Preparation and Biological Activity of 2-[4-(Thiazol-2-yl)phenyl]propionic Acid Derivatives Inhibiting Cyclooxygenase

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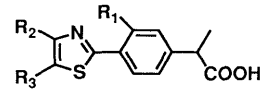
A series of 2-[4-(thiazol-2-yl)phenyl]propionic acids substituted at various positions were prepared by the reaction of diethyl 2-methyl-2-(4-thiocarbamoylphenyl)malonates with α-bromoaldehyde diethyl acetals or α-haloketones followed by hydrolysis of esters. The inhibition of prostaglandin H synthetase (cyclooxygenase) was assayed by use of an enzyme preparation from guinea pig polymorphonuclear leukocytes. Examination of the structure–activity relationship of these compounds indicated that the substitution pattern with halogens at position 3 (R_1) of the benzene ring and a methyl group in position 4 (R_2) and/or 5 (R_3) of the thiazole ring were favorable for inhibitory activity. The compounds bearing bulky alkyl or polar functional groups at the R_2 position were weak inhibitors. The potent inhibitors of cyclooxygenase were tested for their ability to reduce carrageenin-induced inflammation of rat paws. These derivatives had strong anti-inflammatory activity based on their strong inhibition of cyclooxygenase, with some exceptions, including those with a thiomethyl group at R_1.

Keywords structure–activity relationship; cyclooxygenase inhibition; anti-inflammatory; carrageenin-induced inflammation; thiazole derivative; phenylpropionic acid

The anti-inflammatory activity of non-steroidal anti-inflammatory compounds is related to their ability to inhibit cyclooxygenase.[1] The relationship between the inhibition of carrageenin-induced edema and that of prostaglandin biosynthesis *in vivo* (the reduction of urinary prostaglandin E_2 excretion) has been clearly defined.[2] In addition, the relationship between inhibitions of the edema induction and prostaglandin biosynthesis *in vitro* with cyclooxygenase preparations has been explained not directly but in conjunction with such physicochemical parameters of the molecule as hydrophobicity in terms of log *P*, *P* being the 1-octanol/water partition coefficient.[3] The mechanism of cyclooxygenase inhibition has been extensively studied by the use of a purified preparation of prostaglandin H synthetase.[4]

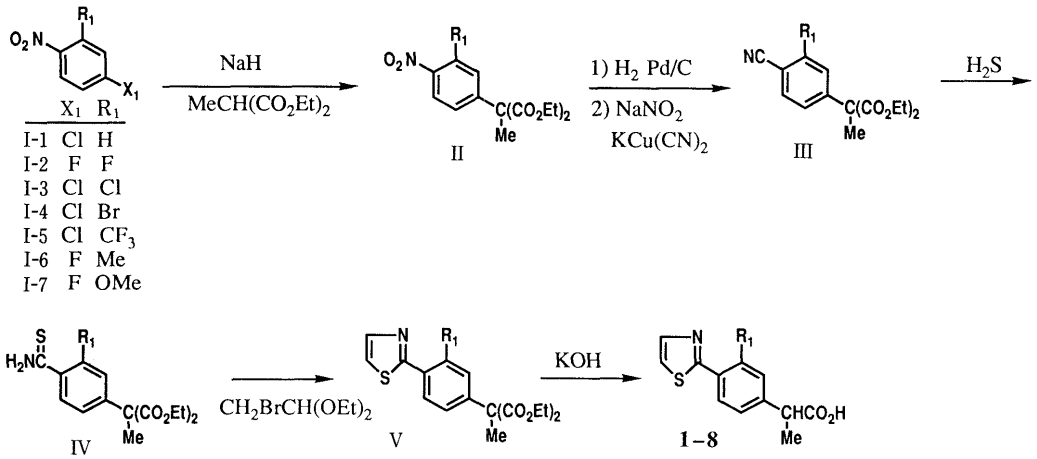
A number of 2-arylpropionic acids such as ibuprofen[5] and flurbiprofen[6] are anti-inflammatory agents. Some analogs containing the thiazole ring in the aryl moiety or as a part of the substituents are anti-inflammatory.[7] Being interested in further exploration of anti-inflammatory arylpropionic acids with thiazole rings, we synthesized a number of substituted 2-[4-(thiazol-2-yl)phenyl]propionic acids. We found that these compounds inhibit cyclooxygenase to various extents depending upon the substitution. In this report, we describe the synthesis of these compounds and the relationship between their structure and cyclooxygenase inhibition. Some compounds that strongly inhibited this enzyme also had strong anti-inflammatory activity in suppressing carrageenin-induced edema in rats.



R_1 = H, F, Cl, Br, CF_3, Me, OMe, SMe, OH, NO_2, NH_2

R_2 = H, Me, Et, iso-Pr, Bu, acetyl, Ph, vinyl, allyl, CH_2OH, CH_2OMe, $CONH_2$, CONHMe, $CONMe_2$, CF_3

R_3 = H, Me, Et $R_2, R_3 = -(CH_2)_n-$; $n = 3, 4$



R_1 = H, F, Cl, Br, CF_3, Me, OCH_3, SMe

Chart 1

Chemistry

The compounds were synthesized by Hantzsch thiazole synthesis.[8] The 2-[3-substituted-4-(thiazol-2-yl)phenyl]-propionic acids **1**—**8** were prepared as shown in Chart 1. The diethyl 2-methyl-2-(3-substituted-4-nitrophenyl)malonates, II-1, II-3, II-4, and II-5, were obtained by the reaction of the corresponding 4-chloro-2-substituted-nitrobenzenes, I-1, I-3, I-4, and I-5, with diethyl methyl malonate. The malonates, II-2, II-6, and II-7, were also obtained by the reaction of 4-fluoro-2-substituted-nitrobenzenes, I-2, I-6, and I-7. 4-Chloro-2-bromonitrobenzene, I-4, was derived from 4-chloro-2-aminonitrobenzene by use of the Sandmeyer reaction.[9] 4-Fluoro-2-methoxynitrobenzene, I-7, were derived from 4-fluoro-2-hydroxynitrobenzene by use of methylation. Diethyl 2-methyl-2-(3-methylthio-4-nitrophenyl)malonate (II-8), was obtained by the reaction of diethyl 2-(3-chloro-4-nitrophenyl)-2-methylmalonate (II-3), with methanethiol derived from dimethyldisulfide and tri-*n*-butylphosphine.

Catalytic hydrogenation of compounds II gave amino derivatives that were converted by use of the Sandmeyer reaction to cyano derivatives III, which were easily converted to thioamide derivatives IV. The thioamides were converted to thiazole derivatives V by use of Hantzsch thiazole synthesis followed by hydrolysis to give compounds **1**—**8**. 2-[3-Hydroxy-4-(thiazol-2-yl)phenyl]propionic acid (**9**), was derived from the demethylation[10] of the corresponding methoxy derivative **7**. For the synthesis of **10**, we used another method (Chart 2), because methyl 4-cyano-3-nitrobenzoate was not obtained by the Sandmeyer reaction of methyl 4-amino-3-nitrobenzoate. Methyl 4-carbamoyl-3-nitrobenzoate (VII), was prepared by selective esterification of nitroterephthalic acid followed by amidation. The carbamoyl group obtained was converted to a thiazole group by reaction with phosphorous pentasulfide followed by Hantzsch thiazole synthesis. The benzoate VIII obtained was converted to compound **10** by Wolf rearrangement[11] followed by hydrolysis. The amino derivative **11** was prepared by the reduction of the nitro group of IX followed by hydrolysis.

Derivatives bearing various substituents at R_1, R_2, and R_3 (**12**—**17**, **28**—**35**, **38**—**43**, and **46**—**47**) were also synthesized by Hantzsch thiazole synthesis[8] (Chart 3). 1-Chloro-3-methylbutan-2-one and 1-chlorohexan-2-one were prepared by the diazomethane-mediated chloromethylation[12] of the corresponding carboxylic acid chlorides. 2-Bromopentan-3-one and 2-bromocyclohexanone were prepared by the bromination[13] of the correspond-

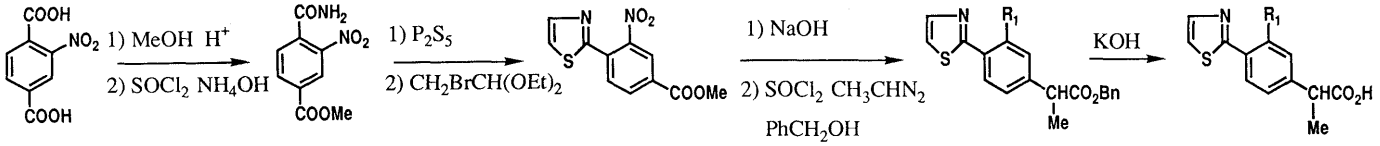
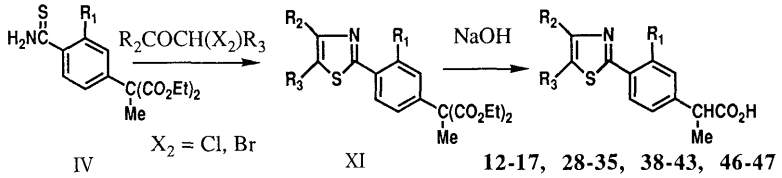


