 1710	1.90 (2H, qn, J=7.5 Hz), 2.34 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 5.32 (1H, d, J=7 Hz), 5.59 (1H, d, J=7 Hz), 6.97 (2H, t, J=8.5 Hz), 7.01 (2H, d, J=6 Hz), 7.03 (2H, d, J=6 Hz), 7.08—7.12 (2H, m), 7.18—7.24 (3H, m), 7.63 (2H, dd, J=8.5, 5 Hz)
6l	3328, 1706	1.92 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 5.31 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 7.00 (2H, d, J=8.5 Hz), 7.03 (2H, d, J=8.5 Hz), 7.07—7.14 (2H, m), 7.19—7.25 (3H, m), 7.42 (2H, d, J=9 Hz), 7.47 (2H, d, J=9 Hz)
6m	3328, 1704	1.91 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.37 (3H, s), 2.60 (2H, t, J=7.5 Hz), 5.09 (1H, d, J=7 Hz), 5.54 (1H, d, J=7 Hz), 7.02 (4H, s), 7.07—7.12 (2H, m), 7.14 (2H, d, J=8 Hz), 7.16—7.24 (3H, m), 7.55 (2H, d, J=8 Hz)
6n	3324, 1704	1.90 (2H, qn, J=7.5 Hz), 2.34 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 3.82 (3H, s), 5.19 (1H, d, J=7 Hz), 5.53 (1H, d, J=7 Hz), 6.79 (2H, d, J=9 Hz), 7.02 (4H, s), 7.08—7.13 (2H, m), 7.16—7.24 (3H, m), 7.59 (2H, d, J=9 Hz)
6o	3284, 1708[b]	1.93 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.65 (2H, t, J=7.5 Hz), 4.03 (2H, s), 5.12 (1H, d, J=8 Hz), 5.69 (1H, d, J=8 Hz), 7.03 (2H, d, J=8 Hz), 7.15 (2H, d, J=8 Hz), 7.18 (2H, d, J=8 Hz), 7.18—7.37 (8H, m)
6p	3296, 1716	1.93 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.65 (2H, t, J=7.5 Hz), 2.66 (3H, s), 5.32 (1H, d, J=7.5 Hz), 5.73 (1H, d, J=7.5 Hz), 7.16 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=8.5 Hz), 7.27—7.38 (5H, m)
6q	3276, 1708	1.91 (2H, qn, J=7.5 Hz), 2.34 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 5.48 (1H, d, J=8 Hz), 5.77 (1H, d, J=8 Hz), 6.88 (1H, dd, J=11.5, 8 Hz), 6.98—7.24 (3H, m), 7.06 (4H, s), 7.26 (2H, d, J=9 Hz), 7.58 (2H, d, J=9 Hz)
6r	3296, 1706	1.91 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 5.33 (1H, d, J=7.5 Hz), 5.57 (1H, d, J=7.5 Hz), 6.83 (1H, d, J=10 Hz), 6.88—6.95 (2H, m), 6.97 (2H, d, J=8 Hz), 7.02 (2H, d, J=8 Hz), 7.20 (1H, td, J=8, 7 Hz), 7.29 (2H, d, J=9 Hz), 7.57 (2H, d, J=9 Hz)
6s	3276, 1702	1.25 (1H, s), 1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 5.55 (1H, s), 6.92 (2H, t, J=8.5 Hz), 6.96 (2H, d, J=8 Hz), 7.03 (2H, d, J=8 Hz), 7.11 (2H, dd, J=8.5, 5.5 Hz), 7.29 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=8.5 Hz)[c]
6t	3264, 1706	1.91 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 5.31 (1H, d, J=7.5 Hz), 5.55 (1H, d, J=7.5 Hz), 6.95 (2H, d, J=8 Hz), 7.03 (2H, d, J=8 Hz), 7.07 (2H, d, J=8.5 Hz), 7.20 (2H, d, J=8.5 Hz), 7.30 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz)
6u	3320, 1706	1.91 (2H, qn, J=7.5 Hz), 2.29 (3H, s), 2.35 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 5.16—5.30 (1H, m), 5.55 (1H, d, J=7.5 Hz), 6.97 (2H, d, J=8 Hz), 7.02 (4H, s), 7.02 (2H, d, J=8 Hz), 7.26 (2H, d, J=8.5 Hz), 7.54 (2H, d, J=8.5 Hz)
6v	3260, 1716	1.91 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.5 Hz), 5.34 (1H, d, J=7 Hz), 5.62 (1H, d, J=7 Hz), 6.96 (2H, d, J=8 Hz), 7.06 (2H, d, J=8 Hz), 7.28 (2H, d, J=8.5 Hz), 7.29 (2H, d, J=9 Hz), 7.49 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=9 Hz)
6w	3260, 1712	1.86 (2H, qn, J=7.5 Hz), 2.28 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 5.75 (1H, s), 6.63 (1H, d, J=3.5 Hz), 6.83 (1H, dd, J=5, 3.5 Hz), 7.01 (2H, d, J=8 Hz), 7.06 (2H, d, J=8 Hz), 7.25 (1H, dd, J=5, 1 Hz), 7.29 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz)[d]
6x	3268, 1704	1.86 (2H, qn, J=7.5 Hz), 2.27 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 5.57 (1H, s), 5.97 (1H, d, J=3.5 Hz), 6.21 (1H, dd, J=3.5, 2 Hz), 7.03 (2H, d, J=8.5 Hz), 7.08 (2H, d, J=8.5 Hz), 7.31 (1H, d, J=2 Hz), 7.33 (2H, d, J=8.5 Hz), 7.60 (2H, d, J=8.5 Hz)[d]
6y	3336, 1708	1.93 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 2.93 (1H, dd, J=14, 7 Hz), 3.02 (1H, dd, J=14, 7 Hz), 4.52 (1H, q, J=7 Hz), 5.01 (1H, d, J=7 Hz), 6.95—7.00 (6H, m), 7.16—7.24 (5H, m), 7.40 (2H, d, J=8.5 Hz)
6z	3328, 1706	1.93 (2H,qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.5 Hz), 2.97 (1H, dd, J=14.5, 6 Hz), 3.01 (1H, dd, J=14.5, 8.5 Hz), 4.55 (1H, m), 5.15 (1H, d, J=6.5 Hz), 6.88—7.00 (3H, m), 7.01 (2H, d, J=8.5 Hz), 7.04 (2H, d, J=8.5 Hz), 7.15—7.22 (1H, m), 7.19 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz)

Table 4. (continued)

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
6aa	3300, 1714	1.92 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 2.97 (1H, dd, J=13.5, 7 Hz), 3.01 (1H, dd, J=13.5, 7 Hz), 4.52 (1H, q, J=7 Hz), 5.09 (1H, d, J=7 Hz), 6.62 (1H, br d, J=8 Hz), 6.76 (1H, br d, J=8 Hz), 6.88 (1H, td, J=8, 2.5 Hz), 6.94 (2H, d, J=8 Hz), 7.00 (2H, d, J=8 Hz), 7.15 (1H, td, J=8, 6 Hz), 7.22 (2H, d, J=8.5 Hz), 7.44 (2H, d, J=8.5 Hz)
6ab	3304, 1714	1.92 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 2.96 (1H, dd, J=14, 7 Hz), 2.99 (1H, dd, J=14, 7 Hz), 4.50 (1H, q, J=7 Hz), 4.89 (1H, br s), 6.85—6.93 (6H, m), 6.99 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz), 7.44 (2H, d, J=8.5 Hz)
6ac	3296, 1710	1.92 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 2.94 (1H, dd, J=14, 7 Hz), 2.99 (1H, dd, J=14, 7 Hz), 4.49 (1H, q, J=7 Hz), 4.97 (1H, d, J=7 Hz), 6.87 (2H, d, J=8.5 Hz), 6.92 (2H, d, J=8 Hz), 6.99 (2H, d, J=8 Hz), 7.14 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz)
6ad	3324, 1714	1.93 (2H, qn, J=7.5 Hz), 2.31 (3H, s), 2.37 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.5 Hz), 2.84 (1H, dd, J=14, 8.5 Hz), 2.98 (1H, dd, J=14, 6 Hz), 4.47 (1H, td, J=8.5, 6 Hz), 4.92 (1H, d, J=6 Hz), 6.83 (2H, d, J=8 Hz), 6.98 (2H, d, J=8 Hz), 7.00 (4H, s), 7.19 (2H, d, J=8.5 Hz), 7.39 (2H, d, J=8.5 Hz)
6ae	3276, 1706	1.36 (3H, d, J=7 Hz), 1.84 (2H, qn, J=7.5 Hz), 2.26 (2H, t, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 4.42 (1H, q, J=7 Hz), 6.94 (2H, d, J=8 Hz), 6.97 (2H, d, J=8 Hz), 7.30 (2H, d, J=9 Hz), 7.53 (2H, d, J=9 Hz)[d]
6af	3264, 1696	1.77 (2H, qn, J=7.5 Hz), 2.19 (2H, t, J=7.5 Hz), 2.54 (2H, t, J=7.5 Hz), 3.98 (2H, d, J=6 Hz), 7.07 (2H, d, J=8 Hz), 7.11 (2H, d, J=8 Hz), 7.59 (2H, d, J=8.5 Hz), 7.75 (2H, d, J=8.5 Hz), 8.11 (1H, t, J=6 Hz)[a]
22a	3268, 1706	1.11—1.37 (4H,m), 1.49—1.60 (2H, m), 1.62—1.83 (2H, m), 2.30 (2H, t, J=7.5 Hz), 4.29 (1H, q, J=7.5 Hz), 5.26 (1H, d, J=7.5 Hz), 6.96 (2H, dd, J=7.5, 1.5 Hz), 7.08—7.18 (3H, m), 7.23 (2H, d, J=9 Hz), 7.49 (2H, d, J=9 Hz)
22b	3264, 1708	1.08—1.33 (6H, m), 1.50—1.62 (2H, m), 1.62—1.82 (2H, m), 2.32 (2H, t, J=7.5 Hz), 4.28 (1H, q, J=7.5 Hz), 5.21 (1H, d, J=7.5 Hz), 6.97 (2H, dd, J=7.5, 2 Hz), 7.10—7.17 (3H, m), 7.23 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)
22c	3296, 1710	1.00—1.40 (8H, m), 1.48—1.85 (4H, m), 2.33 (2H, t, J=7.5 Hz), 4.29 (1H, q, J=7.5 Hz), 5.26 (1H, d, J=7.5 Hz), 6.87—7.03 (2H, m), 7.03—7.19 (3H, m), 7.22 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz)

