# Studies on Anti-inflammatory Agents. VI.[1] Synthesis and Pharmacological Properties of 2,3-Diarylthiophenes

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**A series of novel 5-substituted-2,3-diarylthiophenes has been synthesized and found to be active in the rat adjuvant arthritis (AA) model and/or in the yeast-induced hyperalgesia (Randall–Selitto) assay. Among the compounds synthesized herein, 2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)thiophene (6a) exhibited the most potent activities on AA, collagen-induced arthritis (CIA) and the delayed-type hypersensitivity response to type II collagen. 5-Bromo-2-[4-(methylamino)phenyl]-3-[4-(methylsulfinyl)phenyl]thiophene (38) is also a potent inhibitor of AA, CIA, hyperalgesia and *in vitro* tumor necrosis factor-α production.**

**Key words** anti-inflammatory agent; 2,3-diarylthiophene; antirheumatic activity; analgesic activity; structure–activity relationship

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by painful and swollen joints with possible progression to irreversible joint damage. It is believed to have an underlying autoimmune pathology. The drug treatment initially involves the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and diclofenac. These drugs relieve pain and stiffness, but have no significant effect on immunological responses. Except for the mildest cases, disease-modifying antirheumatic drugs (DMARDs) such as gold salts and D-penicillamine are used to suppress immunological processes and/or joint destruction. New and potentially disease-modifying therapies for RA that have recently come under investigation include tenidap, leflunomide, anti-tumor necrosis factor(TNF)-α antibody, cyclosporin and FK506.[2]

We previously reported a novel compound **1** (FR115068), which was discovered through chemical modification of the anti-inflammatory agent FK3311, and which possesses a broad spectrum of both anti-inflammatory and immunoregulatory activities.[3] Aiming at developing new compounds exerting potent and broad-spectrum activities like **1**, we conducted chemical modification of the structurally distinct thiophene-type agent **2**.[4] Recently, a number of thiophene derivatives, which include selective cyclooxygenase(COX)-2 inhibitors such as 2,3-diarylthiophene **3** and 3,4-diarylthiophene **4**, have been reported.[5] These reports encouraged us to publish our studies on **2**-related 2,3-diarylthiophenes. In this paper, we describe the syntheses and pharmacological activities of the thiophene derivatives represented by the general structure of **5**.

## Chemistry

The syntheses of 5-(perfluoroalkyl, carbamoyl and aminomethyl)thiophenes (**6**, **13**, **15**) are summarized in Chart 1. Perfluoroalkylation of **2** with sodium perfluoroalkane carboxylates and CuI yielded **6**.[6,7] The deoxybenzoin **7** was treated with Vilsmeier reagent, followed by cyclization with thioglycolic acid, to give **9** and **10**.[8] Decarboxylation of **10** in the presence of Cu powder also afforded **9**. Oxidation of **10** with $H_2O_2$ in AcOH gave **11**, which was activated with $PCl_5$ or 1,1′-carbonyldiimidazole ($Im_2CO$) and then treated with the appropriate amines, affording the carboxamides **13**. 5-(Dialkylamino)methyl derivatives **15c—e** were prepared by reduction of **12** and subsequent oxidation *via* **14c—e**. The amino and methylamino groups of **14a, b** were protected, followed by oxidation with *m*-chloroperbenzoic acid (mCPBA) and deprotection with HBr to give **15a, b**.

The syntheses of 5-(acetyl, carboxymethyl and sulfamoyl)thiophenes (**17**, **19**, **20**) and 3-[4-(methylsulfonylamino)phenyl]thiophene **22** are shown in Chart 2. Compound **9** was oxidized and acetylated with acetyl chloride and $TiCl_4$ catalyst to afford **17**. The carboxymethyl de-

