Pergamon

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Bioorganic & Medicinal Chemistry 11 (2003) 4729–4742

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Structure–Activity Relationships of 5-Phenylthiophenecarboxylic Acid Derivatives as Antirheumatic Agents

Toshiya Noguchi,* Masahiro Hasegawa, Kazuyuki Tomisawa and Morihiro Mitsukuchi

Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 403, Yoshino-cho, 1-chome, Kita-ku, Saitama-city, Saitama 330-8530, Japan

Received 7 May 2003; accepted 5 August 2003

Abstract—5-(Phenylthiophene)-3-carboxylic acid (**2a**), a metabolite of esonarimod (**1**), which was developed as a new antirheumatic drug, was considered as a lead compound for new antirheumatic drugs. A new series of **2a** derivatives were synthesized and their characteristic pharmacological effects, that is their antagonistic effect toward interleukin (IL)-1 in mice and the suppressive effect against adjuvant-induced arthritis (AIA) in rats, were evaluated and compared with those of **1**. The structure–activity relationships indicated that [5-(4-bromophenyl)-thiophen-3-yl]acetic acid (**5d**), methyl [5-(4-chlorophenyl)-thiophen-3-yl]acetate (**5h**), and methyl [5-(4-bromophenyl)-thiophen-3-yl]acetate (**5i**) suppressed AIA more potently than **1** and all of the other synthesized compounds.

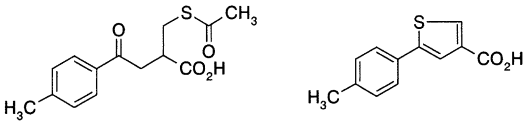
Introduction

Esonarimod, (*R,S*)-2-acetylthiomethyl-4-(4-methylphenyl)-4-oxobutanoic acid (**1**), was originally developed by Taisho Pharmaceutical Co. Ltd. as a new antirheumatic drug.[1,2] Compound **1** has a variety of effects on cellular and mediator events in inflammatory processes, inhibits the production of inflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor-α from human peripheral blood mononuclear cells,[3] and suppresses the development of arthritis in various animal models.[1,3–5] In preclinical and clinical studies, its metabolic fate has been studied in several animal species and in humans.[6] We found that 5-(4-methylphenyl)-thiophene-3-carboxylic acid (**2a**) was a metabolite of **1** that had immunological activity like **1**. The chemical structures of **1** and **2a** are shown in Figure 1. These structural and biological similarities led us to study derivatives of **2a** in the hope of finding new antirheumatic agents. Some thiopheneacetic acid derivatives, such as thiaprofenoic acid (**3**), have already been developed as nonsteroidal anti-inflammatory drugs.[7] Furthermore, thiophenealkanoic acid (**4**) has been reported to exhibit immunological activity.[8] The structures of these compounds are illustrated in Figure 2. In connection with these reports, we were interested in the activity of (5-phenylthiophene)acetic acid derivatives and (5-phenylthiophene)propionic acid derivatives (**5–9**).

In this report, we describe the synthesis of new chemically modified phenylthiophene derivatives, examine their immunological effects, and discuss the structure–activity relationships (SARs).

Chemistry

The structures of the prepared compounds **2**, **5–9** are illustrated in Figure 3. Compounds **2** were 5-phenyl-3-carboxylic acid derivatives. Compounds **5–9** were (5-phenylthiophen-3-yl)acetic acid, 3-(5-phenylthiophen-3-yl)propionic acid, 5-phenylthiophene-2-carboxylic acid, (5-phenylthiophen-2-yl)acetic acid, and 2-(5-phe-



Esonarimod (**1**) **2a**

Figure 1.

*Corresponding author. Tel.: +81-48-663-1111; e-mail: t.noguchi@po.rd.taisho.co.jp

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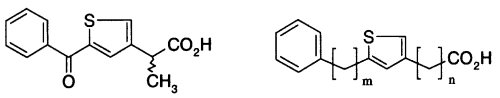
doi:10.1016/j.bmc.2003.08.009



3 4

Figure 2.

nylthiophen-3-yl)propionic acid derivatives, respectively. Compounds **2**, **5**, **6** and **9** were newly synthesized. Compounds **7** and **8** were previously known and their anti-inflammatory and hypolipidemic activities have been described previously, while their immunological effects have not been reported.[9–14]

5-Phenylthiophene-3-carboxylic acid derivatives (**2a–v**) were synthesized from 2-acetylthiomethyl-4-phenyl-4-oxobutanoic acid derivatives (**1**, **10a–g**), which were obtained previously by our group (Scheme 1),[2] as starting materials. Treatment of **1**, **10a–g** with H_2SO_4 and alcohol gave the corresponding esters of dihydrothiophene derivatives (**11a–l**),[6] which were oxidized with 2,3-dihydro-5,6-dicyano-1,4-benzoquinone (DDQ) to give esters of 5-phenylthiophene-3-carboxylic acid derivatives (**2b–m**).[15] Hydrolysis of **2b–m** gave free carboxylic acid derivatives (**2a**,**n–t**). Benzyl or isopropyl esters of 5-(4-bromophenylthiophene)-3-carboxylic acids (**2u**,**v**) were obtained by esterification of **2p** with the corresponding bromide.

The preparation of 5-phenylthiophene-2-carboxylic acid (**7a**) and its methyl ester (**7b**) is shown in Scheme 2. The rhodanine adduct, 5-cinnamylidenerhodanine (**14**), was prepared by known methods.[16] Hydrolysis and treatment of **14** with H_2O_2 gave the disulfide (**15**). Oxidation of **15** with iodine gave **7a**. Treatment with H_2SO_4 and methanol gave **7b**. The synthetic pathway to other 5-phenylthiophene-2-carboxylic acid derivatives (**7c–h**) is outlined in Scheme 3. 2-Phenylthiophene derivatives (**20a–c**) were obtained by three-step reactions from the corresponding benzene derivatives (**16a–c**). Vilsmeier reaction of **20a–c** with *N*,*N*-dimethylformamide (DMF) and $POCl_3$ gave aldehydes (**21a–c**), which were oxidized to the target compounds (**7c–e**) with Ag_2O.[17] Treatment of **7c–e** with H_2SO_4 and methanol gave the corresponding methyl esters (**7f–h**).

Scheme 4 shows the synthetic route to (5-phenylthiophen-3-yl)acetic acid derivatives (**5a–i**).[18] Condensation of 2-phenylthiolan-4-on (**24**) with cyanoacetic acid and then decarbonylation with DDQ gave (5-phenylthiophen-3-yl)acetonitrile (**25a**). Compound **24** was obtained by two-step reactions from ethyl cinnamate (**22**).[19] Reduction of **2b**,**f**,**h**,**l** with $LiAlH_4$ and treatment with $SOCl_2$ gave the corresponding chlorides (**26a–d**), which were treated with KCN to give the respective (5-phenylthiophen-3-yl)acetonitrile derivatives (**25b–e**). Compounds **5a–e** were obtained by hydrolysis of **25a–e**. Treatment of **5a–e** with H_2SO_4 and methanol gave the corresponding methyl esters (**5f–i**).

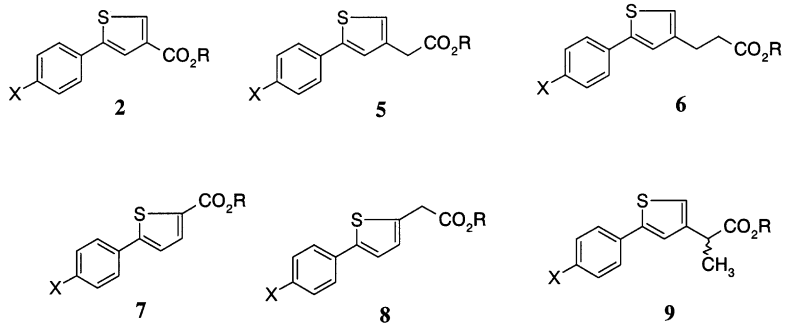
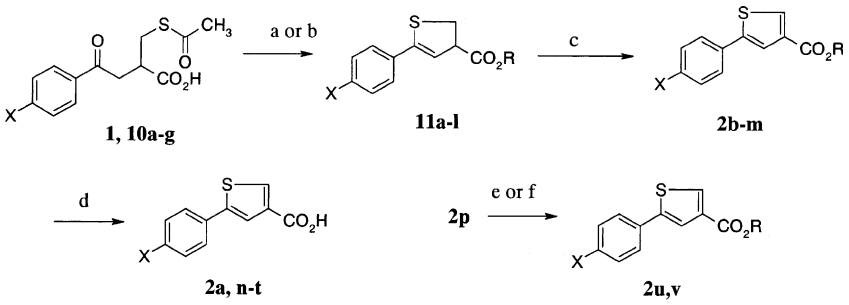
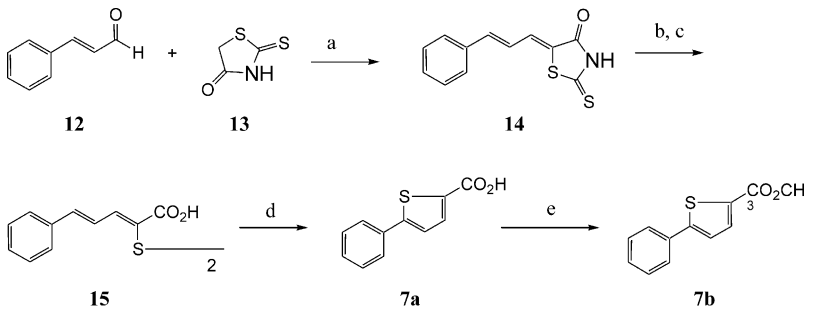


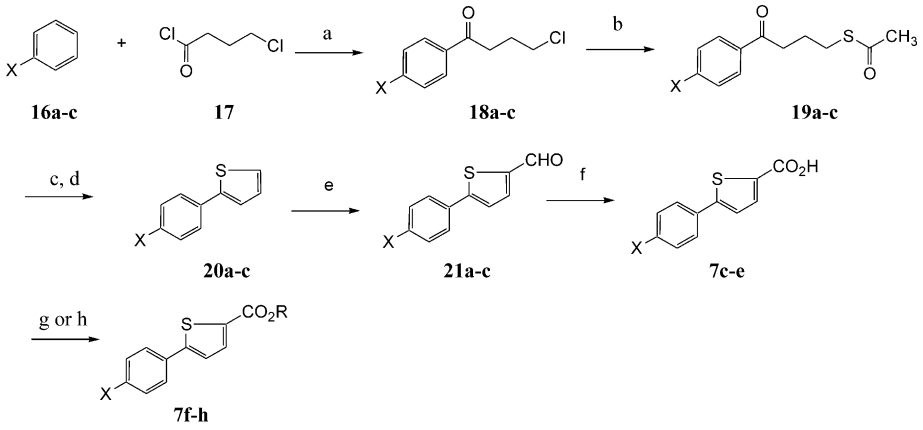
Figure 3.