Chart 2



R_1=H, Cl, F; R_2=Me, Et, iso-Pr, Bu, acetyl, phenyl ; R_3=H, Me, Et

Chart 3

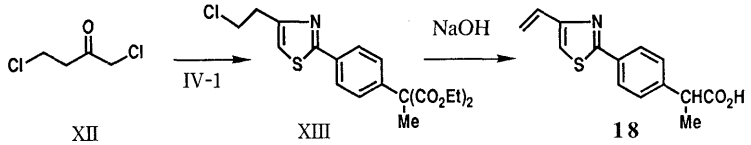


Chart 4

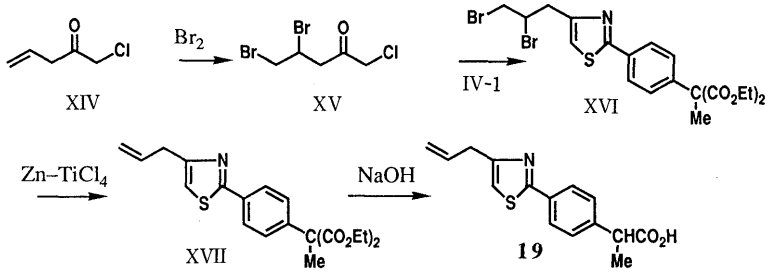


Chart 5

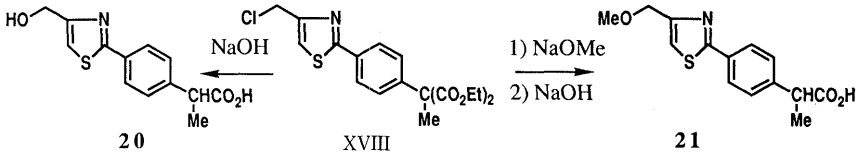


Chart 6

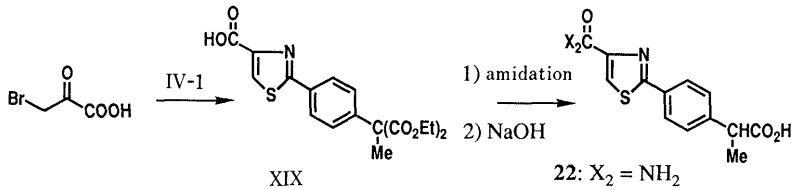


Chart 7

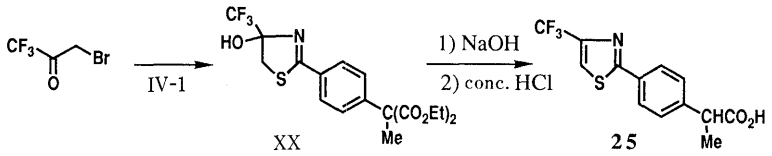


Chart 8

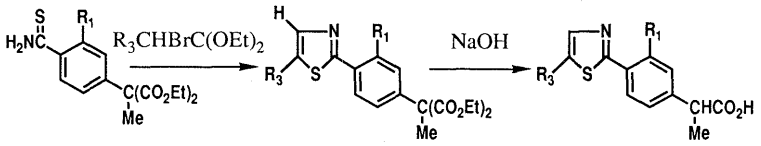


Chart 9

ing silyl enol ether. 2-[4-(4-Vinylthiazol-2-yl)phenyl]propionic acid (**18**), was prepared by the dehydrochlorination of chloroethyl thiazole XIII, which was prepared by the reaction of 1,4-dichlorobutan-2-one XII with thioamide IV-1 (Chart 4). 1,4-Dichlorobutan-2-one XII, was also prepared by the diazomethane-mediated chloromethylation[12] of 3-chloropropionyl chloride. 2-[4-(4-Allylthiazol-2-yl)phenyl]propionic acid (**19**) was prepared by debromination[14] and a subsequent hydrolysis of diethyl 2-[4-[4-(2,3-dibromopropyl)thiazol-2-yl]phenyl]-2-methylmalonate (XVI), which was prepared by the reaction of 1-chloro-4,5-dibromopentan-2-one, XV, with thioamide IV-1 (Chart 5). Compound XV was prepared by the bromination of 1-chloro-4-penten-3-one, XIV.[15] The compounds with CH_2OH (**20**) and CH_2OMe (**21**) as R_2 substituents were synthesized by alkali hydrolysis or methanolysis followed by hydrolysis of diethyl 2-[4-(4-chloromethylthiazol-2-yl)phenyl]-2-methylmalonate (XVIII), which was prepared by the reaction of 1,3-dichloropropan-2-one with thioamide IV-1 (Chart 6). The compounds with $CONH_2$ (**22**), CONHMe (**23**), or $CON(Me)_2$ (**24**) as R_2 substituents were synthesized by the amidation of diethyl 2-[4-(4-carboxythiazol-2-yl)phenyl]-2-methylmalonate (XIX), which was prepared by the reaction of 3-bromopyruvic acid with thioamide IV-1 (Chart 7). The compound with CF_3 as its R_2 substituent, **25**, was synthesized by hydrolysis and a subsequent dehydration of diethyl 2-methyl-2-[4-(4-trifluoromethyl-4-hydroxy-2-thiazolin-2-yl)phenyl]malonate (XX), which was prepared by the reaction of 1,1,1-trifluoromethyl-3-bromopropan-2-one with thioamide IV-1 (Chart 8).

The derivatives with methyl or ethyl as their R_3 substituent (**26**—**27**, **36**—**37**, and **44**—**45**) were synthesized by the method used for the preparation of **1**—**8** (Chart 9). α-Halo-acetals used in these reactions were synthesized by the method of Rasmussen and Bøwadt.[16]

The compounds synthesized here and their mp and analytical data are shown in Table I.

Results and Discussion

Inhibitory activity of each compound was examined in terms of the 50% inhibitory concentration, I_{50}, for the production of thromboxane B_2 and prostaglandin E_2 from arachidonic acid in the 10000 × *g* supernatant fraction from guinea pig polymorphonuclear leukocytes by use of a procedure reported elsewhere.[17] The degree of inhibition of the enzyme by the compounds is listed in Table I. The anti-inflammatory activity of the compounds that strongly inhibited cyclooxygenase was evaluated in terms of effects on carrageenin-induced paw edema in rats as described in

TABLE I. Physicochemical and Biological Data of 2-[4-(Thiazol-2-yl)phenyl]propionic Acid Derivatives

No.	R_1	R_2	R_3	mp (°C)[a]	Recrystn. solvent[b]	Formula	Analysis (%) Calcd (Found)			I_{50}[c] (M)
							C	H	N	
1	H	H	H	149—151	A	$C_{12}H_{11}NO_2S$	61.78 (61.80)	4.75 4.58	6.00 5.88)	2.75×10^{-6}
2	F	H	H	152—154	B	$C_{12}H_{10}FNO_2S$	57.36 (57.18)	4.01 3.93	5.57 5.60)	2.50×10^{-7}
3	Cl	H	H	81— 82	C	$C_{12}H_{10}ClNO_2S$	53.84 (53.75)	3.77 3.63	5.23 5.19)	2.00×10^{-7}
4	Br	H	H	137—138	B	$C_{12}H_{10}BrNO_2S$	46.17 (46.13)	3.23 3.13	4.49 4.35)	1.00×10^{-7}
5	CF_3	H	H	103—105	A	$C_{13}H_{10}F_3NO_2S$	51.83 (51.91)	3.35 3.27	4.65 4.57)	3.00×10^{-7}
6	Me	H	H	82.5— 84	B	$C_{13}H_{13}NO_2S$	63.14 (63.04)	5.30 5.11	5.66 5.54)	2.00×10^{-6}
7	OMe	H	H	Liquid		$C_{13}H_{13}NO_3S$	59.30 (59.13)	4.98 5.08	5.32 5.04)	5.20×10^{-6}
8	SMe	H	H	84— 85	B	$C_{13}H_{13}NO_2S_2$	55.89 (55.73	4.69 4.58	5.01 4.87)	3.00×10^{-7}
9	OH	H	H	107.5—108.5	B	$C_{12}H_{11}NO_3S$	250.0537[f] (250.0503)			6.00×10^{-7}
10	NO_2	H	H	111—113	B	$C_{12}H_{10}N_2O_4S$	51.79 (51.80	3.62 3.54	10.07 9.94)	2.90×10^{-6}
11	NH_2	H	H	165.5—167	B	$C_{12}H_{12}N_2O_2S$	58.05 (58.02	4.87 4.77	11.28 11.55)	1.00×10^{-6}
12	H	Me	H	181—182	B	$C_{13}H_{13}NO_2S$	248.0744 (248.0711)			7.20×10^{-7}
13	H	Et	H	125—127	B	$C_{14}H_{15}NO_2S$	64.34 (64.29	5.79 5.59	5.36 5.27)	3.00×10^{-6}
14	H	iso-Pr	H	146—148	A	$C_{15}H_{17}NO_2S$	65.43 (65.14	6.22 6.20	5.09 4.95)	1.63×10^{-5}
15	H	Bu	H	73—74.5	A	$C_{16}H_{19}NO_2S$	66.41 (66.37	6.62 6.67	4.84 4.87)	1.05×10^{-4}
16	H	Acetyl	H	155.5—156.5	A	$C_{14}H_{13}NO_3S$	61.08 (60.93	4.76 4.65	5.09 5.16)	1.05×10^{-4}
17	H	Ph	H	157.5—159	B	$C_{18}H_{15}NO_2S$	69.88 (70.01	4.89 4.80	4.53 4.54)	3.60×10^{-5}
18	H	Vinyl	H	114—115	B	$C_{14}H_{13}NO_2S$	260.0744 (260.0705)			2.10×10^{-6}
19	H	Allyl	H	Amorph.	B	$C_{15}H_{15}NO_2S$	65.91 (65.62	5.53 5.46	5.12 5.02)	1.30×10^{-5}
20	H	CH_2OH	H	132—134	B	$C_{13}H_{13}NO_3S$	59.30 (59.45	4.98 4.92	5.32 5.25)	1.60×10^{-5}
21	H	CH_2OMe	H	98—100	B	$C_{14}H_{15}NO_3S$	60.63 (60.36	5.45 5.27	5.05 4.94)	3.00×10^{-5}
22	H	$CONH_2$	H	245—247	D	$C_{13}H_{12}N_2O_3S$	56.51 (56.40	4.38 4.38	10.14 9.89)	7.50×10^{-4}
23	H	CONHMe	H	188—189	E	$C_{14}H_{14}N_2O_3S$	57.92 (58.11	4.86 4.86	9.65 9.63)	1.02×10^{-3}
24	H	$CONMe_2$	H	155.5—158	B	$C_{15}H_{16}N_2O_3S$	59.19 (58.91	5.30 5.20	9.20 9.16)	9.20×10^{-4}
25	H	CF_3	H	142—144	B	$C_{13}H_{10}F_3NO_2S$	51.83 (51.75	3.35 3.17	4.65 4.54)	8.20×10^{-6}
26	H	H	Me	159—160.5	A	$C_{13}H_{13}NO_2S$	248.0744 (248.0713)			5.50×10^{-6}
27	H	H	Et	130—132	A	$C_{14}H_{15}NO_2S$	64.34 (64.28	5.79 5.75	5.36 5.26)	3.20×10^{-6}
28	H	Me	Me	173.5—175.5	F	$C_{14}H_{15}NO_2S$	64.34 (64.34	5.79 5.77	5.36 5.33)	1.00×10^{-6}
29	H	Et	Me	144—145	A	$C_{15}H_{17}NO_2S$	65.43 (65.15	6.22 6.28	5.09 5.11)	1.02×10^{-5}
30	H	CH_2CH_2[d]	CH_2[d]	194.5—195.5	E	$C_{15}H_{15}NO_2S$	65.91 (65.65	5.53 5.40	5.12 4.89)	7.00×10^{-7}
31	H	CH_2CH_2[e]	CH_2CH_2[e]	187—188	A	$C_{16}H_{17}NO_2S$	288.1057 (288.1094)			7.00×10^{-7}
32	F	Me	H	141—143	A	$C_{13}H_{12}FNO_2S$	58.86 (58.91	4.56 4.48	5.28 5.29)	1.00×10^{-7}
33	F	Et	H	114—116	C	$C_{14}H_{14}FNO_2S$	60.20 (60.08	5.05 5.22	5.01 5.03)	1.20×10^{-6}