a) DMSO-d_6. *b*) Liquid. *c*) $CDCl_3$–CD_3OD. *d*) CD_3OD.

trachea, we examined the inhibitory effect on U-46619-induced contraction of guinea-pig trachea *in vitro*, and the inhibitory effect on U-46619-induced bronchoconstriction in guinea-pig after oral administration *in vivo*. Compounds **6h** and **6y** were very potent *in vitro* and *in vivo*. In particular, **6y** exhibited 100 times higher activity than the reference compound **2**. We further examined the TXA_2 synthase inhibitory effect and the leukotriene D_4 (LTD_4) antagonistic effect. The TXA_2 synthase inhibitory effect was evaluated with human platelet membrane fraction. It was found that both **6h** and **6y** exhibited this activity. LTD_4 antagonistic effect was evaluated in terms of the inhibitory effect on LTD_4-induced contraction of guinea-pig ileum. It became apparent that **6h** also possessed weak LTD_4 antagonistic activity. It is thought favorable for an antithrombotic agent or antiasthmatic agent, that the compound should possess TXA_2 synthase inhibitory activity and/or LTD_4 antagonistic activity, together with TXA_2 antagonistic activity.[12]

In conclusion, we have disclosed that **6y** possesses very strong TXA_2 antagonistic activity and TXA_2 synthase inhibitory activity, and that **6h** possesses LTD_4 antagonistic activity, together with TXA_2 antagonistic activity and TXA_2 synthase inhibitory activity. Further pharmacological evaluations of **6h** and **6y** are planned to cast light on the potential of these compounds as antithrombotic agents and/or antiasthmatic agents.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus without correction. IR spectra were recorded using a Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra were measured with JEOL EX-270 (270 MHz) and JEOL A-500 (500 MHz) spectrometers using tetramethylsilane as an internal standard. MS were measured on a JEOL DX-300 mass spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. Merck Kieselgel 60 (70—230 mesh) was used for column chromatography. All extracts were dried over Na_2SO_4 and concentrated under reduced pressure.

Methyl 4-(4-Benzoylphenyl)butyrate (7g, R^2=Ph, A=4-Propyl) Anhydrous aluminum chloride (44.9 g, 0.337 mol) was added portionwise to a solution of methyl 4-phenylbutyrate (30.0 g, 0.168 mol) and benzoyl chloride (23.7 g, 0.169 mol) in CS_2 (200 ml) under ice-cooling, and the mixture was refluxed for 4 h. After cooling, the reaction mixture was poured into ice water and extracted with CH_2Cl_2. The extract was washed successively with water and aqueous K_2CO_3, dried and concentrated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2–hexane (2:1)→CH_2Cl_2] to afford the title compound (24.0 g, 51%) as a pale yellow oil. IR (liq.): 1738, 1658 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (2H, qn, J=7.5 Hz), 2.36 (2H, t, J=7.5 Hz), 2.74 (2H, t, J=7.5 Hz), 3.67 (3H, s), 7.29 (2H, d, J=8.5 Hz), 7.37—7.67 (3H, m), 7.70—7.87 (2H, m), 7.78 (2H, d, J=8.5 Hz). High-resolution MS m/z: Calcd for $C_{18}H_{18}O_3$: 282.1255. Found: 282.1249.

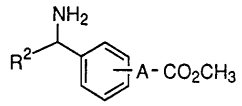
Other ketones **7** were prepared similarly from the corresponding acid chlorides and methyl phenylalkanoates. ω-(3-Benzoylphenyl)alkanoates (**7**, R^2=Ph, A=3-alkyl) were prepared according to the literature.[13]

Methyl 4-[4-(Hydroxyphenylmethyl)phenyl]butyrate (8g, R^2=Ph, A=4-Propyl) $NaBH_4$ (1.88 g, 49.7 mmol) was added portionwise to a suspension of methyl 4-(4-benzoylphenyl)butyrate (**7g**, R^2=Ph, A=4-propyl; 14.0 g, 49.6 mmol) in MeOH (150 ml) under ice-cooling, and the mixture was stirred at room temperature for 30 min. MeOH was evaporated off under reduced pressure, and the residue was diluted with water and extracted with Et_2O. The extract was washed successively with dilute HCl and water, dried and concentrated to yield the title compound (12.7 g, 90%) as a colorless oil. IR (liq.): 3464 (OH), 1738 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.92 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 3.63 (3H, s), 5.79 (1H, s), 7.06—7.43 (7H, m), 7.13 (2H, d, J=8 Hz). High-resolution MS m/z: Calcd for $C_{18}H_{20}O_3$: 284.1412. Found: 284.1431.

Other alcohols **8** were prepared similarly from the corresponding ketones **7** in 63—100% yields.

Methyl 4-[4-(Chlorophenylmethyl)phenyl]butyrate (9g, R^2=Ph, A=4-Propyl) Thionyl chloride (4.04 ml, 55.4 mmol) was added dropwise to a solution of **8g** (R^2=Ph, A=4-propyl; 12.4 g, 43.6 mmol) in benzene (40 ml) under ice-cooling, and the mixture was refluxed for 1 h. The solvent was evaporated off under reduced pressure, and the residue was taken up in Et_2O. This solution was washed with water. The Et_2O layer

