# Synthesis of [[(Benzenesulfonamido)alkyl]phenyl]alkanoic Acid Derivatives Containing Pyridyl or Imidazolyl Groups and Their Thromboxane $A_2$ Receptor Antagonistic and Thromboxane $A_2$ Synthase Inhibitory Activities

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**As part of our search for a dual inhibitor possessing both thromboxane $A_2$ ($TXA_2$) receptor antagonistic and $TXA_2$ synthase inhibitory activities, some [[(benzenesulfonamido)alkyl]phenyl]alkanoic acid derivatives possessing a pyridyl or imidazolyl group were synthesized. Their $TXA_2$ receptor antagonistic and $TXA_2$ synthase inhibitory activities were evaluated in terms of the inhibitory effects on U-46619-induced guinea-pig platelet aggregation and on thromboxane $B_2$ ($TXB_2$) production in human platelets, respectively. It was found that 3-[4-[2-(1-imidazolyl)-1-(4-chlorobenzenesulfonamido)ethyl]phenyl]propionic acid (22a), containing an imidazolyl group, is a well-balanced dual inhibitor having both $TXA_2$ receptor antagonistic activity ($IC_{50}=0.31\ \mu M$) and $TXA_2$ synthase inhibitory activity ($IC_{50}=0.39\ \mu M$).**

**Key words** synthesis; dual inhibitor; thromboxane $A_2$; thromboxane $A_2$ receptor antagonistic activity; thromboxane $A_2$ synthase inhibitory activity

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.[1] Thus, efforts have been made to develop $TXA_2$ receptor antagonists (TXRAs) or $TXA_2$ synthase inhibitors (TXSIs) as candidate antithrombotic or anti-asthmatic agents, and some promising compounds are under clinical trial for the treatment of thrombosis and asthma.[2]

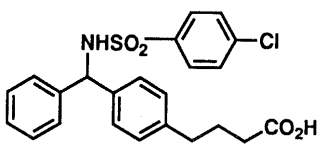
TXSIs possess the advantage of increasing the beneficial (anti-thrombotic) prostaglandins (PGs), such as $PGI_2$ or $PGD_2$, *via* temporarily accumulated $PGH_2$, which is an endoperoxide precursor of $TXA_2$, when they inhibit the biosynthesis of $TXA_2$.[3] But the first clinical results with TXSI have been disappointing.[4] One of the major reasons may be that $PGH_2$ itself has a strong platelet-aggregating effect and bronchoconstricting action, like $TXA_2$, which binds to the same receptor as $TXA_2$.[5] On the other hand, TXRAs antagonize the actions of both $TXA_2$ and $PGH_2$, and it was reported that a combination of TXSI and TXRA was more effective than either agent alone.[6] Recently, efforts have been made to develop dual inhibitors having both TXRA and TXSI activities.[7]

In the previous paper, we disclosed that compound **1** possesses strong TXRA and weak TXSI activities.[8] We have conducted structural modification of **1** in order to obtain better balanced dual inhibitors. Representative TXSIs, such as ozagrel (**2**)[2d] or isbogrel (**3**),[2e] contain a pyridyl or imidazolyl group together with a carboxyl group as structural features, both of which have been found to be mandatory for TXSI activity. Another characteristic feature is that a six- to nine- carbon chain between the imidazolyl and the carboxyl groups is favorable for activity.[2d,9] Therefore, we envisioned that replacement of the benzene ring with a pyridine or imidazole ring in **1** would enhance TXSI activity with retention of the TXRA activity. This paper deals with the synthesis and the pharmacological effects of novel benzenesulfonamide derivatives containing a pyridyl or imidazolyl group (**10a—i**, **22a, b**, **29a, b**) and imidazole derivatives (**13a—c**).

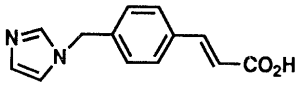
## Synthesis

The derivatives containing the pyridyl group (**10a—i**) were synthesized as shown in Chart 2. Reduction of the ketones (**4a—e**) with sodium borohydride gave the corresponding alcohols (**5a—e**). Chlorination of **5a—e** with thionyl chloride afforded **6a—e**, which were treated with sodium azide to yield the azides (**7a—e**). Hydrogenation of **7a—e** gave the amines (**8a—e**), which were condensed with various benzenesulfonyl chlorides, followed by alkaline hydrolysis to afford the desired compounds **10a—i**.

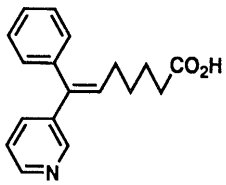
The derivatives containing the imidazolyl group (**13a—**




**1**




ozagrel (**2**)




isbogrel (**3**)

Chart 1

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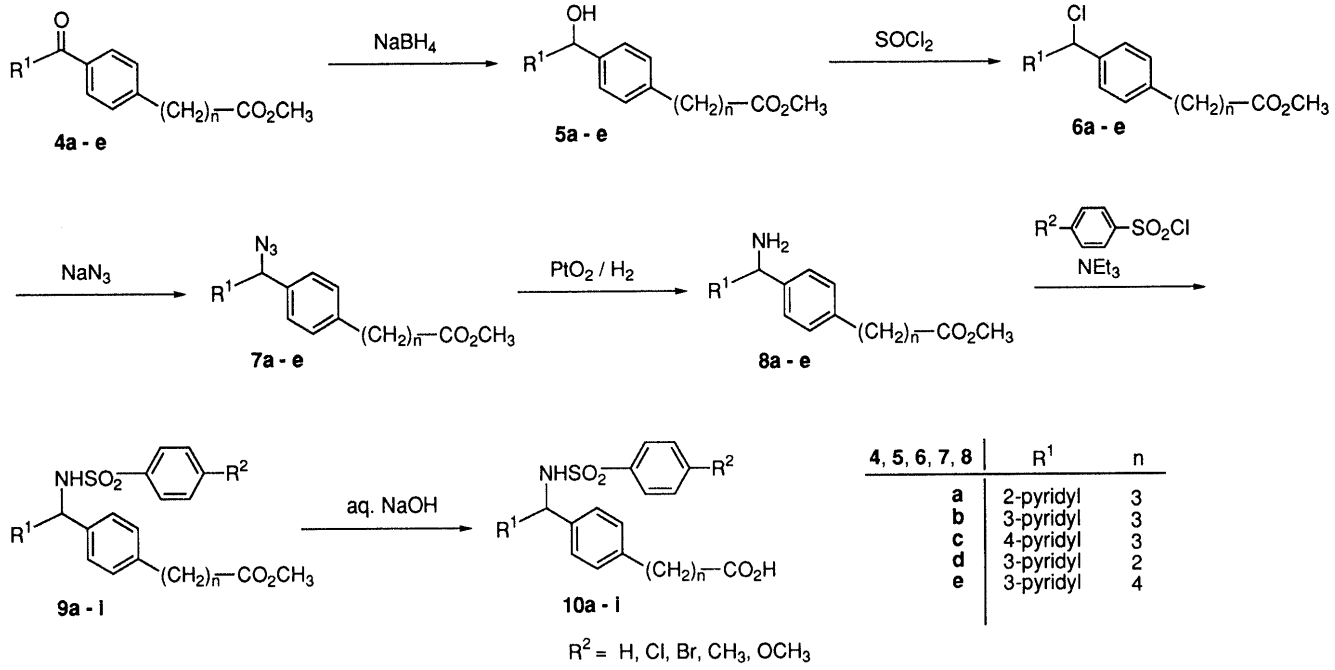



| 4, 5, 6, 7, 8 | $R^1$ | n |
|---|---|---|
| a | 2-pyridyl | 3 |
| b | 3-pyridyl | 3 |
| c | 4-pyridyl | 3 |
| d | 3-pyridyl | 2 |
| e | 3-pyridyl | 4 |