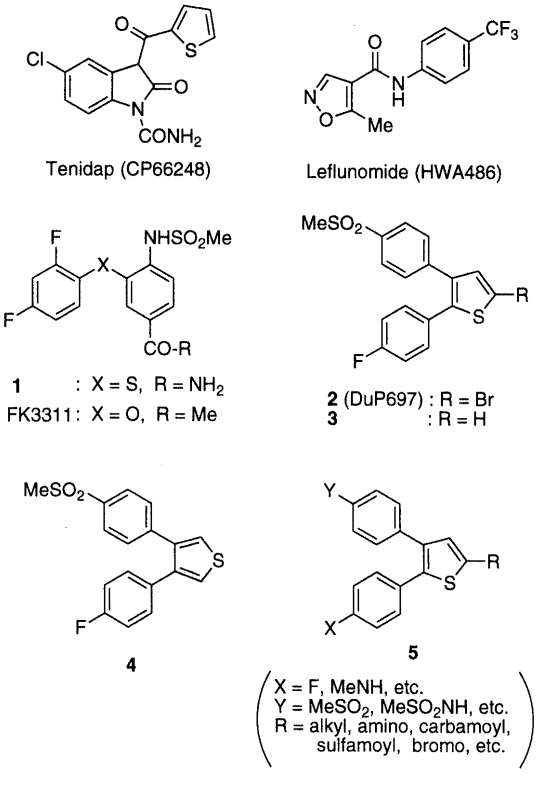


Fig. 1

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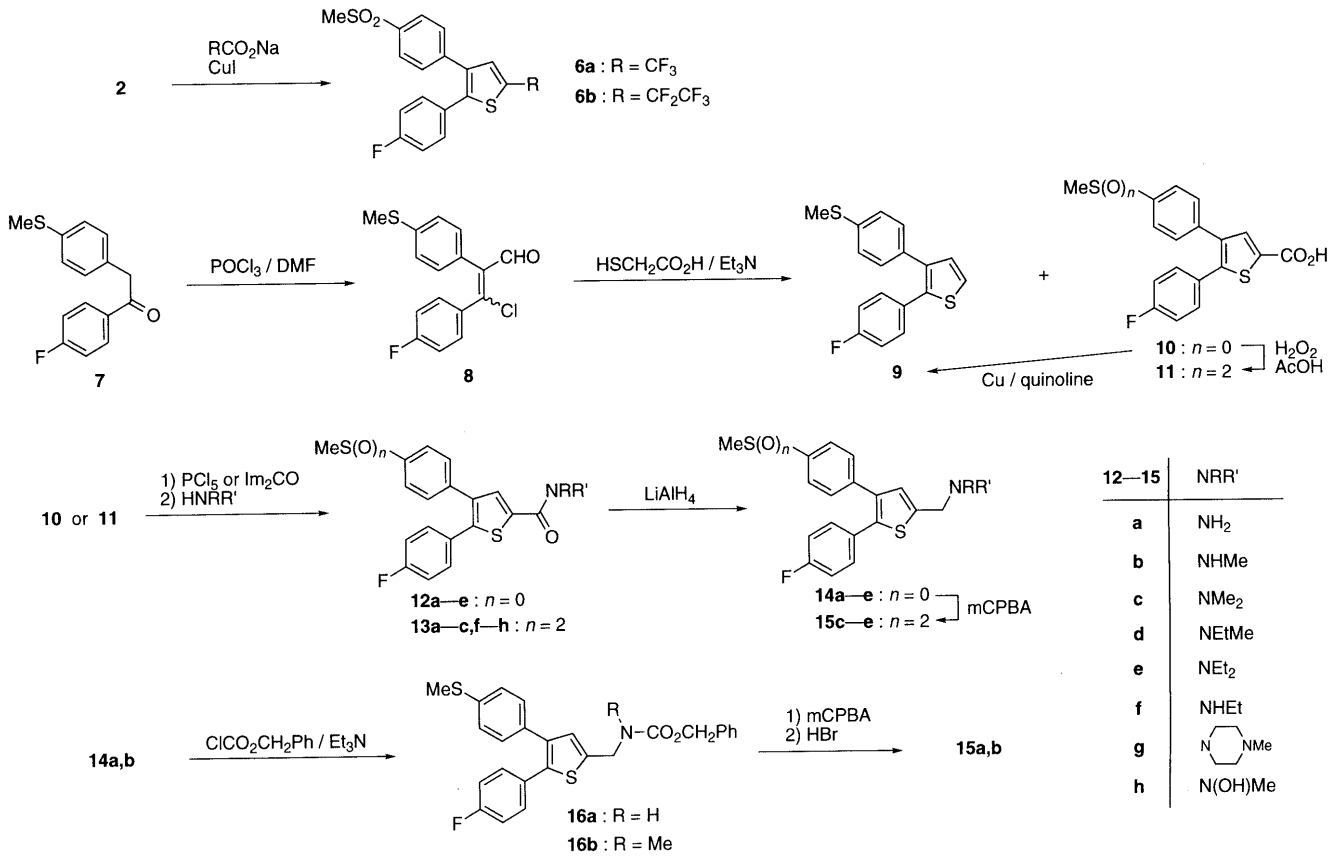



Chart 1

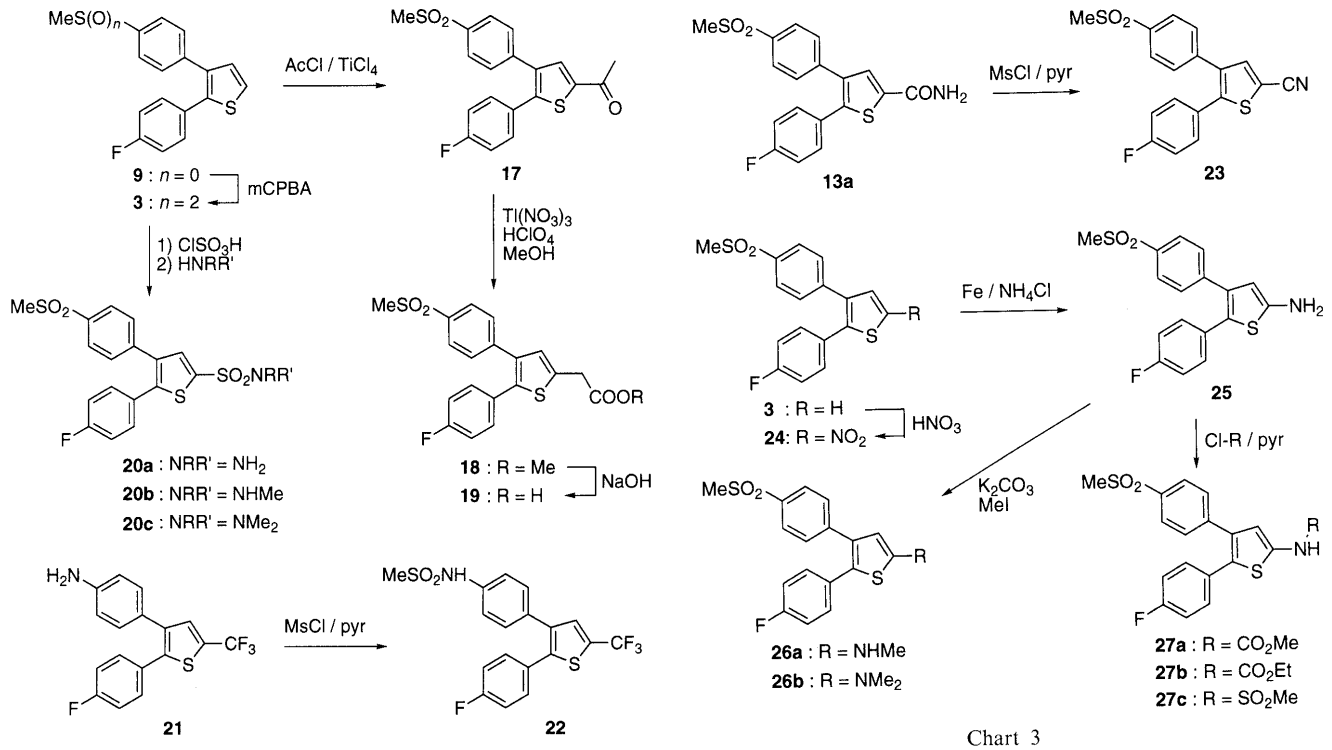



Chart 2

Chart 3

rivative **19** was obtained by oxidative rearrangement of **17** by the method of McKillop *et al.*[9] and subsequent hydrolysis of the ester **18**. Chlorosulfonylation and amidation of **3** gave the sulfamoyl derivatives **20**. Similarly, methylsulfonylation of the amino derivative **21** yielded **22**.[10] The nitrile **23** was prepared by dehydration of the amide **13a** (Chart 3).[11] 5-(Substituted amino)thiophenes (**26**, **27**) were synthesized *via* the amino derivative **25**, which was obtained from **3** by nitration and reduction with Fe.