TABLE I. (continued)

No.	R_1	R_2	R_3	mp (°C)[a]	Recrystn. solvent[b]	Formula	Analysis (%) Calcd (Found) C	H	N	I_{50}[c] (M)
34	F	iso-Pr	H	116—117.5	A	$C_{15}H_{16}FNO_2S$	61.42 (61.43)	5.50 (5.50)	4.78 (4.74)	3.40×10^{-5}
35	F	Bu	H	60— 62	A	$C_{16}H_{18}FNO_2S$	62.52 (62.40)	5.90 (5.86)	4.56 (4.45)	5.10×10^{-5}
36	F	H	Me	113—113.5	G	$C_{13}H_{12}FNO_2S$	58.86 (58.58)	4.56 (4.50)	5.28 (5.16)	3.00×10^{-7}
37	F	H	Et	118.5—119	A	$C_{14}H_{14}FNO_2S$	60.20 (60.10)	5.05 (5.13)	5.01 (5.01)	9.00×10^{-7}
38	F	Me	Me	163.5—164.5	C	$C_{14}H_{14}FNO_2S$	60.20 (60.39)	5.05 (4.95)	5.01 (4.96)	2.00×10^{-7}
39	F	Et	Me	136—137.5	A	$C_{15}H_{16}FNO_2S$	61.42 (61.16)	5.50 (5.45)	4.78 (4.78)	4.20×10^{-6}
40	Cl	Me	H	141—143	C	$C_{13}H_{12}ClNO_2S$	55.42 (55.39)	4.29 (4.16)	4.97 (5.04)	1.00×10^{-7}
41	Cl	Et	H	111—112	C	$C_{14}H_{14}ClNO_2S$	56.85 (57.00	4.77 4.78)	4.74 4.79)	7.00×10^{-7}
42	Cl	iso-Pr	H	101—102	A	$C_{15}H_{16}ClNO_2S$	310.0668 (310.0707		312.0638 312.0643)	3.40×10^{-5}
43	Cl	Bu	H	88—89	C	$C_{16}H_{18}ClNO_2S$	59.34 (59.20	5.60 5.59)	4.33 4.40)	6.20×10^{-5}
44	Cl	H	Me	106—107	C	$C_{13}H_{12}ClNO_2S$	55.42 (55.35)	4.29 4.34)	4.97 4.97)	6.00×10^{-8}
45	Cl	H	Et	120—121	A	$C_{14}H_{14}ClNO_2S$	56.85 (56.71	4.77 4.66)	4.74 4.77)	2.00×10^{-7}
46	Cl	Me	Me	158—159	C	$C_{14}H_{14}ClNO_2S$	56.85 (56.80	4.77 4.77)	4.74 4.75)	8.00×10^{-7}
47	Cl	Et	Me	102—103	C	$C_{15}H_{16}ClNO_2S$	58.15 (58.29	5.21 5.08)	4.52 4.45)	1.20×10^{-6}
	Ibuprofen									1.01×10^{-6}
	Indomethacin									1.00×10^{-7}

a) Compounds that did not show a sharp mp are denoted 'amorph.' *b*) Solvents: A, chloroform–hexane; B, AcOEt–hexane; C, ether–hexane; D, water; E, chloroform–hexane–methanol; F, AcOEt; G, AcOEt–chloroform–hexane. *c*) Concentration for 50% inhibition of cyclooxygenase from guinea pig leukocytes. Each value represents the mean of at least two experiments. *d*) The R_2 and R_3 substituents form a cyclopentane ring. *e*) The R_2 and R_3 substituents form a cyclohexane ring. *f*) High mass data. The upper value was calculated and the lower one was found. The values are for $M+H^+$ (measured by the SI-MS-positive mode).

TABLE II. Anti-inflammatory Activity of 2-[4-(Thiazol-2-yl)phenyl]propionic Acid Derivatives

Compound	Anti-edematous effect ED_{40}[a] (mg/kg)	Cyclooxygenase inhibition I_{50}[b] (M)
1	13	2.8×10^{-6}
3	3	2.0×10^{-7}
8	343	3.0×10^{-7}
32	4	1.0×10^{-7}
36	19	3.0×10^{-7}
38	8	2.0×10^{-7}
40	4	1.0×10^{-7}
44	112	6.0×10^{-8}
Ibuprofen	15	1.0×10^{-6}
Indomethacin	2	1.0×10^{-7}

a) 40% Effective dose. *b*) 50% inhibitory concentration.

the Experimental section. The tested compounds were given orally. Their anti-edematous effect was expressed as the 40% effective dose (ED_{40}, as mg/kg; Table II).

When R_2 and R_3 were not substituted, the effect on cyclooxygenase inhibition of the substituent R_1 in the benzene ring was to increase inhibition by halogens **2**—**4**, trifluoromethyl **5**, methylthio **8**, and hydroxy **9**. There was little change in the inhibition with methyl **6**, methoxy **7**, nitro **10**, and amino **11**. When R_1 and R_3 were not substituted and R_2 was methyl **12**, inhibition was greater than with unsubstituted **1**, but compounds with an R_2 group bulkier than ethyl **13** or vinyl **18** (isopropyl **14**, butyl **15**, acetyl **16**, phenyl **17**, and allyl **19**) caused weaker inhibition. The activity of compounds where R_2 was hydroxymethyl (**20**), methoxymethyl (**21**), amide (**22**—**24**), or trifluoromethyl (**25**) was low. Compound **29**, in which R_2 is ethyl and R_3 is methyl, caused less inhibition than the fused-ring analogs **30** and **31**, which were about four times as active as the unsubstituted **1**. Introduction of fluorine (**32**—**39**) and chlorine (**40**—**47**) into the R_1 position increased inhibition compared with the corresponding compounds lacking an R_1 substituent except when isopropyl was the R_2 substituent, in compounds **34** and **42**, which had about half the activity of the R_1 unsubstituted compound **14**. In general, inhibition increased 2—10 times when fluorine or chlorine was introduced into the R_1 substituent. In particular, compound **44**, in which R_1 is Cl, R_2 is H, and R_3 is Me, caused more inhibition than indomethacin. The effect of the R_1 substituent was not directly linked with any physicochemical substituent property in an obvious pattern, but some steric effect requiring a limited size seemed to be important for the R_2 substituent. That the introduction of halogens into the R_1 position increased inhibition by about the same extent could mean

that the effects of the R_1 and R_2 substituents were additive. Some other factor may affect the activity of compounds in which R_2 is isopropyl.