Chart 2

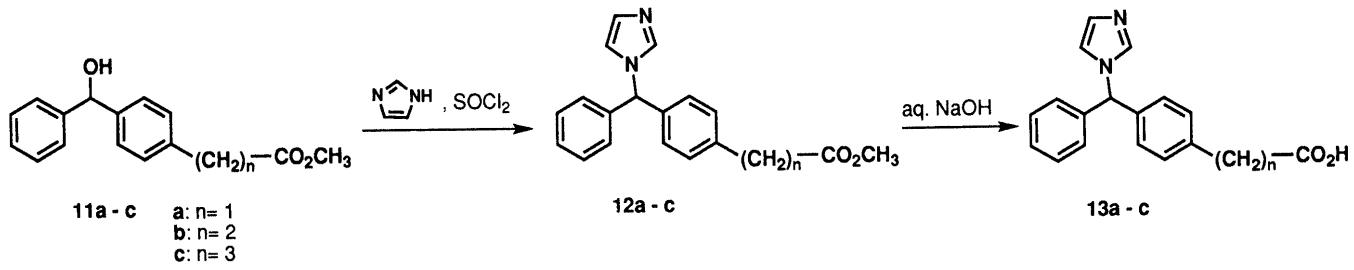



Chart 3

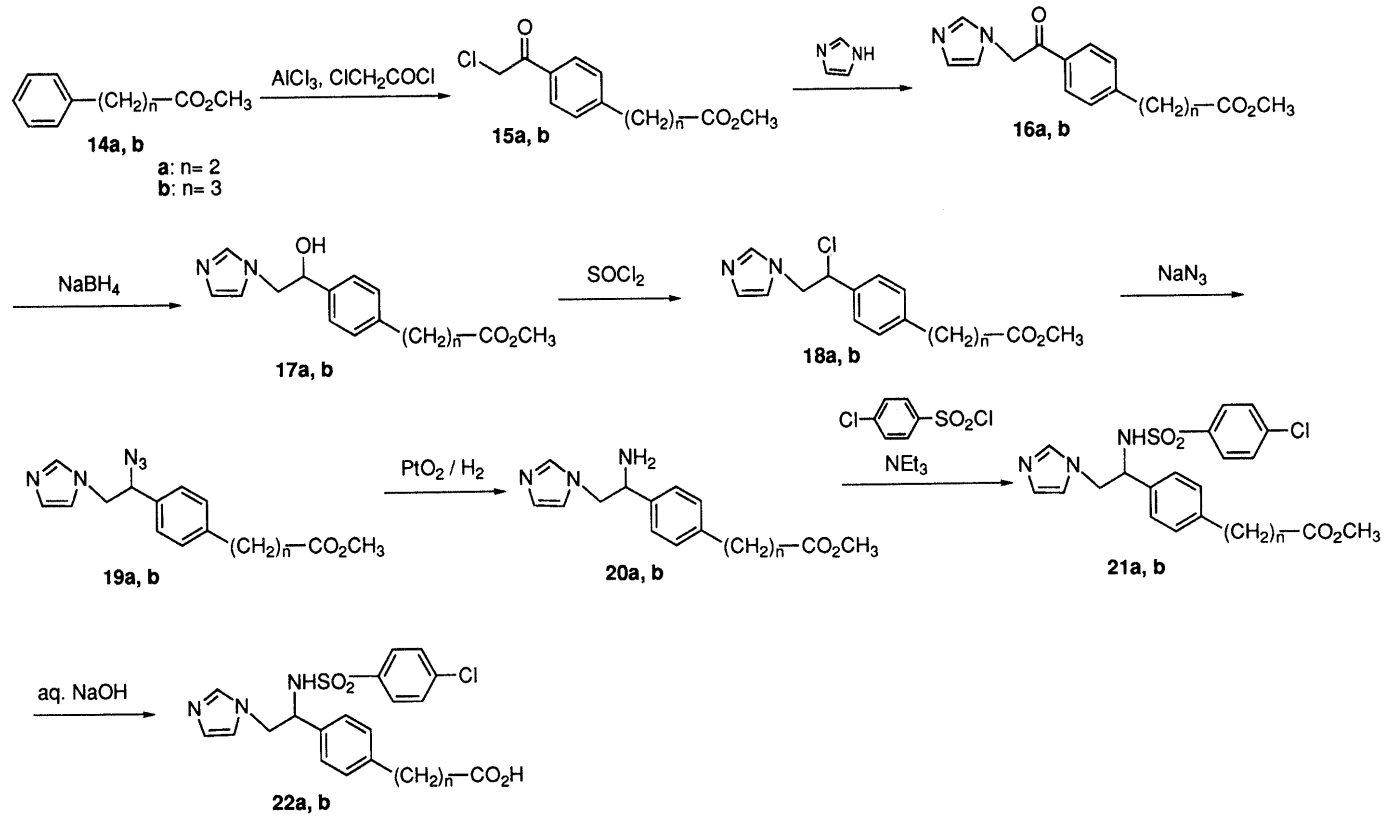



Chart 4

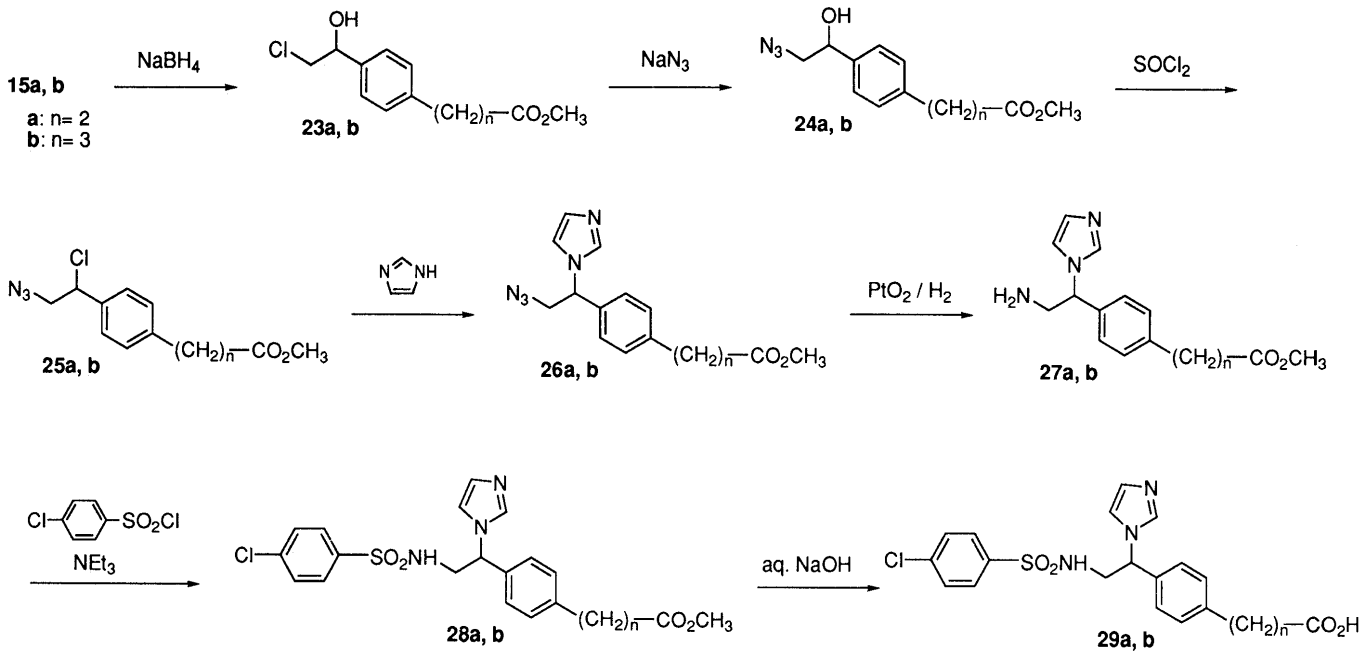



Chart 5

c) were synthesized as shown in Chart 3. Reaction of the alcohols (**11a—c**)[8] with imidazole and thionyl chloride gave **12a—c**, followed by alkaline hydrolysis to afford the desired compounds **13a—c**. Compounds **22a, b** were synthesized as shown in Chart 4. The Friedel–Crafts reaction of phenylalkanoates (**14a, b**) with chloroacetyl chloride in the presence of anhydrous aluminum chloride provided the chloroketones (**15a, b**). Condensation of **15a, b** with imidazole afforded **16a, b**, which were reduced with sodium borohydride to yield the alcohols (**17a, b**). The desired compounds **22a, b** were prepared from **17a, b** in 5 steps, similarly to **10a—i**. Compounds **29a, b** were synthesized as shown in Chart 5. Reduction of the chloroketones (**15a, b**) with sodium borohydride gave the alcohols (**23a, b**), which were treated with sodium azide to yield the azides (**24a, b**). After chlorination of **24a, b** with thionyl chloride, the chlorides (**25a, b**) were condensed with imidazole to afford **26a, b**. The desired compounds **29a, b** were prepared from **26a, b** in 3 steps, similarly to **10a—i**.

## Pharmacological Results and Discussion

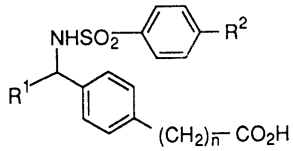
TXRA and TXSI activities of the synthetic compounds were estimated in terms of the inhibitory effects on U-46619[10]-induced guinea-pig platelet aggregation and on $TXB_2$ production in human platelets, respectively. The activities are given as $IC_{50}$ values in Tables 1—3.

First of all, we evaluated the pharmacological effects of the benzenesulfonamide derivatives containing a pyridyl group (**10a—i**). In the case of **10a—c**, which differ in substitution position on the pyridine ring, we expected that the TXSI activity of the 3-pyridyl compound (**10b**) would be stronger, based on the reported structure–activity relationships of TXSIs.[9b] However, **10a—c** showed similar TXSI activities to **1**. The TXRA activity of **10b**, the most potent of the three, was almost equal to that of **1**. Compounds **10f** and **10g**, having a methyl or a methoxy group at the $R^2$ position, were slightly more potent than **1** in terms of TXSI activity, while **10b, d, e** were as potent as, or slightly less potent than **1**. The TXRA activity of **10b** was slightly stronger than that of **1**, but the other compounds were less potent. Compounds **10b, h, i**, with different lengths of carbon chain attached to the carboxyl group, showed the following features. (i) TXSI activity of the ethyl chain compound (**10h**) was five times more potent than that of **1**. (ii) TXSI activities of the propyl and butyl chain compounds (**10b, i**) were as potent as that of **1**. (iii) TXRA activity of **10h** was much weaker than that of **1**. In conclusion, we have not yet found a good dual inhibitor among the benzenesulfonamide compounds containing a pyridyl group.

Next, we evaluated the pharmacological effects of the imidazole compounds. As a preliminary examination, we evaluated the pharmacological effects of the imidazole compounds (**13a—c**) without the benzenesulfonamido group, to investigate the influence of TXSI activities owing to the imidazolyl group. TXSI activities of **13a—c** were much stronger than that of **1**, and the ethyl chain compound (**13b**) was the most potent among those examined. The activity of **13b** was 500 times greater than that of **1** and comparable to that of ozagrel (**2**). However, the TXRA activity of each compound disappeared, probably because of the lack of the benzenesulfonamido group, which is important for TXRA activity.[2a]

Since we had confirmed enhancement of TXSI activity by introduction of the imidazolyl group, we next examined the pharmacological effects of the benzenesulfonamide derivatives containing the imidazolyl group (**22a, b, 29a, b**). The ethyl chain compound (**22a**) was about 10 times more potent than the propyl chain compound (**22b**) and 5 times more potent than **1** in terms of TXSI activity. On the other hand, the carbon chain length of the carboxyl group had little influence on TXRA activity, and **22a** and **22b** were each as potent as **1**. These results indicated that **22a** might be a well-balanced dual inhibitor having both TXRA and TXSI activities. The ethyl chain compound (**29a**), showed about 5 times stronger TXSI activity than the propyl chain

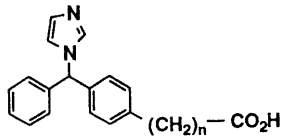
Table 1. Physicochemical and Pharmacological Data for Pyridyl-Substituted Sulfonamides **10a—i**




| Compd. No. | $R^{1}$ [a] | $R^2$ | $n$ | Yield [b] (%) | mp (°C) (Recryst. solv.) [c] | Formula | Analysis (%) Calcd (Found) C | H | N | $IC_{50}$ (μM) TX [d] antagonism | TX [e] synthase |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **10a** | 2-Py | Cl | 3 | 90 | 126—126.5 (IE) | $C_{22}H_{21}ClN_2O_4S$ | 59.39 (59.46 | 4.76 4.77 | 6.30 6.31) | 0.76 | 2.00 |
| **10b** | 3-Py | Cl | 3 | 84 | 183—185 (E) | $C_{22}H_{21}ClN_2O_4S$ | 59.39 (59.30 | 4.76 4.83 | 6.30 6.27) | 0.40 | 2.00 |
| **10c** | 4-Py | Cl | 3 | 90 | 182—183 (M) | $C_{22}H_{21}ClN_2O_4S$ | 59.39 (59.27 | 4.76 4.70 | 6.30 6.26) | 2.51 | 2.00 |
| **10d** | 3-Py | H | 3 | 80 | 164—167 (E) | $C_{22}H_{22}N_2O_4S$ | 64.27 (64.32 | 5.40 5.55 | 6.82 6.66) | 1.58 | 2.51 |
| **10e** | 3-Py | Br | 3 | 83 | 192—195 (M) | $C_{22}H_{21}BrN_2O_4S$ | 53.99 (53.83 | 4.33 4.38 | 5.72 5.67) | 0.50 | 2.51 |
| **10f** | 3-Py | $CH_3$ | 3 | 77 | 165—167 (E) | $C_{23}H_{24}N_2O_4S$ | 65.07 (64.96 | 5.70 5.93 | 6.60 6.56) | 0.79 | 1.58 |
| **10g** | 3-Py | $OCH_3$ | 3 | 77 | 166—167.5 (E) | $C_{23}H_{24}N_2O_5S$ | 62.71 (62.45 | 5.49 5.70 | 6.36 6.27) | 1.58 | 1.00 |
| **10h** | 3-Py | Cl | 2 | 84 | 210—212.5 (M) | $C_{21}H_{19}ClN_2O_4S$ | 58.53 (58.48 | 4.44 4.36 | 6.50 6.52) | 31.6 | 0.40 |
| **10i** | 3-Py | Cl | 4 | 87 | 201—203 (M) | $C_{23}H_{23}ClN_2O_4S$ | 60.19 (60.17 | 5.05 4.93 | 6.10 6.07) | 0.50 | 1.60 |
| **1** | Ph | Cl | 3 | — | 153—155.5 (EA–IE) | $C_{23}H_{22}ClNO_4S$ | 62.23 (62.10 | 4.99 5.03 | 3.16 2.97) | 0.20 | 2.00 |

*a*) Abbreviations: Py, pyridyl; Ph, phenyl. *b*) Yield from **9a—i**. *c*) Abbreviations: IE, isopropyl ether; E, ethanol; M, methanol; EA, ethyl acetate. *d*) Concentration needed to inhibit U-46619 (2 μg/ml)-induced platelet-aggregation in guinea-pig platelet-rich plasma (PRP) by 50%. *e*) Concentration needed to inhibit by 50% $TXB_2$ production in human platelets.

Table 2. Physicochemical and Pharmacological Data for Imidazolyl Derivatives **13a—c**



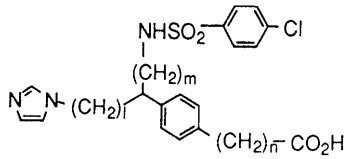

| Compd. No. | $n$ | Yield [a] (%) | mp (°C) (Recryst. solv.) [b] | Formula | Analysis (%) Calcd (Found) C | H | N | $IC_{50}$ (μM) TX [c] antagonism | TX [d] synthase |
|---|---|---|---|---|---|---|---|---|---|
| **13a** | 1 | 88 | 177—179 (E) | $C_{18}H_{16}N_2O_2$ | 73.96 (73.91 | 5.52 5.61 | 9.58 9.37) | >100 | 0.02 |
| **13b** | 2 | 82 | 138—139 (E–DE) | $C_{19}H_{18}N_2O_2$ | 74.49 (74.36 | 5.92 5.94 | 9.14 8.98) | >100 | 0.0040 |
| **13c** | 3 | 77 | 150—151.5 (M–IE) | $C_{20}H_{20}N_2O_2$ | 74.98 (74.87 | 6.29 6.11 | 8.74 8.67) | >100 | 0.35 |
| **2** | | | | | | | | N.T. [e] | 0.0079 |

*a*) Yield from **12a—c**. *b*) See footnote *c* in Table 1. DE, diethyl ether. *c*) See footnote *d* in Table 1. *d*) See footnote *e* in Table 1. *e*) Not tested.

compound (**29b**) or **1**, but its TXRA activity was weaker than that of **1**.

We estimated the most stable conformation of **22a**, which possesses well-balanced dual inhibitory activity, by molecular mechanics calculation using Nemesis (version 2.0, Oxford Molecular Ltd.) and compared it with the stable conformation[11a] of $TXA_2$ (in Fig. 1, the conformation of (*S*)-**22a** is indicated, as a matter of convenience). The most stable conformation of **22a** is a "hairpin form,"[8,11] in which the two benzene rings are arranged nearly in parallel to each other. Thus, the sulfonamido group is predicted to be fixed. An oxygen atom of the sulfonamido group approximately matched the C15-hydroxy of the ω-chain of $TXA_2$ when the carboxyl group of **22a** was superimposed on that of $TXA_2$. This result is similar to that for **1** in the preceding paper.[8] Further, the imidazole ring of **22a** was located close to the oxane ring moiety of $TXA_2$. It was considered that

Table 3. Physicochemical and Pharmacological Data for Imidazolyl-Substituted Sulfonamides **22a**, **b** and **29a**, **b**




| Compd. No. | *l* | *m* | *n* | Yield[a] (%) | mp (°C) (Recryst. solv.)[b] | Formula | Analysis (%) Calcd (Found) | | | $IC_{50}$ (μM) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N | TX[c] antagonism | TX[d] synthase |
| **22a** | 1 | 0 | 2 | 82 | 215—216.5 (M) | $C_{20}H_{20}ClN_3O_4S$ | 55.36 (55.25 | 4.65 4.58 | 9.68 9.68) | 0.31 | 0.39 |
| **22b** | 1 | 0 | 3 | 74 | 196—198 (M) | $C_{21}H_{22}ClN_3O_4S$ | 54.13 (54.38 | 5.19 5.03 | 9.02 9.01) | 0.25 | 3.02 |
| **29a** | 0 | 1 | 2 | 94 | Amorphous | $C_{20}H_{20}ClN_3O_4S$ | | — | | 2.70 | 0.40 |
| **29b** | 0 | 1 | 3 | 90 | 182—185 (M–A) | $C_{21}H_{22}ClN_3O_4S$ | 56.31 (56.44 | 4.95 4.91 | 9.38 9.27) | 0.62 | 1.86 |

*a*) Yield from **21a**, **b** and **28a**, **b**. *b*) See footnote *c* in Table 1. A, acetone. *c*) See footnote *d* in Table 1. *d*) See footnote *e* in Table 1.