Table 5. Spectral Data for Amines **11a—w**



11a – w

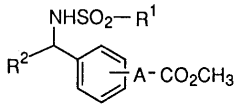
Compd. No.	$R^{2a)}$	A	Yield[b] (%)	IR (liq.) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
11a	Ph	3-CH(CH_3)	84	3384, 3320, 1736	1.45—1.50 (3H, m), 1.50—1.90 (2H, br s), 3.62—3.65 (3H, m), 3.71 (1H, q, J=7 Hz), 5.20 (1H, s), 7.14—7.39 (9H, m)
11b	Ph	3-CH_2	82	3380, 3312, 1738	1.50—1.90 (2H, br s), 3.60 (2H, s), 3.68 (3H, s), 5.20 (1H, s), 7.12—7.39 (9H, m)
11c	Ph	3-$(CH_2)_2$	90	3380, 1738	1.73 (2H, br s), 2.60 (2H, t, J=8 Hz), 2.92 (2H, t, J=8 Hz), 3.64 (3H, s), 5.18 (1H, s), 7.04—7.08 (1H, s), 7.19—7.38 (8H, m)
11d	Ph	3-$(CH_2)_3$	87	3380, 3312, 1738	1.71 (2H, br s), 1.93 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.18 (1H, s), 7.02—7.06 (1H, m), 7.16—7.39 (8H, m)
11e	Ph	4-CH_2	100	3380, 1736	2.59 (2H, br), 3.59 (2H, s), 3.67 (3H, s), 5.22 (1H, s), 7.11—7.42 (9H, m)
11f	Ph	4-$(CH_2)_2$	84	3380, 1738	1.94 (2H, br s), 2.59 (2H, t, J=8 Hz), 2.91 (2H, t, J=8 Hz), 3.65 (3H, s), 5.17 (1H, s), 7.10—7.38 (9H, m)
11g	Ph	4-$(CH_2)_3$	97	3384, 1736	1.93 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.32 (2H, br s), 2.61 (2H, t, J=7.5 Hz), 3.64 (3H, s), 5.19 (1H, s), 7.06—7.46 (7H, m), 7.11 (2H, d, J=8.5 Hz)
11h	Ph	4-$(CH_2)_4$	87	3384, 3316, 1738	1.51—1.75 (4H, m), 1.90 (2H, s), 2.32 (2H, t, J=7 Hz), 2.59 (2H, t, J=7 Hz), 3.65 (3H, s), 5.18 (1H, s), 7.11 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.17—7.41 (5H, m)
11i	2-F-Ph	4-$(CH_2)_3$	63	3384, 3320, 1738	1.90 (2H, s), 1.93 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.48 (1H, s), 6.99 (1H, ddd, J=10.5, 8, 1.5 Hz), 7.08—7.28 (2H, m), 7.12 (2H, d, J=8 Hz), 7.31 (2H, d, J=8 Hz), 7.45 (1H, td, J=8, 2 Hz)
11j	3-F-Ph	4-$(CH_2)_3$	84	3384, 3316, 1738	1.86 (2H, s), 1.93 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.17 (1H, s), 6.83—6.97 (1H, m), 7.02—7.30 (3H, m), 7.12 (2H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz)
11k	4-F-Ph	4-$(CH_2)_3$	87	3384, 3316, 1736	1.83—2.01 (4H, m), 2.32 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.17 (1H, s), 6.98 (2H, t, J=8.5 Hz), 7.12 (2H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz), 7.34 (2H, dd, J=8.5, 5.5 Hz)
11l	4-Cl-Ph	4-$(CH_2)_3$	89	3384, 3316, 1738	1.93 (2H, qn, J=8 Hz), 2.32 (2H, t, J=8 Hz), 2.62 (2H, t, J=8 Hz), 3.65 (3H, s), 5.18 (1H, s), 7.12 (2H, d, J=8.5 Hz), 7.25 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.32 (2H, d, J=8.5 Hz)
11m	4-CH_3-Ph	4-$(CH_2)_3$	84	3384, 3320, 1738	1.88 (2H, s), 1.92 (2H, qn, J=7.5 Hz), 2.31 (3H, s), 2.31 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.15 (1H, s), 7.11 (2H, d, J=8 Hz), 7.11 (2H, d, J=6.5 Hz), 7.25 (2H, d, J=8 Hz), 7.28 (2H, d, J=6.5 Hz)
11n	4-CF_3-Ph	4-$(CH_2)_3$	80	3388, 3320, 1738	1.93 (2H, qn, J=7.5 Hz), 1.80—2.20 (2H, br), 2.32 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.24 (1H, s), 7.13 (2H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz), 7.51 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz)
11o	2-Thi	4-$(CH_2)_3$	83	3384, 3312, 1736	1.94 (2H, qn, J=7.5 Hz), 2.02 (2H, br s), 2.32 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.39 (1H, s), 6.83 (1H, d, J=3.5 Hz), 6.91 (1H, dd, J=5, 3.5 Hz), 7.15 (2H, d, J=8 Hz), 7.19 (1H, dd, J=5, 1 Hz), 7.33 (2H, d, J=8 Hz)
11p	2-Fur	4-$(CH_2)_3$	63	3376, 3304, 1738	1.95 (2H, qn, J=7.5 Hz), 2.00—2.38 (2H, br), 2.33 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.14 (1H, s), 6.10 (1H, d, J=3 Hz), 6.30 (1H, dd, J=3, 2 Hz), 7.16 (2H, d, J=8 Hz), 7.29 (2H, d, J=8 Hz), 7.34 (1H, s)
11q	Bn	4-$(CH_2)_3$	76	3380, 3300, 1738	1.73 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 2.83 (1H, dd, J=13.5, 9 Hz), 3.01 (1H, dd, J=13.5, 5 Hz), 3.67 (3H, s), 4.17 (1H, dd, J=9, 5 Hz), 7.08—7.17 (4H, m), 7.19—7.22 (1H, m), 7.26—7.29 (4H, m)
11r	2-F-Bn	4-$(CH_2)_3$	81	3384, 3308, 1738	1.85 (2H, br s), 1.94 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 2.88 (1H, dd, J=13.5, 8.5 Hz), 3.03 (1H, dd, J=13.5, 5.5 Hz), 3.67 (3H, s), 4.21 (1H, dd, J=8.5, 5.5 Hz), 6.99—7.22 (4H, m), 7.13 (2H, d, J=8 Hz), 7.27 (2H, d, J=8 Hz)
11s	3-F-Bn	4-$(CH_2)_3$	85	3380, 3310, 1738	1.48 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 2.82 (1H, dd, J=13.5, 8.5 Hz), 2.97 (1H, dd, J=13.5, 5 Hz), 3.67 (3H, s), 4.16 (1H, m), 6.84—6.96 (4H, m), 7.14 (2H, d, J=8 Hz), 7.21—7.26 (1H, m), 7.25 (2H, d, J=8 Hz)
11t	4-F-Bn	4-$(CH_2)_3$	89	3384, 3320, 1738	1.45 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 2.80 (1H, dd, J=13.5, 8.5 Hz), 2.94 (1H, dd, J=13.5, 5.5 Hz), 3.67 (3H, s), 4.12 (1H, dd, J=8.5, 5.5 Hz), 6.95 (2H, t, J=8.5 Hz), 7.09 (2H, dd, J=8.5, 3.5 Hz), 7.13 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz)
11u	4-Cl-Bn	4-$(CH_2)_3$	88	3384, 3308, 1738	1.86 (2H, br s), 1.95 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 2.83 (1H, dd, J=13.5, 8.5 Hz), 2.95 (1H, dd, J=13.5, 5.5 Hz), 3.67 (3H, s), 4.13 (1H, dd, J=8.5, 5.5 Hz), 7.05 (2H, d, J=8.5 Hz), 7.13 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.5 Hz)

Table 5. (continued)

Compd. No.	$R^{2a)}$	A	Yield[b] (%)	IR (liq.) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
11v	4-CH_3-Bn	4-$(CH_2)_3$	94	3380, 3300, 1738	1.95 (2H, qn, J=7.5 Hz), 2.32 (3H, s), 2.33 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 2.75 (1H, dd, J=14, 9 Hz), 2.96 (1H, dd, J=14, 5 Hz), 3.67 (3H, s), 4.14 (1H, dd, J=9, 5 Hz), 7.07 (2H, d, J=7.5 Hz), 7.09 (2H, d, J=7.5 Hz), 7.14 (2H, d, J=7.5 Hz), 7.28 (2H, d, J=7.5 Hz)
11w	CH_3	4-$(CH_2)_3$	73	3376, 3312, 1738	1.39 (3H, d, J=6.5 Hz), 1.90—1.99 (2H, br), 1.95 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 3.66 (3H, s), 4.10 (1H, q, J=6.5 Hz), 7.14 (2H, d, J=8 Hz), 7.27 (2H, d, J=8 Hz)

a) See footnote *a* in Table 2. *b*) Yield from azides (**10**).