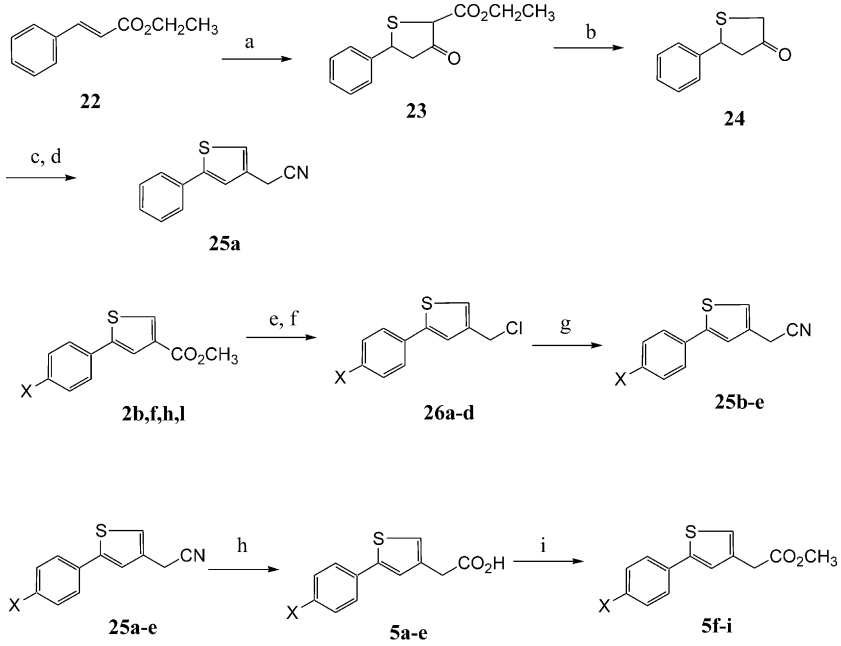
Scheme 1. Compounds: **1**, X = CH_3; **10a**, X = H; **10b**, X = Cl; **10c**, X = Br; **10d**, X = CH_2CH_3; **10e**, X = $CH(CH_3)_2$; **10f**, X = OCH_3; **10g**, X = cyclohexyl; **11a**, X = CH_3, R = CH_3; **11b**, X = CH_3, R = CH_2CH_3; **11c**, X = H, R = CH_3; **11d**, X = H, R = CH_2CH_3; **11e**, X = Cl, R = CH_3; **11f**, X = Cl, R = CH_2CH_3; **11g**, X = Br, R = CH_3; **11h**, X = Br, R = CH_2CH_3; **11i**, X = CH_2CH_3, R = CH_3; **11j**, X = $CH(CH_3)_2$, R = CH_3; **11k**, X = OCH_3, R = CH_3; **11l**, X = cyclohexyl, R = CH_3; **2b**, X = CH_3, R = CH_3; **2c**, X = CH_3, R = CH_2CH_3; **2d**, X = H, R = CH_3; **2e**, X = H, R = CH_2CH_3; **2f**, X = Cl, R = CH_3; **2g**, X = Cl, R = CH_2CH_3, **2h**, X = Br, R = CH_3; **2i**, X = Br, R = CH_2CH_3; **2j**, X = CH_2CH_3, R = CH_3; **2k**, X = $CH(CH_3)_2$, R = CH_3; **2l**, X = OCH_3, R = CH_3; **2m**, X = cyclohexyl, R = CH_3; **2n**, X = H; **2a**, X = CH_3; **2o**, X = Cl; **2p**, X = Br; **2q**, X = CH_2CH_3; **2r**, X = $CH(CH_3)_2$; **2s**, X = OCH_3; **2t**, X = cyclohexyl; **2u**, X = Br, R = $CH(CH_3)2$; **2v**, X = Br, R = CH_2Ph. Reagents and conditions: (a) CH_3OH, H_2SO_4, reflux; (b) CH_3CH_2OH, H_2SO_4, reflux; (c) DDQ, benzene, rt; (d) KOH, THF, H_2O, rt; (e) PhBr, K_2CO_3, DMF, rt; (f) $(CH_3)_2CHBr$, K_2CO_3, DMF, rt.



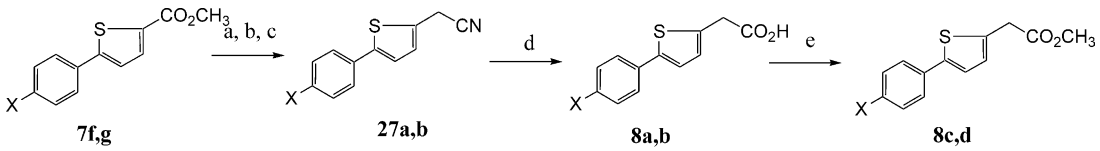
Scheme 2. Reagents and conditions: (a) AcONa, AcOH, reflux; (b) NaOH, H_2O, 80 °C; (c) H_2O_2, pyridine, H_2O, 3 °C; (d) I_2, dioxane, ethanol, rt; (e) H_2SO_4, CH_3OH, reflux.



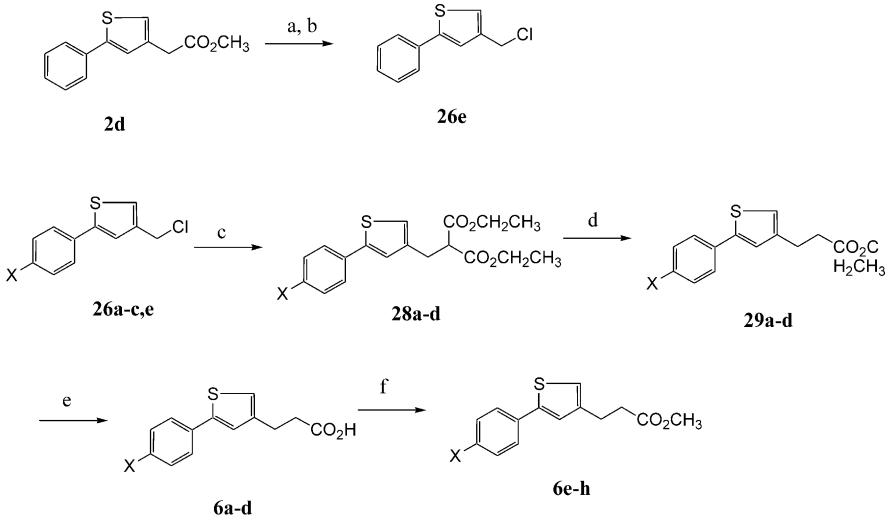
Scheme 3. Compounds: **16a**, X = Cl; **16b**, X = Br, **16c**, X = CH_3; **18a**, X = Cl; **18b**, X = Br, **18c**, X = CH_3; **19a**, X = Cl; **19b**, X = Br, **19c**, X = CH_3; **20a**, X = Cl; **20b**, X = Br, **20c**, X = CH_3; **21a**, X = Cl, **21b**, X = Br; **21c**, X = CH_3; **7c**, X = Cl; **7d**, X = Br; **7e**, X = CH_3; **7f**, X = Cl, R = CH_3; **7g**, X = Br, R = CH_3; **7h**, X = CH_3, R = CH_2CH_3. Reagents and conditions: (a) $AlCl_3$, CS_2, rt; (b) AcSK, DMF, 5 °C; (c) H_2SO_4, CH_3OH, reflux; (d) chloranil, benzene, reflux; (e) $POCl_3$, DMF, 1,2-dichloroethane, reflux; (f) Ag_2O, NaOH, H_2O, 50 °C; (g) H_2SO_4, methanol, toluene, reflux; (h) H_2SO_4, ethanol, toluene, reflux.



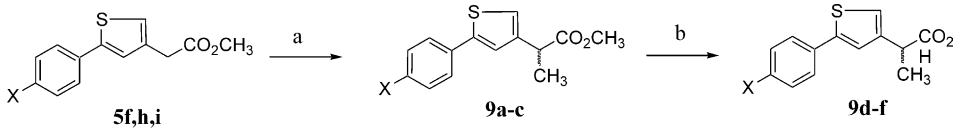
Scheme 4. Compounds: **26a**, X = CH_3; **26b**, X = Cl; **26c**, X = Br; **26d**, X = OCH_3; **25b**, X = CH_3; **25c**, X = Cl; **25d**, X = Br; **25e**, X = OCH_3; **5a**, X = H; **5b**, X = CH_3; **5c**, X = Cl; **5d**, X = Br; **5e**, X = OCH_3; **5f**, X = H; **5g**, X = CH_3; **5h**, X = Cl; **5i**, X = Br. Reagents and conditions: (a) ethyl thioglycolate, $NaOCH_2CH_3$, ethanol, THF, rt; (b) H_2SO_4, acetic acid, H_2O, reflux; (c) cyanoacetic acid, acetic acid, piperidine, benzene, reflux; (d) DDQ, toluene, rt; (e) $LiAlH_4$, ether, reflux; (f) $SOCl_2$, THF, $[(CH_3)_2N]_3PO$, rt; (g) KCN, 18-crown-6, CH_3CN, rt; (h) KOH, ethanol, H_2O, reflux; H_2SO_4, methanol, reflux.



Scheme 5. Compounds: **27a**, X = Cl; **27b**, X = Br; **8a**, X = Cl; **8b**, X = Br, **8c** X = Cl, **8d**, X = Br. Reagents and conditions: (a) $LiAlH_4$, $(CH_3CH_2)_2O$, reflux; (b) $SOCl_2$, THF, $[(CH_3)_2N]_3PO$, rt; (c) KCN, 18-crown-6, CH_3CN, rt; (d) KOH, ethanol, H_2O, reflux; (e) H_2SO_4, methanol, reflux.



Scheme 6. Compounds: **28a**, X = H; **28b**, X = CH_3; **28c**, X = Cl; **28d**, X = Br; **29a**, X = H; **29b**, X = CH_3; **29c**, X = Cl; **29d**, X = Br; **6a**, X = H; **6b**, X = CH_3; **6c**, X = Cl; **6d**, X = Br; **6e**, X = H; **6f**, X = CH_3; **6g**, X = Cl; **6h**, X = Br. Reagents and conditions; (a) $LiAlH_4$, ether, reflux; (b) $SOCl_2$, THF, $[(CH_3)_2N]_3PO$, rt; (c) diethyl malonate, $NaOCH_2CH_3$, ethanol, reflux; (d) NaCl, DMSO, H_2O, reflux; (e) NaOH, methanol, H_2O, rf; (f) H_2SO_4, methanol, reflux.



Scheme 7. Compounds: **9a**, X = H; **9b**, X = Cl; **9c**, X = Br; **9d**, X = H; **9e**, X = Cl; **9f**, X = Br. Reagents and conditions: (a) CH_3I, NaH, DMF, 0 °C; (b) KOH, CH_3OH, THF, H_2O rt.

The same reaction sequence was applied to **7f,g** to give (5-phenylthiophen-2-yl)acetic acid derivatives (**8a–d**) (Scheme 5).

The preparation of 3-(5-phenylthiophen-3-yl)propionic acid derivatives (**6a–h**) is shown in Scheme 6.[20] Condensation of the chlorides (**26a–d**), intermediates of **5b–e**, and diethyl malonate with sodium ethoxide gave diesters (**28a–d**),[21] which were treated with dimethylsulfoxide (DMSO), NaCl and hydrolysis to give free carboxylic acids (**6a–d**), respectively.[22] Methyl esters (**6e–h**) were obtained from **6a–d** with H_2SO_4 and methanol.