5-Bromo-2-[4-(methylamino)phenyl]thiophene **38** was obtained as shown in Chart 4. The deoxybenzoin **30** was

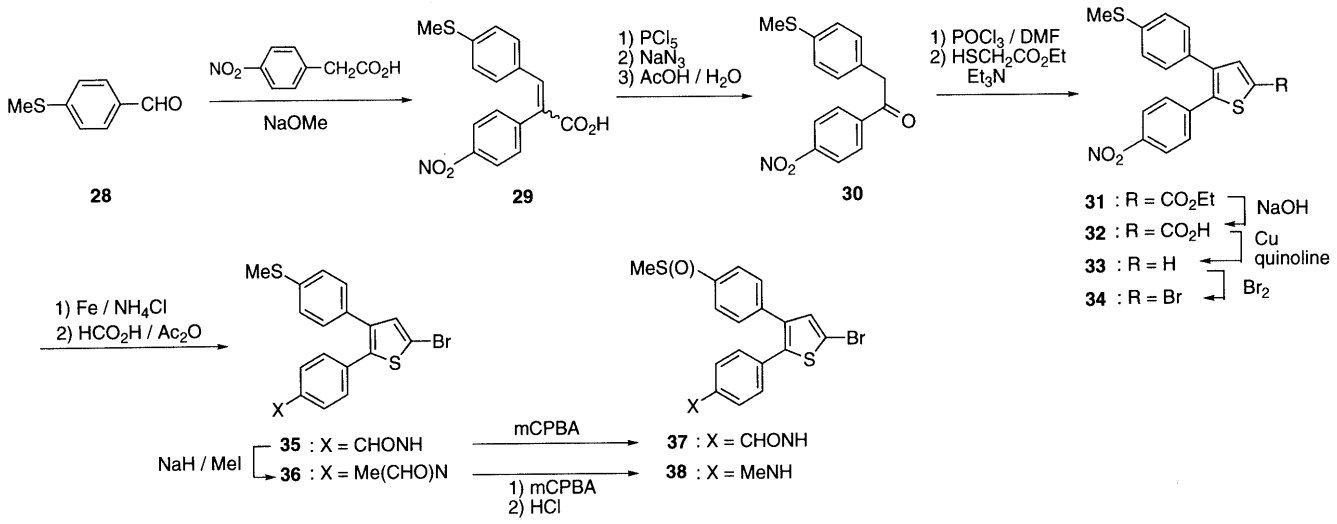



Chart 4

prepared by the method of Bender and Hill.[12] Reaction of **30** with Vilsmeier reagent and ethyl thioglycolate, hydrolysis, decarboxylation, and subsequent bromination with bromine afforded the 5-bromothiophene derivative **34**. The methylamino derivative **38** was prepared from **34** by reduction, protection with a formyl group, methylation, careful oxidation with mCPBA, and deprotection *via* **35** and **36**. The formylamino intermediate **35** was oxidized to give **37**.

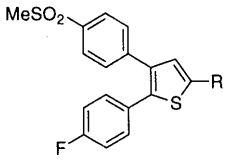
## Results and Discussion

The compounds synthesized in this study were first tested for anti-inflammatory and analgesic activities through oral administration to rats. The chronic anti-inflammatory activity was assessed in terms of inhibition of adjuvant arthritis (AA). The analgesic activity against inflammation-related pain was evaluated as relative potency in the yeast-induced hyperalgesia (Randall–Selitto) assay. The test results are summarized in Tables 1—3.

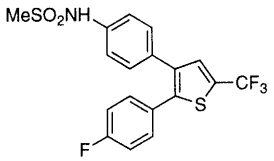
As a first step in the chemical modification of **2**, we investigated various 5-substituted thiophene derivatives to find alternative substituents to the bromine of **2**. Table 1 shows the results for perfluoro, amino and carboxy alkyl derivatives (**6**, **15**, **19**). Perfluoro compounds **6a**, **b** exhibited very potent inhibitory activities toward AA (98% and 88% inhibition at 10 mg/kg, respectively). Amino and carboxy compounds (**15b—e**, **19**) also showed potent anti-inflammatory activities. Among these active compounds, **6a** was selected as a lead compound because of its exceptionally strong anti-inflammatory activity ($ED_{50}$ = 0.030 mg/kg). The (methylsulfonyl)phenyl moiety at the 3-position of the thiophene ring of **6a** was replaced with a (methylsulfonylamino)phenyl group, in the expectation that broader-spectrum activities, such as those of **1**, would be obtained. The resultant compound **22** also significantly suppressed AA. Moreover, perfluoro (**6**, **22**), amino (**15a, c, d**) and carboxy (**19**) alkyl derivatives exhibited moderate analgesic activities.

Various carbamoyl and sulfamoyl derivatives (**13**, **20**) were investigated as shown in Table 2. *N*-Methyl and *N*-unsubstituted derivatives (**13b**, **20a, b**) exhibited the most potent anti-inflammatory activity. Bulky substituents

Table 1. Investigation of 5-(Substituted alkyl) Derivatives




6,15 and 19




22

| Compd. | R | Adjuvant arthritis % inhibition[a] (10 mg/kg *p.o.*) | Randall–Selitto relative potency[b] (32 mg/kg *p.o.*) |
|---|---|---|---|
| **6a** | $CF_3$ | 98[c] | 1.20[d] |
| **6b** | $CF_2CF_3$ | 88[c] | 1.13 |
| **15a**[e] | $CH_2NH_2$ | 43[d] | 1.30[c] |
| **15b**[e] | $CH_2NHMe$ | 86[c] | 1.03 |
| **15c**[f] | $CH_2NMe_2$ | 79[c] | 1.19[d] |
| **15d**[f] | $CH_2NMeEt$ | 73[c] | 1.33[c] |
| **15e** | $CH_2NEt_2$ | 66[c,g] | 1.06 |
| **19** | $CH_2COOH$ | 78[c] | 1.27[c] |
| **22** | | 73[c,h] | 1.17 |

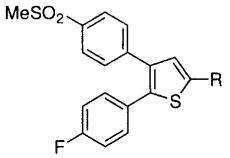
*a*) Uninjected paw. *b*) Ratio of the pain threshold in the treated *vs.* control animals. *c*) $p<0.01$. *d*) $p<0.05$, significant difference from control (Student's *t*-test). *e*) HBr salt. *f*) HCl salt. *g*) 3.2 mg/kg. *h*) 7 mg/kg.