Table 6. Physicochemical Data for Sulfonamides **12a—af**



12a – af

Compound No.	$R^{1a)}$	$R^{2a)}$	A	Yield (%)	mp (°C) (Recryst. solv.)[b]	Formula[c]
12a	4-Cl-Ph	Ph	3-CH(CH_3)	91	Oil	—
12b	4-Cl-Ph	Ph	3-CH_2	87	123.5—124 (EA–IE)	$C_{22}H_{20}ClNO_4S$
12c	4-Cl-Ph	Ph	3-$(CH_2)_2$	78	114—115.5 (EA–IE)	$C_{23}H_{22}ClNO_4S$
12d	4-Cl-Ph	Ph	3-$(CH_2)_3$	86	Oil	—
12e	4-Cl-Ph	Ph	3-$(CH_2)_4$	97	Oil	—
12f	4-Cl-Ph	Ph	4-CH_2	86	Oil	—
12g	4-Cl-Ph	Ph	4-$(CH_2)_2$	64	Oil	—
12h	4-Cl-Ph	Ph	4-$(CH_2)_3$	74	Oil	—
12i	4-Cl-Ph	Ph	4-$(CH_2)_4$	71	Oil	—
12j	Ph	Ph	4-$(CH_2)_3$	72	Oil	—
12k	4-F-Ph	Ph	4-$(CH_2)_3$	74	Oil	—
12l	4-Br-Ph	Ph	4-$(CH_2)_3$	51	100.5—102 (DE–IE)	$C_{24}H_{24}BrNO_4S$
12m	4-CH_3-Ph	Ph	4-$(CH_2)_3$	74	Oil	—
12n	4-CH_3O-Ph	Ph	4-$(CH_2)_3$	59	Oil	—
12o	Bn	Ph	4-$(CH_2)_3$	94	Oil	—
12p	CH_3	Ph	4-$(CH_2)_3$	94	Oil	—
12q	4-Cl-Ph	2-F-Ph	4-$(CH_2)_3$	53	Oil	—
12r	4-Cl-Ph	3-F-Ph	4-$(CH_2)_3$	40	87—88 (E)	$C_{24}H_{23}ClFNO_4S$
12s	4-Cl-Ph	4-F-Ph	4-$(CH_2)_3$	57	89.5—91 (M–IE)	$C_{24}H_{23}ClFNO_4S$
12t	4-Cl-Ph	4-Cl-Ph	4-$(CH_2)_3$	81	Oil	—
12u	4-Cl-Ph	4-CH_3-Ph	4-$(CH_2)_3$	61	89.5—90.5 (E–IE)	$C_{25}H_{26}ClNO_4S$
12v	4-Cl-Ph	4-CF_3-Ph	4-$(CH_2)_3$	80	105—106 (M–IE)	$C_{25}H_{23}ClF_3NO_4S$
12w	4-Cl-Ph	2-Thi	4-$(CH_2)_3$	44	115.5—117.5 (E)	$C_{22}H_{22}ClNO_4S_2$
12x	4-Cl-Ph	2-Fur	4-$(CH_2)_3$	41	96—97.5 (EA–IE)	$C_{22}H_{22}ClNO_5S$
12y	4-Cl-Ph	Bn	4-$(CH_2)_3$	71	93.5—94 (EA–IE)	$C_{25}H_{26}ClNO_4S$
12z	4-Cl-Ph	2-F-Bn	4-$(CH_2)_3$	91	97—98 (EA–IE)	$C_{25}H_{25}ClFNO_4S$
12aa	4-Cl-Ph	3-F-Bn	4-$(CH_2)_3$	82	88—90 (EA–IE)	$C_{25}H_{25}ClFNO_4S$
12ab	4-Cl-Ph	4-F-Bn	4-$(CH_2)_3$	85	104.5—106 (EA–IE)	$C_{25}H_{25}ClFNO_4S$
12ac	4-Cl-Ph	4-Cl-Bn	4-$(CH_2)_3$	88	108—109.5 (EA–IE)	$C_{25}H_{25}Cl_2NO_4S$
12ad	4-Cl-Ph	4-CH_3-Bn	4-$(CH_2)_3$	93	109.5—110.5 (EA–IE)	$C_{26}H_{28}ClNO_4S$
12ae	4-Cl-Ph	CH_3	4-$(CH_2)_3$	81	92—93 (EA–IE)	$C_{19}H_{22}ClNO_4S$
12af	4-Cl-Ph	H	4-$(CH_2)_3$	48	75.5—76 (IE)	$C_{19}H_{22}ClNO_4S$

a) See footnote *a* in Table 2. *b*) See footnote *b* in Table 2. DE, diethyl ether. *c*) See footnote *b* in Table 1.

was dried and concentrated to yield the title compound (12.5 g, 95%) as a colorless oil. IR (liq.): 1738 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.94 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 3.65 (3H, s), 6.11 (1H, s), 7.15 (2H, d, J=8.5 Hz), 7.20—7.46 (7H, m). High-resolution MS *m/z*: Calcd for $C_{18}H_{19}ClO_2$: 302.1074, 304.1044. Found: 302.1094, 304.1063.

Other chlorides **9** were prepared similarly from the corresponding alcohols **8** in 89—100% yields.

Methyl 4-[4-(Azidophenylmethyl)phenyl]butyrate (10g, R^2=Ph, A=4-Propyl) A suspension of **9g** (R^2=Ph, A=4-propyl; 12.0 g, 39.6 mmol) and sodium azide (5.20 g, 80.0 mmol) in *N*,*N*-dimethylformamide (DMF) (60 ml) was heated at 50—60 °C for 4 h. After cooling, the reaction mixture was diluted with water and extracted with Et_2O. The extract was washed with water, dried and concentrated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2–hexane (1 : 1)] to yield **10g** (10.8 g, 88%) as a colorless oil. IR (liq.): 2104 (N_3), 1738 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.94 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.68 (1H, s), 7.10—7.39 (9H, m). High-resolution MS *m/z*: Calcd for $C_{18}H_{19}N_3O_2$: 309.1477. Found: 309.1495.

Other azides **10**, except **10p** (R^2=2-furyl, A=4-propyl), were prepared similarly from the corresponding chlorides **9** in 62—100% yields.