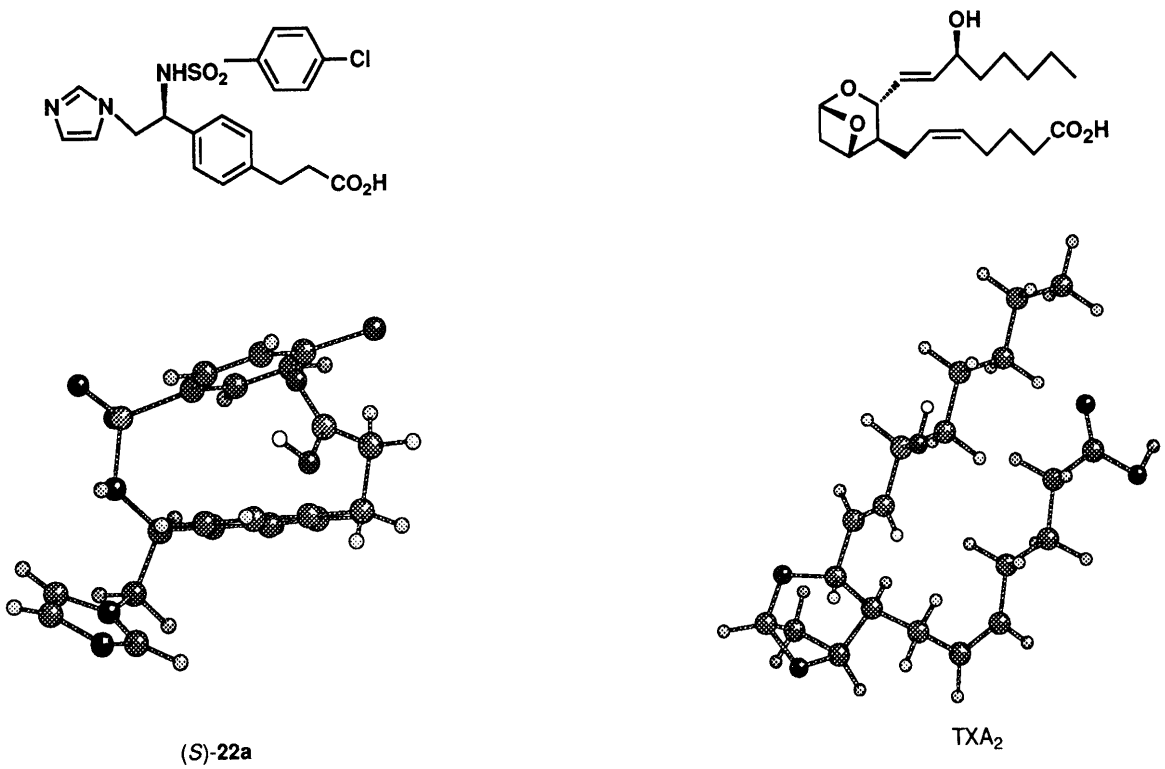



Fig. 1. The Stable Conformations of (*S*)-**22a** and $TXA_2$

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 (*S*)-**22a** were selected with a conformational search around single bonds rotated by 360° in 30° increments. The stable conformation was determined by energy minimization of initial conformations. For $TXA_2$, the stable conformation was determined in a similar manner using torsion angles described in the literature.[11a)]

these structural features could account for the strong TXRA activity of **22a**.

In conclusion, we found **22a**, a novel, well-balanced dual inhibitor having both TXRA and TXSI activities. Further pharmacological evaluations of **22a** are planned to evaluate its suitability as an antithrombotic agent and/or antiasthmatic agent.

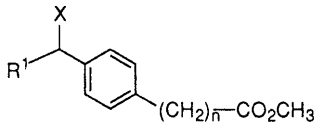
## Experimental

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 and high-resolution MS were measured on a JEOL DX-300 mass spectrometer. Merck Kieselgel 60 (70—230 mesh) was used for column chromatography. All extracts were dried over $Na_2SO_4$.

**Methyl 4-[4-[Hydroxy(2-pyridyl)methyl]phenyl]butyrate (5a)** $NaBH_4$ (0.67 g, 17.6 mmol) was added portionwise to a solution of methyl 4-[4-(2-pyridylcarbonyl)phenyl]butyrate (**4a** 5.00 g, 17.6 mmol) in MeOH (50 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 dissolved in dilute HCl and washed with $Et_2O$. The aqueous layer was made alkaline with $K_2CO_3$ and extracted with $Et_2O$. The extract was washed with water, dried and concentrated. The residue was purified by column chromatography [$SiO_2$, AcOEt–$CH_2Cl_2$ (2:1)] to yield **5a** (3.95 g, 79%) as a colorless oil.

Alcohols (**5b—e**) were prepared similarly from the corresponding

Table 4. Physicochemical Data for **5a—e**, **6a—e**, **7a—e**, **8a—e**




| Compd. No. | $R^{1}$ [a] | X | n | Yield [b] (%) | mp (°C) (Recryst. solv.) [c] | Formula | Analysis (%) Calcd C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | 2-Py | OH | 3 | 79 | Oil | $C_{17}H_{19}NO_3$ | 285.1365 [d] | | | 285.1355 | | |
| **5b** | 3-Py | OH | 3 | 62 | 85—86 (EA–IE) | $C_{17}H_{19}NO_3$ | 71.56 | 6.71 | 4.91 | 71.69 | 6.79 | 4.93 |
| **5c** | 4-Py | OH | 3 | 51 | 82—83.5 (EA–IE) | $C_{17}H_{19}NO_3$ | 71.56 | 6.71 | 4.91 | 71.57 | 6.55 | 4.95 |
| **5d** | 3-Py | OH | 2 | 56 | 91—91.5 (EA–IE) | $C_{16}H_{17}NO_3$ | 70.83 | 6.32 | 5.16 | 70.82 | 6.28 | 5.10 |
| **5e** | 3-Py | OH | 4 | 49 | 78—80 (EA–IE) | $C_{18}H_{21}NO_3$ | 72.22 | 7.07 | 4.68 | 72.07 | 7.12 | 4.65 |
| **6a** | 2-Py | Cl | 3 | 97 | Oil | $C_{17}H_{18}ClNO_2$ | 303.1026, 305.0997 [d] | | | 303.1027, 305.1005 | | |
| **6b** | 3-Py | Cl | 3 | 95 | Oil | $C_{17}H_{18}ClNO_2$ | 303.1026, 305.0997 [d] | | | 303.1032, 305.1008 | | |
| **6c** | 4-Py | Cl | 3 | 99 | Oil | $C_{17}H_{18}ClNO_2$ | 303.1026, 305.0997 [d] | | | 303.1021, 305.1010 | | |
| **6d** | 3-Py | Cl | 2 | 90 | Oil | $C_{16}H_{16}ClNO_2$ | 289.0870, 291.0840 [d] | | | 289.0866, 291.0854 | | |
| **6e** | 3-Py | Cl | 4 | 97 | Oil | $C_{18}H_{20}ClNO_2$ | 317.1183, 319.1153 [d] | | | 317.1165, 319.1171 | | |
| **7a** | 2-Py | $N_3$ | 3 | 99 | Oil | $C_{17}H_{18}N_4O_2$ | 310.1430 [d] | | | 310.1442 | | |
| **7b** | 3-Py | $N_3$ | 3 | 96 | Oil | $C_{17}H_{18}N_4O_2$ | 310.1430 [d] | | | 310.1432 | | |
| **7c** | 4-Py | $N_3$ | 3 | 86 | Oil | $C_{17}H_{18}N_4O_2$ | 310.1430 [d] | | | 310.1427 | | |
| **7d** | 3-Py | $N_3$ | 2 | 94 | Oil | $C_{16}H_{16}N_4O_2$ | 296.1273 [d] | | | 296.1264 | | |
| **7e** | 3-Py | $N_3$ | 4 | 88 | Oil | $C_{18}H_{20}N_4O_2$ | 324.1586 [d] | | | 324.1588 | | |
| **8a** | 2-Py | $NH_2$ | 3 | 84 | Oil | $C_{17}H_{20}N_2O_2$ | 284.1525 [d] | | | 284.1529 | | |
| **8b** | 3-Py | $NH_2$ | 3 | 95 | Oil | $C_{17}H_{20}N_2O_2$ | 284.1525 [d] | | | 284.1534 | | |
| **8c** | 4-Py | $NH_2$ | 3 | 96 | Oil | $C_{17}H_{20}N_2O_2$ | 284.1525 [d] | | | 284.1518 | | |
| **8d** | 3-Py | $NH_2$ | 2 | 75 | Oil | $C_{16}H_{18}N_2O_2$ | 270.1368 [d] | | | 270.1370 | | |
| **8e** | 3-Py | $NH_2$ | 4 | 89 | Oil | $C_{18}H_{22}N_2O_2$ | 298.1681 [d] | | | 298.1678 | | |

*a*) See footnote *a* in Table 1. *b*) Yield from **4a—e**, **5a—e**, **6a—e**, **7a—e**. *c*) See footnote *c* in Table 1. *d*) High-resolution MS data.

ketones (**4b—e**). Physicochemical data for **5a—e** are summarized in Tables 4 and 5.

**Methyl 4-[4-[Chloro(2-pyridyl)methyl]phenyl]butyrate (6a)** Thionyl chloride (3.55 ml, 49.8 mmol) was added dropwise to a solution of **5a** (7.11 g, 24.9 mmol) in benzene (35 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 h. The solvent was evaporated off under reduced pressure, and the residue was taken up in $CH_2Cl_2$. This solution was washed successively with aqueous $NaHCO_3$ solution and water. The extract was dried and concentrated to yield **6a** (7.34 g, 97%) as a pale violet oil.

Chlorides (**6b—e**) were prepared similarly from the corresponding alcohols (**5b—e**). Physicochemical data for **6a—e** are summarized in Tables 4 and 5.

**Methyl 4-[4-[Azido(2-pyridyl)methyl]phenyl]butyrate (7a)** A suspension of **6a** (7.34 g, 24.2 mmol) and sodium azide (3.14 g, 48.3 mmol) in *N*,*N*-dimethylformamide (DMF) (40 ml) was heated at 40 °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 to yield **7a** (7.40 g, 99%) as a pale brown oil.

Azides (**7b—e**) were prepared similarly from the corresponding chlorides (**6b—e**). Physicochemical data for **7a—e** are summarized in Tables 4 and 5.

**Methyl 4-[4-[Amino(2-pyridyl)methyl]phenyl]butyrate (8a)** A suspension of **7a** (5.00 g, 16.1 mmol) and $PtO_2$ (50 mg) in MeOH (50 ml) was hydrogenated at ambient temperature under a hydrogen atmosphere (1 atm) for 6 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 $Et_2O$. The extract was washed with water, dried and concentrated to yield **8a** (3.86 g, 84%) as a pale yellow oil.

Amines (**8b—e**) were prepared similarly from the corresponding azides (**7b—e**). Physicochemical data for **8a—e** are summarized in Tables 4 and 5.

**Methyl 4-[4-[(4-Chlorobenzenesulfonamido)(2-pyridyl)methyl]phenyl]butyrate (9a)** 4-Chlorobenzenesulfonyl chloride (2.82 g, 13.4 mmol) was added portionwise to a solution of **8a** (3.80 g, 13.4 mmol) and triethylamine (2.05 ml, 14.7 mmol) in $CH_2Cl_2$ (38 ml) under ice-cooling. The mixture was stirred at room temperature for 1 h, and then washed successively with water, aqueous $K_2CO_3$ solution and water. The extract was dried and concentrated to yield **9a** (5.33 g, 87%) as pale yellow crystals, which were recrystallized from EtOH to give colorless prisms.

Sulfonamides (**9b—i**) were prepared in a similar manner to that described above. Physicochemical data for **9a—i** are summarized in Tables 6 and 7.

**4-[4-[(4-Chlorobenzenesulfonamido)(2-pyridyl)methyl]phenyl]butyric Acid (10a)** A solution of **9a** (3.00 g, 6.54 mmol) and 2 N NaOH (12 ml) in MeOH (30 ml) was stirred at room temperature for 5 h. After evaporation of the solvent under reduced pressure, the residue was diluted with water, adjusted to pH 5 with dilute HCl, and then extracted with $CH_2Cl_2$. The extract was washed with water, dried and concentrated to yield **10a** (2.62 g, 90%) as colorless crystals, which were recrystallized from isopropyl ether (iso-$Pr_2O$) to give colorless plates.

Sulfonamides (**10b—i**) were prepared in a similar manner to that described above. Physicochemical data for **10a—i** are summarized in Tables 1 and 8.