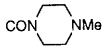
(*e.g.*, **13c, f—h, 20c**) gave less active compounds, but introduction of bulky carbamoyl groups resulted in fairly potent analgesic activities (**13c, g, h**). Among the substituted amino derivatives (**26**, **27**) in Table 2, only carbamates **27a, b** showed potent anti-inflammatory activities. On the other hand, the sterically small and electron-withdrawing cyano (**23**) and nitro (**24**) derivatives very strongly inhibited AA.

In the previous paper,[1] we reported on the 1-[4-(methylamino)phenyl]pyrazole derivative **39** (Table 3), which possessed not only potent anti-inflammatory ($ED_{50}$ = 0.30 mg/kg) and analgesic ($ED_{30}$ = 11 mg/kg) activities, but also hydrophilic character. We tried the introduction of the methylamino moiety of **39** in the present study, as depicted in Table 3. Compound **38** and its synthetic intermediate **37** significantly inhibited both AA and pain in the Randall–Selitto assay; in particular, the activities of **38** were superior to those of **39**.

Based on the above evaluation and additional dose–

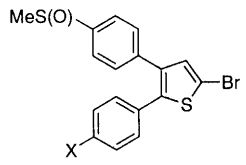
Table 2. Investigation of 5-Carbamoyl, Sulfamoyl, Amino and Miscellaneous Derivatives



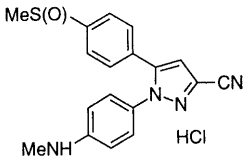

| Compd. | R | Adjuvant arthritis % inhibition[a] (10 mg/kg *p.o.*) | Randall–Selitto relative potency[b] (32 mg/kg *p.o.*) |
|---|---|---|---|
| **13b** | CONHMe | 74[c] | 1.31[c] |
| **13c** | $CONMe_2$ | 31 | 1.40[c] |
| **13f** | CONHEt | 49[d] | 1.18 |
| **13g** |  | 57[d] | 1.32[c] |
| **13g** | CON NMe | 57[d] | 1.32[c] |
| **13h** | CON(OH)Me | 22 | 1.41[c] |
| **20a** | $SO_2NH_2$ | 84[c] | 1.28[d] |
| **20b** | $SO_2NHMe$ | 89[c] | 1.01 |
| **20c** | $SO_2NMe_2$ | 60[c] | 1.09 |
| **26a** | NHMe | 16[e] | NT |
| **26b** | $NMe_2$ | 57[d,e] | NT |
| **27a** | $NHCO_2Me$ | 81[c] | 1.15[d] |
| **27b** | $NHCO_2Et$ | 79[c] | 1.09 |
| **27c** | $NHSO_2Me$ | 53[c] | 1.17 |
| **17** | COMe | 47[d] | 1.41[c] |
| **23** | CN | 96[c,e] | 0.98[f] |
| **24** | $NO_2$ | 87[c,e] | 1.08 |

*a*—*d*) Refer to Table 1. *e*) 3.2 mg/kg. *f*) 10 mg/kg. NT: Not tested.

Table 3. Investigation of 2-[4-(Substituted amino)phenyl] Derivatives




**37,38**




**39**

| Compd. | X | Adjuvant arthritis % inhibition[a] (3.2 mg/kg *p.o.*) | Randall–Selitto relative potency[b] (10 mg/kg *p.o.*) |
|---|---|---|---|
| **37** | CHONH | 76[c] | 1.26[d] |
| **38** | MeNH | 93[c] | 1.35[c] |
| **39**[e] | | 74[c] | 1.30[c] |

*a*—*d*) Refer to Table 1. *e*) Ref. 1.

response studies, **6a** and **38** were chosen for further investigation. Compounds **6a** and **38** reduced chronic inflammation in the AA model with $ED_{50}$ values of 0.030 and 0.32 mg/kg, respectively(Table 4). They also exhibited analgesic activity in the Randall–Selitto assay with $ED_{30}$ values of 58 and 5.4 mg/kg, respectively. These data indicated that both **6a** and **38** had potency equivalent to that of standard NSAIDs such as indomethacin, but were devoid of gastrointestinal toxicity. The data in Table 4, furthermore, indicate that **6a** and **2** are selective COX-2 inhibitors. On the other hand, the COX-inhibitory activity of **38** was marginal.

To evaluate further the antirheumatic activities of **6a** and **38**, we examined the effect on the type II collagen-induced arthritis (CIA) model in mice in comparison

Table 4. Anti-inflammatory, Analgesic and COX-Inhibitory Activities of **6a**, **38** and Reference Compounds

| | **6a** | **38** | **2**[a] | Indomethacin |
|---|---|---|---|---|
| Adjuvant arthritis[b] | | | | |
| $ED_{50}$ (mg/kg *p.o.*)[c] | 0.030 | 0.32 | 0.085 | 0.15 |
| $UD_{50}$ (mg/kg *p.o.*)[d] | >3.2 | >3.2 | >3.2 | 0.069 |
| Safety Index[e] | >106 | >10 | >38 | 0.46 |
| Randall–Selitto[b] | | | | |
| $ED_{30}$ (mg/kg *p.o.*) | 58 | 5.4 | 1.3 | 3.4 |
| Cyclooxygenase[f] | | | | |
| COX-1 ($IC_{50}$, $\mu$M) | 5.6 | 96 | 11 | 0.23 |
| COX-2 ($IC_{50}$, $\mu$M) | 0.072 | >10 | 0.020 | 0.61 |
| Selectivity[g] | 77 | | 550 | 0.38 |

*a*) Synthesized according to ref. 8. *b*) In rats. *c*) Uninjected paw. *d*) The median dose for production of GI lesions. *e*) $UD_{50}/ED_{50}$. *f*) *In vitro* (human). *g*) Selectivity = $IC_{50}$ (COX-1)/$IC_{50}$ (COX-2).