Table 7. Spectral Data for Sulfonamides **12a—af**

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
12a	3280, 1736[a]	1.37—1.43 (3H, m), 3.55—3.65 (1H, m), 3.64 (3H, s), 5.21 (1H, d, J=7.5 Hz), 5.59—5.65 (1H, m), 6.94—7.24 (9H, m), 7.26 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=8.5 Hz)
12b	3264, 1730	3.51 (2H, s), 3.68 (3H, s), 5.26 (1H, d, J=7.5 Hz), 5.61 (1H, d, J=7.5 Hz), 6.95—7.24 (9H, m), 7.26 (2H, d, J=8.5 Hz), 7.54 (2H, d, J=8.5 Hz)
12c	3256, 1730	2.52 (2H, t, J=8 Hz), 2.82 (2H, t, J=8 Hz), 3.64 (3H, s), 5.29 (1H, d, J=7 Hz), 5.59 (1H, d, J=7 Hz), 6.90—6.95 (2H, m), 7.02—7.16 (4H, m), 7.19—7.28 (5H, m), 7.54 (2H, d, J=8.5 Hz)
12d	3280, 1736[a]	1.85 (2H, qn, J=7.5 Hz), 2.28 (2H, t, J=7.5 Hz), 2.52 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.25 (1H, d, J=7.5 Hz), 5.60 (1H, d, J=7.5 Hz), 6.87—6.93 (2H, m), 7.00—7.05 (1H, m), 7.08—7.16 (3H, m), 7.20—7.24 (3H, m), 7.26 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=8.5 Hz)
12e	3284, 1738[a]	1.50—1.64 (4H, m), 2.32 (2H, t, J=7 Hz), 2.51 (2H, t, J=7 Hz), 3.67 (3H, s), 5.22 (1H, d, J=7.5 Hz), 5.60 (1H, d, J=7.5 Hz), 6.85—7.28 (9H, m), 7.26 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=8.5 Hz)
12f	3280, 1736[a]	3.57 (2H, s), 3.69 (3H, s), 5.24 (1H, d, J=7 Hz), 5.60 (1H, d, J=7 Hz), 7.01—7.29 (11H, m), 7.54 (2H, d, J=8.5 Hz)
12g	3284, 1738[a]	2.57 (2H, t, J=8 Hz), 2.88 (2H, t, J=8 Hz), 3.66 (3H, s), 5.36 (1H, d, J=7.5 Hz), 5.58 (1H, d, J=7.5 Hz), 6.99—7.27 (11H, m), 7.54 (2H, d, J=9 Hz)
12h	3284, 1736[a]	1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.24 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.92—7.30 (11H, m), 7.54 (2H, d, J=8.5 Hz)
12i	3284, 1738[a]	1.50—1.73 (4H, m), 2.33 (2H, t, J=7 Hz), 2.56 (2H, t, J=7 Hz), 3.66 (3H, s), 5.21 (2H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.98 (2H, d, J=8.5 Hz), 7.01 (2H, d, J=8.5 Hz), 7.07—7.18 (2H, m), 7.18—7.23 (3H, m), 7.25 (2H, d, J=8.5 Hz), 7.54 (2H, d, J=8.5 Hz)
12j	3288, 1736[a]	1.88 (2H, qn, J=7.5 Hz), 2.28 (2H, t, J=7.5 Hz), 2.56 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.32 (1H, d, J=7.5 Hz), 5.58 (1H, d, J=7.5 Hz), 7.06—7.52 (12H, m), 7.66 (2H, dd, J=8.5, 1.5 Hz)
12k	3284, 1738[a]	1.89 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.19 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.97 (2H, t, J=8.5 Hz), 7.01 (4H, s), 7.07—7.26 (5H, m), 7.63 (2H, dd, J=8.5, 5 Hz)
12l	3232, 1744, 1706	1.91 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.09 (1H, d, J=7.5 Hz), 5.60 (1H, d, J=7.5 Hz), 7.00 (2H, d, J=8 Hz), 7.03 (2H, d, J=8 Hz), 7.08—7.13 (2H, m), 7.20—7.25 (3H, m), 7.43 (2H, d, J=8.5 Hz), 7.47 (2H, d, J=8.5 Hz)
12m	3284, 1736[a]	1.89 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.37 (3H, s), 2.57 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.07 (1H, d, J=7 Hz), 5.54 (1H, d, J=7 Hz), 7.00 (4H, s), 6.94—7.24 (7H, m), 7.55 (2H, d, J=8.5 Hz)
12n	3288, 1736[a]	1.89 (2H, qn, J=7.5 Hz), 2.29 (2H, t, J=7.5 Hz), 2.57 (2H, t, J=7.5 Hz), 3.66 (3H, s), 3.83 (3H, s), 5.07 (1H, d, J=7 Hz), 5.53 (1H, d, J=7 Hz), 6.79 (2H, d, J=9 Hz), 7.01 (4H, s), 7.07—7.24 (5H, m), 7.59 (2H, d, J=9 Hz)
12o	3288, 1736[a]	1.94 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.64 (2H, t, J=7.5 Hz), 3.65 (3H, s), 4.03 (2H, s), 4.81 (1H, d, J=8 Hz), 5.70 (1H, d, J=8 Hz), 7.04 (2H, d, J=7.5 Hz), 7.16 (2H, d, J=8.5 Hz), 7.18 (2H, d, J=8.5 Hz), 7.20—7.37 (8H, m)
12p	3288, 1736[a]	1.94 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 2.67 (3H, s), 3.66 (3H, s), 5.01 (1H, d, J=7.5 Hz), 5.73 (1H, d, J=7.5 Hz), 7.16 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz), 7.20—7.39 (5H, m)
12q	3284, 1738[a]	1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.31 (1H, d, J=7.5 Hz), 5.77 (1H, d, J=7.5 Hz), 6.89 (1H, dd, J=10.5, 8.5 Hz), 6.95—7.25 (3H, m), 7.06 (4H, s), 7.26 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz)
12r	3232, 1716	1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.31 (1H, d, J=7.5 Hz), 5.57 (1H, d, J=7.5 Hz), 6.84 (1H, td, J=7.5, 2.5 Hz), 6.88—6.95 (2H, m), 6.96 (2H, d, J=8.5 Hz), 7.03 (2H, d, J=8.5 Hz), 7.20 (1H, td, J=8, 7 Hz), 7.28 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz)
12s	3240, 1706	1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.23 (1H, d, J=7 Hz), 5.57 (1H, d, J=7 Hz), 6.92 (2H, t, J=8.5 Hz), 6.96 (2H, d, J=8 Hz), 7.02 (2H, d, J=8 Hz), 7.10 (2H, dd, J=8.5, 5 Hz), 7.28 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz)
12t	3280, 1738[a]	1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 3.67 (3H, s), 5.09 (1H, d, J=7.5 Hz), 5.55 (1H, d, J=7.5 Hz), 6.94 (2H, d, J=8.5 Hz), 7.03 (2H, d, J=8.5 Hz), 7.07 (2H, d, J=8.5 Hz), 7.21 (2H, d, J=8.5 Hz), 7.30 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz)
12u	3268, 1738, 1718	1.90 (2H, qn, J=7.5 Hz), 2.29 (3H, s), 2.30 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.13 (1H, d, J=7.5 Hz), 5.55 (1H, d, J=7.5 Hz), 6.97 (2H, d, J=8 Hz), 7.01 (4H, s), 7.02 (2H, d, J=8 Hz), 7.25 (2H, d, J=9.5 Hz), 7.54 (2H, d, J=9.5 Hz)
12v	3260, 1732	1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.18 (1H, d, J=7.5 Hz), 5.62 (1H, d, J=7.5 Hz), 6.94 (2H, d, J=8.5 Hz), 7.05 (2H, d, J=8.5 Hz), 7.28 (2H, d, J=8 Hz), 7.29 (2H, d, J=8.5 Hz), 7.49 (2H, d, J=8 Hz), 7.56 (2H, d, J=8.5 Hz)
12w	3264, 1744	1.91 (2H, qn, J=7.5 Hz), 2.32 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 3.67 (3H, s), 5.31 (1H, d, J=7.5 Hz), 5.81 (1H, d, J=7.5 Hz), 6.70 (1H, d, J=3.5 Hz), 6.84 (1H, dd, J=5, 3.5 Hz), 7.03 (2H, d, J=8 Hz), 7.08 (2H, d, J=8 Hz), 7.18 (1H, dd, J=5, 1 Hz), 7.27 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz)
12x	3228, 1720	1.91 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 3.67 (3H, s), 5.28 (1H, d, J=8 Hz), 5.63 (1H, d, J=8 Hz), 6.00 (1H, d, J=3 Hz), 6.20 (1H, dd, J=3, 2 Hz), 7.05 (2H, d, J=8 Hz), 7.09 (2H, d, J=8 Hz), 7.23 (1H, d, J=2 Hz), 7.30 (2H, d, J=9 Hz), 7.58 (2H, d, J=9 Hz)
12y	3232, 1710	1.91 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 2.93 (1H, dd, J=14, 8 Hz), 3.02 (1H, dd, J=14, 6 Hz), 3.68 (3H, s), 4.53 (1H, dd, J=8, 6 Hz), 4.88 (1H, d, J=7 Hz), 6.94—6.99 (6H, m), 7.19—7.21 (5H, m), 7.40 (2H, d, J=8.5 Hz)
12z	3228, 1712	1.91 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 2.97 (1H, dd, J=14, 7 Hz), 3.03 (1H, dd, J=14, 9 Hz), 3.68 (3H, s), 4.52—4.59 (1H, m), 4.99—5.10 (1H, m), 6.89—7.00 (3H, m), 7.00 (2H, d, J=8 Hz), 7.03 (2H, d, J=8 Hz), 7.15—7.20 (1H, m), 7.18 (2H, d, J=8.5 Hz), 7.42 (2H, d, J=8.5 Hz)
12aa	3276, 1736, 1722	1.90 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.57 (2H, t, J=7.5 Hz), 2.96 (1H, dd, J=14, 7.5 Hz), 3.00 (1H, dd, J=14, 7.5 Hz), 3.68 (3H, s), 4.52 (1H, q, J=7.5 Hz), 5.09 (1H, d, J=7.5 Hz), 6.63 (1H, br d, J=8 Hz), 6.76 (1H, br d, J=8 Hz), 6.87 (1H, td, J=8, 2.5 Hz), 6.92 (2H, d, J=8.5 Hz), 6.97 (2H, d, J=8.5 Hz), 7.14 (1H, td, J=8, 6 Hz), 7.21 (2H, d, J=8.5 Hz), 7.44 (2H, d, J=8.5 Hz)

Table 7. (continued)

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
12ab	3280, 1738, 1720	1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.57 (2H, t, J=7.5 Hz), 2.95 (1H, dd, J=14, 7 Hz), 2.98 (1H, dd, J=14, 7 Hz), 3.68 (3H, s), 4.50 (1H, q, J=7 Hz), 4.93 (1H, d, J=7 Hz), 6.83—6.92 (4H, m), 6.89 (2H, d, J=8 Hz), 6.96 (2H, d, J=8 Hz), 7.22 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz)
12ac	3300, 1726	1.90 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 2.94 (1H, dd, J=14, 7 Hz), 2.98 (1H, dd, J=14, 7 Hz), 3.68 (3H, s), 4.50 (1H, q, J=7 Hz), 4.96 (1H, d, J=7 Hz), 6.87 (2H, d, J=8.5 Hz), 6.90 (2H, d, J=8 Hz), 6.98 (2H, d, J=8 Hz), 7.13 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz), 7.42 (2H, d, J=8.5 Hz)
12ad	3272, 1718	1.91 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.31 (3H, s), 2.59 (2H, t, J=7.5 Hz), 2.84 (1H, dd, J=14, 8.5 Hz), 2.98 (1H, dd, J=14, 6 Hz), 3.68 (3H, s), 4.49 (1H, m), 4.79 (1H, d, J=6 Hz), 6.83 (2H, d, J=8 Hz), 6.97—7.03 (6H, m), 7.19 (2H, d, J=8.5 Hz), 7.39 (2H, d, J=8.5 Hz)
12ae	3260, 1722	1.44 (3H, d, J=6.5 Hz), 1.90 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 3.68 (3H, s), 4.49 (1H, br s), 4.85 (1H, br s), 6.97 (2H, d, J=8 Hz), 6.99 (2H, d, J=8 Hz), 7.30 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz)
12af[b]	3276, 1728	1.25 (3H, t, J=7 Hz), 1.91 (2H, qn, J=7.5 Hz), 2.29 (2H, t, J=7.5 Hz), 2.61 (2H, t, J=7.5 Hz), 4.12 (2H, q, J=7 Hz), 4.12 (2H, s), 4.69 (1H, br s), 7.09 (4H, s), 7.46 (2H, d, J=8.5 Hz), 7.78 (2H, d, J=8.5 Hz)

a) Liquid. *b*) Ethyl ester.