The anti-inflammatory activity of compounds **3**, **8**, **32**, **36**, **38**, **40**, and **44**, which caused inhibition about 10 times as strong as that of the unsubstituted compound **1**, was measured with compound **1** as the reference (Table II). Compounds **3**, **32**, and **40** had strong anti-inflammatory activity, comparable to that of indomethacin, but the anti-inflammatory activity of **8** (R_1 = SMe and $R_2 = R_3 = H$) and **44** (R_1 = Cl, R_2 = H, and R_3 = Me) was very low despite their strong inhibition of cyclooxygenase. The potent anti-inflammatory activity of **3**, **32**, and **40** matched the strength of their inhibition of cyclooxygenase. The low anti-inflammatory activity of **8** may be because the thiomethyl group is unstable *in vivo*. The reason for the low activity of **44** is not known, but some pharmacokinetic property may be involved, because the R_2-unsubstituted compounds **36** and **44** both had low activity. The results indicated that factors controlling pharmacokinetic properties and the metabolic stability of the molecule[1] could explain relationships between cyclooxygenase inhibition and carrageenin-induced paw edema in rats. The cyclooxygenase inhibition and anti-inflammatory activity of ibuprofen, which are shown in Table II, are lower than those of our selected compounds (Table II). Thiazole moiety should be important in exhibiting not only potent cyclooxygenase inhibition but also potent anti-inflammatory activity. A detailed pharmacological study is in progress.

Experimental

Cyclooxygenase Inhibition Inhibition of cyclooxygenase was assayed as described previously.[17]

Carrageenin Edema in Rat Paw The experiment with rats was done by the method of Winter *et al.*[18] with five or six Sprague–Dawley rats per group, starved for 24 h beforehand. Thirty minutes after the administration of water (4 ml), the test drugs were administered orally. After another 30 min, 0.1 ml of carrageenin was injected subcutaneously into the plantar surface of the left hind paw, and 3h later, the volume of the edema was measured. The anti-edematous effect of the drugs was expressed as a 40% effective dose (ED_{40}).

Analyses Melting points were determined with a Yanaco melting point apparatus and are uncorrected. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a Bruker AC-200 NMR spectrometer with tetramethylsilane as the internal standard; chemical shifts are given on the δ (ppm) scale. Infrared (IR) spectra were obtained on a Shimadzu IR-420 spectrometer.

Syntheses: 2-[4-(Thiazol-2-yl)phenyl]propionic Acid (1) 1) Diethyl 2-Methyl-2-(4-nitrophenyl)malonate (II-1): To a suspension of NaH (12.0 g, 60% in mineral oil) in *N*,*N*-dimethylformamide (200 ml, DMF), diethyl methylmalonate (49.8 g) in DMF (20 ml) was added dropwise for 1 h at 0°C. After stirring of the mixture for 30 min at room temperature, 1-chloro-4-nitrobenzene (40.9 g) in DMF (80 ml) was added dropwise for 20 min and the resultant solution was stirred at room temperature for 30 min and then at 90 °C for 2 h. The solution was then cooled to room temperature, poured into ice-water and extracted with hexane–ether (1 : 1). The extract was washed with water and brine, in that order, and dried over $MgSO_4$. After evaporation of the solvent, II-1 was collected by distillation under reduced pressure (43.6 g, 57%), bp 159—161 °C/0.3 mmHg. IR (neat): 3015, 1730, 1605, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.27 (6H, t, J=7.1 Hz), 1.90 (3H, s), 4.26 (4H, q, J=7.1 Hz), 7.58 (2H, d, J=9.1 Hz), 8.21 (2H, d, J=9.1 Hz).

2) Diethyl 2-(4-Cyanophenyl)-2-methylmalonate (III-1): Compound II-1 (10.5 g) in ethyl acetate (100 ml, AcOEt) was hydrogenated over 10% palladium on carbon (1.9 g, Pd–C) under atmospheric pressure at room temperature for 4 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was used in the next step. To a cooled (3 °C) mixture of the amine obtained (9.2 g) in water (70 ml), 12 N HCl (9.8 ml) was added for 5 min. After the mixture was stirred for 10 min, sodium nitrite (2.6 g) in water (15 ml) was added dropwise for 15 min to maintain the temperature of the solution at 2—3 °C. Stirring was continued for another 20 min. Then sodium carbonate (2.6 g) in water (20 ml) was added to adjust the pH of the solution to about 6. The solution obtained was added dropwise for 10 min at 3 °C to a solution of potassium dicyanocuprate prepared by the mixture of cuprous cyanide (6.1 g) and potassium cyanide (8.9 g) in water (70 ml). The mixture was left for 1.5 h at 3 °C and then at 50 °C for 2 h. After being cooled to room temperature, the mixture was poured into water and extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane to give III-1 (5.8 g, 60%). IR (neat): 2200, 1725, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.1 Hz), 1.87 (3H, s), 4.25 (4H, q, J=7.1 Hz), 7.51 (2H, d, J=8.7 Hz), 7.65 (2H, d, J=8.7 Hz).

3) Diethyl 2-Methyl-2-(4-thiocarbamoylphenyl)malonate (IV-1): To a solution of compound III-1 (5.7 g) in DMF (70 ml) containing triethylamine (3.5 ml), hydrogen sulfide was bubbled at 90 °C for 30 min and the solution was then stirred at 90 °C for 30 min. After being cooled to room temperature, the reaction mixture was poured into water and extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane and recrystallized from chloroform–hexane to give IV-1 (6.0 g, 93%). IR (KBr): 3090, 1725, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.2 Hz), 1.87 (3H, s), 4.24 (4H, q, J=7.2 Hz), 7.22 (1H, NH), 7.42 (2H, d, J=8.7 Hz), 7.64 (1H, NH), 7.84 (2H, d, J=8.7 Hz).

4) Diethyl 2-Methyl-2-[4-(thiazol-2-yl)phenyl]malonate (V-1): A solution of IV-1 (1.93 g) and bromoacetaldehyde diethylacetal (1.56 g) in acetic acid (10 ml) containing *p*-toluenesulfonic acid (75 mg) was heated at 100 °C for 1.5 h. After removal of the solvent under reduced pressure, the residue was diluted with AcOEt. The organic layer was washed with saturated sodium bicarbonate solution and brine, and dried over $MgSO_4$, in that order. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane to give V-1 (1.6 g, 78%). IR (neat) cm^{-1} 1720, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.1 Hz), 1.90 (3H, s), 4.25 (4H, q, J=7.1 Hz), 7.33 (1H, d, J=3.3 Hz), 7.47 (2H, d, J=8.6 Hz), 7.87 (1H, d, J=3.3 Hz), 7.95 (2H, d, J=8.6 Hz).

5) 2-[4-(Thiazol-2-yl)phenyl]propionic Acid (**1**): A solution of V-1 (1.5 g) in ethanol (10 ml) containing KOH (0.99 g) was heated at reflux for 1.5 h. After removal of the solvent, the residue was dissolved in water (100 ml) and the solution obtained was washed with AcOEt. The aqueous layer was cooled to 0 °C, acidified to pH 1 with 12 N HCl and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane and recrystallized from chloroform–hexane to give **1** (0.56 g, 53%). IR (KBr): 3150—2150, 1690, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.54 (3H, d, J=7.2 Hz), 3.79 (1H, q, J=7.2 Hz), 7.32 (1H, d, J=3.3 Hz), 7.40 (2H, d, J=8.3 Hz), 7.7—8.2 (4H, m).

2-[3-Fluoro-4-(thiazol-2-yl)phenyl]propionic Acid (2) The procedure used for the preparation of **1** was repeated with 2,4-difluoronitrobenzene as a starting material and dimethylsulfoxide was used as a solvent for the synthesis of diethyl 2-(3-fluoro-4-nitrophenyl)-2-methylmalonate. Yields of I-2 to II-2, II-2 to III-2, III-2 to IV-2, IV-2 to V-2, and V-2 to **2** were 80, 57, 83, 45, and 41%, respectively. The spectra of compound **2** were as follows. IR (KBr): 3100—2300, 1700, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.45 (3H, d, J=7. 1 Hz), 3.77 (1H, q, J=7.1 Hz), 7.2—7.3 (2H, m), 7.7—7.8 (1H, m), 7.9—8.0 (1H, m), 8.1—8.3 (1H, m).

2-[3-Chloro-4-(thiazol-2-yl)phenyl]propionic Acid (3) The procedure used for the preparation of **1** was repeated with 2,4-dichloronitrobenzene as a starting material. Yields of I-3 to II-3, II-3 to III-3, III-3 to IV-3, IV-3 to V-3, and V-3 to **3** were 53, 63, 98, 75, and 84% respectively. The spectra of compound **3** were as follows. IR (KBr): 3250—2200, 1690, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.54 (3H, d, J=7.2 Hz), 3.76 (1H, q, J=7.2 Hz), 7.33 (1H, dd, J=8.2, 1.8 Hz), 7.47 (1H, d, J=1.8 Hz), 7.50 (1H, d, J=3.4 Hz), 7.97 (1H, d, J=3.4 Hz), 8.09 (1H, d, J=8.2 Hz), 7.7—8.6 (1H, OH).