**Methyl 4-[(1-Imidazolyl)phenylmethyl]phenylacetate (12a)** Thionyl chloride (0.86 ml, 11.8 mmol) was added dropwise to a solution of imidazole (3.27 g, 48 mmol) in $CH_3CN$ (30 ml), and the mixture was stirred at room temperature for 10 min. A solution of methyl 4-(hydroxyphenylmethy)phenylacetate (**11a**) (3.07 g, 12 mmol) in $CH_3CN$ (15 ml) was added to the reaction mixture, and the whole was refluxed for 1.5 h. After evaporation of the solvent under reduced pressure, the residue was diluted with aqueous $K_2CO_3$ solution, and extracted with $Et_2O$. The $Et_2O$ layer was extracted with dilute HCl, and the aqueous layer was made alkaline with $K_2CO_3$ and extracted with $Et_2O$. The extract was washed, dried and concentrated. The residue was purified by column chromatography [$SiO_2$, $CH_2Cl_2$–MeOH (100 : 1→50 : 1)] to yield **12a** (1.78 g, 48%) as a colorless oil. IR (liq.): 1738 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.63 (2H, s), 3.70 (3H, s), 6.51 (1H, s), 6.85 (1H, s), 7.00—7.15 (5H, m), 7.28 (2H, d, $J$=8 Hz), 7.30—7.40 (3H, m), 7.42 (1H, s). MS *m/z*: 306 ($M^+$).

Compounds **12b** and **12c** were prepared similarly from the corresponding alcohols **11b** and **11c**, respectively.

**Methyl 3-[4-[(1-Imidazolyl)phenylmethyl]phenyl]propionate (12b)** Colorless oil, yield 55%. IR (liq.): 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.63 (2H, t, $J$=8 Hz), 2.96 (2H, t, $J$=8 Hz), 3.67 (3H, s), 6.49 (1H,

Table 5. Spectral Data for **5a—e**, **6a—e**, **7a—e**, **8a—e**

| Compd. No. | IR (liq.) $cm^{-1}$ | MS *m/z* $M^+$ | $^1$H-NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|
| **5a** | 3396, 1738 | 285 | 1.93 (2H, qn, *J*=7.5 Hz), 2.31 (2H, t, *J*=7.5 Hz), 2.63 (2H, t, *J*=7.5 Hz), 3.65 (3H, s), 5.78 (1H, s), 7.15 (2H, d, *J*=8.5 Hz), 7.19 (1H, d, *J*=8 Hz), 7.23 (1H, dd, *J*=8, 5 Hz), 7.30 (2H, d, *J*=8.5 Hz), 7.66 (1H, td, *J*=8, 1.5 Hz), 8.58 (1H, d, *J*=5 Hz) |
| **5b** | 3176, 1734[a)] | 285 | 1.94 (2H, qn, *J*=7.5 Hz), 2.32 (2H, t, *J*=7.5 Hz), 2.47 (1H, br s), 2.64 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 5.86 (1H, s), 7.17 (2H, d, *J*=8 Hz), 7.25 (1H, dd, *J*=8, 5 Hz), 7.28 (2H, d, *J*=8 Hz), 7.70 (1H, dt, *J*=8, 2 Hz), 8.49 (1H, dd, *J*=5, 2 Hz), 8.62 (1H, d, *J*=2 Hz) |
| **5c** | 3124, 1734[a)] | 285 | 1.93 (2H, qn, *J*=7.5 Hz), 2.31 (2H, t, *J*=7.5 Hz), 2.63 (2H, t, *J*=7.5 Hz), 3.14 (1H, br s), 3.65 (3H, s), 5.78 (1H, s), 7.16 (2H, d, *J*=8.5 Hz), 7.25 (2H, d, *J*=8.5 Hz), 7.35 (2H, d, *J*=6 Hz), 8.49 (2H, d, *J*=6 Hz) |
| **5d** | 3148, 1734[a)] | 271 | 2.61 (2H, t, *J*=8 Hz), 2.78 (1H, br s), 2.95 (2H, t, *J*=8 Hz), 3.66 (3H, s), 5.85 (1H, s), 7.19 (2H, d, *J*=8 Hz), 7.25 (1H, dd, *J*=8, 5 Hz), 7.29 (2H, d, *J*=8 Hz), 7.69 (1H, dt, *J*=8, 2 Hz), 8.47 (1H, dd, *J*=5, 2 Hz), 8.59 (1H, d, *J*=2 Hz) |
| **5e** | 3176, 1744[a)] | 299 | 1.58—1.70 (4H, m), 2.32 (2H, t, *J*=7.5 Hz), 2.61 (2H, t, *J*=7.5 Hz), 2.69 (1H, br s), 3.65 (3H, s), 5.85 (1H, s), 7.16 (2H, d, *J*=8 Hz), 7.24 (1H, dd, *J*=8, 5 Hz), 7.27 (2H, d, *J*=8 Hz), 7.70 (1H, dt, *J*=8, 2 Hz), 8.47 (1H, dd, *J*=5, 2 Hz), 8.60 (1H, d, *J*=2 Hz) |
| **6a** | 1738 | 303, 305 (3:1) | 1.93 (2H, qn, *J*=7.5 Hz), 2.32 (2H, t, *J*=7.5 Hz), 2.63 (2H, t, *J*=7.5 Hz), 3.65 (3H, s), 6.16 (1H, s), 7.16 (2H, d, *J*=8.5 Hz), 7.21 (1H, ddd, *J*=8, 5, 1 Hz), 7.39 (2H, d, *J*=8.5 Hz), 7.57 (1H, d, *J*=8 Hz), 7.72 (1H, td, *J*=8, 1.5 Hz), 8.57 (1H, dd, *J*=5, 1.5 Hz) |
| **6b** | 1736 | 303, 305 (3:1) | 1.95 (2H, qn, *J*=7.5 Hz), 2.33 (2H, t, *J*=7.5 Hz), 2.65 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 6.12 (1H, s), 7.19 (2H, d, *J*=8.5 Hz), 7.31 (2H, d, *J*=8.5 Hz), 7.33 (1H, dd, *J*=8, 5 Hz), 7.80 (1H, dt, *J*=8, 2 Hz), 8.55 (1H, d, *J*=5 Hz), 8.65 (1H, br s) |
| **6c** | 1738 | 303, 305 (3:1) | 1.95 (2H, qn, *J*=7.5 Hz), 2.33 (2H, t, *J*=7.5 Hz), 2.65 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 6.02 (1H, s), 7.18 (2H, d, *J*=8 Hz), 7.27 (2H, d, *J*=8 Hz), 7.37 (2H, d, *J*=6 Hz), 8.60 (2H, d, *J*=6 Hz) |
| **6d** | 1738 | 289, 291 (3:1) | 2.63 (2H, t, *J*=8 Hz), 2.95 (2H, t, *J*=8 Hz), 3.67 (3H, s), 6.12 (1H, s), 7.21 (2H, d, *J*=8 Hz), 7.31 (2H, d, *J*=8 Hz), 7.33 (1H, dd, *J*=8, 5 Hz), 7.80 (1H, dt, *J*=8, 2 Hz), 8.55 (1H, dd, *J*=5, 2 Hz), 8.64 (1H, d, *J*=2 Hz) |
| **6e** | 1736 | 317, 319 (3:1) | 1.59—1.71 (4H, m), 2.33 (2H, t, *J*=7.5 Hz), 2.63 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 6.12 (1H, s), 7.17 (2H, d, *J*=8 Hz), 7.30 (2H, d, *J*=8 Hz), 7.31 (1H, dd, *J*=8, 5 Hz), 7.78 (1H, dt, *J*=8, 2 Hz), 8.54 (1H, dd, *J*=5, 2 Hz), 8.64 (1H, d, *J*=2 Hz) |
| **7a** | 2104, 1736 | 310 | 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), 5.77 (1H, s), 7.18 (2H, d, *J*=8 Hz), 7.21 (1H, ddd, *J*=8, 5, 1 Hz), 7.28 (2H, d, *J*=8 Hz), 7.36 (1H, d, *J*=8 Hz), 7.70 (1H, td, *J*=8, 1.5 Hz), 8.59 (1H, dd, *J*=5, 1.5 Hz) |
| **7b** | 2104, 1738 | 310 | 1.95 (2H, qn, *J*=7.5 Hz), 2.33 (2H, t, *J*=7.5 Hz), 2.65 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 5.72 (1H, s), 7.20 (2H, d, *J*=6 Hz), 7.21 (2H, d, *J*=6 Hz), 7.30 (1H, dd, *J*=8, 5 Hz), 7.64 (1H, dt, *J*=8, 2 Hz), 8.56 (1H, dd, *J*=5, 2 Hz), 8.58 (1H, d, *J*=2 Hz) |
| **7c** | 2108, 1736 | 310 | 1.82 (2H, qn, *J*=7.5 Hz), 2.29 (2H, t, *J*=7.5 Hz), 2.59 (2H, t, *J*=7.5 Hz), 3.57 (3H, s), 6.11 (1H, s), 7.23 (2H, d, *J*=8.5 Hz), 7.27 (2H, d, *J*=8.5 Hz), 7.34 (2H, d, *J*=6 Hz), 8.56 (2H, d, *J*=6 Hz) |
| **7d** | 2104, 1738 | 296 | 2.63 (2H, t, *J*=7.5 Hz), 2.95 (2H, t, *J*=7.5 Hz), 3.67 (3H, s), 5.72 (1H, s), 7.22 (4H, s), 7.30 (1H, dd, *J*=8, 5 Hz), 7.64 (1H, dt, *J*=8, 2 Hz), 8.56 (1H, dd, *J*=5, 2 Hz), 8.58 (1H, d, *J*=2 Hz) |
| **7e** | 2104, 1736 | 324 | 1.60—1.71 (4H, m), 2.33 (2H, t, *J*=7.5 Hz), 2.63 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 5.72 (1H, s), 7.20 (4H, s), 7.32 (1H, dd, *J*=8, 5 Hz), 7.66 (1H, dt, *J*=8, 2 Hz), 8.56 (1H, dd, *J*=5, 2 Hz), 8.59 (1H, d, *J*=2 Hz) |
| **8a** | 3376, 3300, 1736 | 284 | 1.93 (2H, qn, *J*=7.5 Hz), 2.20 (2H, br s), 2.31 (2H, t, *J*=7.5 Hz), 2.61 (2H, t, *J*=7.5 Hz), 3.65 (3H, s), 5.22 (1H, s), 7.12—7.15 (1H, m), 7.13 (2H, d, *J*=8 Hz), 7.25 (1H, d, *J*=7.5 Hz), 7.31 (2H, d, *J*=8 Hz), 7.59 (1H, td, *J*=7.5, 2 Hz), 8.56 (1H, d, *J*=4 Hz) |
| **8b** | 3372, 3304, 1736 | 284 | 1.80—2.10 (2H, br), 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), 5.23 (1H, s), 7.14 (2H, d, *J*=8 Hz), 7.23 (1H, dd, *J*=8, 5 Hz), 7.28 (2H, d, *J*=8 Hz), 7.70 (1H, dt, *J*=8, 2 Hz), 8.47 (1H, dd, *J*=5, 2 Hz), 8.64 (1H, d, *J*=2 Hz) |
| **8c** | 3372, 3300, 1732 | 284 | 1.65—1.98 (2H, br), 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), 5.15 (1H, s), 7.14 (2H, d, *J*=8 Hz), 7.24 (2H, d, *J*=8 Hz), 7.32 (2H, d, *J*=6 Hz), 8.52 (2H, d, *J*=6 Hz) |
| **8d** | 3372, 3300, 1734 | 270 | 1.76 (2H, br s), 2.61 (2H, t, *J*=8 Hz), 2.93 (2H, t, *J*=8 Hz), 3.66 (3H, s), 5.23 (1H, s), 7.16 (2H, d, *J*=8 Hz), 7.23 (1H, dd, *J*=8, 5 Hz), 7.29 (2H, d, *J*=8 Hz), 7.69 (1H, dt, *J*=8, 2 Hz), 8.48 (1H, dd, *J*=5, 2 Hz), 8.64 (1H, d, *J*=2 Hz) |
| **8e** | 3380, 3304, 1738 | 298 | 1.56—1.71 (4H, m), 1.76 (2H, br s), 2.32 (2H, t, *J*=7.5 Hz), 2.60 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 5.22 (1H, s), 7.13 (2H, d, *J*=8 Hz), 7.23 (1H, dd, *J*=8, 5 Hz), 7.27 (2H, d, *J*=8 Hz), 7.70 (1H, dt, *J*=8, 2 Hz), 8.47 (1H, dd, *J*=5, 2 Hz), 8.64 (1H, d, *J*=2 Hz) |

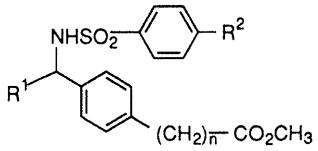
*a*) KBr.

s), 6.85 (1H, s), 7.03 (2H, d, *J*=8 Hz), 7.05—7.15 (3H, m), 7.20 (2H, d, *J*=8 Hz), 7.30—7.40 (3H, m), 7.45 (1H, s). MS *m/z*: 320 ($M^+$).

**Methyl 4-[4-[(1-Imidazolyl)phenylmethyl]phenyl]butyrate (12c)** Colorless oil, yield 56%. IR (liq.): 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.95 (2H, qn, *J*=7.5 Hz), 2.33 (2H, t, *J*=7.5 Hz), 2.65 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 6.48 (1H, s), 6.84 (1H, s), 7.03 (2H, d, *J*=8 Hz), 7.09—7.11 (3H, m), 7.17 (2H, d, *J*=8 Hz), 7.33—7.37 (3H, m), 7.40 (1H, s). MS *m/z*: 334 ($M^+$). High-resolution MS *m/z*: Calcd for $C_{21}H_{22}N_2O_2$: 334.1681. Found: 334.1683.