The synthesis of 2-(5-phenylthiophen-3-yl)propionic acid derivatives (**9a–f**) is shown in Scheme 7.[20] Treatment of **5f,h,i** with methyl iodide gave **9a–c**, which were hydrolyzed with KOH to give free carboxylic acids (**9d–f**).

Results and Discussion

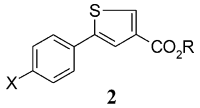
These compounds were evaluated for their antagonistic effect toward IL-1 in mice and their suppressive effect on adjuvant-induced arthritis (AIA) in rats. In rheumatoid arthritis (RA) patients, IL-1 production is induced in synovial cells and peripheral blood, and IL-1 elicits various inflammatory symptoms, such as the proliferation of synovial cells, stimulation of osteoclasts, and degradation of cartilage and bone.[23,24] AIA is also useful for studies of anti-inflammatory or immunosuppressive effects.[25]

The activities of **2**, **5–9** toward IL-1 and AIA are shown in Tables 1–3. Table 1 shows the results of a SAR study on the effect of the substituent (X) at the *para* position of the phenyl ring and the substituent (R) at the carboxylic acid in type **2** compounds, in comparison to the results with **1**. In SAR studies of **1** derivatives, the substituent on the phenyl ring increased the activity toward AIA in the order *para* > *meta* > *ortho*.[2] Consequently, the substituent on the phenyl ring was fixed at the *para* position in this chemical modification. The effects of **2** with various substituents, that is X = H, CH_3, Cl, Br, cyclohexyl, CH_2CH_3, and OCH_3; R = H, CH_3, CH_2CH_3, CH_2Ph, and $CH(CH_3)_2$, were tested. Type **2** compounds generally showed a slightly stronger IL-1

antagonistic effect than **1**. Although somewhat less potent than **1**, **2** suppressed AIA when X was halogen. When X = methyl, **2** was slightly active against AIA, but other X gave reduced activities. Thus, the antagonistic effect against IL-1 is dependent on the nature of X: Cl, Br > CH_3 > > others. With regard to R, free carboxylic acid (R = H) and methyl ester (R = CH_3) were effective against AIA. However, ethyl ester, benzyl ester, and isopropyl ester had less of an effect on AIA. This result suggests that X = halogen, such as Cl or Br, is potent against AIA.

The results of a SAR study on the effect of the distance between the thiophene ring and carboxylic acid are shown in Table 2. Compounds of type **2**, **5**, **6** and **9** were evaluated. Compounds of type **5** had stronger antagonistic effects against IL-1 and suppressed AIA more than **1** and **2**. Compounds **5d**, **5h**, and **5i** were the most potent of all the synthesized compounds **2**, **5**–**9** against AIA. On the other hand, compounds of type **6** had reduced antagonistic effects against IL-1 and suppressive effects against AIA. While type **9** compounds were active against AIA, they showed no IL-1 antagonistic effect. These results showed that the distance between the thiophene ring and carboxylic acid (number of methylenes = *n*) was very important for the antagonistic effect toward IL-1 and the suppression of AIA. The activities increased in the order *n* = 1, 0, 2. Furthermore, ramification of methylene was judged invalid.

Table 1. Activities of type **2** toward IL-1 antagonistic effect and AIA



2

No.	X	R	IL-1	AIA	
			IC_{50} (μM)[a]	% suppression[b]	Activity rank[c]
2a	CH_3	H	81.1	23.7	1
2b	CH_3	CH_3	21.7	34.9	2
2c	CH_3	CH_2CH_3	—	2.5	0
2d	H	CH_3	51.5	—	—
2e	H	CH_2CH_3	66.7	3.2	0
2o	Cl	H	50.4	50.5	3
2f	Cl	CH_3	34.7	47.8	3
2g	Cl	CH_2CH_3	17.2	3.3	0
2p	Br	H	73.0	52.7	3
2h	Br	CH_3	63.0	48.7	3
2i	Br	CH_2CH_3	14.8	22.5	1
2u	Br	$CH(CH_3)_2$	10.8	8.7	0
2v	Br	$PhCH_2$	—	24.7	2
2t	Cyclohexyl	H	12.2	13.1	1
2m	Cyclohexyl	CH_3	2.3	13.4	1
2q	CH_2CH_3	H	—	13.1	1
2r	$CH(CH_3)_2$	H	—	18.4	1
2s	OCH_3	H	48.7	0	0
1			105.5	57.3	4

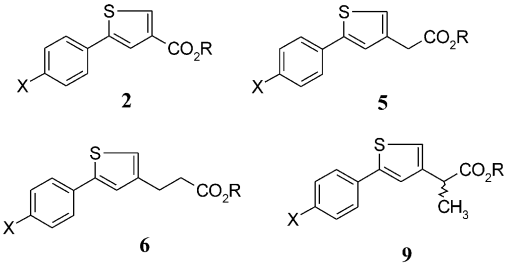
[a]Concentration of drug inhibiting IL-1 generation by 50% of control value. IC_{50} values were calculated by least-squares method.
[b]The edema volume of foot pads of rats with developing AIA. The edema of both hind paws was calculated as percentages with respect to the control value.
[c]The activity rank of AIA was defined as follows. When AIA was 0–10, 10–25, 25–40, 40–55, 55–70, 70–85, and more than 85%, the activity rank was classified into 0, 1, 2, 3, 4, 5 and 6, respectively.

Table 3 shows the results of a SAR study on the placement of the carboxylic acid at the 2- and 3-positions of the thiophene ring (types **2** and **7**) and the distance between the thiophene ring and carboxylic acid (types **5** and **8**). Although placement of the carboxylic acid did not appear to strongly affect the activities, the IL-1 antagonistic effect of type **7** compounds was slightly greater than that of **1**. Type **5** and **8** compounds also had stronger antagonistic effects toward IL-1 suppressive effects against AIA than **1** or types **2** and **7**. However, type **5** compounds were slightly more potent than **8**.

Conclusion

Several analogues of **2a**, a metabolite of esonarimod (**1**), which was developed as an antirheumatic agent, were

Table 2. Activities of type **2**, **5**, **6**, and **9** toward IL-1 antagonistic effect and AIA

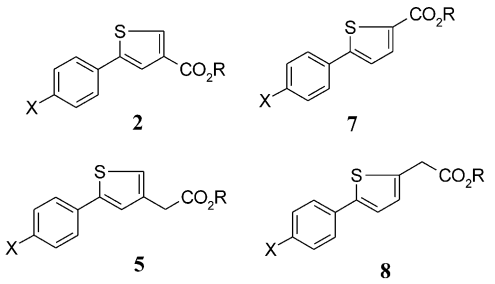


2 **5** **6** **9**

No.	X	R	IL-1	AIA	
			IC_{50} (μM)[a]	% suppression[b]	Activity rank[c]
2d	H	CH_3	51.5	—	—
5a	H	H	26.1	69.2	4
5f	H	CH_3	41.0	69.9	4
6a	H	H	—	22.1	1
6e	H	CH_3	384.5	26.3	2
9d	H	H	138.0	83.2	5
9a	H	CH_3	212.2	—	—
2a	CH_3	H	81.1	23.7	1
2b	CH_3	CH_3	21.7	34.9	2
5b	CH_3	H	79.9	5.5	0
5g	CH_3	CH_3	24.7	12.1	1
6b	CH_3	H	135.8	14.7	1
6f	CH_3	CH_3	116.9	−13.7	0
2o	Cl	H	50.4	50.5	3
2f	Cl	CH_3	34.7	47.8	3
5c	Cl	H	21.0	56.6	4
5h	Cl	CH_3	25.9	89.0	6
6c	Cl	H	103.7	37.9	2
6g	Cl	CH_3	129.3	44.2	3
9e	Cl	H	100.0	57.5	4
9b	Cl	CH_3	78.4	67.1	4
2p	Br	H	73.0	52.7	3
2h	Br	CH_3	63.0	48.7	3
5d	Br	H	29.0	99.7	6
5i	Br	CH_3	21.8	98.0	6
6d	Br	H	125.7	38.9	2
6h	Br	CH_3	161.9	−2.1	0
9f	Br	H	96.0	46.7	3
9c	Br	CH_3	202.4	57.5	4

[a]See footnotes in Table 1.
[b]See footnotes in Table 1.
[c]See footnotes in Table 1.

Table 3. Activities of type **2**, **5**, **7**, and **8** toward IL-1 antagonistic effect and AIA



No.	X	R	IL-1	AIA	
			IC_{50} (μM)[a]	% suppression[b]	Activity rank[c]
2d	H	CH_3	51.5	—	—
7a	H	H	45.1	14.3	1
7b	H	CH_3	—	35.9	2
2a	CH_3	H	81.1	23.7	1
2b	CH_3	CH_3	21.7	34.9	2
7e	CH_3	H	13.5	17.1	1
7h	CH_3	CH_2CH_3	—	−1.6	0
2o	Cl	H	50.4	50.5	3
2f	Cl	CH_3	34.7	47.8	3
7c	Cl	H	29.7	74.0	5
7f	Cl	CH_3		13.9	1
5c	Cl	H	21.0	56.6	4
5h	Cl	CH_3	25.9	89.0	6
8a	Cl	H	14.4	45.2	3
8c	Cl	CH_3	26.1	75.7	5
2p	Br	H	73.0	52.7	3
2h	Br	CH_3	63.0	48.7	3
7d	Br	H	16.5	62.6	4
7g	Br	CH_3	38.1	76.9	5
5d	Br	H	29.0	99.7	6
5i	Br	CH_3	21.8	98.0	6
8b	Br	H	26.1	49.8	3
8d	Br	CH_3	19.0	80.8	5

[a]See footnotes in Table 1.
[b]See footnotes in Table 1.
[c]See footnotes in Table 1.

synthesized. The antagonistic effects of these compounds toward IL-1 and their suppressive effects against AIA were evaluated and compared with those of **1**. Regarding, the substituent on the phenyl ring at the *para* position (X) and the carboxylic acid (R), a SAR study indicated that a halogen (X = Cl or Br) and free carboxylic acid or methyl ester (R = H or CH_3) substituents, respectively, are important for these activities and that R = CH_2CH_3, CH_2Ph or $CH(CH_3)_2$ appears to reduce these activities. Placement of carboxylic acid at the 2- or 3-position of the thiophene ring does not appear to affect these activities. However, the distance between the thiophene ring and carboxylic acid (number of methylenes = *n*) greatly affects the activities: the activities increase in the order *n* = 1, 0, 2. Furthermore 3-(5-phenylthiophene)acrylic acid derivatives, in which the methylene chain was ramified, were judged invalid. Hence, the SAR indicated that [5-(4-bromophenyl)-thiophen-3-yl]acetic acid (**5d**), methyl [5-(4-chlorophenyl)-thiophen-3-yl]acetate (**5h**), and methyl [5-(4-bromophenyl)-thiophen-3-yl]acetate (**5i**) were more potent toward AIA than **1** and all of the other synthesized compounds.