Table 5. Effects of **6a**, **38** and Reference Compounds on Type II Collagen-induced Arthritis and DTH Response in Mice

| Compd. | Dose (mg/kg *p.o.*) | CIA (% inhibition) | | DTH response % inhibition |
|---|---|---|---|---|
| | | Arthritic index | Anti C II Ab[a] | |
| **6a** | 0.1 | 56[b] | −3 | NT |
| | 1 | 76[b] | 9 | 68[b] |
| | 10 | 89[b] | 32[c] | 79[b] |
| **38** | 1 | 12 | 21 | 1 |
| | 3.2 | 47[c] | 21 | NT |
| | 10 | 61[b] | 26 | 0 |
| **2**[d] | 1 | 44 | 2 | 39[b] |
| | 3.2 | 79[b] | 22 | 38[b] |
| | 10 | 65[c] | 17 | 37[b] |
| **1**[e] | 10 | 41[b] | 51[b] | NT |
| | 100 | 43[b] | 61[b] | NT |

*a*) Anti-type II collagen antibody. *b*) $p<0.01$. *c*) $p<0.05$ *vs.* control (Student's *t*-test). *d*) Ref. 8. *e*) Ref. 3. NT: Not tested.

with **1** and **2**. As shown in Table 5, the thiophenes (**6a**, **38**, **2**) suppressed the severity of arthritis measured in terms of the arthritic index more potently than **1**; 56% inhibition was observed even at a dose as low as 0.1 mg/kg of **6a**. Since the induction of arthritis in CIA is closely associated with a high level of both humoral and cellular immunity to type II collagen, the effects of the compounds on these immune responses to collagen were tested. Although **1** reduced the level of anti-collagen antibody in association with the inhibition of the arthritic index, neither **6a**, **38** nor **2** was effective in reducing the plasma level of anti-collagen antibody. This suggested that the suppression of arthritis by these compounds was not due to the reduction of anti-collagen antibody. We next investigated their effects on the cellular immunity to type II collagen monitored in terms of the delayed-type hypersensitivity (DTH) response. Compound **6a** strongly inhibited the DTH response to type II collagen. On the other hand, **38** and **2** showed no or moderate activities.

TNF-$\alpha$ is one of the cytokines critically involved in cellular immunity. Interestingly, **38** as well as **2** strongly inhibited TNF-$\alpha$ production by human peripheral blood mononuclear cells (PBMC) stimulated with lipopolysaccharide (LPS), as shown in Table 6, while indomethacin was inactive(up to 10 $\mu$g/ml). Taken together, the results

Table 6. Effects of **38** and **2** on the Production of TNF-α from Human PBMC

| Compd. | % Inhibition[a] | | |
|---|---|---|---|
| | 0.1 μg/ml | 1 μg/ml | 10 μg/ml |
| **38** | 40 | 86 | 100 |
| **2** | 13 | 81 | 101 |

a) Average values of duplicate experiments.

in Tables 5 and 6 indicate that **6a** and **38** suppressed the arthritic induction in CIA through the inhibition of cellular immunity to collagen.

In conclusion, the chemical modification of **2** has led to the novel compounds **6a** and **38**, which possess a broad spectrum of both anti-inflammatory and immunoregulatory activities, as shown in the AA, Randall–Selitto, COX, CIA, DTH response and TNF-α production assays. These activities suggest that thiophene derivatives such as **6a** or **38** have potential not only to reduce arthritic inflammation and pain, but also to ameliorate immunological abnormalities of RA in the clinic.

## Experimental

Melting points were measured on a Mitamura capillary melting-point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-408 spectrophotometer. $^1$H-NMR spectra were taken with a Varian EM-390 or a Bruker AC-200 instrument using tetramethylsilane as an internal standard. Electron impact MS were obtained with a Hitachi M80 mass spectrometer. Organic extracts were dried over anhydrous $MgSO_4$. Column chromatography was performed using Kieselgel 60 (70—230 mesh, E. Merck).

**2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-thiophene (6a)** A mixture of **2** (7.2 g, 17.5 mmol),[8] $CF_3COONa$ (9.4 g, 67.4 mmol) and CuI (6.5 g, 33.7 mmol) in *N*,*N*-dimethylacetamide (109 ml) was refluxed for 5 h. $CH_2Cl_2$ (200 ml) and 1.5 N HCl (200 ml) were added. The insoluble material was removed by filtration and the filtrate was separated. The organic layer was washed with $H_2O$, dried and evaporated. The residue was chromatographed (toluene–EtOAc, 50 : 1) over silica gel to yield **3** (3.2 g, 55%) and a crude mixture of **6a** and **3** (3.0 g). Concentrated $HNO_3$ (2 ml) was added dropwise to 3.0 g of the crude mixture in $Ac_2O$ (50 ml), and the whole was stirred at 0 °C for 2 h. $NaHCO_3$ (1.0 g) was added and the whole was evaporated. The residue was chromatographed (toluene–EtOAc, 50 : 1) over silica gel and the product was recrystallized from EtOH to give **6a** (1.04 g, 15%) as pale brown crystals, mp 145—146 °C. IR (Nujol): 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 3.20 (3H, s), 7.1—8.0 (9H, m). MS *m/z* : 400 ($M^+$). *Anal.* Calcd for $C_{18}H_{12}F_4O_2S_2$: C, 53.99; H, 3.02. Found: C, 54.47; H, 3.21. Compound **24** (0.6 g, 9%), a by-product of the reaction, was obtained after the second column chromatography.

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(pentafluoroethyl)thiophene (**6b**): This compound was prepared similarly to **6a**, mp 183—185 °C (toluene–EtOAc). IR (Nujol): 1600, 1550, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 3.25 (3H, s), 7.1—8.0 (9H, m). MS *m/z* : 450 ($M^+$). *Anal.* Calcd for $C_{19}H_{12}F_6O_2S_2$: C, 50.67; H, 2.69. Found: C, 51.56; H, 2.71.