Methyl 4-[4-[Azido(2-furyl)methyl]phenyl]butyrate (10p, R^2=2-Furyl, A=4-Propyl) Methanesulfonyl chloride (1.45 g, 12.7 mmol) was added dropwise to a solution of **8p** (R^2=2-furyl, A=4-propyl; 3.48 g, 12.7 mmol) and triethylamine (1.95 ml, 14.0 mmol) in DMF (20 ml) at −20—−15 °C, and the mixture was stirred at −15—0 °C for 20 min. Sodium azide (2.06 g, 31.6 mmol) was added to the reaction mixture at 0 °C, and the whole was stirred at room temperature for 30 min, then diluted with water and extracted with Et_2O. The extract was washed with water, dried and concentrated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2–hexane (5:1)] to yield the title compound (1.59 g, 42%) as a pale yellow oil. IR (liq.): 2104 (N_3), 1738 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (2H, qn, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 2.66 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.62 (1H, s), 6.20 (1H, d, J=3 Hz), 6.34 (1H, dd, J=3, 2 Hz), 7.20 (2H, d, J=8 Hz), 7.29 (2H, d, J=8 Hz), 7.42 (1H, d, J=2 Hz). High-resolution MS m/z: Calcd for $C_{16}H_{17}N_3O_3$: 299.1270. Found: 299.1275.

Methyl 4-[4-[(Aminophenylmethyl)phenyl]butyrate (11g) A suspension of **10g** (R^2=Ph, A=4-propyl; 7.00 g, 22.6 mmol) and PtO_2 (180 mg) in MeOH (70 ml) was hydrogenated at ambient temperature under a hydrogen atmosphere (1 atm) for 5 h. The catalyst was filtered off, and the filtrate was concentrated to yield **11g** (6.20 g, 97%) as a colorless oil. IR (liq.): 3384 (NH_2), 1736 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (2H, qn, J=7.5 Hz), 2.31 (2H, t, J=7.5 Hz), 2.32 (2H, br s), 2.61 (2H, t, J=7.5 Hz), 3.64 (3H, s), 5.19 (1H, s), 7.06—7.46 (7H, m), 7.11 (2H, d, J=8.5 Hz). High-resolution MS m/z: Calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1564.

Other amines **11** were prepared similarly from the corresponding azides **10**. Physicochemical data are summarized in Table 5.

Methyl 4-[4-[(4-Chlorobenzenesulfonamido)phenylmethyl]phenyl]-butyrate (12h) A solution of 4-chlorobenzenesulfonyl chloride (1.86 g, 8.81 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a solution of **11g** (2.50 g, 8.82 mmol) and triethylamine (1.35 ml, 9.68 mmol) in CH_2Cl_2 (10 ml) under ice-cooling. The mixture was stirred at room temperature for 30 min, and then washed successively with dilute HCl and water. The CH_2Cl_2 layer was dried and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2) to yield **12h** (3.00 g, 74%) as a colorless oil. IR (liq.): 3284 (NH), 1736 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (2H, qn, J=7.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.58 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.24 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.92—7.30 (11H, m), 7.54 (2H, d, J=8.5 Hz).

Other sulfonamides **12** were prepared in a similar manner to that described above. Physicochemical data are summarized in Tables 6 and 7.

4-[4-[(4-Chlorobenzenesulfonamido)phenylmethyl]phenyl]butyric Acid (6h) A solution of **12h** (2.70 g, 5.9 mmol) and 2 N NaOH (6 ml) in MeOH (7 ml) was stirred at room temperature for 3 h. After evaporation of the solvent under reduced pressure, the residue was diluted with water and acidified with dilute HCl, and then extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated to yield **6h** (2.10 g, 80%) as colorless crystals, which were recrystallized from a mixture of isopropyl ether (iso-Pr_2O) and AcOEt to give colorless needles, mp 153—155.5 °C. IR (KBr): 3284 (NH), 1706 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.91 (2H, qn, J=7.5 Hz), 2.35 (2H, t, J=7.5 Hz), 2.60 (2H, t, J=7.5 Hz), 5.40 (1H, d, J=7.5 Hz), 5.59 (1H, d, J=7.5 Hz), 6.82—7.40 (11H, m), 7.54 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{23}H_{22}ClNO_4S$: C, 62.23; H, 4.99; N, 3.16. Found: C, 62.10; H, 5.03; N, 2.97.

Other sulfonamides **6** were prepared in a similar manner to that described above. Physicochemical data are summarized in Tables 1, 2 and 4.

2-(3-Benzoylphenyl)-1,3-dioxolane (14) and 2-[3-(Hydroxyphenylmethyl)phenyl]-1,3-dioxolane (15) A solution of 2-(3-bromophenyl)-1,3-dioxolane[7] (**13**; 53.0 g, 0.231 mol) in dry tetrahydrofuran (THF) (50 ml) was added dropwise to a suspension of Mg (5.62 g, 0.231 mol) in dry THF (150 ml) at 50—60 °C, and the mixture was stirred at room temperature for 1 h. A solution of benzaldehyde (24.6 g, 0.232 mol) in dry THF (50 ml) was added dropwise to the reaction mixture under ice-cooling. The mixture was stirred at room temperature for 0.5 h, quenched with aqueous NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried and concentrated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2–hexane (1:1)→CH_2Cl_2]. The first eluent afforded **14** (32.0 g, 54%) as a pale yellow oil, and the later eluent yielded **15** (5.92 g, 10%) as a pale yellow oil. **14**: IR (liq.): 1662 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.92—4.08 (4H, m), 5.84 (1H, s), 7.52—7.80 (9H, m). High-resolution MS m/z: Calcd for $C_{16}H_{14}O_3$: 254.0943. Found: 254.0949. **15**: IR (liq.): 3432 (OH) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.91—4.06 (4H, m), 5.69 (1H, s), 5.71 (1H, s), 7.17—7.46 (9H, m). High-resolution MS m/z: Calcd for $C_{16}H_{16}O_3$: 256.1099. Found: 256.1103.

2-[3-(Hydroxyphenylmethyl)phenyl]-1,3-dioxolane (15) $NaBH_4$ (4.76 g, 0.126 mol) was added portionwise to a solution of **14** (32.0 g, 0.126 mol) in MeOH (200 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 h. MeOH was evaporated off under reduced pressure, and the residue was diluted with water and extracted with Et_2O. The extract was washed with brine, dried and concentrated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2→CH_2Cl_2–AcOEt (10:1)] to yield **15** (32.3 g, 100%) as a pale yellow oil. This product was identical with the Grignard reaction product **15**.

2-[3-(Azidophenylmethyl)phenyl]-1,3-dioxolane (16) Methanesulfonyl chloride (17.3 g, 0.151 mol) was added dropwise to a solution of **15** (32.3 g, 0.126 mol) and triethylamine (22.9 ml, 0.164 mol) in CH_2Cl_2 (200 ml) at −5—0 °C for 30 min. The mixture was stirred at the same temperature for 30 min. The solvent was evaporated off under reduced pressure. A suspension of the residue and sodium azide (20.5 g, 0.315 mol) in dry DMF (200 ml) was stirred at room temperature for 30 min and stirring was continued at 40 °C for 30 min. The reaction mixture was diluted with water and extracted with Et_2O. The extract was washed with brine, dried and concentrated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2–hexane (2:1)] to yield **16** (11.4 g, 31%) as a pale yellow oil. IR (liq.): 2104 (N_3) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.90—4.06 (4H, m), 5.72 (1H, s), 6.11 (1H, s), 7.29—7.44 (9H, m). High-resolution MS m/z: Calcd for $C_{16}H_{15}N_3O_2$: 281.1164. Found: 281.1158.

3-(Azidophenylmethyl)benzaldehyde (17) A mixture of **16** (11.4 g, 40.5 mmol) and dilute HCl (35 ml) in THF (100 ml) was stirred at room

temperature for 1 h. The solvent was evaporated off under reduced pressure. The residue was taken up in benzene and washed with water. The benzene layer was dried and concentrated to yield **17** (9.02 g, 94%) as a colorless oil. IR (liq.): 2104 (N_3), 1704 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.79 (1H, s), 7.25—7.62 (7H, m), 7.79—7.90 (2H, m), 10.03 (1H, s). High-resolution MS *m/z*: Calcd for $C_{14}H_{11}N_3O$: 237.0902. Found: 237.0899.

5-[3-(Azidophenylmethyl)phenyl]pent-4-enoic Acid (18) *tert*-BuOK (4.73 g, 42.2 mmol) was added portionwise to a suspension of (3-carboxypropyl)triphenylphosphonium chloride (8.10 g, 21.0 mmol) in dry THF (60 ml) at 0 °C, and the mixture was stirred at the same temperature for 30 min. A solution of **17** (2.50 g, 10.5 mmol) in dry THF (25 ml) was added dropwise to the reaction mixture at 0 °C. The whole was stirred at the same temperature for 1 h, poured into water, and washed with benzene. The aqueous layer was acidified with dilute HCl and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2–AcOEt (2 : 1)] to yield **18** (1.64 g, 54%) as a pale yellow oil. IR (liq.): 2104 (N_3), 1714 (C=O) cm^{-1}. High-resolution MS *m/z*: Calcd for $C_{18}H_{17}N_3O_2$: 307.1321. Found: 307.1310.