**4-[(1-Imidazolyl)phenylmethyl]phenylacetic Acid (13a)** A solution of **12a** (1.66 g, 5.42 mmol) and 2 N NaOH (5.4 ml) in MeOH (8 ml) was refluxed for 1 h. After evaporation of the solvent under reduced pressure, the residue was diluted with water, adjusted to pH 5 with dilute HCl, and then extracted with $CH_2Cl_2$. The extract was dried and concentrated to yield **13a** (1.39 g, 88%) as colorless crystals, which were recrystallized from EtOH to give colorless prisms, mp 177—179 °C. IR (KBr): 1714

Table 6. Physicochemical Data for Pyridyl-Substituted Sulfonamides **9a—i**




| Compd. No. | $R^{1a)}$ | $R^2$ | $n$ | Yield[b] (%) | mp (°C) (Recryst. solv.)[c] | Formula | Analysis (%) Calcd C | Calcd H | Calcd N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **9a** | 2-Py | Cl | 3 | 87 | 97.5—98.5 (E) | $C_{23}H_{23}ClN_2O_4S$ | 60.19 | 5.05 | 6.10 | 60.25 | 5.03 | 6.05 |
| **9b** | 3-Py | Cl | 3 | 58 | Oil | $C_{23}H_{23}ClN_2O_4S$ | 458.1067, 460.1038[d] | | | 458.1072, 460.1049 | | |
| **9c** | 4-Py | Cl | 3 | 32 | 134.5—135 (E) | $C_{23}H_{23}ClN_2O_4S$ | 60.19 | 5.05 | 6.10 | 60.10 | 5.07 | 6.06 |
| **9d** | 3-Py | H | 3 | 47 | Oil | $C_{23}H_{24}N_2O_4S$ | 424.1457[d] | | | 424.1442 | | |
| **9e** | 3-Py | Br | 3 | 58 | Oil | $C_{23}H_{23}BrN_2O_4S$ | 502.0562, 504.0542[d] | | | 502.0570, 504.0546 | | |
| **9f** | 3-Py | $CH_3$ | 3 | 60 | Oil | $C_{24}H_{26}N_2O_4S$ | 438.1613[d] | | | 438.1629 | | |
| **9g** | 3-Py | $OCH_3$ | 3 | 57 | Oil | $C_{24}H_{26}N_2O_5S$ | 454.1562[d] | | | 454.1555 | | |
| **9h** | 3-Py | Cl | 2 | 43 | 161—162.5 (E) | $C_{22}H_{21}ClN_2O_4S$ | 59.39 | 4.76 | 6.30 | 59.42 | 4.61 | 6.32 |
| **9i** | 3-Py | Cl | 4 | 55 | 132—133.5 (E–IE) | $C_{24}H_{25}ClN_2O_4S$ | 60.94 | 5.33 | 5.92 | 61.03 | 5.31 | 5.89 |

*a*) See footnote *a* in Table 1. *b*) Yield from **8a—e**. *c*) See footnote *c* in Table 1. *d*) High-resolution MS data.

Table 7. Spectral Data for Pyridyl-Substituted Sulfonamides **9a—i**

| Compd. No. | IR (liq.) $cm^{-1}$ | MS $m/z$ $M^+$ | $^1$H-NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|
| **9a** | 3092, 1734[a)] | 458, 460 (3 : 1) | 1.88 (2H, qn, $J$=7.5 Hz), 2.30 (2H, t, $J$=7.5 Hz), 2.55 (2H, t, $J$=7.5 Hz), 3.66 (3H, s), 5.58 (1H, d, $J$=5.5 Hz), 6.97 (2H, d, $J$=8.5 Hz), 7.01—7.10 (2H, m), 7.05 (2H, d, $J$=8.5 Hz), 7.14—7.21 (1H, m), 7.19 (2H, d, $J$=8.5 Hz), 7.51—7.59 (1H, m), 7.53 (2H, d, $J$=8.5 Hz), 8.48 (1H, d, $J$=5 Hz) |
| **9b** | 3272, 1736 | 458, 460 (3 : 1) | 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), 5.63 (2H, s), 6.97 (2H, d, $J$=8.5 Hz), 7.05 (2H, d, $J$=8.5 Hz), 7.22 (1H, dd, $J$=8, 5 Hz), 7.30 (2H, d, $J$=9 Hz), 7.56 (1H, dt, $J$=8, 2 Hz), 7.59 (2H, d, $J$=9 Hz), 8.43 (1H, br s), 8.48 (1H, d, $J$=5 Hz) |
| **9c** | 3268, 1730[a)] | 458, 460 (3 : 1) | 1.90 (2H, qn, $J$=7.5 Hz), 2.31 (2H, t, $J$=7.5 Hz), 2.59 (2H, t, $J$=7.5 Hz), 3.67 (3H, s), 5.54 (1H, d, $J$=7.5 Hz), 5.64 (1H, d, $J$=7.5 Hz), 6.90 (2H, d, $J$=8 Hz), 7.05 (2H, d, $J$=8 Hz), 7.18 (2H, d, $J$=5.5 Hz), 7.33 (2H, d, $J$=8.5 Hz), 7.61 (2H, d, $J$=8.5 Hz), 8.48 (2H, d, $J$=5.5 Hz) |
| **9d** | 3272, 1736 | 424 | 1.89 (2H, qn, $J$=7.5 Hz), 2.28 (2H, t, $J$=7.5 Hz), 2.58 (2H, t, $J$=7.5 Hz), 3.66 (3H, s), 5.53 (1H, d, $J$=7 Hz), 5.60 (1H, d, $J$=7 Hz), 6.95 (2H, d, $J$=8.5 Hz), 7.03 (2H, d, $J$=8.5 Hz), 7.17 (1H, dd, $J$=8.5, 5 Hz), 7.36 (2H, t, $J$=8 Hz), 7.49 (1H, t, $J$=8 Hz), 7.55 (1H, d, $J$=8.5 Hz), 7.69 (2H, dd, $J$=8, 1.5 Hz), 8.36 (1H, br s), 8.44 (1H, d, $J$=5 Hz) |
| **9e** | 3268, 1736 | 502, 504 (1 : 1) | 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), 5.61 (1H, d, $J$=7.5 Hz), 5.92 (1H, d, $J$=7.5 Hz), 6.96 (2H, d, $J$=8 Hz), 7.04 (2H, d, $J$=8 Hz), 7.17 (1H, dd, $J$=7.5, 5 Hz), 7.45 (2H, d, $J$=9 Hz), 7.50 (2H, d, $J$=9 Hz), 7.52 (1H, dt, $J$=7.5, 2 Hz), 8.39 (1H, d, $J$=2 Hz), 8.44 (1H, dd, $J$=5, 2 Hz) |
| **9f** | 3276, 1738 | 438 | 1.89 (2H, qn, $J$=7.5 Hz), 2.29 (2H, t, $J$=7.5 Hz), 2.38 (3H, s), 2.59 (2H, t, $J$=7.5 Hz), 3.66 (3H, s), 5.29 (1H, d, $J$=7.5 Hz), 5.56 (1H, d, $J$=7.5 Hz), 6.96 (2H, d, $J$=8 Hz), 7.04 (2H, d, $J$=8 Hz), 7.14 (1H, dd, $J$=7.5, 5 Hz), 7.17 (2H, d, $J$=8.5 Hz), 7.55—7.59 (1H, m), 7.58 (2H, d, $J$=8.5 Hz), 8.37 (1H, br s), 8.45 (1H, d, $J$=5 Hz) |
| **9g** | 3272, 1736 | 454 | 1.89 (2H, qn, $J$=7.5 Hz), 2.29 (2H, t, $J$=7.5 Hz), 2.58 (2H, t, $J$=7.5 Hz), 3.65 (3H, s), 3.83 (3H, s), 5.54 (1H, d, $J$=7 Hz), 5.65 (1H, d, $J$=7 Hz), 6.81 (2H, d, $J$=9 Hz), 6.97 (2H, d, $J$=8.5 Hz), 7.04 (2H, d, $J$=8.5 Hz), 7.15 (1H, dd, $J$=7.5, 5 Hz), 7.54 (1H, dt, $J$=7.5, 2 Hz), 7.61 (2H, d, $J$=9 Hz), 8.36 (1H, d, $J$=2 Hz), 8.42 (1H, dd, $J$=5, 2 Hz) |
| **9h** | 1736[a)] | 444, 446 (3 : 1) | 2.59 (2H, t, $J$=7.5 Hz), 2.90 (2H, t, $J$=7.5 Hz), 3.67 (3H, s), 5.30 (1H, d, $J$=7 Hz), 5.61 (1H, d, $J$=7 Hz), 6.97 (2H, d, $J$=8 Hz), 7.08 (2H, d, $J$=8 Hz), 7.17 (1H, dd, $J$=8, 5 Hz), 7.31 (2H, d, $J$=8.5 Hz), 7.50 (1H, dt, $J$=8, 2 Hz), 7.58 (2H, d, $J$=8.5 Hz), 8.38 (1H, d, $J$=2 Hz), 8.47 (1H, dd, $J$=5, 2 Hz) |
| **9i** | 1738[a)] | 472, 474 (3 : 1) | 1.56—1.68 (4H, m), 2.33 (2H, t, $J$=7.5 Hz), 2.57 (2H, t, $J$=7.5 Hz), 3.66 (3H, s), 5.34 (1H, d, $J$=7 Hz), 5.61 (1H, d, $J$=7 Hz), 6.94 (2H, d, $J$=8.5 Hz), 7.04 (2H, d, $J$=8.5 Hz), 7.17 (2H, dd, $J$=8, 5 Hz), 7.30 (2H, d, $J$=8.5 Hz), 7.51 (1H, dt, $J$=8, 2 Hz), 7.58 (2H, d, $J$=8.5 Hz), 8.40 (1H, d, $J$=2 Hz), 8.46 (1H, dd, $J$=5, 2 Hz) |

*a*) KBr.