**3-Chloro-3-(4-fluorophenyl)-2-[4-(methylthio)phenyl]propenal (8)** A mixture of $POCl_3$ (20.6 ml, 221 mmol) and *N*,*N*-dimethylformamide (DMF) (22.8 ml, 295 mmol) in $ClCH_2CH_2Cl$ (74 ml) was stirred at room temperature for 30 min, then a solution of **7** (38.3 g, 148 mmol)[13] in $ClCH_2CH_2Cl$ (139 ml) was added. The whole was refluxed for 10 h, cooled, washed twice with $H_2O$, dried, and evaporated. The residue was washed with toluene to give **8** (28.8 g, 64%) as a pale brown solid.[14] IR (Nujol): 1680, 1600, 1500 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.53 (3H, s), 6.9—7.8 (8H, m), 9.68 (1H, s).

**2-(4-Fluorophenyl)-3-[4-(methylthio)phenyl]thiophene (9) and 2-(4-Fluorophenyl)-3-[4-(methylthio)phenyl]thiophene-5-carboxylic Acid (10)** A mixture of **8** (16 g, 52.2 mmol), thioglycolic acid (3.81 ml, 54.7 mmol) and $Et_3N$ (16 ml, 115 mmol) in pyridine (80 ml) was stirred at 70 °C for 1 h and then refluxed for 3 h. The solvent was evaporated, and the residue was dissolved in a mixture of EtOAc and $H_2O$. The organic layer was separated, washed with dilute HCl, dried and evaporated. The oily residue (20 g) was chromatographed[15] over silica gel to afford **9** (5.8 g, 37%) and **10** (10.8 g, 60%).[14] **9**: mp 81—83 °C, off-white solid. IR (Nujol): 1600, 1505 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 6.8—7.5 (10H, m). MS *m/z*: 300 ($M^+$). **10**: Pale brown solid. IR (Nujol): 2500, 1680, 1600, 1540, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 2.50 (3H, s), 7.1—7.5 (8H, m), 7.80 (1H, s).

A mixture of **10** (17.7 g, 51.3 mmol) and Cu powder (3.6 g, 56.7 mmol) in quinoline (31 ml) was refluxed for 5 h. EtOAc was added and the whole was filtered. The filtrate was washed successively with $H_2O$, dilute HCl and $H_2O$, dried and evaporated. The residue was recrystallized from EtOH to give **9** (13.3 g, 86%) as pale brown crystals. The IR, $^1$H-NMR, MS and melting point were identical with those of **9** synthesized above.

**2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-carboxylic Acid (11)** A mixture of **10** (10.8 g, 31.4 mmol) and $H_2O_2$ (30%; 9.3 ml, 81.6 mmol) in AcOH (108 ml) was stirred at 70 °C for 3 h. The mixture was cooled to 5 °C, and the precipitates were collected and recrystallized from EtOH to afford **11** (8.1 g, 68%) as pale yellow crystals, mp 264—265 °C. IR (Nujol): 1680, 1600, 1545, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 3.28 (3H,s), 7.1—8.1 (9H, m). MS *m/z*: 376 ($M^+$). *Anal.* Calcd for $C_{18}H_{13}FO_4S_2 \cdot 1/2H_2O$: C, 56.09; H, 3.66. Found: C, 56.12; H, 3.64.

***N*-Methyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-carboxamide (13b)** A mixture of **11** (7.1 g, 18.8 mmol) and $PCl_5$ (4.1 g, 19.8 mmol) in toluene (100 ml) and tetrahydrofuran (THF) (25 ml) was stirred at room temperature for 1 h, then concentrated to dryness to give the acid chloride (8.1 g) as a pale yellow solid. IR (film): 1750, 1600, 1540, 1510 cm$^{-1}$.

The above acid chloride (1.4 g) was added to a stirred mixture of 25% $MeNH_2$ (2 ml), THF (15 ml) and $H_2O$ (5 ml) at 5 °C. The resultant mixture was stirred at room temperature for 2 h. EtOAc and $H_2O$ were added, and the organic layer was separated, washed with $H_2O$, dried and evaporated. The residue was chromatographed ($CHCl_3$–EtOAc, 1 : 1) over silica gel and the product was crystallized from $Et_2O$ to give **13b** (1.0 g, 81%) as colorless crystals, mp 169—170 °C. IR(Nujol): 3450, 1650, 1600, 1550, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 2.83 (3H, d, $J$=4 Hz), 3.26 (3H, s), 7.2—8.1 (9H, m), 8.4—8.8 (1H, m). MS *m/z*: 389 ($M^+$), 359. *Anal.* Calcd for $C_{19}H_{16}FNO_3S_2$: C, 58.59; H, 4.14; N, 3.60. Found: C, 58.34; H, 4.40; N, 3.54.

The following compounds were prepared from **11** in the same manner as described for **13b**.

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-carboxamide (**13a**): mp 233—234 °C (EtOH–EtOAc), off-white crystals. IR (Nujol): 3480, 3200, 1675, 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 3.28 (3H, s), 7.2—8.1 (11H, m). MS *m/z*: 375 ($M^+$), 357. *Anal.* Calcd for $C_{18}H_{14}FNO_3S_2$: C, 57.58; H, 3.76; N, 3.73. Found: C, 57.54; H, 4.07; N, 3.54.

*N*-Hydroxy-*N*-methyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-carboxamide (**13h**): mp 95—98 °C (iso-$Pr_2O$), pale brown powder. IR (Nujol): 1600, 1540, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 3.24 (3H, s), 3.32 (3H, s), 7.2—8.0 (9H, m), 10.78 (1H, s). MS *m/z*: 405 ($M^+$). *Anal.* Calcd for $C_{19}H_{16}FNO_4S_2 \cdot 1/2H_2O$: C, 55.06; H, 3.89; N, 3.37. Found: C, 55.18; H, 4.12; N, 2.93.