Methyl 5-[3-(Azidophenylmethyl)phenyl]pent-4-enoate (19) A suspension of **18** (1.48 g, 4.82 mmol), iodomethane (0.42 ml, 6.75 mmol) and K_2CO_3 (0.73 g, 5.30 mmol) in DMF (10 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with Et_2O. The extract was washed with brine, dried and concentrated to yield **19** (1.51 g, 97%) as a colorless oil. IR (liq.): 2104 (N_3), 1738 (C=O) cm^{-1}. High-resolution MS *m/z*: Calcd for $C_{19}H_{19}N_3O_2$: 321.1477. Found: 321.1478.

Methyl 5-[3-(Aminophenylmethyl)phenyl]valerate (20) A suspension of **19** (1.50 g, 4.67 mmol) and 5% Pd–C (120 mg) in MeOH (40 ml) was hydrogenated at ambient temperature under a hydrogen atmosphere (3 atm) for 10 h. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The residue was dissolved in dilute HCl and washed with Et_2O. The aqueous layer was made alkaline with K_2CO_3 and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated to yield **20** (1.05 g, 76%) as a colorless oil. IR (liq.): 3384, 3300 (NH_2), 1738 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.69 (4H, m), 2.31 (2H, t, J=7 Hz), 2.22—2.54 (2H, br), 2.59 (2H, t, J=7 Hz), 3.65 (3H, s), 5.20 (1H, s), 7.15—7.39 (9H, m). High-resolution MS *m/z*: Calcd for $C_{19}H_{23}NO_2$: 297.1729. Found: 297.1721.

4-[4-(Azidophenylmethyl)phenyl]butyric Acid (21) A solution of **10g** (0.50 g, 1.62 mmol) and 2 N NaOH (2 ml) in MeOH (10 ml) was stirred at room temperature for 4.5 h. After evaporation of the solvent under reduced pressure, the residue was successively diluted with water and acidified with dilute HCl, and then extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated to yield **21** (0.46 g, 96%) as a pale yellow oil. IR (liq.): 2104 (N_3), 1706 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.95 (2H, qn, J=7.5 Hz), 2.37 (2H, t, J=7.5 Hz), 2.66 (2H, t, J=7.5 Hz), 5.68 (1H, s), 7.17 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz), 7.26—7.37 (5H, m). High-resolution MS *m/z*: Calcd for $C_{17}H_{17}N_3O_2$: 295.1321. Found: 295.1325.

Optical Resolution of Racemic 4-[4-(Azidophenylmethyl)phenyl]butyric Acid [(+)-21 and (−)-21] (*S*)-(−)-1-Phenylethylamine (27.9 g, 0.223 mol) was added to a solution of racemic **21** (65.9 g, 0.223 mol) in AcOEt (150 ml), and the mixture was allowed to stand at room temperature. The crystals deposited were collected by filtration to give the crude salt of (+)-**21** with (*S*)-(−)-1-phenylethylamine (70.0 g) as colorless crystals, which were recrystallized six times from AcOEt to leave the pure salt of (+)-**21** with (*S*)-(−)-1-phenylethylamine (13.7 g, 15%) as colorless needles, mp 118—121 °C. $[\alpha]_D^{20}$ +15.8° (c=1, MeOH). *Anal.* Calcd for $C_{17}H_{17}N_3O_2 \cdot C_8H_{11}N$: C, 72.09; H, 6.78; N, 13.45. Found: C, 72.21; H, 6.82; N, 13.42. The salt of (+)-**21** (13.0 g, 31.2 mmol) was converted in the usual manner to the free acid (+)-**21** (8.70 g, 94%) as a colorless oil. IR (liq.): 2104 (N_3), 1710 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.95 (2H, qn, J=7.5 Hz), 2.37 (2H, t, J=7.5 Hz), 2.66 (2H, t, J=7.5 Hz), 5.68 (1H, s), 7.17 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz), 7.28—7.37 (5H, m). MS *m/z*: 295 (M^+). $[\alpha]_D^{20}$ +19.3° (c=1, MeOH). The filtrate containing the crude salt of (−)-**21** was concentrated. The residue was treated by conventional means to provide recovered free acid (36.8 g, 0.125 mol). This compound was diluted in AcOEt (120 ml) and (*R*)-(+)-1-phenylethylamine (15.1 g, 0.125 mol) was added to the AcOEt solution. The mixture was allowed to stand at room temperature, and the crystals deposited were collected by filtration to give the crude salt of (−)-**21** with (*R*)-(+)-1-phenylethylamine (24.0 g) as colorless crystals. These were recrystallized six times from AcOEt to give the pure salt of (−)-**21** with (*R*)-(+)-1-phenylethylamine (11.1 g, 12%) as colorless needles, mp 117—120 °C. $[\alpha]_D^{20}$ −15.3° (c=1, MeOH). *Anal.* Calcd for $C_{17}H_{17}N_3O_2 \cdot C_8H_{11}N$: C, 72.09; H, 6.78; N, 13.45. Found: C, 72.19; H, 6.80; N, 13.46. The salt of (−)-**21** (10.5 g, 25.2 mmol) was converted in the usual manner to the free acid (−)-**21** (7.17 g, 96%) as a colorless oil. $[\alpha]_D^{20}$ −19.2° (c=1, MeOH). IR, ^{1}H-NMR and MS spectra of (−)-**21** were in agreement with those of (+)-**21**.

(+)- and (−)-Methyl 4-[(4-Azidophenylmethyl)phenyl]butyrate [(+)-10g and (−)-10g] A mixture of (+)-**21** (5.29 g, 17.9 mmol), iodomethane (1.45 ml, 23.3 mmol) and K_2CO_3 (2.72 g, 19.7 mmol) in DMF (30 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with Et_2O. The extract was washed with water, dried and concentrated to yield (+)-**10g** (5.14 g, 93%) as a colorless oil. $[\alpha]_D^{20}$ +19.6° (c=1, MeOH). High-resolution MS *m/z*: Calcd for $C_{18}H_{19}N_3O_2$: 309.1477. Found: 309.1474. In a similar manner to that described above, (−)-**10g** was obtained as a colorless oil (6.77 g, 94%) from (−)-**21** (6.84 g, 23.2 mmol). $[\alpha]_D^{20}$ −19.4° (c=1, MeOH). High-resolution MS *m/z*: Calcd for $C_{18}H_{19}N_3O_2$: 309.1477. Found: 309.1485. IR, ^{1}H-NMR and MS data for (+)-**10g** and (−)-**10g** were in agreement with those for **10g**.

(+)- and (−)-Methyl 4-[4-(Aminophenylmethyl)phenyl]butyrate [(+)-11g and (−)-11g] In a similar manner to that described for **11g**, (+)-**11g** and (−)-**11g** were obtained from (−)-**10g** and (+)-**10g**, respectively. (+)-**11g**: 85% (yield), colorless oil, $[\alpha]_D^{20}$ +1.1° (c=1, MeOH). High-resolution MS *m/z*: Calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1568. (−)-**11g**: 89% (yield), colorless oil, $[\alpha]_D^{20}$ −1.3° (c=1, MeOH). High-resolution MS *m/z*: Calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1754.

(+)- and (−)-Methyl 4-[4-[(4-Chlorobenzenesulfonamido)phenylmethyl]phenyl]butyrate [(+)-12h and (−)-12h] In a similar manner to that described for **12h**, (+)-**12h** and (−)-**12h** were obtained from (−)-**11g** and (+)-**11g**, respectively. (+)-**12h**: 86% (yield), colorless prisms, mp 66—68.5 °C (Et_2O–iso-Pr_2O), $[\alpha]_D^{20}$ +8.3° (c=1, MeOH). *Anal.* Calcd for $C_{24}H_{24}ClNO_4S$: C, 62.94; H, 5.28; N, 3.06. Found: C, 62.84; H, 5.30; N, 2.98. (−)-**12h**: 83% (yield), colorless prisms, mp 66.5—68 °C (Et_2O–iso-Pr_2O), $[\alpha]_D^{20}$ −8.3° (c=1, MeOH). *Anal.* Calcd for $C_{24}H_{24}ClNO_4S$: C, 62.94; H, 5.28; N, 3.06. Found: C, 63.01; H, 5.34; N, 3.13.