2-[3-Bromo-4-(thiazol-2-yl)phenyl]propionic Acid (4) The procedure used for the preparation of **1** was repeated with 2-bromo-4-chloronitrobenzene. 2-Bromo-4-chloronitrobenzene was prepared by the reported method[9] by use of cuprous bromide (93%). Yields of I-4 to II-4, II-4 to III-4, III-4 to IV-4, IV-4 to V-4, and V-4 to **4** were 51, 9, 86, 80, and 71%, respectively. The spectra of compound **4** were as follows. IR (KBr): 3100—2320, 1700, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.42 (3H, d,

J=7.2 Hz), 3.80 (1H, q, J=7.2 Hz), 7.45 (1H, dd, J=8.2, 1.7 Hz), 7.73 (1H, d, J=1.7 Hz), 7.92 (1H, d, J=3.2 Hz), 7.9—8.1 (2H, m), 11.7—13.0 (1H, br, OH).

2-[4-(Thiazol-2-yl)-3-trifluoromethylphenyl]propionic Acid (5) The procedure used for the preparation of **1** was repeated with 4-chloro-2-trifluoromethylnitrobenzene as a starting material. Yields of I-5 to II-5, II-5 to III-5, III-5 to IV-5, IV-5 to V-5, and V-5 to **5** were 97, 41, 54, 48, and 53% respectively. The spectra of compound **5** were as follows. IR (KBr): 3200—2300, 1720, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.44 (3H, d, J=7.1 Hz), 3.95 (1H, q, J=7.1 Hz), 7.71 (2H, m), 7.82 (1H, m), 7.93 (1H, d, J=3.2 Hz), 7.98 (1H, d, J=3.2 Hz), 12.6 (1H, OH).

2-[3-Methyl-4-(thiazol-2-yl)phenyl]propionic Acid (6) The procedure used for preparation of **1** was repeated with 4-fluoro-2-methylnitrobenzene as a starting material. Yields of I-6 to II-6, II-6 to III-6, III-6 to IV-6, IV-6 to V-6, and V-6 to **6** were 82, 71, 69, 90, and 37%, respectively. The spectra of compound **6** were as follows. IR (KBr): 3000—2300, 1700, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.52 (3H, d, J=7.2 Hz), 2.53 (3H, s), 3.74 (1H, q, J=7.2 Hz), 7.2—7.3 (2H, m), 7.39 (1H, d, J=3.3 Hz), 7.64 (1H, d, J=7.8 Hz), 7.93 (1H, d, J=3.3 Hz).

2-[3-Methoxy-4-(thiazol-2-yl)phenyl]propionic Acid (7) The procedure used for preparation of **1** was repeated with 4-fluoro-2-methoxynitrobenzene as a starting material. 4-Fluoro-2-methoxynitrobenzene was synthesized as follows. A mixture of 4-fluoro-2-hydroxynitrobenzene (9.2 g), tetrabutylammonium hydrogen sulfate (0.99 g), 1 N NaOH (61 ml), dichloromethane (61 ml), and dimethylsulfate (6.1 ml) was stirred at room temperature for 67 h. After the reaction, the mixture was diluted with dichloromethane. The organic layer was washed with water and brine, and dried over $MgSO_4$, in that order. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane to give 4-fluoro-2-methoxynitrobenzene I-7 (9.4 g, 94%). IR (KBr): 1620, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 3.98 (3H, s), 6.74 (1H, m), 6.82 (1H, m), 7.96 (1H, m).

Yields of I-7 to II-7, II-7 to III-7, III-7 to IV-7, IV-7 to V-7, and V-7 to **7** were 93, 90, 63, 58, and 98% respectively. The spectra of compound **7** were as follows. IR ($CHCl_3$) cm^{-1}: 3200—2800, 1710, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.55 (3H, d, J=7.2 Hz), 3.78 (1H, q, J=7.2 Hz), 3.99 (3H, s), 6.99 (1H, d, J=1.7 Hz), 7.05 (1H, dd, J=8.1, 1.7 Hz), 7.37 (1H, d, J=3.3 Hz), 7.92 (1H, d, J=3.3 Hz), 8.24 (1H, d, J=8.1 Hz), 9.5 (1H, OH).

2-[3-Methylthio-4-(thiazol-2-yl)phenyl]propionic Acid (8) 1) Diethyl 2-Methyl-2-(3-methylthio-4-nitrophenyl)malonate (II-8): To a solution of dimethyldisulfide (3.4 ml) in ethanol (85 ml) and water (10 ml) was added tri-*n*-butylphosphine (9.8 ml) for 10 min at 0 °C. After stirring of the mixture of 30 min at 0 °C and 70 min at room temperature, diethyl 2-(3-chloro-4-nitrophenyl)-2-methylmalonate (II-3, 8.5 g) in ethanol (50 ml) and 1 N NaOH (38 ml) were added to the solution one after another, each taking 15 min at 0 °C. The solution was stirred for 40 min at 0 °C and then for 4.1 h at room temperature. The solution was extracted with AcOEt and the organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane to give compound II-8 (7.5 g, 86%). IR (KBr): 1720, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.28 (6H, t, J=7.2 Hz), 1.90 (3H, s), 2.49 (3H, s), 4.26 (4H, q, J=7.2 Hz), 7.26 (1H, dd, J=8.8, 2.0 Hz), 7.45 (1H, d, J=2.0 Hz), 8.23 (1H, d, J=8.8 Hz). The procedure used for preparation of **1** was repeated with 2-methyl-2-(3-methylthio-4-nitrophenyl)malonate II-8. Yields of II-8 to III-8, III-8 to IV-8, IV-8 to V-8, and V-8 to **8** were 60, 96, 80, and 60% respectively. The spectra of compound **8** were as follows. IR(KBr): 3600—2300, 1710, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.47 (3H, d, J=7.1 Hz), 2.48 (3H, s), 3.79 (1H, q, J=7.1 Hz), 7.21 (1H, dd, J=8.1, 1.6 Hz), 7.36 (1H, d, J=1.6 Hz), 7.80 (1H, d, J=8.1 Hz), 7.83 (1H, d, J=3.3 Hz), 7.96 (1H, d, J=3.3 Hz), 11—13 (1H, OH).

2-[3-Hydroxy-4-(thiazol-2-yl)phenyl]propionic Acid (9) To a mixture of aluminum chloride[10] (18.7 g), sodium iodide (21.1 g) in dry acetonitrile (270 ml), and dry dichloromethane (135 ml), **7** (1.85 g) in acetonitrile (10 ml) and dichloromethane (5 ml) was added for 10 min at 0 °C. The reaction mixture was stirred at reflux for 11 h, poured into ice-water, and extracted with AcOEt. The organic layer was washed with 1 N sodium thiosulfate solution, water, and brine, in that order, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with chloroform–methanol and recrystallized from AcOEt–hexane to give compound **9** (1.05 g, 60%). IR (KBr): 3300—2500, 2700, 1685, 1620, 1585 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.38 (3H, d, J=7.1 Hz), 3.67 (1H, q, J=7.1 Hz), 6.89 (1H, dd, J=8.1, 1.5 Hz), 6.97 (1H, d, J=1.5 Hz), 7.73 (1H, d, J=3.3 Hz), 7.92 (1H, d, J=3.3 Hz), 7.99 (1H, d, J=8.1 Hz), 11—12 (1H, OH), 12—13 (1H, OH).

2-[3-Nitro-4-(thiazol-2-yl)phenyl]propionic Acid (10) 1) Methyl 4-Carbamoyl-3-nitrobenzoate (VII): A solution of nitroterephthalic acid (20.0 g) in dry methanol (100 ml) and concentrated sulfuric acid (10 ml) was stirred at reflux for 1 h. After evaporation of the solvent, the residue was poured into $NaHCO_3$ and the aqueous layer was washed with chloroform. After the solution was acidified to pH 2 with 2 N HCl, the solution was extracted with AcOEt. The organic layer was washed with water and brine, in that order, and over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized from AcOEt–hexane to give the ester (14.7 g), mp 132—133 °C. A solution of the ester (7.2 g) in thionyl chloride (62 ml) containing 2—3 drops of DMF was stirred at reflux for 3 h. After removal of excess thionyl chloride by distillation, the residue (7.83 g) was used in the next step. To a solution of 28% ammonium hydroxide (30 ml) and 1 N NaOH (3 ml) was added the acid chloride (6.88 g) in dichloromethane (30 ml), and the mixture was stirred at room temperature for 1.5 h. The precipitated solid was collected by filtration and dried to give VII (5.9 g, 64%). IR (KBr): 3360, 3100, 1720, 1660, 1540 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.93 (3H, s), 7.78 (1H, d, J=7.9 Hz), 7.86 (1H, NH), 8.28 (1H, NH), 8.29 (1H, dd, J=7.9, 1.6 Hz), 8.44 (1H, d, J=1.6 Hz).

2) Methyl 3-Nitro-4-(thiazol-2-yl)benzoate (VIII): A solution of VII (4.95 g) and phosphorous pentasulfide (2.0 g) in dioxane (200 ml) was stirred at reflux for 1 h. After filtration of the reaction mixture, the filtrate was concentrated under reduced pressure. The residue obtained was chromatographed on silica gel with AcOEt–hexane to give thioamide (4.35 g). The thioamide was converted by the procedure used for the synthesis of V-1 to give VIII (2.6 g, 46%). IR (KBr): 3100, 1715, 1540 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 4.00 (3H, s), 7.54 (1H, d, J=3.2 Hz), 7.86 (1H, d, J=8.0 Hz), 7.96 (1H, d, J=3.2 Hz), 8.29 (1H, dd, J=8.0, 1.6 Hz), 8.43 (1H, d, J=1.6 Hz).