Table 8. Spectral Data for Pyridyl-Substituted Sulfonamides **10a—i**

| Compd. No. | IR (KBr) $cm^{-1}$ | MS *m/z* $M^+$ | $^1$H-NMR ($CD_3OD$) $\delta$ (ppm) |
|---|---|---|---|
| **10a** | 3168, 1696 | 444, 446 (3:1) | 1.83 (2H, qn, *J*=7.5 Hz), 2.24 (2H, t, *J*=7.5 Hz), 2.56 (2H, t, *J*=7.5 Hz), 5.60 (1H, s), 7.02 (4H, s), 7.17—7.22 (1H, m), 7.29—7.35 (1H, m), 7.32 (2H, d, *J*=9 Hz), 7.61 (2H, d, *J*=9 Hz), 7.66 (1H, td, *J*=7.5, 2 Hz), 8.37 (1H, d, *J*=4.5 Hz) |
| **10b** | 3256, 1698 | 444,446 (3:1) | 1.85 (2H, qn, *J*=7.5 Hz), 2.26 (2H, t, *J*=7.5 Hz), 2.59 (2H, t, *J*=7.5 Hz), 5.67 (1H, s), 7.01 (2H, d, *J*=8 Hz), 7.06 (2H, d, *J*=8 Hz), 7.31 (1H, dd, *J*=8.5, 5 Hz), 7.34 (2H, d, *J*=9 Hz), 7.61 (2H, d, *J*=9 Hz), 7.65 (1H, d, *J*=8.5 Hz), 8.35 (1H, br s), 8.37 (1H, d, *J*=5 Hz) |
| **10c** | 3212, 1696 | 269 ($M^+ - C_6H_4ClSO_2$) | 1.84 (2H, qn, *J*=7.5 Hz), 2.26 (2H, t, *J*=7.5 Hz), 2.58 (2H, t, *J*=7.5 Hz), 5.60 (1H, s), 6.97 (2H, d, *J*=8.5 Hz), 7.04 (2H, d, *J*=8.5 Hz), 7.28 (2H, d, *J*=4.5 Hz), 7.34 (2H, d, *J*=8.5 Hz), 7.62 (2H, d, *J*=8.5 Hz), 8.39 (2H, d, *J*=4.5 Hz) |
| **10d** | 3260, 1702 | 411 ($M^+ + 1$) | 1.84 (2H, qn, *J*=7.5 Hz), 2.24 (2H, t, *J*=7.5 Hz), 2.57 (2H, t, *J*=7.5 Hz), 5.65 (1H, s), 7.00 (2H, d, *J*=8 Hz), 7.04 (2H, d, *J*=8 Hz), 7.29 (1H, dd, *J*=8, 5 Hz), 7.35 (2H, t, *J*=8 Hz), 7.47 (1H, t, *J*=8 Hz), 7.64 (1H, dt, *J*=8, 2 Hz), 7.68 (2H, dd, *J*=8, 1.5 hz), 8.32 (1H, d, *J*=2 Hz), 8.34 (1H, dd, *J*=5, 2 Hz) |
| **10e** | 3256, 1696 | 444, 446 (1:1, $M^+ - CO_2$) | 1.86 (2H, qn, *J*=7.5 Hz), 2.27 (2H, t, *J*=7.5 Hz), 2.59 (2H, t, *J*=7.5 Hz), 5.66 (1H, s), 7.00 (2H, d, *J*=8.5 Hz), 7.06 (2H, d, *J*=8.5 Hz), 7.31 (1H, dd, *J*=8, 5 Hz), 7.49 (2H, d, *J*=9 Hz), 7.54 (2H, d, *J*=9 Hz), 7.65 (1H, d, *J*=8 Hz), 8.35 (1H, d, *J*=2 Hz), 8.37 (1H, dd, *J*=5, 2 Hz) |
| **10f** | 3256, 1706 | 425 ($M^+ + 1$) | 1.84 (2H, qn, *J*=7.5 Hz), 2.25 (2H, t, *J*=7.5 Hz), 2.35 (3H, s), 2.58 (2H, t, *J*=7.5 Hz), 5.61 (1H, s), 7.00 (2H, d, *J*=8.5 Hz), 7.05 (2H, d, *J*=8.5 Hz), 7.16 (2H, d, *J*=8 Hz), 7.29 (1H, dd, *J*=7.5, 5 Hz), 7.54 (2H, d, *J*=8 Hz), 7.63 (1H, dt, *J*=7.5, 2 Hz), 8.31 (1H, d, *J*=2 Hz), 8.34 (1H, dd, *J*=5, 2 Hz) |
| **10g** | 3256, 1700 | 441 ($M^+ + 1$) | 1.84 (2H, qn, *J*=7.5 Hz), 2.25 (2H, t, *J*=7.5 Hz), 2.58 (2H, t, *J*=7.5 Hz), 3.81 (3H, s), 5.59 (1H, s), 6.85 (2H, d, *J*=8.5 Hz), 7.01 (2H, d, *J*=8.5 Hz), 7.06 (2H, d, *J*=8.5 Hz), 7.30 (1H, dd, *J*=8, 5 Hz), 7.59 (2H, d, *J*=8.5 Hz), 7.64 (1H, d, *J*=8 Hz), 8.32 (1H, br s), 8.34 (1H, d, *J*=5 Hz) |
| **10h** | 3252, 1698 | 255 ($M^+ - C_6H_4ClSO_2$) | 2.55 (2H, t, *J*=7.5 Hz), 2.85 (2H, t, *J*=7.5 Hz), 5.66 (1H, s), 7.01 (2H, d, *J*=7 Hz), 7.09 (2H, d, *J*=7 Hz), 7.31 (1H, dd, *J*=8, 5 Hz), 7.34 (2H, d, *J*=8.5 Hz), 7.61 (2H, d, *J*=8.5 Hz), 7.64 (1H, d, *J*=8 Hz), 8.34 (1H, s), 8.36 (1H, d, *J*=5 Hz) |
| **10i** | 3256, 1696 | 458, 460 (3:1) | 1.54—1.64 (4H, m), 2.31 (2H, t, *J*=7 Hz), 2.57 (2H, t, *J*=7 Hz), 5.66 (1H, s), 6.99 (2H, d, *J*=8 Hz), 7.04 (2H, d, *J*=8 Hz), 7.31 (1H, dd, *J*=8, 5 Hz), 7.33 (2H, d, *J*=9 Hz), 7.61 (2H, d, *J*=9 Hz), 7.65 (1H, d, *J*=8 Hz), 8.35 (1H, d, *J*=2 Hz), 8.37 (1H, dd, *J*=5, 2 Hz) |

(C=O) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.57 (2H, s), 6.83 (1H, s), 6.95 (1H, s), 7.05—7.15 (5H, m), 7.28 (2H, d, *J*=8 Hz), 7.30—7.40 (3H, m), 7.61 (1H, s). MS *m/z*: 292 ($M^+$). *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.91; H, 5.61; N, 9.37.

Compounds **13b** and **13c** were prepared similarly from **12b** and **12c**, respectively.

**3-[4-[(1-Imidazolyl)phenylmethyl]phenyl]propionic Acid (13b)** Colorless crystals, mp 138—139 °C (EtOH–$Et_2O$), yield 82%. IR (KBr): 1710 (C=O) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.53 (2H, t, *J*=7.5 Hz), 2.83 (2H, t, *J*=7.5 Hz), 6.80 (1H, s), 6.95 (1H, s), 7.00—7.15 (5H, m), 7.24 (2H, d, *J*=8 Hz), 7.30—7.40 (3H, m), 7.61 (1H, s). MS *m/z*: 306 ($M^+$). *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.36; H, 5.94; N, 8.98.

**4-[4-[(1-Imidazolyl)phenylmethyl]phenyl]butyric Acid (13c)** Colorless needles, mp 150—151.5 °C (MeOH–iso-$Pr_2O$), yield 77%. IR (KBr): 1710 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.96 (2H, qn, *J*=7.5 Hz), 2.34 (2H, t, *J*=7.5 Hz), 2.67 (2H, t, *J*=7.5 Hz), 6.47 (1H, s), 6.85 (1H, s), 7.01 (2H, d, *J*=8.5 Hz), 7.07—7.09 (2H, m), 7.11 (1H, s), 7.18 (2H, d, *J*=8.5 Hz), 7.34—7.36 (3H, m), 7.49 (1H, s). MS *m/z*: 320 ($M^+$). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.87; H, 6.11; N, 8.67.

**Methyl 3-(4-Chloroacetylphenyl)propionate (15a)** Anhydrous aluminum chloride (11.9 g, 89.2 mol) was added portionwise to a solution of methyl 3-phenylpropionate (**14a**) (7.33 g, 44.6 mmol) in $CS_2$ (22 ml), and then chloroacetyl chloride (3.55 ml, 44.6 mmol) was added dropwise to the mixture under ice-cooling. The reaction mixture was stirred at room temperature for 16 h. After removal of the organic layer by decantation, the residue was taken up in $CH_2Cl_2$. This solution was poured into ice water and extracted with $CH_2Cl_2$. The extract was washed successively with aqueous $K_2CO_3$ solution and water, then dried and concentrated. The residual crystals were washed with iso-$Pr_2O$ to yield **15a** (9.45 g, 88%) as pale yellow crystals, which were recrystallized from iso-$Pr_2O$ to give colorless columns, mp 89—90.5 °C. IR (KBr): 1732, 1698 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.67 (2H, t, *J*=7.5 Hz), 3.03 (2H, t, *J*=7.5 Hz), 3.67 (3H, s), 4.69 (2H, s), 7.33 (2H, d, *J*=8 Hz), 7.89 (2H, d, *J*=8 Hz). MS *m/z*: 240, 242 (3:1, $M^+$). *Anal.* Calcd for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44. Found: C, 60.02; H, 5.38.

Compound **15b** was prepared similarly from methyl 4-phenylbutyrate (**14b**).

**Methyl 4-(4-Chloroacetylphenyl)butyrate (15b)** Colorless needles, mp 45—45.5 °C (iso-$Pr_2O$), yield 67%. IR (KBr): 1738, 1696 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.99 (2H, qn, *J*=7.5 Hz), 2.35 (2H, t, *J*=7.5 Hz), 2.73 (2H, t, *J*=7.5 Hz), 3.67 (3H, s), 4.69 (2H, s), 7.31 (2H, d, *J*=8.5 Hz), 7.89 (2H, d, *J*=8.5 Hz). MS *m/z*: 254, 256 (3:1, $M^+$). *Anal.* Calcd for $C_{13}H_{15}ClO_3$: C, 61.30; H, 5.94. Found: C, 61.32; H, 6.04.

**Methyl 3-[4-[(1-Imidazolyl)acetyl]phenyl]propionate (16a)** The mixture of **15a** (7.22 g, 30.1 mmol) and imidazole (5.11 g, 75.1 mmol) in toluene (40 ml) was heated at 70 °C for 2 h. After evaporation of the solvent under reduced pressure, the residue was diluted, made alkaline with aqueous $K_2CO_3$ solution, and extracted with $CH_2Cl_2$. The extract was washed with water, dried and concentrated. The residue was purified by column chromatography [$SiO_2$, $CH_2Cl_2$–MeOH (30:1→20:1)] to yield **16a** (5.62 g, 69%) as pale yellow crystals, which were recrystallized from AcOEt to give pale yellow plates, mp 109.5—110.5 °C. IR (KBr): 1730, 1698 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.68 (2H, t, *J*=7.5 Hz), 3.04 (2H, t, *J*=7.5 Hz), 3.67 (3H, s), 5.37 (2H, s), 6.94 (1H, s), 7.14 (1H, s), 7.37 (2H, d, *J*=8 Hz), 7.51 (1H, s), 7.91 (2H, d, *J*=8 Hz). MS *m/z*: 272 ($M^+$). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.18; H, 5.92; N, 10.24.

Compound **16b** was prepared similarly from **15b**.

**Methyl 4-[4-[(1-Imidazolyl)acetyl]phenyl]butyrate (16b)** Colorless scales, mp 90—91 °C (AcOEt–iso-$Pr_2O$), yield 59%. IR (KBr): 1738, 1698 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.99 (2H, qn, *J*=7.5 Hz), 2.35 (2H, t, *J*=7.5 Hz), 2.75 (2H, t, *J*=7.5 Hz), 3.68 (3H, s), 5.38 (2H, s), 6.95 (1H, s), 7.14 (1H, s), 7.34 (2H, d, *J*=8 Hz), 7.51 (1H, s), 7.90 (2H, d, *J*=8 Hz). MS *m/z*: 286 ($M^+$). *Anal.* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.21; H, 6.48; N, 9.68.

**Methyl 3-[4-[1-Hydroxy-2-(1-imidazolyl)ethyl]phenyl]propionate (17a)** Compound **17a** was prepared from **16a** in the same manner as **5a**. Colorless scales, mp 99.5—101.5 °C (AcOEt), yield 86%. IR (KBr): 3124 (OH), 1738 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.63 (2H, t, *J*=7.5 Hz), 2.95 (2H, t, *J*=7.5 Hz), 3.67 (3H, s), 4.06 (1H, dd, *J*=14,

8 Hz), 4.11 (1H, dd, $J$=14, 4.5 Hz), 4.89 (1H, dd, $J$=8, 4.5 Hz), 6.88 (1H, s), 6.92 (1H, s), 7.20 (2H, d, $J$=8 Hz), 7.24 (2H, d, $J$=8 Hz), 7.34 (1H, s). MS $m/z$: 274 ($M^+$). *Anal.* Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.54; H, 6.78; N, 10.15.

**Methyl 4-[4-[1-Hydroxy-2-(1-imidazolyl)ethyl]phenyl]butyrate (17b)** Compound **17b** was prepared from **16b** in the same manner as **5a**. Colorless scales, mp 112—113 °C (AcOEt), yield 88%. IR (KBr): 3120 (OH), 1738 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.95 (2H, qn, $J$=7.5 Hz), 2.33 (2H, t, $J$=7.5 Hz), 2.65 (2H, t, $J$=7.5 Hz), 3.67 (3H, s), 4.06—4.14 (2H, m), 4.91 (1H, dd, $J$=7.5, 4 Hz), 6.90 (1H, s), 6.97 (1H, s), 7.18 (2H, d, $J$=8 Hz), 7.23 (2H, d, $J$=8 Hz), 7.38 (1H, s). MS $m/z$: 288 ($M^+$). *Anal.* Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.64; H, 7.13; N, 9.68.

**Methyl 3-[4-[1-Chloro-2-(1-imidazolyl)ethyl]phenyl]propionate (18a)** Compound **18a** was prepared from **17a** in the same manner as **6a**. Colorless oil, yield 100%. IR (liq.): 1734 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.63 (2H, t, $J$=8 Hz), 2.95 (2H, t, $J$=8 Hz), 3.67 (3H, s), 4.37 (1H, dd, $J$=14.5, 6.5 Hz), 4.45 (1H, dd, $J$=14.5, 6.5 Hz), 5.00 (1H, t, $J$=6.5 Hz), 6.80 (1H, s), 7.01 (1H, s), 7.20 (4H, s), 7.31 (1H, s). MS $m/z$: 292, 294 (3:1, $M^+$). High-resolution MS $m/z$: Calcd for $C_{15}H_{17}ClN_2O_2$: 292.0979, 294.0949. Found: 292.0970, 294.0934.

**Methyl 4-[4-[1-Chloro-2-(1-imidazolyl)ethyl]phenyl]butyrate (18b)** Compound **18b** was prepared from **17b** in the same manner as **6a**. Pale yellow oil, yield 100%. IR (liq.): 1734 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.95 (2H, qn, $J$=7.5 Hz), 2.33 (2H, t, $J$=7.5 Hz), 2.65 (2H, t, $J$=7.5 Hz), 3.67 (3H, s), 4.39 (1H, dd, $J$=14.5, 6 Hz), 4.46 (1H, dd, $J$=14.5, 7 Hz), 5.02 (1H, t, $J$=7 Hz), 6.82 (1H, s), 7.02 (1H, s), 7.18 (2H, d, $J$=8 Hz), 7.21 (2H, d, $J$=8 Hz), 7.38 (1H, s). MS $m/z$: 306, 308 (3:1, $M^+$). High-resolution MS $m/z$: Calcd for $C_{16}H_{19}ClN_2O_2$: 306.1135, 308.1105. Found: 306.1121, 308.1103.