(+)- and (−)-4-[4-[(4-Chlorobenzenesulfonamido)phenylmethyl]phenyl]butyric Acid [(+)-6h and (−)-6h] In a similar manner to that described for **6h**, (+)-**6h** and (−)-**6h** were obtained from (+)-**12h** and (−)-**12h**, respectively. (+)-**6h**: 97% (yield), colorless crystals, mp 135—137.5 °C (80% aqueous MeOH). $[\alpha]_D^{20}$ +9.0° (c=1, MeOH). *Anal.* Calcd for $C_{23}H_{22}ClNO_4S$: C, 62.23; H, 4.99; N, 3.16. Found: C, 62.11; H, 4.93; N, 3.14. Optical purity (by HPLC): 98.8% ee. (−)-**6h**: 95% (yield), colorless prisms, mp 135.5—137.5 °C (75% aqueous MeOH), $[\alpha]_D^{20}$ −9.3° (c=1, MeOH). *Anal.* Calcd for $C_{23}H_{22}ClNO_4S$: C, 62.23; H, 4.99; N, 3.16. Found: C, 62.21; H, 4.97; N, 3.25. Optical purity (by HPLC): >99% ee.

Optical Resolution of Racemic 4-[4-[1-(4-Chlorobenzenesulfonamido)-2-phenylethyl]phenyl]butyric Acid [(+)-6y or (−)-6y] Racemic **6y** (10.0 g, 21.8 mmol) and quinidine (7.08 g, 21.8 mmol) were dissolved in AcOEt (70 ml) by heating, and the mixture was allowed to stand at room temperature. The crystals deposited were collected by filtration to give the crude salt of (−)-**6y** with quinidine (8.02 g) as colorless crystals, which were recrystallized from MeOH to afford the pure salt of (−)-**6y** with quinidine (6.37 g, 37%) as colorless prisms, mp 181.5—183.5 °C. $[\alpha]_D^{20}$ +93.6° (c=1, MeOH). *Anal.* Calcd for $C_{24}H_{24}ClNO_4S \cdot C_{20}H_{24}N_2O_2$: C, 67.55; H, 6.18; N, 5.37. Found: C, 67.48; H, 6.17; N, 5.50. The quinidine salt (6.15 g, 7.86 mmol) was converted in the usual manner to the free acid (−)-**6y** (3.14 g, 87%) as colorless needles. mp 173.5—174 °C (90% aqueous EtOH). $[\alpha]_D^{20}$ −40.3° (c=1, MeOH). *Anal.* Calcd for $C_{24}H_{24}ClNO_4S$: C, 62.94; H, 5.28; N, 3.06. Found: C, 62.94; H, 5.19; N, 3.17. Optical purity (by HPLC): >99% ee. The filtrate containing the crude salt of (+)-**6y** with quinidine was concentrated. The residue was treated by conventional means to provide recovered free acid (5.00 g, 10.9 mmol). This free acid and quinine (3.92 g, 10.9 mmol) were dissolved in AcOEt (40 ml) by heating, and the mixture was allowed to stand at room temperature. The crystals deposited were collected by filtration to give the crude salt of (+)-**6y** with quinine (7.50 g) as colorless crystals. These were recrystallized from EtOH to afford the pure salt of (+)-**6y** with quinine (6.50 g, 38%) as colorless prisms, mp 174—176 °C. $[\alpha]_D^{20}$ −63.7° (c=1, MeOH). *Anal.* Calcd for $C_{24}H_{24}ClNO_4S \cdot C_{20}H_{24}N_2O_2$:

C, 67.55; H, 6.18; N, 5.37. Found: C, 67.42; H, 6.16; N, 5.43. The quinine salt (6.00 g, 7.67 mmol) was converted in the usual manner to the free acid (+)-**6y** (3.06 g, 87%) as colorless needles. mp 173—174 °C (90% aqueous EtOH). $[\alpha]_D^{20}$ +40.2° (c=1, MeOH). *Anal.* Calcd for $C_{24}H_{24}ClNO_4S$: C, 62.94; H, 5.28; N, 3.06. Found: C, 62.89; H, 5.30; N, 3.26. Optical purity (by HPLC): >99% ee.

HPLC Analysis Chromatographic conditions were as follows: column, Chiralcel OD-H (4.6 mm i.d. × 250 mm); column temperature, room temperature; mobile phase, hexane–dry EtOH (4:1) containing 0.1% trifluoroacetic acid; flow rate, 0.75 ml/min; detector, UV at 230 nm; retention time, (+)-**6h**, 19 min; (−)-**6h**, 15 min; (+)-**6y**, 9 min; (−)-**6y**, 10 min.

Inhibitory Effect on U-46619-Induced Guinea-Pig Platelet Aggregation Blood was collected from the abdominal aorta of guinea-pigs (about 400 g wt.) into 1/10 volume of 3.8% sodium citrate, and then platelet-rich plasma (PRP: 6×10^5 cells/μl) was obtained by centrifugation. PRP (190 μl) in a cuvette was incubated with 1 μl of dimethyl sulfoxide (DMSO) solution of test compounds for 2 min at 37 °C in an aggregometer (Hema Tracer I; Niko Bioscience). A 10 μl aliquot of U-46619 (Cayman), a TXA_2/prostaglandin H_2 receptor agonist and potent platelet aggregation inducer, was added to PRP to give a final concentration of 2 μg/ml, and platelet aggregation was measured with an aggregometer. The IC_{50} values were calculated graphically from the concentration–% inhibition relations.

Inhibitory Effect on U-46619-Induced Contraction of Guinea-Pig Trachea Male Hartley guinea-pigs were killed and the trachea was removed immediately. Each trachea was cut into spiral strips (3 × 20 mm). Each preparation was suspended in a 10 ml organ bath containing modified Krebs–Henseleit solution of the following composition: 118 mM NaCl, 4.7 mM KCl, 2.6 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 24.9 mM $NaHCO_3$, 11.1 mM glucose. The tissue baths were maintained at 37 ± 1 °C and continuously aerated with 95% O_2–5% CO_2. The resting tension was 1.5 g. Each preparation was equilibrated for 60 min by washing with the medium every 15 min and pretreated with 3×10^{-6} M indomethacin to remove the influence of cyclooxygenase products on the responses to various agonists. Contractile responses were recorded as a change of isometric tension by using a force displacement transducer (Orientec, T7-30-240). The U-46619 concentration–response curve was constructed by means of cumulative increases in bath concentration of the agonist. The preparation was then washed at regular intervals until the resting base line had been recovered returned. After an appropriate rest period, the U-46619 concentration–response curve was obtained again in the presence of a test drug. Compounds were added 5 min before the addition of the agonist. The pK_b values of each test compound were calculated according to the method of Furchgott.[14]

Inhibitory Effect on U-46619-Induced Bronchoconstriction in Guinea-Pig Bronchoconstriction was evaluated by the method of Konzett and Rössler.[15] Male Hartley guinea-pigs (about 400 g wt.) were anesthetized with urethane (1.5 g/kg, i.p.) and ventilated on an artificial respirator (Model 683; Harvard). Overflow volume against a pressure of approximately 12 cm H_2O was measured by a sensor (Model 7020; Ugo basile) as an index of bronchoconstriction. Guinea-pigs which had been starved for 24 h were treated orally with 0.3 mg/kg (5 ml/kg) of test compound suspended in 5% gum Arabic. After 2 h, animals were treated with U-46619 (4 μg/kg; Cayman) through the cervical vein, and the maximal response was measured. The inhibition rates against the control group based on the response rate normalized to complete closure as 100% were calculated.

Inhibitory Effect on TXA_2 Synthase Commercial human platelet membrane fraction Eldan-Technologies (100 μg/ml, 285 μl) as a source of TXA_2 synthase, a DMSO solution of test compound (10 μl) and 100 μg/ml (5 μl) of prostaglandin H_2 (Cayman) were mixed and allowed to react for 3 min at 25 °C. The produced thromboxane B_2 (TXB_2), a stable metabolite of TXA_2, was determined by an Radioimmunoassay (RIA) method (TXB_2 quantification kit; Du Pont/MEN Research Products). The IC_{50} values were calculated graphically.

Inhibitory Effect on LTD_4-Induced Contraction of Guinea-Pig Ileum Ileum (approximately 20 mm) was suspended in a 10 ml organ bath containing Tyrode solution of the following composition: 137 mM NaCl, 4 mM KCl, 2.7 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.4 mM NaH_2PO_4, 11.9 mM $NaHCO_3$, 5.0 mM glucose. The tissue baths were maintained at 30 ± 0.5 °C and continuously aerated with 95% O_2–5% CO_2. These studies were also carried out with indomethacin (1×10^{-6}) to exclude the influence of cyclooxygenase products on the responses to various agonists. Contractile responses were recorded by using an isotonic transducer (Nihon Kohden, TD112S). The LTD_4 (3×10^{-10} M)-induced contraction was obtained. After an appropriate rest period, LTD_4-induced contraction was repeated in the presence of a test compound. The compound (3×10^{-7} M) was added 5 min before the addition of agonist. The values of the maximal response were measured. The inhibition rates were determined for each compound.

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