***N*,*N*-Dimethyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-carboxamide (13c)** A mixture of **11** (1.0 g, 2.66 mmol) and 1,1′-carbonyldiimidazole (0.45 g, 2.8 mmol) in THF (15 ml) was refluxed for 2 h. $Me_2NH \cdot HCl$ (0.3 g, 3.68 mmol) and $K_2CO_3$ (0.39 g, 2.8 mmol) were added, and the resultant mixture was stirred at room temperature for 2 h and then refluxed for 2 h. EtOAc was added, and the mixture was washed successively with $H_2O$, aqueous $NaHCO_3$, $H_2O$ and dilute HCl, dried and evaporated. The residue was recrystallized from EtOH to give **13c** (0.76 g, 71%) as pale yellow crystals, mp 172—173 °C. IR (Nujol): 1605, 1545, 1490 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 3.21 (3H, s), 3.27 (6H, s), 7.0—8.1 (9H, m). MS *m/z* : 403 ($M^+$), 359. *Anal.* Calcd for $C_{20}H_{18}FNO_3S_2$: C, 59.53; H, 4.50; N, 3.47. Found: C, 59.38; H, 4.53; N, 3.36.

The following compounds were obtained from **10** or **11** in the same manner as described for **13c**.

*N*,*N*-Dimethyl-2-(4-fluorophenyl)-3-[4-(methylthio)phenyl]thiophene-5-carboxamide (**12c**): Oil.[14] IR (film): 2920, 1620, 1600, 1540 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.51 (3H, s), 3.28 (6H, s), 6.8—7.5 (9H, m). MS *m/z*: 371 ($M^+$), 327.

*N*-Ethyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-carboxamide (**13f**): mp 149—151 °C (EtOH), colorless needles. IR (Nujol): 3400, 1640, 1550, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.14 (3H, t, $J$=7 Hz), 3.25 (3H, s), 3.2—3.4 (2H, m), 7.1—7.6 (6H, m), 7.90 (2H, d, $J$=8 Hz), 7.96 (1H, s), 8.60 (1H, t, $J$=6 Hz). MS $m/z$: 403 ($M^+$). *Anal.* Calcd for $C_{20}H_{18}FNO_3S_2$: C, 59.53; H, 4.50; N, 3.47. Found: C, 59.71; H, 4.50; N, 3.50.

1-{2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thenoyl}-4-methylpiperazine (**13g**): mp 68—72 °C ($CHCl_3$), off-white powder. IR (Nujol): 1610, 1545, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.12 (3H, s), 2.37 (4H, br s), 3.23 (3H, s), 3.72 (4H, br s), 7.1—8.0 (9H, m). MS $m/z$: 458 ($M^+$). *Anal.* Calcd for $C_{23}H_{23}FN_2O_3S_2 \cdot 1/2H_2O$: C, 59.08; H, 4.96; N, 5.99. Found: C, 59.34; H, 5.08; N, 5.35.

***N,N*-Dimethyl-2-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-5-thenylamine (14c)** A solution of **12c** (1.95 g, 5.26 mmol) in benzene (15 ml) was added dropwise to an ice-cooled suspension of $LiAlH_4$ (0.27 g, 7 mmol) in $Et_2O$ (10 ml). The mixture was refluxed for 9 h and cooled. Then 4 N NaOH (10 ml) was added dropwise, and EtOAc was added to the mixture. The insoluble material was removed by filtration and the filtrate was washed with $H_2O$, dried and evaporated. The residue was chromatographed (toluene–EtOAc, 2:1) over silica gel to afford **14c** (1.5 g, 78%) as a yellow oil.[14] IR (film): 2770, 1600, 1510 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.35 (6H, s), 2.50 (3H, s), 3.66 (2H, s), 6.8—7.5 (9H, m). MS $m/z$: 357 ($M^+$), 313.

***N,N*-Dimethyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thenylamine Hydrochloride (15c)** A mixture of **14c** (1.4 g, 4 mmol) and mCPBA (2.6 g, 12 mmol) in $CH_2Cl_2$ (25 ml) was stirred overnight. The insoluble material was removed by filtration, and the filtrate was washed with aqueous $NaHCO_3$, dried and evaporated. The residue was dissolved in 30% HCl in MeOH (1 ml) and the solvent was evaporated. The residue was pulverized with $Et_2O$ to give **15c** (1.4 g, 81%) as a pale brown powder, mp 192—194 °C. IR (Nujol): 3400, 2550, 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.23 (3H, s), 3.55 (6H, s), 5.25 (2H, s), 7.2—8.1 (9H, m). MS $m/z$: 389 ($M^+$), 345. *Anal.* Calcd for $C_{20}H_{20}FNO_2S_2 \cdot HCl \cdot H_2O$: C, 54.10; H, 5.22; N, 3.15. Found: C, 53.64; H, 4.74; N, 3.09.

The following compounds were prepared from **14d** or **14e**[10] in the same manner as described for **15c**.

*N*-Ethyl-*N*-methyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thenylamine Hydrochloride (**15d**): mp 95—100 °C (dec.) (EtOH), off-white solid. IR (Nujol): 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.40 (3H, t, $J$=8 Hz), 3.20 (3H, s), 3.37 (3H, s), 3.77 (2H, q, $J$=8 Hz), 5.15 (2H, s), 7.1—8.0 (9H, m). MS $m/z$: 403 ($M^+$), 345. *Anal.* Calcd for $C_{21}H_{22}FNO_2S_2 \cdot HCl \cdot 2H_2O$: C, 53.05; H, 4.63; N, 2.94. Found: C, 52.87; H, 4.83; N, 2.57.

*N,N*-Diethyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thenylamine (**15e**): mp 98—102 °C (hexane–EtOAc), pale yellow powder. IR (Nujol): 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.20 (6H, t, $J$=7 Hz), 3.0—3.3 (4H, m), 3.23 (3H, s), 4.52 (2H, s), 7.1—7.9 (9H, m). MS $m/z$: 417 ($M^+$), 345. *Anal.* Calcd for $C_{22}H_{24}FNO_2S_2 \cdot 5/2H_2O$: C, 57.14; H, 5.20; N, 3.03. Found: C, 57.52; H, 5.68; N, 2.80.