Experimental

Chemistry

Melting points were determined by a Buchi 535 melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1760 spectrometer. ^1H NMR spectra were recorded on a Varian VXL-200 spectrometer. Chemical shifts are reported in ppm (δ) values, as determined using a JEOL JMS-SIX102 spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400. TLC was performed on silica gel precoated plates (Merck, Kieselgel 60F254). Column chromatography was performed over silica gel (Wako, Wako gel C-200). 2-Acetylthiomethyl-(4-methylphenyl)-4-oxobutanoic acid (**1**), 2-acetylthiomethyl-4-phenyl-4-oxobutanoic acid (**10a**), 2-acetylthiomethyl-(4-chlorophenyl)-4-oxobutanoic acid (**10b**), 2-acetylthiomethyl-(4-bromophenyl)-4-oxobutanoic acid (**10c**), 2-acetylthiomethyl-(4-ethylphenyl)-4-oxobutanoic acid (**10d**) 2-acetylthiomethyl - (4 - isopropylphenyl) - 4 - oxobutanoic acid (**10e**), 2-acetylthiomethyl-(4-methoxyphenyl)-4-oxobutanoic acid (**10f**), and 2-acetylthiomethyl-(4-cyclohexylphenyl)-4-oxobutanoic acid (**10g**) were synthesized as described in the literature.[2]

General procedure for preparation of methyl 5-(4-methylphenyl)thiophene-3-carboxylate (2b–m)

To a solution of **1**, **10a–g** (17.4 mmol) in methanol (20 mL) was slowly added a solution of concd H_2SO_4 (1.5 mL) in methanol (2.0 mL). The mixture was stirred under reflux for 5 h, and then methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed successively with satd $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was concentrated under reduced pressure to give a residue, which was recrystallized from solvents or purified by silica gel column chromatography to give dihydrothiophene (**11a–l**).

To a solution of **11a–l** (11.7 mmol) in benzene (10 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2.92 g, 12.9 mmol), and the mixture was stirred at room temperature for 1.5 h. The precipitate was filtered and washed with benzene. The filtrate and washings were combined and washed successively with satd $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. The benzene solution was evaporated under reduced pressure to give a residue, which was recrystallized from solvents or purified by silica gel column chromatography to give **2b–m**. However, three compounds **2j–l** were made for next steps without identification of the structures.

Methyl 5-(4-methylphenyl)thiophene-3-carboxylate (2b). Compound **2b** was prepared from **1** and methanol, and recrystallized from diethylether–hexane as colorless needles. Yield, 64% from **1**; mp: 80–82 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ 2.37 (s, 3H), 3.89 (s, 3H), 7.20 (d, 2H, *J* = 8 Hz), 7.50 (d, 2H, *J* = 8 Hz), 7.68 (d, 1H, *J* = 1 Hz), 7.99 (d, 2H, *J* = 1 Hz). IR (KBr) cm^{-1}: 1702. MS *m*/*z* 232 (M^+). Anal. calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.21; H, 5.17.

Ethyl 5-(4-methylphenyl)thiophene-3-carboxylate (2c). Compound **2c** was prepared from **1** and ethanol, and recrystallized from ethyl acetate–hexane as a white powder. Yield, 63% from **1**; mp: 35–37 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.40 (t, 3H, J=7 Hz), 2.39 (s, 3H), 4.35 (q, 2H, J=7 Hz), 7.20 (d, 2H, J=8 Hz), 7.51 (d, 2H, J=8 Hz), 7.66 (d, 1H, J=1 Hz), 8.00 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1708. MS m/z 246 (M^+). Anal. calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.30; H, 5.74.

Methyl 5-phenylthiophene-3-carboxylate (2d). Compound **2d** was prepared from **10a** and methanol, and recrystallized from ethyl acetate–hexane as colorless needles. Yield, 83% from **10a**; mp: 91–92 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.89 (s, 3H), 7.27–7.45 (m, 3H), 7.61 (m, 2H), 7.72 (d, 1H, J=1 Hz), 8.02 (1H, d, J=1 Hz). IR (KBr) cm^{-1}: 1710. MS m/z 218 (M^+). Anal. calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 65.98; H, 4.79.

Ethyl 5-phenylthiophene-3-carboxylate (2e). Compound **2e** was prepared from **10a** and ethanol, and purified by silica gel chromatography as a pale yellow oil. Yield from **10a**, 83%; ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.40 (t, 3H, J=7 Hz), 4.35 (q, 2H, J=7 Hz), 7.30–7.45 (m, 3H), 7.61 (d, 2H, J=8 Hz), 7.71 (d, 1H, J=1 Hz), 8.02 (d, 1H, J=1 Hz). IR (neat) cm^{-1}: 1718. MS m/z 232 (M^+). Anal. calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21. Found: C, 67.07; H, 5.10.

Methyl 5-(4-chlorophenyl)thiophene-3-carboxylate (2f). Compound **2f** was prepared from **10b** and methanol, and recrystallized from diethylether–hexane as pale yellow needles. Yield, 74% from **10b**; mp: 68–70 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.87 (s, 3H), 7.35 (d, 2H, J=8 Hz), 7.52 (d, 2H, J=8 Hz), 7.68 (d, 1H, J=1 Hz), 8.03 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1707. MS m/z 252 (M^+). Anal. calcd for $C_{12}H_9ClO_2S$: C, 57.02; H, 3.59. Found: C, 56.93; H, 3.44.

Ethyl 5-(4-chlorophenyl)thiophene-3-carboxylate (2g). Compound **2g** was prepared from **10b** and ethanol, and recrystallized from diethylether–hexane as pale yellow needles. Yield, 71% from **10b**; mp: 69–70 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.39 (t, 3H, J=7 Hz), 4.35 (q, 2H, J=7 Hz), 7.36 (d, 2H, J=8 Hz), 7.55 (d, 2H, J=8 Hz), 7.69 (d, 1H, J=1 Hz), 8.02 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1708. MS m/z 266 (M^+). Anal. calcd for $C_{13}H_{11}ClO_2S$: C, 58.54; H, 4.16. Found: C, 58.64; H, 4.07.

Methyl 5-(4-bromophenyl)thiophene-3-carboxylate (2h). Compound **2h** was prepared from **10c** and methanol, and recrystallized from diethylether–hexane as a white powder. Yield, 88% from **10c**; mp: 90–93 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.89 (s, 3H), 7.43–7.57 (m, 4H), 7.70 (d, 1H, J=1 Hz), 8.03 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1718. MS m/z 297 (M^+). Anal. calcd for $C_{12}H_9BrO_2S$: C, 48.50; H, 3.05. Found: C, 48.52; H, 2.96.

Ethyl 5-(4-bromophenyl)thiophene-3-carboxylate (2i). Compound **2i** was prepared from **10c** and ethanol, and recrystallized from diethylether–hexane as colorless needles. Yield, 83% from **10c**; mp: 77–79 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.40 (t, 3H, J=7 Hz), 4.44 (q, 2H, J=7 Hz), 7.43–7.57 (m, 4H), 7.70 (d, 1H, J=1 Hz), 8.05 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1718, 1708. MS m/z 311 (M^+). Anal. calcd for $C_{13}H_{11}BrO_2S$: C, 50.17; H, 3.56. Found: C, 50.33; H, 3.43.

Methyl 5-(4-ethylphenyl)thiophene-3-carboxylate (2j). Compound **2j** was prepared from **10d** and methanol, and recrystallized from diethylether–hexane as colorless needles. Yield, 80% from **10d**; mp: 63–67 °C.

Methyl 5-(4-isopropylphenyl)thiophene-3-carboxylate (2k). Compound **2k** was prepared from **10e** and methanol, and recrystallized from diethylether–hexane as a white powder. Yield, 82% from **10e**; mp: 33–34 °C.

Methyl 5-(4-methoxyphenyl)thiophene-3-carboxylate (2l). Compound **2l** was prepared from **10f** and methanol, and recrystallized from diethylether–hexane as a white powder. Yield, 78% from **10f**; mp: 100–101 °C.

Methyl 5-(4-cyclohexylphenyl)thiophene-3-carboxylate (2m). Compound **2m** was prepared from **10g** and methanol, and recrystallized from diethylether–hexane as a white powder. Yield, 81% from **10g**; mp: 94–95 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.20–1.60 (m, 5H), 1.70–2.00 (m, 5H), 2.45–2.65 (m, 1H), 3.89 (s, 1H), 7.24 (d, 2H, J=8 Hz), 7.53 (d, 2H, J=8 Hz), 7.67 (d, 1H, J=1 Hz), 8.00 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1717. MS m/z 300 (M^+). Anal. calcd for $C_{18}H_{20}O_2S$: C, 71.97; H, 6.71. Found: C, 71.80; H, 6.75.

General procedure for preparation of 2a,n–t

To a solution of **2b–m** (11.1 mmol) in tetrahydrofuran (THF) (10 mL) was added a solution of KOH (2.50 g, 37.9 mmol) in methanol (5.0 mL) and water (1.0 mL). The mixture was stirred at room temperature for 4 h. The resulting solution was acidified with 10% HCl, and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed successively with sat. $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was recrystallized from solvents to give **2a**,**n–t**.

5-(4-Methylphenyl)thiophene-3-carboxylic acid (2a). Compound **2a** was prepared from **2b**, and recrystallized from toluene as colorless prisms. Yield, 87%; mp: 192–193 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 2.38 (s, 3H), 7.22 (d, 2H, J=8 Hz), 7.51 (d, 2H, J=8 Hz), 7.70 (d, 1H, J=1 Hz), 8.13 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 2599, 1671. MS m/z 218 (M^+). Anal. calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 66.09; H, 4.53.

5-Phenylthiophene-3-carboxylic acid (2n). Compound **2n** was prepared from **2d**, and recrystallized from ethyl acetate–hexane as colorless crystals. Yield, 89%; mp: 180–181 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 7.39–7.48 (m, 3H), 7.62 (d, 2H, J=9 Hz), 7.77 (d, 1H, J=1 Hz), 8.18 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1671. MS m/z

204 (M^+). Anal. calcd for $C_{11}H_8O_2S$: C, 64.68; H, 3.95. Found: C, 64.42; H, 3.81.

5-(4-Chlorophenyl)thiophene-3-carboxylic acid (2o). Compound **2o** was prepared from **2f**, and recrystallized from ethyl acetate–hexane as colorless crystals. Yield, 86%; mp: 204–206 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 7.40 (d, 2H, J=8 Hz), 7.55 (d, 2H, J=8 Hz), 7.73 (d, 1H, J=1 Hz), 8.18 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 3112, 2597, 1671. MS m/z 238 (M^+). Anal. calcd for $C_{11}H_7ClO_2S$: C, 55.35; H, 2.96. Found: C, 55.49; H, 2.89.

5-(4-Bromophenyl)thiophene-3-carboxylic acid (2p). Compound **2p** was prepared from **2h**, and recrystallized from ethyl acetate as colorless prisms. Yield, 84%; mp: 212–213 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 7.48 (d, 2H, J=9 Hz), 7.52 (d, 2H, J=9 Hz), 7.73 (d, 1H, J=1 Hz), 8.18 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1671, 1538. MS m/z 283 (M^+). Anal. calcd for $C_{11}H_7BrO_2S$: C, 46.66; H, 2.49. Found: C, 46.83; H, 2.40.

5-(4-Ethylphenyl)thiophene-3-carboxylic acid (2q). Compound **2q** was prepared from **2j**, and recrystallized from ethyl acetate as colorless crystals. Yield, 63%; mp: 196–197 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.27 (t, 3H, J=7 Hz), 2.68 (q, 2H, J=7 Hz), 7.24 (d, 2H, J=9 Hz), 7.55 (d, 2H, J=9 Hz), 7.72 (d, 1H, J=1 Hz), 8.14 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 2967, 1673. MS m/z 232 (M^+). Anal. calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.21; H, 5.17.