3) Benzyl 2-[3-Nitro-4-(thiazol-2-yl)phenyl]propionate (IX): The methyl ester (2.61 g) was hydrolyzed by a procedure similar to the synthesis of **1**, giving the benzoic acid (2.2 g). 3-Nitro-4-(thiazol-2-yl)benzoyl chloride was prepared quatitatively by a procedure similar to the synthesis of methyl 4-chloroformyl-3-nitrobenzoate. The acid chloride was converted to IX by a method reported elsewhere.[11] The residue obtained was chromatographed on silica gel with AcOEt–hexane to give IX (1.05 g, 43%). IR (neat): 1715, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.58 (3H, d, J=7.2 Hz), 3.89 (1H, q, J=7.2 Hz), 5.14 (2H, m), 7.2—7.4 (5H, m), 7.47 (1H, d, J=3.3 Hz), 7.56 (1H, dd, J=8.0, 1.8 Hz), 7.68 (1H, d, J=8.0 Hz), 7.75 (1H, d, J=1.8 Hz), 7.90 (1H, d, J=3.3 Hz).

4) 2-[3-Nitro-4-(thiazol-2-yl)phenyl]propionic Acid (**10**): The procedure used for the preparation of **1** was repeated with IX (1.15 g) to obtain **10** (610 mg, 71%). IR (KBr): 3150—2200, 1725, 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.46 (3H, d, J=7.2 Hz), 3.94 (1H, q, J=7.2 Hz), 7.72 (1H, dd, J=8.1, 1.6 Hz), 7.79 (1H, d, J=8.1 Hz), 7.90 (1H, d, J=1.6 Hz), 7.93 (1H, d, J=3.2 Hz), 7.95 (1H, d, J=3.2 Hz), 12.3—13.1 (1H, OH).

2-[3-Amino-4-(thiazol-2-yl)phenyl]propionic Acid (11) 1) Benzyl 2-[3-Amino-4-(thiazol-2-yl)phenyl]propionate (X): The procedure used for the preparation of III-1 was repeated with IX (1.1 g), and platinum oxide (68 mg) in acetic acid (20 ml) to give X (870 mg, 87%). IR (neat): 3430 3300, 1720, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.50 (3H, d, J=7.2 Hz), 3.69 (1H, q, J=7.2 Hz), 5.1—5.2 (2H, m), 6.12 (2H, NH_2), 6.6—6.7 (2H, m), 7.20 (1H, d, J=3.4 Hz), 7.25—7.35 (5H, m), 7.58 (1H, d, J=8.6 Hz), 7.78 (1H, d, J=3.4 Hz).

2) 2-[3-Amino-4-(thiazol-2-yl)phenyl]propionic Acid (**11**): The procedure used for the preparation of **1** was repeated with X (870 mg). After the reaction, the solution was concentrated under reduced pressure and the aqueous layer obtained was acidified with 4 N HCl to pH 4 and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized from AcOEt to give compound **11** (480 mg, 76%). IR (KBr): 3300, 1690, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.34 (3H, d, J=7.1 Hz), 3.54 (1H, q, J=7.1 Hz), 6.53 (1H, dd, J=8.2, 1.6 Hz), 6.75 (1H, d, J=1.6 Hz), 7.00 (2H, NH_2), 7.51 (1H, d, J=8.2 Hz), 7.61 (1H, d, J=3.4 Hz), 7.85 (1H, d, J=3.4 Hz).

2-[4-(4-Methylthiazol-2-yl)phenyl]propionic Acid (12) 1) Diethyl 2-Methyl-2-[4-(4-methylthiazol-2-yl)phenyl]malonate (XI-12): A solution of IV-1 (2.0 g) and chloroacetone (1.32 ml, 90% purity) in dry benzene (40 ml) was stirred at reflux for 3.25 h. The solution was diluted with ether, and the organic layer was washed with water and brine, and dried over $MgSO_4$, in that order. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane to give XI-12 quantitatively. IR (neat): 1730, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.1 Hz), 1.89 (3H, s), 2.51 (3H, s), 4.24 (4H, q, J=7.1 Hz), 6.67 (1H, s), 7.44 (2H, d, J=8.5 Hz), 7.90 (2H, d, J=8.5 Hz).

TABLE III. Yields, IR, and NMR Data for 2-[4-(Thiazol-2-yl)phenyl]propionic Acid Derivatives

No.	Yield (%)[a]	IR (KBr) cm^{-1}	NMR (δ in DMSO-d_6 from TMS)
13	68	3600—2800 1725	1.27 (3H, t, J=7.5 Hz), 1.41 (3H, d, J=7.1 Hz), 2.79 (1H, dq, J=0.7, 7.5 Hz), 3.76 (1H, q, J=7.1 Hz), 7.29 (1H, t, J=0.7 Hz), 7.4—7.5 (2H, m), 7.8—7.9 (2H, m), 12.4 (s, OH)
14[b]	70	3000—2300 1720	1.30 (6H, d, J=6.8 Hz), 1.40 (3H, d, J=7.1 Hz), 3.08 (1H, m), 3.74 (1H, q, J=7.1 Hz), 7.24 (1H, s), 7.40 (2H, d, J=8.3 Hz), 7.85 (2H, d, J=8.3 Hz), 12.4 (s, OH)
15[b]	14	3000—2300 1720	0.92 (3H, t, J=7.2 Hz), 1.2—1.8 (4H, m), 1.40 (3H, d, J=7.1 Hz), 2.75 (2H, t, J=7.2 Hz), 3.74 (1H, q, J=7.1 Hz), 7.28 (1H, s), 7.40 (2H, d, J=7.9 Hz), 7.85 (2H, d, J=7.9 Hz), 12.4 (s, OH)
16	32	3200—2400 1720	1.41 (3H, d, J=7.1 Hz), 2.64 (3H, s), 3.79 (1H, q, J=7.1 Hz), 7.46 (2H, d, J=8.3 Hz), 7.96 (2H, d, J=8.3 Hz), 8.56 (1H, s), 12.4 (s, OH)
17	40	3600—2700 1690	1.41 (3H, d, J=7.1 Hz), 3.76 (1H, q, J=7.1 Hz), 7.3—7.5 (5H, m), 7.9—8.1 (4H, m), 8.15 (1H, s)
28	53	3600—2800 1700	1.39 (3H, d, J=7.1 Hz), 2.31 (3H, s), 2.36 (3H, s), 3.74 (1H, q, J=7.1 Hz), 7.3—7.4 (2H, m), 7.7—7.8 (2H, m), 12.4 (s, OH)
29[c]	22	3000—2300 1720	1.20 (3H, t, J=7.5 Hz), 1.37 (3H, d, J=7.1 Hz), 2.36 (3H, s), 2.64 (2H, q, J=7.5 Hz), 3.70 (1H, q, J=7.1 Hz), 7.35 (2H, d, J=8.1 Hz), 7.77 (2H, d, J=8.1 Hz), 12.4 (s, OH)
30	70	3000—2300 1700	1.39 (3H, d, J=7.1 Hz), 2.47 (2H, m), 2.81 (2H, t, J=7.1 Hz), 2.92 (2H, t, J=7.1 Hz), 3.73 (1H, q, J=7.1 Hz), 7.37 (2H, d, J=8.3 Hz), 7.85 (2H, d, J=8.3 Hz), 12.4 (s, OH)
31[c]	62	3600—3000 1715	1.39 (3H, d, J=7.1 Hz), 1.83 (4H, m), 2.76 (4H, m), 3.72 (1H, q, J=7.1 Hz), 7.37 (2H, d, J=8.1 Hz), 7.80 (2H, d, J=8.1 Hz), 12.4 (s, OH)
32	87	3000—2300 1715	1.39 (3H, d, J=7.2 Hz), 2.43 (3H, s), 3.78 (1H, q, J=7.2 Hz), 7.2—7.4 (2H, m), 7.41 (1H, s), 8.13 (1H, dd, J=8.1, 8.1 Hz), 12.5 (s, OH)
33	68	3000—2300 1710	1.26 (3H, t, J=7.5 Hz), 1.39 (3H, d, J=7.1 Hz), 2.79 (2H, q, J=7.5 Hz), 3.79 (1H, q, J=7.1 Hz), 7.2—7.4 (2H, m), 7.43 (1H, s), 8.14 (1H, dd, J=8.1, 8.1 Hz), 12.6 (s, OH)
34[b]	64	3000—2300 1720	1.31 (6H, d, J=6.9 Hz), 1.42 (3H, d, J=7.1 Hz), 3.12 (1H, m), 3.80 (1H, q, J=7.1 Hz), 7.2—7.4 (2H, m), 7.40 (1H, s), 8.18 (1H, dd, J=8.0, 8.0 Hz), 12.5 (s, OH)
35[b]	50	3000—2300 1720	0.93 (3H, t, J=7.0 Hz), 1.2—1.7 (4H, m), 1.41 (3H, d, J=7.1 Hz), 2.79 (2H, t, J=7.0 Hz), 3.80 (1H, q, J=7.1 Hz), 7.25—7.35 (2H, m), 7.41 (1H, s), 8.16 (1H, dd, J=8.0, 8.0 Hz), 12.6 (s, OH)
38	70	3000—2300 1705	1.38 (3H, d, J=7.1 Hz), 2.31 (3H, s), 2.36 (3H, s), 3.77 (1H, q, J=7.1 Hz), 7.2—7.4 (2H, m), 8.08 (1H, dd, J=8.1, 8.1 Hz), 12.6 (s, OH)
39[c]	45	3000—2300 1710	1.23 (3H, t, J=7.5 Hz), 1.41 (3H, d, J=7.1 Hz), 2.40 (3H, s), 2.70 (2H, q, J=7.5 Hz), 3.78 (1H, q, J=7.1 Hz), 7.2—7.4 (2H, m), 8.12 (1H, dd, J=8.0, 8.0 Hz), 12.5 (s, OH)
40	59	3000—2300 1710	1.39 (3H, d, J=7.1 Hz), 2.44 (3H, s), 3.79 (1H, q, J=7.1 Hz), 7.39 (1H, dd, J=8.2, 1.5 Hz), 7.47 (1H, s), 7.53 (1H, d, J=1.5 Hz), 8.12 (1H, d, J=8.2 Hz), 12.6 (s, OH)
41	57	3100—2250 1710	1.35 (3H, t, J=7.5 Hz), 1.39 (3H, d, J=7.1 Hz), 2.80 (2H, q, J=7.5 Hz), 3.79 (1H, q, J=7.1 Hz), 7.39 (1H, dd, J=8.2, 1.5 Hz), 7.48 (1H, s), 7.53 (1H, d, J=1.5 Hz), 8.12 (1H, d, J=8.2 Hz), 12.6 (s, OH)
42[b]	52	3050—2300 1720	1.28 (6H, d, J=6.9 Hz), 1.39 (3H, d, J=7.1 Hz), 3.09 (1H, m), 3.79 (1H, q, J=7.1 Hz), 7.40 (1H, m), 7.44 (1H, s), 7.52 (1H, m), 8.12 (1H, d, J=8.2 Hz), 12.6 (s, OH)
43[b]	50	3050—2300 1710	0.89 (3H, t, J=7.3 Hz), 1.33 (2H, m), 1.39 (3H, d, J=7.1 Hz), 1.66 (2H, m), 2.76 (2H, t, J=7.3 Hz), 3.78 (1H, q, J=7.1 Hz), 7.3—7.5 (2H, m), 7.52 (1H, d, J=1.4 Hz), 8.12 (1H, d, J=8.2 Hz), 12.6 (s, OH)
46	43	3000—2300 1710	1.38 (3H, d, J=7.1 Hz), 2.32 (3H, s), 2.38 (3H, s), 3.77 (1H, q, J=7.1 Hz), 7.36 (1H, m), 7.49 (1H, m), 8.09 (1H, d, J=8.2 Hz), 12.6 (s, OH)
47[c]	54	3050—2300 1710	1.20 (3H, t, J=7.5 Hz), 1.39 (3H, d, J=7.1 Hz), 2.39 (3H, s), 2.68 (2H, q, J=7.5 Hz), 3.77 (1H, q, J=7.1 Hz), 7.37 (1H, dd, J=8.2, 1.5 Hz), 7.50 (1H, d, J=1.5 Hz), 8.10 (1H, d, J=8.2 Hz), 12.6 (s, OH)