**Methyl 3-[4-[1-Azido-2-(1-imidazolyl)ethyl]phenyl]propionate (19a)** Compound **19a** was prepared from **18a** in the same manner as **7a**. Pale yellow oil, yield 80%. IR (liq.): 2112 ($N_3$), 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.64 (2H, t, $J$=8 Hz), 2.97 (2H, t, $J$=8 Hz), 3.68 (3H, s), 4.11 (2H, d, $J$=6.5 Hz), 4.74 (1H, t, $J$=6.5 Hz), 6.87 (1H, s), 7.05 (1H, s), 7.16 (2H, d, $J$=8 Hz), 7.24 (2H, d, $J$=8 Hz), 7.36 (1H, s). MS $m/z$: 299 ($M^+$). High-resolution MS $m/z$: Calcd for $C_{15}H_{17}N_5O_2$: 299.1382. Found: 299.1390.

**Methyl 4-[4-[1-Azido-2-(1-imidazolyl)ethyl]phenyl]butyrate (19b)** Compound **19b** was prepared from **18b** in the same manner as **7a**. Pale yellow oil, yield 91%. IR (liq.): 2112 ($N_3$), 1734 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.96 (2H, qn, $J$=7.5 Hz), 2.34 (2H, t, $J$=7.5 Hz), 2.67 (2H, t, $J$=7.5 Hz), 3.68 (3H, s), 4.11—4.13 (2H, m), 4.75 (1H, t, $J$=6.5 Hz), 6.88 (1H, s), 7.05 (1H, s), 7.16 (2H, d, $J$=8.5 Hz), 7.22 (2H, d, $J$=8.5 Hz), 7.42 (1H, s). MS $m/z$: 313 ($M^+$). High-resolution MS $m/z$: Calcd for $C_{16}H_{19}N_5O_2$: 313.1539. Found: 313.1551.

**Methyl 3-[4-[1-Amino-2-(1-imidazolyl)ethyl]phenyl]propionate (20a)** Compound **20a** was prepared from **19a** in the same manner as **8a**. Pale brown oil, yield 91%. IR (liq.): 3368 ($NH_2$), 1734 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.55 (2H, br s), 2.63 (2H, t, $J$=8 Hz), 2.95 (2H, t, $J$=8 Hz), 3.68 (3H, s), 4.02 (1H, dd, $J$=14, 8 Hz), 4.09 (1H, dd, $J$=14, 5 Hz), 4.25 (1H, dd, $J$=8, 5 Hz), 6.87 (1H, s), 7.04 (1H, s), 7.19 (2H, d, $J$=8 Hz), 7.22 (2H, d, $J$=8 Hz), 7.38 (1H, s). MS $m/z$: 274 ($M^+$+1).

**Methyl 4-[4-[1-Amino-2-(1-imidazolyl)ethyl]phenyl]butyrate (20b)** Compound **20b** was prepared from **19b** in the same manner as **8a**. Pale brown oil, yield 92%. IR (liq.): 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.88 (2H, br s), 1.95 (2H, qn, $J$=7.5 Hz), 2.33 (2H, t, $J$=7.5 Hz), 2.65 (2H, t, $J$=7.5 Hz), 3.67 (3H, s), 4.04 (1H, dd, $J$=14, 8 Hz), 4.10 (1H, dd, $J$=14, 5 Hz), 4.26 (1H, dd, $J$=8, 5 Hz), 6.87 (1H, s), 7.04 (1H, s), 7.17 (2H, d, $J$=8 Hz), 7.22 (2H, d, $J$=8 Hz), 7.42 (1H, s). MS $m/z$: 288 ($M^+$+1).

**Methyl 3-[4-[1-(4-Chlorobenzenesulfonamido)-2-(1-imidazolyl)ethyl]phenyl]propionate (21a)** Compound **21a** was prepared from **20a** in the same manner as **9a**. Pale yellow prisms, mp 168—169 °C (MeOH–$Et_2O$), yield 49%. IR (KBr): 1738 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.58 (2H, t, $J$=7.5 Hz), 2.88 (2H, t, $J$=7.5 Hz), 3.68 (3H, s), 4.22—4.31 (2H, m), 4.66 (1H, t, $J$=6 Hz), 6.64 (1H, s), 6.91 (2H, d, $J$=8.5 Hz), 6.92 (1H, s), 7.02 (2H, d, $J$=8.5 Hz), 7.24 (2H, d, $J$=8.5 Hz), 7.29 (1H, s), 7.52 (2H, d, $J$=8.5 Hz). *Anal.* Calcd for $C_{21}H_{22}ClN_3O_4S$: C, 56.31; H, 4.95; N, 9.38. Found: C, 56.33; H, 5.01; N, 9.26. MS $m/z$: 366 ($M^+ - C_4H_5N_2$).

**Methyl 4-[4-[1-(4-Chlorobenzenesulfonamido)-2-(1-imidazolyl)ethyl]phenyl]butyrate (21b)** Compound **21b** was prepared from **20b** in the same manner as **9a**. Pale yellowish brown oil, yield 61%. IR (liq.): 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.89 (2H, qn, $J$=7.5 Hz), 2.30 (2H, t, $J$=7.5 Hz), 2.58 (2H, t, $J$=7.5 Hz), 3.68 (3H, s), 4.28 (2H, d, $J$=6 Hz), 4.65 (1H, t, $J$=6 Hz), 6.63 (1H, s), 6.87 (2H, d, $J$=8.5 Hz), 6.92 (1H, s), 7.00 (2H, d, $J$=8.5 Hz), 7.25 (2H, d, $J$=8.5 Hz), 7.26 (1H, s), 7.54 (2H, d, $J$=8.5 Hz). MS $m/z$: 461, 463 (3:1, $M^+$). High-resolution MS $m/z$: Calcd for $C_{22}H_{24}ClN_3O_4S$: 461.1176, 463.1147. Found: 461.1190, 463.1136.

**3-[4-[1-(4-Chlorobenzenesulfonamido)-2-(1-imidazolyl)ethyl]phenyl]-propionic Acid (22a)** Compound **22a** was prepared from **21a** in the same manner as **10a**. Pale yellow plates, mp 215—216.5 °C (MeOH), yield 82%. IR (KBr): 3136 (NH), 1650—1700 (br, C=O) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.47 (2H, t, $J$=7.5 Hz), 2.74 (2H, t, $J$=7.5 Hz), 4.09 (2H, d, $J$=8 Hz), 4.59 (1H, q, $J$=8 Hz), 6.75 (1H, s), 7.01 (2H, d, $J$=8 Hz), 7.05 (1H, s), 7.07 (2H, d, $J$=8 Hz), 7.33 (2H, d, $J$=9 Hz), 7.38 (2H, d, $J$=9 Hz), 7.45 (1H, s), 8.45 (1H, d, $J$=9 Hz). MS $m/z$: 352 ($M^+ - C_4H_5N_2$). *Anal.* Calcd for $C_{20}H_{20}ClN_3O_4S$: C, 55.36; H, 4.65; N, 9.68. Found: C, 55.25; H, 4.58; N, 9.68.

**4-[4-[1-(4-Chlorobenzenesulfonamido)-2-(1-imidazolyl)ethyl]phenyl]butyric Acid (22b)** Compound **22b** was prepared from **21b** in the same manner as **10a**. Pale yellow crystals, mp 196—198 °C (MeOH), yield 73%. IR (KBr): 1700 (C=O) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.75 (2H, qn, $J$=7.5 Hz), 2.18 (2H, t, $J$=7.5 Hz), 2.50 (2H, t, $J$=7.5 Hz), 4.10 (2H, d, $J$=7.5 Hz), 4.60 (1H, q, $J$=7.5 Hz), 6.76 (1H, s), 6.96 (2H, d, $J$=8 Hz), 7.05 (1H, s), 7.07 (2H, d, $J$=8 Hz), 7.31 (2H, d, $J$=8.5 Hz), 7.40 (2H, d, $J$=8.5 Hz), 7.45 (1H, s), 8.46 (1H, d, $J$=9 Hz). MS $m/z$: 366 ($M^+ - C_4H_5N_2$). *Anal.* Calcd for $C_{21}H_{22}ClN_3O_4S \cdot H_2O$: C, 54.13; H, 5.19; N, 9.02. Found: C, 54.38; H, 5.03; N, 9.01.

**Methyl 3-[4-(2-Chloro-1-hydroxyethyl)phenyl]propionate (23a)** $NaBH_4$ (2.23 g, 58.9 mmol) was added portionwise to a solution of **15a** (18.9 g, 78.5 mmol) in MeOH (130 ml) under ice-cooling, and the mixture was stirred at the same 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 water, dried and concentrated to yield **23a** (18.6 g, 98%) as a pale yellow oil. IR (liq.): 3464 (OH), 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.61 (1H, d, $J$=3 Hz), 2.63 (2H, t, $J$=7.5 Hz), 2.95 (2H, t, $J$=7.5 Hz), 3.64 (1H, dd, $J$=11.5, 9 Hz), 3.67 (3H, s), 3.73 (1H, dd, $J$=11.5, 3.5 Hz), 4.86—4.89 (1H, m), 7.21 (2H, d, $J$=8 Hz), 7.31 (2H, d, $J$=8 Hz). MS $m/z$: 242, 244 (3:1, $M^+$). High-resolution MS $m/z$: Calcd for $C_{12}H_{15}ClO_3$: 242.0710, 244.0680. Found: 242.0709, 244.0678.

Compound **23b** was prepared similarly from **15b**.

**Methyl 4-[4-(2-Chloro-1-hydroxyethyl)phenyl]butyrate (23b)** Pale yellow oil, yield 97%. IR (liq.): 3460 (OH), 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.95 (2H, qn, $J$=7.5 Hz), 2.33 (2H, t, $J$=7.5 Hz), 2.62 (1H, d, $J$=3 Hz), 2.65 (2H, t, $J$=7.5 Hz), 3.64 (1H, dd, $J$=11, 9 Hz), 3.67 (3H, s), 3.73 (1H, dd, $J$=11, 3.5 Hz), 4.85—4.90 (1H, m), 7.19 (2H, d, $J$=8 Hz), 7.31 (2H, d, $J$=8 Hz). MS $m/z$: 256, 258 (3:1, $M^+$). High-resolution MS $m/z$: Calcd for $C_{13}H_{17}ClO_3$: 256.0866, 258.0837. Found: 256.0869, 258.0825.

**Methyl 3-[4-(2-Azido-1-hydroxyethyl)phenyl]propionate (24a)** A suspension of **23a** (14.0 g, 57.7 mmol) and sodium azide (7.50 g, 0.115 mol) in DMF (60 ml) was heated at 90 °C for 2.5 h. After cooling, the reaction mixture was diluted with water and extracted with $Et_2O$. The extract was washed with water, dried and concentrated to yield **24a** (13.3 g, 93%) as a pale yellow oil. IR (liq.): 3464 (OH), 2108 ($N_3$), 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.31 (1H, d, $J$=3 Hz), 2.63 (2H, t, $J$=7.5 Hz), 2.95 (2H, t, $J$=7.5 Hz), 3.43 (1H, dd, $J$=13, 3.5 Hz), 3.48 (1H, dd, $J$=13, 8.5 Hz), 3.67 (3H, s), 4.84—4.87 (1H, m), 7.21 (2H, d, $J$=8.5 Hz), 7.30 (2H, d, $J$=8.5 Hz). MS $m/z$: 193 ($M^+ - CH_2N_3$).

Compound **24b** was prepared similarly from **23b**.

**Methyl 4-[4-(2-Azido-1-hydroxyethyl)phenyl]butyrate (24b)** Pale yellow oil, yield 99%. IR (liq.): 3464 (OH), 2108 ($N_3$), 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.95 (2H, qn, $J$=7.5 Hz), 2.31—2.34 (3H, m), 2.65 (2H, t, $J$=7.5 Hz), 3.43 (1H, dd, $J$=12.5, 4 Hz), 3.48 (1H, dd, $J$=12.5, 8 Hz), 3.67 (3H, s), 4.84—4.87 (1H, m), 7.19 (2H, d, $J$=8 Hz), 7.29 (2H, d, $J$=8 Hz). MS $m/z$: 207 ($M^+ - CH_2N_3$).

**Methyl 3-[4-(2-Azido-1-chloroethyl)phenyl]propionate (25a)** Thionyl chloride (3.61 ml, 49.4 mmol) was added dropwise to a solution of **24a** (13.3 g, 53.4 mmol) in $CH_2Cl_2$ (50 ml) under ice-cooling, and the mixture was stirred at 40 °C for 1 h. The solvent was evaporated off under reduced pressure to give **25a** (13.2 g, 100%) as a pale yellow oil. IR (liq.): 2112 ($N_3$), 1738 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.63 (2H, t, $J$=8 Hz), 2.96 (2H, t, $J$=8 Hz), 3.67 (3H, s), 3.68 (1H, dd, $J$=13, 6 Hz), 3.75 (1H, dd, $J$=13, 8 Hz), 4.95 (1H, t, $J$=7 Hz), 7.23 (2H, d, $J$=8.5 Hz), 7.33 (2H, d, $J$=8.5 Hz). MS $m/z$: 211, 213 (3:1, $M^+ - CH_2N_3$).

Compound **25b** was prepared similarly from **24b**.