5-(4-Isopropylphenyl)thiophene-3-carboxylic acid (2r). Compound **2r** was prepared from **2k**, and recrystallized from ethyl acetate as colorless crystals. Yield, 75%; mp: 204–205 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.27 (d, 6H, J=6 Hz), 2.94 (septet, 1H, J=6 Hz), 7.27 (d, 2H, J=8 Hz), 7.55 (d, 2H, J=8 Hz), 7.70 (d, 1H, J=1 Hz), 8.13 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 2963, 1675. MS m/z 246 (M^+). Anal. calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.35; H, 5.81.

5-(4-Methoxyphenyl)thiophene-3-carboxylic acid (2s). Compound **2s** was prepared from **2l**, and recrystallized from ethyl acetate–hexane as a white powder. Yield, 44%; mp: 197 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.85 (s, 3H), 6.93 (d, 2H, J=8 Hz), 7.55 (d, 2H, J=8 Hz), 7.63 (d, 1H, J=1 Hz), 8.09 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 3106, 1668. MS m/z 234 (M^+). Anal. calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30. Found: C, 61.39; H, 4.22.

5-(4-Cyclohexylphenyl)thiophene-3-carboxylic acid (2t). Compound **2t** was prepared from **2m**, and recrystallized from ethyl acetate as colorless crystals. Yield, 65%; mp: >300 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.33–1.55 (m, 5H), 1.70–2.00 (m, 5H), 2.45–2.60 (m, 1H), 7.24 (d, 2H, J=8 Hz), 7.53 (d, 2H, J=8 Hz), 7.70 (d, 1H, J=1 Hz), 8.12 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 2927, 1668. MS m/z 286 (M^+). Anal. calcd for $C_{17}H_{18}O_2S$: C, 71.29; H, 6.33. Found: C, 71.28; H, 6.29.

General procedure for preparation of 2u,v

To a solution of **2p** (2.83 g, 10.0 mmol) in DMF (30 mL) was added benzylbromide or isopropylbromide (32.5 mmol) and K_2CO_3 (2.70 g, 19.5 mmol) at room temperature. The mixture was stirred at 60 °C for 4 h. Water (30 mL) was added to the resulting solution, which was then extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was concentrated under reduced pressure to give a residue, which was recrystallized from solvents to give **2u,v**.

Isopropyl 5-(4-bromophenyl)thiophene-3-carboxylate (2u). Compound **2u** was prepared from isopropylbromide, and recrystallized from hexane as colorless needles. Yield, 77%; mp: 77–79 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.37 (d, 6H, J=6 Hz), 5.21 (septet, 1H, J=6 Hz), 7.45–7.57 (m, 4H), 7.70 (d, 1H, J=1 Hz), 8.02 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1715. MS m/z 325 (M^+). Anal. calcd for $C_{14}H_{13}BrO_2S$: C, 57.92; H, 3.51. Found: C, 57.92; H, 3.38.

Benzyl 5-(4-bromophenyl)thiophene-3-carboxylate (2v). Compound **2v** was prepared from benzylbromide, and recrystallized from diethylether–hexane as colorless needles. Yield, 77%; mp: 63–66 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 5.33 (m, 2H), 7.34–7.55 (m, 9H), 7.71 (d, 1H, J=1 Hz), 8.08 (d, 1H, J=1 Hz). IR (KBr) cm^{-1}: 1714. MS m/z 373 (M^+). Anal. calcd for $C_{18}H_{13}BrO_2S$: C, 57.92; H, 3.51. Found: C, 57.92; H, 3.38.

General procedure for preparation of 5a–e

To a solution of sodium metal (4.6 g, 200 mmol) in ethanol (100 mL) was added ethyl thioglycolate (21.6 g, 180 mmol) under ice cooling, and the mixture was allowed to stand at room temperature for 20 min. Ethyl cinnamate (**22**) (31.7 g, 180 mmol) was then added. The reaction mixture was stirred at room temperature for 2 h. The ethanol solution was concentrated under reduced pressure to give a residue, which was refluxed with 1.5 mol/L H_2SO_4 (100 mL) for 3 h. The resulting solution was extracted with diethylether, washed successively with water, satd $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. The diethylether solution was evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography to afford ethyl 5-phenylthiolane-3-on-2-carboxylate (**23**) (29.3 g, 65%). To a solution of 4.5 mol/L H_2SO_4 (80 mL) and acetic acid (200 mL) was added **23** (29.3 g, 117 mmol), and the mixture was stirred under reflux for 1 h. Acetic acid was removed under reduced pressure, and the mixture was extracted with diethylether. The extract was washed successively with water and brine and dried over anhydrous $MgSO_4$ to give a residue, which was purified by silica gel column chromatography to give 5-phenylthiolane-3-on (**24**) (17.9 g, 86%) as pale yellow crystals. To a solution of **24** (2.33 g, 13.1 mmol) and cyanoacetic acid (2.00 g, 23.5 mmol) in benzene (50 mL) was added acetic acid (1.0 mL) and piperidine (1.0 mL), and the mixture was stirred under reflux for 6 h. The resulting solution was washed successively with water, 5% HCl, satd $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. The benzene solution was evaporated under reduced pressure to give a residue, which was dissolved in toluene (30 mL), and then DDQ (3.20 g, 14.1 mmol) was added. The mixture was stirred under

reflux for 1 h, and the precipitate was filtered and washed with toluene. The filtrate and washings were combined and washed successively with satd $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. The toluene solution was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography and then recrystallized from diethylether–hexane to give (5-phenylthiophen-3-yl)acetonitrile (**25a**) (1.65 g, 63%) as colorless crystals.

To a suspended solution of $LiAlH_4$ (4.00 g, 105 mmol) and diethylether (200 mL) was slowly added **2b**,**f**,**h**,**l** (103 mmol), and the mixture was stirred under reflux for 0.5 h. The reaction mixture was quenched with 1% HCl (20 mL), and extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was dissolved in THF (200 mL) and hexamethylphosphoric triamide (HMPA) (40 mL), and thionyl chloride (15.0 mL, 206 mmol) was added. The reaction mixture was stirred at room temperature for 0.5 h, and then evaporated under reduced pressure to give a residue. To the residue was added water (300 mL), and the mixture was extracted with diethylether. The extract was washed successively with water and brine, and dried over anhydrous $MgSO_4$. The diethylether solution was evaporated under reduced pressure to give crude chloride (**26a–d**), which was dissolved in acetonitrile (200 mL). Potassium cyanide (8.00 g, 123 mmol) and 18-crown-6 (2.00 g, 7.57 mmol) was added, and the solution was stirred overnight at room temperature. The reaction mixture was poured into water (200 mL) and extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography, and then recrystallized from diethylether- hexane to give acetonitrile derivatives (**25b–e**) (65–80%).

To a solution of **25a–e** (49.1 mmol) in ethanol (30 mL) was added KOH (25.0 g, 379 mmol) in water (50 mL) at room temperature with stirring. The reaction mixture was refluxed for 1 h. The reaction mixture was poured into 10% HCl (200 mL) and extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was recrystallized from ethyl acetate to give **5a–e**.

(5-Phenylthiophen-3-yl)acetic acid (5a). Compound **5a** was prepared from **22**, and recrystallized from ethyl acetate as pale yellow crystals. Yield, 95%; mp: 154–155 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.70 (s, 2H), 7.11 (m, 1H), 7.15–7.45 (m, 4H), 7.59 (d, 2H, $J=9$ Hz). IR (KBr) cm^{-1}: 3094, 1698. MS m/z 218 (M^+). Anal. calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 66.07; H, 4.52.

[5-(4-Methylphenyl)thiophen-3-yl]acetic acid (5b). Compound **5b** was prepared from **2b**, and recrystallized from ethyl acetate as pale yellow crystals. Yield, 76%; mp: 149 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 2.35 (s, 3H), 3.67 (s, 2H), 7.06 (d, 1H, $J=2$ Hz), 7.15 (d, 2H, $J=9$ Hz), 7.19 (d, 1H, $J=2$ Hz), 7.45 (d, 2H, $J=9$ Hz). IR (KBr) cm^{-1}: 2917, 1698. MS m/z 232 (M^+). Anal. calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.32; H, 5.19.

[5-(4-Chlorophenyl)thiophen-3-yl]acetic acid (5c). Compound **5c** was prepared from **2f**, and recrystallized from ethyl acetate as colorless crystals. Yield, 92%; mp: 151 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.69 (s, 2H), 7.11 (d, 1H, $J=2$ Hz), 7.23 (d, 2H, $J=2$ Hz), 7.33 (d, 2H, $J=9$ Hz), 7.50 (d, 2H, $J=9$ Hz). IR (KBr) cm^{-1}: 3091, 1698. MS m/z 252 (M^+). Anal. calcd for $C_{12}H_9ClO_2S$: C, 57.02; H, 3.59. Found: C, 57.00; H, 3.44.

[5-(4-Bromophenyl)thiophen-3-yl]acetic acid (5d). Compound **5d** was prepared from **2h**, and recrystallized from ethyl acetate as colorless crystals. Yield, 94%; mp: 164 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.69 (s, 2H), 7.11 (d, 1H, $J=2$ Hz), 7.23 (d, 2H, $J=1$ Hz), 7.43 (d, 2H, $J=8$ Hz), 7.50 (d, 2H, $J=8$ Hz). IR (KBr) cm^{-1}: 3090, 1698. MS m/z 252 (M^+). Anal. calcd for $C_{12}H_9BrO_2S$: C, 48.50; H, 3.05. Found: C, 48.49; H, 2.94.

[5-(4-Methoxyphenyl)thiophen-3-yl]acetic acid (5e). Compound **5e** was prepared from **2l**, and recrystallized from ethyl acetate as colorless crystals. Yield, 90%; mp: 149 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.57 (s, 2H), 3.78 (s, 3H), 6.97 (d, 2H, $J=9$ Hz), 7.20 (s, 1H), 7.25 (s, 1H), 7.54 (d, 2H, $J=9$ Hz). IR (KBr) cm^{-1}: 3090, 1698. MS m/z 248 (M^+). Anal. calcd for $C_{13}H_{12}O_3S$: C, 62.88; H, 4.87. Found: C, 62.95; H, 4.80.

General procedure for preparation of 5f–i

To a solution of conc H_2SO_4 (3 mL) in methanol (30 mL) was added **5a–e** (27.5 mmol), the mixture was stirred under reflux for 2 h, and then methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed successively with sat. $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography or recrystallized from solvents to give **5f–i**.

Methyl (5-phenylthiophen-3-yl)acetate (5f). Compound **5f** was prepared from **5a**, and purified by silica gel column chromatography as a pale yellow oil. Yield, 99%; ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.64 (s, 2H), 3.72 (s, 3H), 7.07 (m, 1H), 7.13–7.40 (m, 4H), 7.58 (d, 2H, $J=9$ Hz). IR (KBr) cm^{-1}: 3060, 1737. MS m/z 232 (M^+). Anal. calcd for $C_{12}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 66.98; H, 5.12.