a) Yields from the corresponding thioamides (IV-1, IV-2, or IV-3). *b*) α-Haloketones used in these reactions were prepared from isobutyryl chloride (for the syntheses of **14**, **34**, and **42**) or valeryl chloride (for the syntheses of **15**, **35**, and **43**) by use of diazomethane-mediated chloromethylation.[12] *c*) α-Haloketones used in these reactions were prepared by the bromination[13] of the silyl enol ether of cyclohexanone (for the synthesis of **31**) or 3-pentanone (for the syntheses of **29**, **39**, and **47**).

2) 2-[4-(4-Methylthiazol-2-yl)phenyl]propionic Acid (**12**): The procedure used for the preparation of **1** was repeated with XI-12 (2.1 g) and 1 N NaOH (25 ml) in ethanol (10 ml) to obtain **12** (1.1 g, 74%). IR (KBr): 3000—2800, 1720, 1600, 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.37 (3H, d, J=7.1 Hz), 2.40 (3H, d, J=0.7 Hz), 3.73 (1H, q, J=7.1 Hz), 7.29 (1H, m), 7.38 (2H, d, J=8.3 Hz), 7.85 (2H, d, J=8.3 Hz), 12.4 (1H, OH). The compounds **13**—**17**, **28**—**35**, **38**—**43**, and **46**—**47** were prepared as in the synthesis of **12**. The yields and physical properties are summarized in Table III.

2-[4-(4-Vinylthiazol-2-yl)phenyl]propionic Acid (18) 1) Diethyl 2-[4-[4-(2-Chloroethyl)thiazol-2-yl]phenyl]-2-methylmalonate (XIII): The procedure used for the preparation of XI-12 was repeated with IV-1 (1.4 g) and 1,4-dichloro-2-butanone (850 mg: prepared from propionyl chloride by a reported method[12]) in dry benzene (25 ml), giving XIII (970 mg). IR(KBr): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.2 Hz), 1.88 (3H, s), 3.26 (2H, t, J=7.0 Hz), 3.90 (2H, t, J=7.0 Hz), 4.24 (4H, q, J=7.2 Hz), 7.00 (1H, s), 7.45 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=8.6 Hz).

2) 2-[4-(4-Vinylthiazol-2-yl)phenyl]propionic Acid (**18**): The procedure used for the preparation of **12** was repeated with XIII (970 mg) and 1 N NaOH (48.8 ml) in ethanol to obtain **18** (370 mg, 58%). IR (KBr): 3200—2500, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.53 (3H, d, J=7.1 Hz), 3.78 (1H, q, J=7.1 Hz), 5.40 (1H, dd, J=10.8, 1.6 Hz), 6.14 (1H, dd, J=17.3, 1.6 Hz), 6.76 (1H, dd, J=17.3, 10.8 Hz), 7.10 (1H, s), 7.38 (2H, d, J=8.4 Hz), 7.92 (2H, d, J=8.4 Hz).

2-[4-(4-Allylthiazol-2-yl)phenyl]propionic Acid (19) 1) 4,5-Dibromo-1-chloro-2-pentanone (XV): Bromine was added dropwise to a solution of crude 1-chloro-4-penten-2-one (XIV) [prepared from allyltrimethylsilane (1.4 g) and chloroacetonitrile (0.94 ml) by a method published elsewhere[15]] in dichloromethane (100 ml) at −78 °C until the solution turned orange. After the addition ended, the solution was stirred at −60 °C for 30 min. Water added to the solution and the resultant mixture was extracted with ether. The organic layer was washed with $NaHCO_3$, water, and brine, and dried over $MgSO_4$, in that order. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane to give XV (980 mg, 28% based on chloroacetonitrile). IR (neat): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 3.26 (1H, dd, J=17.9, 8.8 Hz), 3.53 (1H, dd, J=17.9, 3.9 Hz), 3.71 (1H, dd, J=10.3, 9.7 Hz), 3.93 (1H, dd, J=10.3, 4.3 Hz), 4.14 (2H, s), 4.5—4.6 (1H, m).

2) Diethyl 2-[4-[4-(2,3-Dibromopropyl)thiazol-2-yl]phenyl]-2-methylmalonate (XVI): The procedure used for preparation of XI-12 was repeated with VI-1 (1.4 g) and XV (1.3 g) in dry benzene (30 ml), giving XVI (1.6 g) quantitatively. IR (neat): 1730, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.1 Hz), 1.89 (3H, s), 3.33 (1H, dd, J=14.9, 7.6 Hz), 3.64 (1H, dd, J=14.9, 5.0 Hz), 3.86 (2H, m), 4.24 (4H, q, J=7.1 Hz), 4.68 (1H, m), 7.10 (1H, s), 7.45 (2H, d, J=8.5 Hz), 7.91 (2H, d, J=8.5 Hz).

TABLE IV. Yields, IR, and NMR Data for 2-[4-(5-Alkylthiazol-2-yl)phenyl]propionic Acids

No.	Yield (%)[a]	IR (KBr) cm^{-1}	NMR (δ in DMSO-d_6 from TMS)
26[b]	35	3000—2300 1700	1.39 (3H, d, J=7.1 Hz), 2.49 (3H, s), 3.72 (1H, q, J=7.1 Hz), 7.38 (2H, d, J=8.0 Hz), 7.56 (1H, s), 7.81 (2H, d, J=8.0 Hz)
27[b]	52	2900—2300 1720	1.29 (3H, t, J=7.5 Hz), 1.40 (3H, d, J=7.1 Hz), 2.87 (2H, q, J=7.5 Hz), 3.72 (1H, q, J=7.1 Hz), 7.38 (2H, d, J=8.2 Hz), 7.58 (1H, s), 7.82 (2H, d, J=8.2 Hz), 12.4 (s, OH)
36[b]	45	3000—2300 1700	1.41 (3H, d, J=7.1 Hz), 2.51 (3H, s), 3.80 (1H, q, J=7.1 Hz), 7.25—7.35 (2H, m), 7.67 (1H, s), 8.12 (1H, dd, J=8.0, 8.0 Hz), 12.4 (1H, OH)
37[b]	31	3200—2300 1720	1.31 (3H, t, J=7.7 Hz), 1.42 (3H, d, J=7.1 Hz), 2.91 (2H, q, J=7.7 Hz), 3.79 (1H, q, J=7.1 Hz), 7.25—7.35 (2H, m), 7.69 (1H, s), 8.13 (1H, dd, J=8.0, 8.0 Hz), 12.5 (1H, OH)
44[b]	54	3200—2300 1690	1.40 (3H, d, J=7.1 Hz), 2.50 (3H, s), 3.79 (1H, q, J=7.1 Hz), 7.38 (1H, m), 7.52 (1H, m), 7.68 (1H, s), 8.09 (1H, d, J=8.2 Hz), 12.6 (1H, OH)
45[b]	57	3050—2200 1715	1.27 (3H, t, J=7.5 Hz), 1.39 (3H, d, J=7.1 Hz), 2.90 (2H, q, J=7.5 Hz), 3.78 (1H, q, J=7.1 Hz), 7.38 (1H, m), 7.52 (1H, m), 7.72 (1H, s), 8.08 (1H, d, J=8.3 Hz), 12.6 (1H, OH)

a) Yields from the corresponding thioamides (IV-1, IV-2, or IV-3). *b*) Dimethyl acetal of 2-bromopropanal (for the syntheses of **26**, **36**, and **44**) and dimethyl acetal of 2-bromobutanal (for the syntheses of **27**, **37**, and **45**) were prepared by a reported method.[16]