**Methyl 4-[4-(2-Azido-1-chloroethyl)phenyl]butyrate (25b)** Pale yellow oil, yield 100%. IR (liq.): 2112 ($N_3$), 1738 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.94 (2H, qn, $J$=7.5 Hz), 2.33 (2H, t, $J$=7.5 Hz), 2.66 (2H, t, $J$=7.5 Hz), 3.67 (3H, s), 3.68 (1H, dd, $J$=13, 7 Hz), 3.75 (1H, dd, $J$=13, 6 Hz), 4.95 (1H, t, $J$=7 Hz), 7.20 (2H, d, $J$=8 Hz), 7.33 (2H, d, $J$=8 Hz). MS $m/z$: 225, 227 (3:1, $M^+ - CH_2N_3$).

**Methyl 3-[4-[2-Azido-1-(1-imidazolyl)ethyl]phenyl]propionate (26a)** A mixture of **25a** (14.3 g, 53.4 mmol) and imidazole (9.09 g, 0.133 mol) in toluene (30 ml) was heated at 110 °C for 2.5 h. After cooling, the reaction mixture was acidified with 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. The residue was purified by column chromatography [$SiO_2$, $CH_2Cl_2$–MeOH (40:1)] to yield **26a** (2.20 g, 14%) as a pale yellowish brown oil. IR (liq.): 2108 ($N_3$), 1734 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.62 (2H, t, $J$=8 Hz), 2.95 (2H, t, $J$=8 Hz), 3.66 (3H, s), 3.93—4.01 (2H, m), 5.31 (1H, dd, $J$=8, 5.5 Hz), 6.99 (1H, s), 7.12 (1H, s), 7.13 (2H, d, $J$=8 Hz), 7.23 (2H, d, $J$=8 Hz), 7.61 (1H, s). MS $m/z$: 299 ($M^+$). High-resolution MS $m/z$: Calcd for $C_{15}H_{17}N_5O_2$: 299.1382. Found: 299.1389.

Compound **26b** was prepared similarly from **25b**.

**Methyl 4-[4-(2-Azido-1-(1-imidazolyl)ethyl]phenyl]butyrate (26b)** Pale reddish brown oil, yield 25%. IR (liq.): 2108 ($N_3$), 1734 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.94 (2H, qn, $J$=7.5 Hz), 2.32 (2H, t, $J$=7.5 Hz), 2.65 (2H, t, $J$=7.5 Hz), 3.66 (3H, s), 3.93—4.01 (2H, m), 5.31 (1H, dd, $J$=8, 5.5 Hz), 6.99 (1H, s), 7.12 (1H, s), 7.13 (2H, d, $J$=8 Hz), 7.20 (2H, d, $J$=8 Hz), 7.61 (1H, s). MS $m/z$: 313 ($M^+$). High-resolution MS $m/z$: Calcd for $C_{16}H_{19}N_5O_2$: 313.1539. Found: 313.1543.

**Methyl 3-[4-[2-Amino-1-(1-imidazolyl)ethyl]phenyl]propionate (27a)** Compound **27a** was prepared from **26a** in the same manner as **8a**. Pale brown oil, yield 87%. IR (liq.): 3380 ($NH_2$), 1736 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.13 (1H, br), 1.68 (1H, br), 2.62 (2H, t, $J$=8 Hz), 2.94 (2H, t, $J$=8 Hz), 3.40 (1H, dd, $J$=14, 6 Hz), 3.45 (1H, dd, $J$=14, 8.5 Hz), 3.67 (3H, s), 5.13 (1H, dd, $J$=8.5, 6 Hz), 7.00 (1H, s), 7.11 (1H, s), 7.12 (2H, d, $J$=8 Hz), 7.20 (2H, d, $J$=8 Hz), 7.63 (1H, s). MS $m/z$: 244 ($M^+ - CH_3N$).

**Methyl 4-[4-[2-Amino-1-(1-imidazolyl)ethyl]phenyl]butyrate (27b)** Compound **27b** was prepared from **26b** in the same manner as **8a**. Pale brown oil, yield 94%. IR (liq.): 3372 ($NH_2$), 1734 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.40 (2H, br), 1.94 (2H, qn, $J$=7.5 Hz), 2.32 (2H, t, $J$=7.5 Hz), 2.64 (2H, t, $J$=7.5 Hz), 3.40 (1H, dd, $J$=15.5, 6 Hz), 3.40 (1H, dd, $J$=15.5, 8.5 Hz), 3.66 (3H, s), 5.13 (1H, dd, $J$=8.5, 6 Hz), 7.00 (1H, s), 7.11 (1H, s), 7.11 (2H, d, $J$=8.5 Hz), 7.17 (2H, d, $J$=8.5 Hz), 7.63 (1H, s). MS $m/z$: 258 ($M^+ - CH_3N$).

**Methyl 3-[4-[2-(4-Chlorobenzenesulfonamido)-1-(1-imidazolyl)ethyl]-phenyl]propionate (28a)** Compound **28a** was prepared from **27a** in the same manner as **9a**. Colorless needles, mp 131—134 °C (AcOEt), yield 29%. IR (KBr): 1744 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.61 (2H, t, $J$=8 Hz), 2.93 (2H, t, $J$=8 Hz), 3.54 (1H, dd, $J$=14.5, 10 Hz), 3.66 (3H, s), 3.68 (1H, dd, $J$=14.5, 4.5 Hz), 5.34 (1H, dd, $J$=10, 4.5 Hz), 6.86 (1H, s), 6.92 (1H, s), 7.07 (2H, d, $J$=8 Hz), 7.19 (2H, d, $J$=8 Hz), 7.43 (1H, s), 7.48 (2H, d, $J$=9 Hz), 7.80 (2H, d, $J$=9 Hz). MS $m/z$: 447, 449 (3:1, $M^+$). *Anal.* Calcd for $C_{21}H_{22}ClN_3O_4S$: C, 56.31; H, 4.95; N, 9.38. Found: C, 56.38; H, 4.96; N, 9.28.

**Methyl 4-[4-[2-(4-Chlorobenzenesulfonamido)-1-(1-imidazolyl)ethyl]-phenyl]butyrate (28b)** Compound **28b** was prepared from **27b** in the same manner as **9a**. Colorless needles, mp 102—103 °C (AcOEt–iso-$Pr_2O$), yield 35%. IR (KBr): 1740 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.92 (2H, qn, $J$=7.5 Hz), 2.31 (2H, t, $J$=7.5 Hz), 2.63 (2H, t, $J$=7.5 Hz), 3.55 (1H, dd, $J$=14.5, 10 Hz), 3.66 (3H, s), 3.68 (1H, dd, $J$=14.5, 4.5 Hz), 5.34 (1H, dd, $J$=10, 4.5 Hz), 6.86 (1H, s), 6.91 (1H, s), 7.07 (2H, d, $J$=8 Hz), 7.16 (2H, d, $J$=8 Hz), 7.43 (1H, s), 7.47 (2H, d, $J$=9 Hz), 7.80 (2H, d, $J$=9 Hz). MS $m/z$: 461, 463 (3:1, $M^+$). *Anal.* Calcd for $C_{22}H_{24}ClN_3O_4S$: C, 57.20; H, 5.24; N, 9.10. Found: C, 57.21; H, 5.04; N, 9.09.

**3-[4-[2-(4-Chlorobenzenesulfonamido)-1-(1-imidazolyl)ethyl]phenyl]-propionic Acid (29a)** Compound **29a** was prepared from **28a** in the same manner as **10a**. Pale yellow amorphous solid, yield 94%. IR (KBr): 1710 (C=O) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.50 (2H, t, $J$=8 Hz), 2.80 (2H, t, $J$=8 Hz), 3.45—3.50 (1H, m), 3.67—3.73 (1H, m), 5.44 (1H, dd, $J$=9, 5.5 Hz), 7.10 (1H, s), 7.20 (2H, d, $J$=8 Hz), 7.25 (2H, d, $J$=8 Hz), 7.41 (1H, s), 7.62 (2H, d, $J$=8.5 Hz), 7.78 (2H, d, $J$=8.5 Hz), 8.10 (1H, t, $J$=6 Hz), 8.20 (1H, s). MS $m/z$: 230 ($M^+ - C_7H_6ClNO_2S$).

**4-[4-[2-(4-Chlorobenzenesulfonamido)-1-(1-imidazolyl)ethyl]phenyl]-butyric Acid (29b)** Compound **29b** was prepared from **28b** in the same manner as **10a**. Colorless needles, mp 182—185 °C (MeOH–acetone), yield 90%. IR (KBr): 1696 (C=O) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.77 (2H, qn, $J$=7.5 Hz), 2.19 (2H, t, $J$=7.5 Hz), 2.56 (2H, t, $J$=7.5 Hz), 3.43—3.48 (1H, m), 3.62—3.67 (1H, m), 5.36 (1H, dd, $J$=9, 5.5 Hz), 6.90 (1H, s), 7.15 (2H, d, $J$=8 Hz), 7.22 (2H, d, $J$=8 Hz), 7.25 (1H, s), 7.62 (2H, d, $J$=8.5 Hz), 7.77 (2H, d, $J$=8.5 Hz), 7.80 (1H, s), 8.03 (1H, t, $J$=6 Hz). MS $m/z$: 447, 449 (3:1, $M^+$). *Anal.* Calcd for $C_{21}H_{22}ClN_3O_4S$: C, 56.31; H, 4.95; N, 9.38. Found: C, 56.44; H, 4.91; N, 9.27.

**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: $6 \times 10^5$ cells/$\mu$l) was obtained by centrifugation. PRP (190 $\mu$l) in a cuvette was incubated with 1 $\mu$l of DMSO solution of a test compound for 2 min at 37 °C in an aggregometer (Hema Tracer I; Niko Bioscience). A 10 $\mu$l aliquot of U-46619 (Cayman), a $TXA_2$/$PGH_2$ receptor agonist and potent platelet aggregation inducer, was added to PRP to give a final concentration of 2 $\mu$g/ml, and platelet aggregation was measured with an aggregometer. The $IC_{50}$ values were calculated graphically from the concentration–% inhibition relations.

**Inhibitory Effect on $TXA_2$ Synthase** Commercial human platelet membrane fraction (Eldan Technologies) (100 $\mu$g/ml, 285 $\mu$l) as a source of $TXA_2$ synthase, a DMSO solution of test compound (10 $\mu$l) and 100 $\mu$g/ml (5 $\mu$l) of $PGH_2$ (Cayman) were mixed and allowed to react for 3 min at 25 °C. The produced $TXB_2$, a stable metabolite of $TXA_2$, was determined by an RIA method ($TXB_2$ quantification kit; Du Pont/NEN Research Products). The IC values were calculated graphically.

## References


1) Hamberg M., Svensson J., Samuelsson B., *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994—2998 (1975); Moncada S., Vane J. R., *Pharmacol. Rev.*, **30**, 293—331 (1979); Coleman R. A., Sheldrich R. L. G., *Br. J. Pharmacol.*, **96**, 688—692 (1989).
2) *a*) Hall S. E., *Med. Res. Rev.*, **11**, 503—579 (1991); *b*) Arimura A., Asanuma F., Kurosawa A., Harada M., *Int. Arch. Allergy Immunol.*, **98**, 239—246 (1992); *c*) Collington E. W., Finch H., "Annual Reports in Medicinal Chemistry," Vol. 25, ed. by Bristol J. A., Academic Press, Inc., New York, 1990, pp. 99—108; *d*) Iizuka K., Akahane K., Momose D., Nakazawa M., Tanouchi T., Kawamura M., Ohyama I., Kajiwara I., Iguchi Y., Okada T., Taniguchi K., Miyamoto T., Hayashi M., *J. Med. Chem.*, **24**, 1139—1148 (1981); *e*) Kato K., Ohkawa S., Terao S., Terashita Z., Nishikawa K., *ibid.*, **28**, 287—294 (1985).
3) Vermylen J., Defreyn G., Carreras L. O., Machin S. J., Schaeren J. V., Verstraete M., *Lancet*, **1981**, 1073—1075.
4) Cross P. E., Dickinson R. P., "Annual Reports in Medicinal Chemistry," Vol. 22, ed. by Bailey D. M., Academic Press, Inc., New York, 1987, pp. 95—105.
5) Mayeux P. R., Morton H. E., Gillard J., Lord A., Morinelli T. A., Boehm A., Mais D. E., Halushka P. V., *Biochem. Biophys. Res. Commun.*, **157**, 733—739 (1988).
6) Gresele P., Deckmyn H., Nenci G. G., Vermylen J., *Trends Pharmacol. Sci.*, **12**, 158—163 (1991).
7) Bhagwat S. S., *Drugs Fut.*, **19**, 765—777 (1994).
8) Sakurai S., Ogawa N., Suzuki T., Kato K., Ohashi T., Yasuda S., Kato H., Ito Y., *Chem. Pharm. Bull.*, **44**, 765—777 (1996).
9) *a*) Yoshimoto T., Yamamoto S., Hayaishi O., *Prostaglandins*, **16**, 529—540 (1978); *b*) Tanouchi T., Kawamura M., Ohyama I., Kajiwara I., Iguchi Y., Okada T., Miyamoto T., Taniguchi K., Hayashi M., *J. Med. Chem.*, **24**, 1149—1155 (1981).
10) Malmsten C., *Life Sci.*, **18**, 169—176 (1976).
11) *a*) Ezumi K., Yamakawa M., Narisada M., *J. Med. Chem.*, **33**, 1117—1122 (1990); *b*) Cozzi P., Giordani A., Menichincheri M., Pillan A., Pinciroli V., Rossi A., Tonani R., Volpi D., Tamburin M., Ferrario R., Fusar D., Salvati P., *ibid.*, **37**, 3588—3604 (1994).