Methyl [5-(4-methylphenyl)thiophen-3-yl]acetate (5g). Compound **5g** was prepared from **5b**, and purified by silica gel column chromatography as a pale yellow oil. Yield, 92%; ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 2.36 (s,

3H), 3.64 (s, 2H), 3.73 (s, 3H), 7.04 (m, 1H), 7.17 (m, 3H), 7.48 (d, 2H, $J=9$ Hz). IR (KBr) cm^{-1}: 2951, 1741. MS m/z 246 (M^+). Anal. calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.06; H, 5.61.

Methyl [5-(4-chlorophenyl)thiophen-3-yl]acetate (5h). Compound **5h** was prepared from **5c**, and recrystallized from diethylether–hexane as pale yellow crystals. Yield, 91%; mp: 38 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 3.65 (s, 2H), 3.73 (s, 3H), 7.09 (m, 1H), 7.22 (d, 1H, $J=2$ Hz), 7.32 (d, 2H, $J=9$ Hz), 7.50 (d, 2H, $J=2$ Hz). IR (KBr) cm^{-1}: 3094, 1747. MS m/z 266 (M^+). Anal. calcd for $C_{13}H_{11}ClO_2S$: C, 58.54; H, 4.16. Found: C, 58.49; H, 4.04.

Methyl [5-(4-bromophenyl)thiophen-3-yl]acetate (5i). Compound **5i** was prepared from **5d**, and recrystallized from diethylether-hexane as pale yellow crystals. Yield, 91%; mp: 59 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 3.64 (s, 2H), 3.72 (s, 3H), 7.10 (m, 1H), 7.24 (d, 1H, $J=2$ Hz), 7.43 (d, 2H, $J=8$ Hz), 7.48 (d, 2H, $J=8$ Hz). IR (KBr) cm^{-1}: 3095, 1746. MS m/z 311 (M^+). Anal. calcd for $C_{12}H_9BrO_2S$: C, 50.18; H, 3.56. Found: C, 50.11; H, 3.43.

General procedure for preparation of 6a–d

Compounds **26e** were prepared from **2d** in a manner analogous to that used for the preparation of **26a–d**. To a solution of sodium metal (2.80 g, 122 mmol) in ethanol (350 mL) was added diethyl malonate (27.7 mL, 182 mmol) at room temperature. After the mixed solution was heated under gentle reflux with stirring, **26b–e** (122 mmol) was added. The whole mixture was refluxed for 1.5 h, and then ethanol was removed under reduced pressure. To the concentrate was added water (100 mL), and the mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography to give diester (**28a–d**) (60–65%). To a solution of **28a–d** (72.9 mmol) in DMSO (150 mL) was added a solution of NaCl (8.80 g, 151 mmol) in water (4.8 mL) at room temperature, and the mixture was stirred under reflux for 5 h. The resulting solution was poured into water (200 mL), and extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give ethyl ester (**29a–d**) (71–88%).

To a solution of **29a–d** (59.0 mmol) in methanol (400 mL) was added NaOH (14.1 g, 353 mmol) in water (100 mL) at room temperature with stirring, and the stirring was continued for 1 h. Methanol was removed under reduced pressure and poured into 5% HCl (100 mL), which was extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was recrystallized from solvents to give **6a–d**.

3-(5-Phenylthiophen-3-yl)propionic acid (6a). Compound **6a** was prepared from **26e**, and recrystallized from ethyl acetate as colorless crystals. Yield, 62%; mp: 134 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 2.71 (t, 2H, $J=8$ Hz), 2.97 (t, 2H, $J=8$ Hz), 6.94 (d, 1H, $J=2$ Hz), 7.17 (d, 1H, $J=2$ Hz), 7.22–7.44 (m, 3H), 7.58 (d, 2H, $J=8$ Hz). IR (KBr) cm^{-1}: 2913, 1685. MS m/z 232 (M^+). Anal. calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.23; H, 5.21.

3-[5-(4-Methylphenyl)thiophen-3-yl]propionic acid (6b). Compound **6b** was prepared from **26a**, and recrystallized from ethyl acetate–hexane as colorless crystals. Yield, 77%; mp: 122 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 2.35 (s, 3H), 2.73 (t, 2H, $J=8$ Hz), 2.95 (t, 2H, $J=8$ Hz), 6.90 (d, 1H, $J=1$ Hz), 7.13 (d, 1H, $J=1$ Hz), 7.15 (d, 2H, $J=8$ Hz), 7.48 (d, 2H, $J=8$ Hz). IR (KBr) cm^{-1}: 3436, 2913, 1693, 1219. MS m/z 246 (M^+). Anal. calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.53; H, 5.70.

3-[5-(4-Chlorophenyl)thiophen-3-yl]propionic acid (6c). Compound **6c** was prepared from **26b**, and recrystallized from ethyl acetate–hexane as colorless crystals. Yield, 64%; mp: 128 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 2.73 (t, 2H, $J=8$ Hz), 2.98 (t, 2H, $J=8$ Hz), 6.95 (d, 1H, $J=1$ Hz), 7.15 (d, 1H, $J=1$ Hz), 7.33 (d, 2H, $J=8$ Hz), 7.50 (d, 2H, $J=8$ Hz). IR (KBr) cm^{-1}: 3436, 2932, 1703, 1217. MS m/z 266 (M^+). Anal. calcd for $C_{13}H_{11}ClO_2S$: C, 58.54; H, 4.16. Found: C, 58.55; H, 4.04.

3-[5-(4-Bromophenyl)thiophen-3-yl]propionic acid (6d). Compound **6d** was prepared from **26c**, and recrystallized from ethyl acetate–hexane as colorless crystals. Yield, 81%; mp: 129 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 2.73 (t, 2H, $J=8$ Hz), 2.98 (t, 2H, $J=8$ Hz), 6.95 (d, 1H, $J=1$ Hz), 7.15 (d, 1H, $J=1$ Hz), 7.30–7.60 (m, 4H). IR (KBr) cm^{-1}: 2916, 1697, 1221. MS m/z 311 (M^+). Anal. calcd for $C_{13}H_{11}BrO_2S$: C, 50.18; H, 3.56. Found: C, 50.17; H, 3.51.

General procedure for preparation of 6e–h. Compound **6e–h** was prepared from **6a–d** in a manner analogous to that used for the preparation of **5f–i**.

Methyl 3-(5-phenylthiophen-3-yl)propionate (6e). Compound **6e** was prepared from **6a**, and recrystallized from diethylether–hexane as colorless crystals. Yield, 94%; mp: 67 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 2.66 (t, 2H, $J=8$ Hz), 2.97 (t, 2H, $J=8$ Hz), 3.70 (s, 3H), 6.93 (d, 1H, $J=2$ Hz), 7.16 (d, 1H, $J=2$ Hz), 7.22–7.44 (m, 3H), 7.58 (d, 2H, $J=8$ Hz). IR (KBr) cm^{-1}: 2949, 1733. MS m/z 246 (M^+). Anal. calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.00; H, 5.72.

Methyl 3-[5-(4-methylphenyl)thiophen-3-yl]propionate (6f). Compound **6f** was prepared from **6b**, and recrystallized from hexane–petroleum ether as pale yellow crystals. Yield, 84%; mp: 60 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 2.35 (s, 3H), 2.65 (t, 2H, $J=8$ Hz), 2.95 (t, 2H, $J=8$ Hz), 3.70 (s, 3H), 6.90 (d, 1H, $J=1$ Hz), 7.10 (d, 1H, $J=1$ Hz), 7.18 (d, 2H, $J=8$ Hz), 7.48 (d, 2H, $J=8$ Hz).

IR (KBr) cm^{-1}: 3461, 2913, 1742. MS *m/z* 260 (M^+). Anal. calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19. Found: C, 69.37; H, 6.14.

Methyl 3-[5-(4-chlorophenyl)thiophen-3-yl]propionate (6g). Compound **6g** was prepared from **6c**, and recrystallized from methanol as colorless crystals. Yield, 83%; mp: 85 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 2.65 (t, 2H, *J* = 8 Hz), 2.95 (t, 2H, *J* = 8 Hz), 3.70 (s, 3H), 6.93 (d, 1H, *J* = 1 Hz), 7.13 (d, 1H, *J* = 1 Hz), 7.33 (d, 2H, *J* = 8 Hz), 7.50 (d, 2H, *J* = 8 Hz). IR (KBr) cm^{-1}: 3448, 2950, 1739, 1171. MS *m/z* 280 (M^+). Anal. calcd for $C_{14}H_{13}ClO_2S$: C, 59.89; H, 4.67. Found: C, 60.00; H, 4.57.

Methyl 3-[5-(4-bromophenyl)thiophen-3-yl]propionate (6h). Compound **6h** was prepared from **6d**, and recrystallized from methanol as colorless crystals. Yield, 73%; mp: 87 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 2.66 (t, 2H, *J* = 8 Hz), 2.95 (t, 2H, *J* = 8 Hz), 3.70 (s, 3H), 6.95 (d, 1H, *J* = 1 Hz), 7.14 (d, 1H, *J* = 1 Hz), 7.38–7.53 (m, 4H). IR (KBr) cm^{-1}: 3449, 2949, 1741, 1170. MS *m/z* 325 (M^+). Anal. calcd for $C_{14}H_{13}BrO_2S$: C, 51.70; H, 4.03. Found: C, 51.84; H, 3.97.

5-Phenylthiophene-2-carboxylic ccid (7a). A suspended solution of rhodanine (**13**) (21.8 g, 163 mmol), sodium acetate (40.3 g, 489 mmol) and cinnamaldehyde (**12**) (21.5 g, 163 mmol) in acetic acid (200 mL) was refluxed for 0.5 h, and then poured into 800 g of ice. The orange solid was collected and recrystallized from toluene to give 24.2 g (60%) of 5-cinnamylidenerhodanine (**14**).

A solution of **14** (10.0 g, 40.4 mmol) in 5% NaOH (50 mL) was stirred at 80 °C for 0.5 h. The resulting solution was filtered through a charcoal pad and cooled to 0 °C, and 10% chilled HCl (50 mL) was added. The precipitate of 2-mercapto-5-phenyl-2,4-pentadienoic acid (6.02 g, 72%) was collected. The crude product was dissolved in pyridine (50 mL) and cooled to 3 °C, and 4.6 mL of 30% hydrogen peroxide was slowly added with stirring. After standing for 5 h, the solution was poured into 10% HCl (300 mL). The resulting solid was collected, washed with water, and dried to give 2.67 g (32%) of 2,2′-dithiobis(5-phenyl-2,4-pentadienoic acid) (**15**).

To a solution of **15** (2.50 g, 6.09 mmol) in chilled ethanol (30 mL) was slowly adde a solution of iodine (1.85 g, 14.6 mmol) in ethanol (5 mL) with stirring. The solution was stirred at room temperature for 2 days, and then poured into chilled water (200 mL) containing sodium bisulfite (5.0 g). After the aqueous supernatant was decanted, the residue was taken up on hot 10% NaOH (100 mL), filtered through a heated Buchner funnel and cooled, to give white crystals of the sodium salt of **7a**. This product was collected, and washed with water and 5% HCl (100 mL). Upon recrystallization from ethyl acetate–hexane, **7a** was obtained as a white powder (1.94 g, 78%). mp: 188–189 °C, ^1H NMR ($CDCl_3$) (200 MHz) δ: 7.33 (d, 1H, *J* = 1 Hz), 7.41 (m, 3H), 7.67 (m, 2H), 7.87 (d, 1H, *J* = 4 Hz), 9.43 (br s, 1H). IR (KBr) cm^{-1}: 3059, 2869, 1704, 1661, 1540. MS *m/z* 204 (M^+). Anal. calcd for $C_{11}H_8O_2S$: C, 64.69; H, 3.95. Found: C, 64.69; H, 3.80.