3) Diethyl 2-[4-(4-Allylthiazol-2-yl)phenyl]-2-methylmalonate (XVII): The reported method[14] was used with XVI (1.0 g), zinc dust (850 mg), and titanium (IV) chloride (0.5 ml) in tetrahydrofuran (10 ml) to give XVII (750 mg of crude product) quantitatively. IR (neat): 1730, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.1 Hz), 1.89 (3H, s), 3.61 (2H, m), 4.23 (4H, q, J=7.1 Hz), 5.1—5.3 (2H, m), 6.0—6.2 (1H, m), 6.92 (1H, s), 7.45 (2H, d, J=8.5 Hz), 7.91 (2H, d, J=8.5 Hz).

4) 2-[4-(4-Allylthiazol-2-yl)phenyl]propionic Acid (**19**): The procedure used for the preparation of **12** was repeated with XVII (1.5 g) and 1N NaOH (12.3 ml) in ethanol (5 ml) to give **19** (850 mg, 76%). IR (KBr): 3000—2400, 1720, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, d, J=7.1 Hz), 3.54 (2H, m), 3.74 (1H, q, J=7.1 Hz), 5.1—5.3 (2H, m), 5.9—6.1 (1H, m), 7.27 (1H, s), 7.39 (2H, d, J=8.3 Hz), 7.86 (2H, d, J=8.3 Hz).

2-[4-(4-Hydroxymethylthiazol-2-yl)phenyl]propionic Acid (20) 1) Diethyl 2-[4-(4-Chloromethylthiazol-2-yl)phenyl]-2-methylmalonate (XVIII): The procedure used for the preparation of XI-12 was repeated with IV-1 (3.3 g) and 1,3-dichloroacetone (1.7 g) in dry benzene (50 ml) to give XVIII (3.7 g, 91%). IR (neat): 1720, 1505 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.1 Hz), 1.89 (3H, s), 4.24 (4H, q, J=7.1 Hz), 4.74 (2H, s), 7.30 (1H, s), 7.46 (2H, d, J=8.4 Hz), 7.86 (2H, d, J=8.4 Hz).

2) 2-[4-(4-Hydroxymethylthiazol-2-yl)phenyl]propionic Acid (**20**): The procedure used for the preparation of **12** was repeated with XVIII (5.2 g) and 1 N NaOH (50 ml) in ethanol (10 ml) to give **20** (800 mg, 22%). IR (KBr): 3400, 3300—2500, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.40 (3H, d, J=7.1 Hz), 3.73 (1H, q, J=7.1 Hz), 4.63 (2H, s), 5.30 (1H, OH), 7.43 (1H, s), 7.41 (2H, d, J=8.2 Hz), 7.87 (2H, d, J=8.2 Hz), 12.5 (1H, OH).

2-[4-(4-Methoxymethylthiazol-2-yl)phenyl]propionic Acid (21) A solution of XVIII (3.2 g) and sodium methoxide (1.4 g) in methanol (50 ml) was stirred at reflux for 2 h. After the reaction, the solution was poured into ice-water and acidified to pH 2 with 1 N HCl. The mixture was extracted with chloroform and the extract was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane to give the 4-methoxymethylthiazole derivative (1.9 g, 66%). The compound obtained was treated by a method similar to that for preparation of **12**, giving **21** (1.3 g, 67%). IR (KBr): 3200—2600, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.54 (3H, d, J=7.1 Hz), 3.49 (3H, s), 3.77 (1H, q, J=7.1 Hz), 4.64 (2H, s), 7.21 (1H, s), 7.37 (2H, d, J=8.2 Hz), 7.87 (2H, d, J=8.2 Hz).

2-[4-(4-Carbamoylthiazol-2-yl)phenyl]propionic Acid (22) 1) Diethyl 2-[4-(4-Carboxythiazol-2-yl)phenyl]-2-methylmalonate (XIX): The procedure used for the preparation of XI-12 was repeated with IV-1 (3.0 g) and 3-bromopyruvic acid (2.1 g) in dry benzene (40 ml) to give XIX (2.6 g, 71%). IR (KBr): 3100—2500, 1720, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.27 (6H, t, J=7.0 Hz), 1.90 (3H, s), 4.24 (4H, q, J=7.0 Hz), 7.50 (2H, d, J=8.6 Hz), 7.97 (2H, d, J=8.6 Hz), 8.29 (1H, s).

2) 2-[4-(4-Carbamoylthiazol-2-yl)phenyl]propionic Acid (**22**): A solution of XIX (1.1 g) and thionyl chloride (3.8 g) in dichloromethane (20 ml) was stirred at reflux for 100 min. After removal of the solvent and thionyl chloride, the residue obtained was added dropwise to 28% ammonium hydroxide (50 ml) at 0 °C. The solution was stirred for 10 min and extracted with AcOEt. The extract was washed with water and brine, and dried over $MgSO_4$, in that order. After evaporation of the solvent, the residue was precipitated from chloroform–hexane. The white solid obtained was converted by a method similar to that used for the preparation of **12** to give **22** (20%). IR (KBr): 3600—3000, 1685, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.41 (3H, d, J=7.0 Hz), 3.76 (1H, q, J=7.0 Hz), 7.44 (2H, d, J=8.2 Hz), 7.67 (1H, NH), 7.85 (1H, NH), 7.99 (2H, d, J=8.2 Hz), 8.27 (1H, s), 12.5 (1H, OH).

2-[4-[4-(*N*-Methylcarbamoyl)thiazol-2-yl]phenyl]propionic Acid (23) This compound was prepared in a similar way as in the synthesis of **22**, with use of methylamine to give **23** (48% from XIX). IR (KBr): 3500—2300, 1710, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.41 (3H, d, J=7.2 Hz), 2.84 (3H, d, J=4.8 Hz), 3.77 (1H, q, J=7.2 Hz), 7.44 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 8.24 (1H, s), 8.46 (1H, q, J=4.8 Hz, NH), 12.4 (1H, OH).

2-[4-[4-(*N*,*N*-Dimethylcarbamoyl)thiazol-2-yl]phenyl]propionic Acid (24) This compound was prepared in a similar way as in the synthesis of **22** with use of dimethylamine to give **24** (49% from XIX). IR (KBr): 3100—2300, 1715, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.41 (3H, d, J=7.2 Hz), 3.03 (3H, s), 3.20 (3H, s), 3.76 (1H, q, J=7.2 Hz), 7.43 (2H, d, J=8.2 Hz), 7.92 (2H, d, J=8.2 Hz), 8.08 (1H, s), 12.4 (1H, OH).

2-[4-(4-Trifluoromethylthiazol-2-yl)phenyl]propionic Acid (25) 1) Diethyl 2-Methyl-2-[4-(4-trifluoromethyl-4-hydroxy-2-thiazolin-2-yl)phenyl]-malonate (XX): The procedure used for preparation of XI-12 was repeated with IV-1 (1.5 g) and 1,1,1-trifluoro-3-bromo-2-propanone (1.2 g) in dry benzene (25 ml) to give XX (1.3 g, 64%). IR (KBr): 3100, 1730, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.26 (6H, t, J=7.1 Hz), 1.68 (3H, s), 3.00 (1H, OH), 3.57 (1H, m), 3.77 (1H, m), 4.25 (4H, q, J=7.1 Hz), 7.45 (2H, d, J=8.7 Hz), 7.90 (2H, d, J=8.7 Hz).

2) 2-[4-(4-Trifluoromethylthiazol-2-yl)phenyl]propionic Acid (**25**): The procedure used for the preparation of **12** was repeated with XX (1.14 g) and 1 N NaOH (9.0 ml) in ethanol (8 ml) to give 2-[4-(4-trifluoromethyl-4-hydroxy-2-thiazolin-2-yl)phenyl]propionic acid (590 mg, 69%). The compound obtained (570 mg) in 12 N HCl (5 ml) was heated at reflux for 170 min. After the reaction, the mixture was extracted with chloroform. The extract was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane and recrystallized from AcOEt–hexane to give **25** (410 mg, 75%). IR (KBr): 3500—2600, 1710, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.55 (3H, d, J=7.2 Hz), 3.80 (1H, q, J=7.2 Hz), 7.42 (2H, d, J=6.7 Hz), 7.72 (1H, m), 7.81 (2H, d, J=6.7 Hz). The compounds **26**, **27**, **36**, **37**, **44**, and **45** were prepared in a similar way as in the synthesis of **1** except that ethanol and acetic acid (1 : 1) were used as solvents for the synthesis of the thiazole ring. The yields and physical properties are summarized in Table IV.

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