Methyl 5-phenylthiophene-2-carboxylate (7b). To a solution of concd H_2SO_4 (0.2 mL) in methanol (5 mL) was added **5a** (1.40 g, 6.85 mmol), and the mixture was stirred under reflux for 0.5 h. Methanol was then removed under reduced pressure. The residue was dissolved in ethyl acetate, washed successively with satd $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to give **7b** (1.26 g, 84%) as a pale yellow oil. ^1H NMR ($CDCl_3$) (200 MHz) δ: 3.90 (s, 3H), 7.29 (d, 1H, *J* = 4 Hz), 7.40 (m, 3H), 7.65 (dd, 2H, *J* = 2, 8 Hz), 7.78 (d, 1H, *J* = 4 Hz). IR (KBr) cm^{-1}: 2980, 1706. MS *m/z* 218 (M^+). Anal. calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 66.04; H, 4.56.

General procedure for preparation of 7c–e

To a suspended solution of $AlCl_3$ (32.3 g, 242 mmol) and chlorobutyryl chloride (**17**) (31.0 g, 220 mmol) in CS_2 (50 mL) was slowly added a solution of **16a–c** (199 mmol) in CS_2 (50 mL) with stirring at room temperature. Stirring was continued for 2.5 h, and the resulting solution was poured into 10% HCl (200 mL) and extracted with ethyl acetate. The extract was washed successively with water, sat. $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography and then recrystallized from cyclohexane/petroleum ether to give chloride (**18a–c**) (51–54%).

To a solution of **18a–c** (103 mmol) in DMF (50 mL) was added a solution of potassium thioacetate (12.4 g, 109 mmol) in DMF (100 mL) at 5 °C with stirring. Stirring was continued for 22 h. The resulting solution was poured into water (300 mL) and extracted with diethylether. The extract was washed successively with 5% HCl, satd $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography and then recrystallized from diethylether–hexane to give thioacetate (**19a–c**) (83–86%).

A solution of **19a–c** (83.0 mmol) in concd H_2SO_4 (13 mL) and methanol (130 mL) was refluxed for 1 h, and then methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed successively with satd $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. The ethyl acetate solution was concentrated under reduced pressure to give a residue which was dissolved in benzene (170 mL), and chloranil (20.6 g, 83.8 mmol) was then added. The mixture was stirred under reflux for 2 h, and then a crystalline precipitate was filtered and washed with benzene. The filtrate and washings were combined and washed successively with 5% KOH, water, and brine, and dried over anhydrous $MgSO_4$. The benzene solution was evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography and then recrystallized from hexane to give phenylthiophene (**20a–c**) (68–73%).

To a solution of DMF (13 mL) and 1,2-dichloroethane (50 mL) was slowly added a solution of $POCl_3$ (15.7 mL, 172 mmol) in 1,2-dichloroethane (50 mL) with stirring over 0.5 h at 0–5 °C. To the reaction mixture was slowly added a solution of **20a–c** (83.6 mmol) in 1,2-dichloroethane (50 mL) over 15 min below 10 °C, and the mixture was stirred under reflux for 17 h. The resulting solution was poured into chilled 50% KOH (20 mL) and extracted with ethyl acetate. The extract was washed successively with 5% HCl, water, and brine, and dried over $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was recrystallized from ethyl acetate–hexane to give formate (**21a–c**) (82–85%).

To a solution of NaOH (5.80 g, 145 mmol) in water (60 mL) was added Ag_2O (13.0 g, 56.1 mmol) in water (60 mL) at room temperature. After stirring for 15 min, **21a–c** (37.4 mmol) was added and the reaction mixture was stirred at room temperature for 0.5 h, and at 50 °C for 4 h. A crystalline precipitate was filtered off and washed with water. The filtrate and washings were combined, poured into chilled 10% HCl (20 mL) and extracted with ethyl acetate and THF. The extract was washed successively with water and brine and dried over anhydrous $MgSO_4$. The organic solution was evaporated under reduced pressure to give a residue, which was recrystallized from solvents to give **7c–e**.

5-(4-Chlorophenyl)thiophene-2-carboxylic acid (7c). Compound **7c** was prepared from chlorobenzene (**16a**), and recrystallized from THF as a white powder. Yield, 86%; mp: 250–252 °C, ^{1}H NMR (DMSO-d_6) (200 MHz) δ: 7.45–7.55 (m, 2H), 7.55–7.65 (m, 1H), 7.70–7.85 (m, 3H), 13.3 (br s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 2812, 2520, 1656, 1534, 1446. MS *m*/*z* 238 (M^+). Anal. calcd for $C_{11}H_7ClO_2S$: C, 55.35; H, 2.96. Found: C, 55.27; H, 2.87.

5-(4-Bromophenyl)thiophene-2-carboxylic acid (7d). Compound **7d** was prepared from bromobenzene (**16b**), and recrystallized from THF–hexane as a white powder. Yield, 76%; mp: 243–245 °C, ^{1}H NMR (DMSO-d_6) (200 MHz) δ: 7.55–7.95 (m, 6H), 13.2 (br s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 2973, 1671, 1535, 1449. MS *m*/*z* 283 (M^+). Anal. calcd for $C_{11}H_7BrO_2S$: C, 46.65; H, 2.49. Found: C, 46.50; H, 2.38.

5-(4-Methylphenyl)thiophene-2-carboxylic acid (7e). Compound **7e** was prepared from bromobenzene (**16c**), and recrystallized from ethyl acetate–hexane as a white powder. Yield, 76%; mp: 208–210 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 2.33 (s, 3H), 7.28 (d, 2H, *J* = 9 Hz), 7.52 (d, 2H, *J* = 4 Hz), 13.1 (br s, 1H). IR (KBr) cm^{-1}: 2857, 2549, 1658, 1539, 1450. MS *m*/*z* 218 (M^+). Anal. calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 65.98; H, 4.48.

General procedure for preparation of 7f–h

To a solution of concd H_2SO_4 (4.3 mL), alcohol (86 mL), and toluene (40 mL) was added **7c–e** (27.2 mmol), and the mixture was stirred under reflux for 7 h. The resulting solution was concentrated under reduced pressure to about 30 mL. The mixture was poured into water and extracted with ethyl acetate. The extract was washed successively with satd $NaHCO_3$, water, and brine and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was recrystallized from ethyl acetate–hexane to give **7f–h**.

Methyl 5-(4-chlorophenyl)thiophene-2-carboxylate (7f). Compound **7f** was prepared from **7c** and methanol, and recrystallized from ethyl acetate–hexane as a white powder. Yield, 86%; mp: 113 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.90 (s, 3H), 7.25 (d, 1H, *J* = 5 Hz), 7.30–7.42 (m, 2H), 7.50–7.60 (m, 2H), 7.75 (d, 1H, *J* = 5 Hz). IR (KBr) cm^{-1}: 3392, 3099, 2951, 1702, 1532, 1447. MS *m*/*z* 252 (M^+). Anal. calcd for $C_{12}H_9ClO_2S$: C, 57.04; H, 3.59. Found: C, 56.61; H, 3.42.

Methyl 5-(4-bromophenyl)thiophene-2-carboxylate (7g). Compound **7g** was prepared from **7d** and methanol, and recrystallized from ethyl acetate–hexane as a white powder. Yield, 83%; mp: 112 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 4.25 (s, 3H), 7.63 (d, 1H, *J* = 5 Hz), 7.80–7.93 (m, 4H), 8.10 (d, 1H, *J* = 5 Hz). IR (KBr) cm^{-1}: 3436, 2929, 1690, 1675, 1582. MS *m*/*z* 297 (M^+). Anal. calcd for $C_{12}H_9BrO_2S$: C, 48.50; H, 3.05. Found: C, 48.45; H, 2.95.

Ethyl 5-(4-methylphenyl)thiophene-carboxylate (7h). Compound **7h** was prepared from **7e** and ethanol, and recrystallized from ethyl acetate–hexane as a white powder. Yield, 95%; mp: 88–89 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.38 (t, 3H, *J* = 7 Hz), 2.36 (s, 3H), 4.35 (q, 2H, *J* = 7 Hz), 7.20 (d, 2H, *J* = 8 Hz), 7.23 (d, 1H, *J* = 4 Hz), 7.52 (d, 2H, *J* = 8 Hz), 7.74 (d, 1H, *J* = 4 Hz). IR (KBr) cm^{-1}: 2982, 1702. MS *m*/*z* 246 (M^+). Anal. calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.24; H, 5.64.

General procedure for preparation of 8a,b

Compounds **8a**,**b** were prepared from **7f**,**g** in a manner analogous to that used for the preparation of **5a–e**.

[5-(4-Chlorophenyl)thiophen-2-yl]acetic acid (8a). Compound **8a** was prepared from **7f**, and recrystallized from ethyl acetate–hexane as colorless crystals. Yield, 66%; mp: 153–155 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.85 (s, 2H), 6.96 (d, 1H, *J* = 5 Hz), 7.18 (d, 1H, *J* = 5 Hz), 7.40–7.50 (m, 2H), 7.60–7.70 (m, 2H), 12.50–12.80 (br s, 1H). IR (KBr) cm^{-1}: 3421, 3044, 1708. MS *m*/*z* 252 (M^+). Anal. calcd for $C_{12}H_9ClO_2S$: C, 57.02; H, 3.59. Found: C, 57.14; H, 3.54.

[5-(4-Bromophenyl)thiophen-2-yl]acetic acid (8b). Compound **8b** was prepared from **7g**, and recrystallized from ethyl acetate- hexane as colorless crystals. Yield, 75%; mp: 158–159 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.88 (s, 2H), 6.93 (d, 1H, *J* = 5 Hz), 7.15 (d, 1H, *J* = 5 Hz), 7.38–7.63 (m, 4H). IR (KBr) cm^{-1}: 3437, 2909, 1712. MS *m*/*z* 297 (M^+). Anal. calcd for $C_{12}H_9BrO_2S$: C, 48.50; H, 3.05. Found: C, 48.54; H, 2.96.

General procedure for preparation of 8c,d

Compounds **8c**,**d** were prepared from **8a**,**b** in a manner analogous to that used for the preparation of **5f–i**.

Methyl [5-(4-chlorophenyl)thiophen-2-yl]acetate (8c). Compound **8c** was prepared from **8a**, and recrystallized from methanol as colorless crystals. Yield, 67%; mp: 75–76 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.75 (s, 3H), 3.85 (s, 2H), 6.90 (d, 1H, J = 5 Hz), 7.13 (d, 1H, J = 5 Hz), 7.28–7.38 (m, 2H), 7.45–7.55 (m, 2H). IR (KBr) cm^{-1}: 3436, 1741. MS m/z 266 (M^+). Anal. calcd for $C_{13}H_{11}ClO_2S$: C, 58.54; H, 4.16. Found: C, 58.63; H, 4.10.

Methyl [5-(4-bromophenyl)thiophen-2-yl]acetate (8d). Compound **8d** was prepared from **8b**, and recrystallized from methanol as colorless crystals. Yield, 97%; mp: 94–95°C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 3.75 (s, 3H), 3.85 (s, 2H), 6.90 (d, 1H, J = 5 Hz), 7.15 (d, 1H, J = 5 Hz), 7.40–7.60 (m, 4H). IR (KBr) cm^{-1}: 3436, 1741. MS m/z 311 (M^+). Anal. calcd for $C_{13}H_{11}BrO_2S$: C, 50.18; H, 3.56. Found: C, 49.97; H, 3.48.

General procedure for preparation of 9a–c

To a solution of **5f**,**h**,**i** (16.8 mmol) in DMF (40 mL) was added NaH (60% oil suspension) (672 mg, 28.0 mmol), and the solution was stirred under ice cooling for 0.5 h. Methyl iodide (1.05 mL, 16.9 mmol) was added, and the stirring was continued for 3 h. The resulting solution was poured into water (50 mL) and extracted with ethyl acetate. The extract was washed successively with water and brine and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography to give **9a–c** (77–83%).

Methyl 2-(5-phenylthiophen-3-yl)propionate (9a). Compound **9a** was prepared from **5f** as a pale yellow oil. Yield, 83%; ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.53 (d, 3H, J = 7 Hz), 3.70 (s, 3H), 3.82 (q, 1H, J = 7 Hz), 7.05–7.65 (m, 7H). IR (neat) cm^{-1}: 2950, 1737. MS m/z 246 (M^+). Anal. calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.23; H, 5.70.

Methyl 2-[5-(4-chlorophenyl)thiophen-3-yl]propionate (9b). Compound **9b** was prepared from **5h** as a pale yellow oil. Yield, 81%; ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.52 (d, 3H, J = 7 Hz), 3.70 (s, 3H), 3.82 (q, 1H, J = 7 Hz), 7.05–7.56 (m, 6H). IR (neat) cm^{-1}: 2950, 1737. MS m/z 280 (M^+). Anal. calcd for $C_{14}H_{13}ClO_2S$: C, 59.89; H, 4.67. Found: C, 59.71; H, 4.57.

Methyl 2-[5-(4-bromophenyl)thiophen-3-yl]propionate (9c). Compound **9c** was prepared from **5i** as a pale yellow oil. Yield, 77%; ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.53 (d, 3H, J = 7 Hz), 3.70 (s, 3H), 3.82 (q, 1H, J = 7 Hz), 7.05–7.55 (m, 6H). IR (neat) cm^{-1}: 2950, 1735. MS m/z 325 (M^+). Anal. calcd for $C_{14}H_{13}BrO_2S$: C, 51.70; H, 4.03. Found: C, 51.63; H, 3.91.

General procedure for preparation of 9d–f

To a solution of **9a–c** (23.5 mmol) in methanol (70 mL) and THF (35 mL) was added a solution of NaOH (1.70 g, 425 mmol) in water (70 mL), and the mixture was stirred overnight at room temperature. The resulting solution was concentrated under reduced pressure, and then poured into 5% HCl (100 mL). The mixture was extracted with ethyl acetate. The extract was washed successively with water and brine and dried over anhydrous $MgSO_4$. The ethyl acetate solution was evaporated under reduced pressure to give a residue, which was recrystallized from ethyl acetate–hexane to give **9d–f**.

2-(5-Phenylthiophen-3-yl)propionic acid (9d). Compound **9d** was prepared from **9a** as colorless crystals. Yield, 92%; mp: 97 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.56 (d, 3H, J = 7 Hz), 3.85 (q, 1H, J = 7 Hz), 7.07–7.70 (m, 7H). IR (KBr) cm^{-1}: 2939, 1704. MS m/z 232 (M^+). Anal. calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21. Found: C, 67.12; H, 5.13.

2-[5-(4-Chlorophenyl)thiophen-3-yl]propionic acid (9e). Compound **9e** was prepared from **9b** as colorless crystals. Yield, 85%; mp: 118 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.55 (d, 3H, J = 7 Hz), 3.83 (q, 1H, J = 7 Hz), 7.08–7.60 (m, 6H). IR (KBr) cm^{-1}: 2981, 1695. MS m/z 266 (M^+). Anal. calcd for $C_{13}H_{11}ClO_2S$: C, 58.53; H, 4.16. Found: C, 58.71; H, 4.04.

2-[5-(4-Bromophenyl)thiophen-3-yl]propionic acid (9f). Compound **9f** was prepared from **9c** as colorless crystals. Yield, 85%; mp: 128 °C, ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 1.55 (d, 3H, J = 7 Hz), 3.84 (q, 1H, J = 7 Hz), 7.10–7.55 (m, 6H). IR (KBr) cm^{-1}: 2979, 1694. MS m/z 311 (M^+). Anal. calcd for $C_{13}H_{11}BrO_2S$: C, 50.17; H, 3.56. Found: C, 49.90; H, 3.44.

Biological methods

IL-1-Induced thymocyte proliferation (assay of the IL-1 antagonistic effect).[23] C3H/HeJ mouse thymus cells were suspended in complete RPMI1640 medium containing 100 U/mL penicillin, 100 μg/mL streptomycin, 5×10^{-5} mol/L 2-mercaptoethanol (Sigma, USA) and 5% fetal bovine serum at a concentration of 3×10^7 cells/mL. Each well of a 96-well culture plate (Nunc Company, USA) contained the test compound in 0.05 mL of medium, 0.05 mL of cell suspension, 0.05 mL of phytohemagglutinin (PHA) (Sigma, USA) solution (24 μg/mL), and 0.05 mL of IL-1β (Genzyme, USA) solution (24 U/mL). After 48 h of incubation at 37 °C in a CO_2 incubator, cells were pulsed with 0.25 μCi of methyl-^{3}H-thymidine (^{3}H-TdR, 6.7 Ci/mmol, Amersham, Japan) for 16 h. The cells were harvested with an automated cell harvester and counted in a beta scintillation counter.

Suppression of AIA.[25] SD rats were inoculated intradermally in the tail with 0.6 mg of heat-killed Mycobacterium butyricum (Difco Laboratories, USA) suspended in 0.1 mL of liquid paraffin. The test compounds, which

were prepared as a suspension in 5% gum arabic solution, were orally administered to the rats at a daily dose of 100 mg/kg for 20 days. In the control group, a 5% gum arabic solution was orally administered to rats after sensitization. Twenty-one days later, the edema volume of the hindpaw of rats in the test compound-treated and control groups was measured to evaluate edema-suppressing activities. The activity toward AIA was ranked as follows. When AIA was 0–10, 10–25, 25–40, 40–55, 55–70, 70–85%, and more than 85%, the activity was classified as 0, 1, 2, 3, 4, 5 and 6, respectively.

References and Notes

1. Takeshita, K.; Fukazawa, I.; Futaki, N.; Kameo, K.; Tomisawa, K.; Otomo, S.; Aihara, H. *Arzneim.-Forsch./Drug Res*. **1988**, *38*, 537.
2. Kameo, K.; Ogawa, K.; Takeshita, K.; Nakaike, S.; Tomisawa, K.; Sota, K. *Chem. Pharm. Bull*. **1988**, *36*, 2050.
3. Takahashi, S.; Inoue, T.; Higaki, M.; Mizushima, Y. *Drugs Exp. Clin. Res*. **1998**, *24*, 67.
4. Yasuda, Y.; Inoue, T.; Takeshita, K. *Drugs Exp. Clin. Res*. **1996**, *22*, 1.
5. Hashimoto, M.; Kobayashi, K.; Yamagata, N.; Katsura, T.; Sugihara, S.; Iwabuchi, H.; Kasama, T.; Kasahara, K.; Takahashi, T.; Takeshita, K.; Otomo, S. *Agents Actions* **1992**, *37*, 99.
6. Noguchi, T.; Onodera, A.; Tomisawa, K.; Yokomori, S. *Heterocycles* **2002**, *57*, 1907.
7. Clemence, F.; Le Martret, O.; Fournex, R.; Dagnaux, G. P. M. *Eur. J. Med. Chem. Ther*. **1974**, *9*, 390.
8. Lautenschläger, H. H.; Parnham, M. J.; Leyck, S.; Winkelmann J.; Brekle, A. Japanese Patent, 202,877, 1985; *Chem. Abstr*. **1986**, *104*, 148724.
9. Heller, H. G.; Oliver, S. N.; Whittal, J.; Johncock, W.; Darcy, P. J.; Trundle C. European Patent, 140,540, 1985; *Chem. Abstr*. **1986**, *104*, 70288.
10. Ito, K.; Spears, G. W.; Takahashi, F.; Yamada, A.; Tomishima, M.; Miyake, H. World Patent, 125,229, 2001; *Chem. Abstr*. **2001**, *134*, 280863.
11. Gallagher, P. T.; Hicks, T. A. European Patent, 259,972, 1988; *Chem. Abstr*. **1988**, *109*, 92763.
12. Rooney, C. S.; Randall, W. C.; Streeter, K. B.; Ziegler, C.; Cragoe, E. J., Jr.; Schwam, H.; Michelson, S. R.; Williams, H. W. R.; Eichler, E.; Duggan, D. E.; Ulm, E. H.; Noll, R. M. *J. Med. Chem*. **1983**, *26*, 700.
13. Fincke, H.; Bohr, H.; Staeger, S. German Patent, 1,919,381, 1969; *Chem. Abstr*. **1970**, *72*, 31599.
14. Beaton, C. M.; Chapman, N. B.; Clarke, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, *22*, 2355.
15. Tomisawa, K.; Kameo, K.; Hatada, Y.; Takahashi, Y.; Hatayama, K. Japanese Patent, 193,990, 1990; *Chem. Abstr*. **1990**, *113*, 231203.
16. Campaigne, E.; White, R. L. J., Jr. *Heterocyclic Chem*. **1988**, *25*, 367.
17. Weston, A. W.; Michaels, R. J., Jr. *Org. Synth*. **1962**, *4*, 915.
18. Tomisawa, K.; Hasegawa, M.; Mitsukuchi, M.; Hatayama, K. World Patent, 9,602,529, 1996; *Chem. Abstr*. **1996**, *125*, 33493.
19. Surrey, A. R.; Hammer, H. F.; Suter, C. M. *J. Am. Chem. Soc*. **1944**, *66*, 1933.
20. Tomisawa, K.; Hasegawa, M.; Mitsukuchi, M.; Hatayama, K. Japanese Patent, 194,476, 1997; *Chem. Abstr*. **1997**, *127*, 190640.
21. Moffett, R. B. *Org. Synthesis* **1962**, *4*, 291.
22. Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett*. **1973**, *14*, 957.
23. Oppenheim, J. J.; Shneyour, A.; Kook, A. I. *J. Immunol*. **1976**, *116*, 1466.
24. Oppenheim, J. J.; Kovacs, E. J.; Matsushima, K.; Durum, S. K. *Immunol. Today* **1986**, *7*, 45.
25. Mohr, W.; Wild, A. *Arzneim.-Forsch./Drug Res*. **1976**, *26*, 1860.