***N*-(Benzyloxycarbonyl)-2-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-5-thenylamine (16a)** Benzyl chloroformate (1.0 ml, 7.0 mmol) was added dropwise to an ice-cooled solution of **14a** (2.1 g, 6.36 mmol)[10] and $Et_3N$ (1.27 ml, 9.12 mmol) in $CH_2Cl_2$ (20 ml). The mixture was stirred at room temperature for 3 h, washed successively with $H_2O$ and aqueous $NaHCO_3$, dried and evaporated. The residue was chromatographed ($CHCl_3$) over silica gel to afford **16a** (1.3 g, 48%) as a yellow oil.[14] $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 4.39 (2H, d, $J$=6 Hz), 5.14 (2H, s), 6.9—7.5 (14H, m), 8.00 (1H, t, $J$=6 Hz). MS $m/z$: 463 ($M^+$).

*N*-(Benzyloxycarbonyl)-*N*-methyl-2-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-5-thenylamine (**16b**): This compound was obtained from **14b**[10] in the same manner as described for **16a**: Yellow oil.[14] $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 2.93 (3H, s), 4.60 (2H, s), 5.14 (2H, s), 7.1—7.4 (14H, m). MS $m/z$: 477 ($M^+$).

**2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thenylamine Hydrobromide (15a)** **16a** (1.3 g, 2.81 mmol) was oxidized with mCPBA (1.3 g, 6.04 mmol) at room temperature overnight, and chromatographed (toluene–EtOAc, 2:1) over silica gel. The resultant sulfone(oil; 0.78 g, 1.58 mmol) was dissolved in 30% HBr in AcOH (10 ml). The solution was stirred at room temperature for 1 h and evaporated. The residue was washed with iso-$Pr_2O$ to give **15a** (0.7 g, 53%) as a white powder, mp >200 °C. IR (Nujol): 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.24 (3H, s), 4.32 (2H, s), 7.1—7.5 (7H, m), 7.80 (2H, d, $J$=8 Hz), 8.37 (2H, br s). MS $m/z$: 361 ($M^+$). *Anal.* Calcd for $C_{18}H_{16}FNO_2S_2 \cdot HBr \cdot 2/3H_2O$: C, 47.58; H, 4.07; N, 3.08. Found: C, 48.02; H, 4.03; N, 2.59.

*N*-Methyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thenylamine Hydrobromide (**15b**): This compound was obtained from **16b** in the same manner as described for **15a**: mp 100—110 °C (dec.) ($Et_2O$). IR (Nujol): 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.64 (3H, s), 3.24 (3H, s), 4.44 (2H, s), 7.2—7.6 (7H, m), 7.90 (2H, d, $J$=8 Hz), 9.00 (2H, br s). MS $m/z$: 375 ($M^+$). *Anal.* Calcd for $C_{19}H_{18}FNO_2S_2 \cdot HBr \cdot H_2O$: C, 48.30; H, 3.84; N, 2.53. Found: C, 48.09; H, 4.13; N, 2.53.

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene (**3**): This compound was obtained from **9** in the same manner as described for **15c**: mp 155—156 °C (EtOH), pale brown solid. IR (Nujol): 1595, 1505 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.23 (3H, s), 7.0—8.0 (10H, m). MS $m/z$: 332 ($M^+$). *Anal.* Calcd for $C_{17}H_{13}FO_2S_2$: C, 61.42; H, 3.94. Found: C, 61.46; H, 3.91.

**5-Acetyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene (17)** $TiCl_4$ (2.7 ml, 24.2 mmol) was added dropwise to a stirred solution of **3** (5.0 g, 15.1 mmol) and AcCl (2.2 ml, 30.2 mmol) in benzene (50 ml) at 5—10 °C. The mixture was stirred at room temperature for 4 h, poured into ice-$H_2O$, and extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$, dried and evaporated. The residue was recrystallized from EtOH–EtOAc to give **17** (3.7 g, 66%) as pale brown crystals, mp 169—172 °C. IR (Nujol): 1670, 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.58 (3H, s), 3.21 (3H, s), 7.0—8.0 (8H, m), 8.11 (1H, s). MS $m/z$: 374 ($M^+$), 359. *Anal.* Calcd for $C_{19}H_{15}FO_3S_2$: C, 60.94; H, 4.04. Found: C, 60.46; H, 4.12.

**Methyl 2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-acetate (18)** A mixture of **17** (1.0 g, 2.67 mmol), $Tl(NO_3)_3 \cdot 3H_2O$ (1.4 g, 3.21 mmol) and 70% $HClO_4$ (3 ml) in MeOH (15 ml) and dioxane (7 ml) was stirred at room temperature for 7 h. The insoluble material was removed by filtration, and $CHCl_3$ and $H_2O$ were added to the filtrate. The organic layer was separated, dried and evaporated to give **18** (1.2 g) as an oil.[14] IR (film): 1740, 1670, 1600, 1510 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.10 (3H, s), 3.81 (3H, s), 3.91 (2H, s), 6.9—8.0 (9H, m). MS $m/z$: 404 ($M^+$), 345.

**2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-acetic Acid (19)** A mixture of **18** (2 g, 4.95 mmol) and 4 N NaOH (3.7 ml, 14.8 mmol) in THF (20 ml) was stirred at room temperature for 1 h. $H_2O$ and toluene were added, and the aqueous layer was separated, acidified with HCl and extracted with EtOAc. The extract was dried and evaporated. The residue was recrystallized from EtOH–$H_2O$ to give **19** (1.6 g, 81%) as pale orange crystals, mp 171—173 °C. IR (Nujol): 1700, 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.24 (3H, s), 3.93 (2H, s), 7.1—8.0 (9H, m). MS $m/z$: 390 ($M^+$), 345. *Anal.* Calcd for $C_{19}H_{15}FO_4S_2$: C, 58.45; H, 3.87. Found: C, 58.18; H, 3.84.

***N*-Methyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-sulfonamide (20b)** **3** (1.1 g, 3.31 mmol) was added portionwise to $ClSO_3H$ (1 ml, 15 mmol) and the resultant mixture was stirred at room temperature for 1 h. The mixture was added to an ice-cooled mixture of 25% $MeNH_2$ (20 ml) and THF (20 ml), and the whole was stirred at 0 °C for 1 h and then extracted with EtOAc. The extract was washed with $H_2O$, dried and evaporated. The residue was chromatographed ($CHCl_3$–MeOH, 20:1) over silica gel and the product was recrystallized from EtOH to give **20b** (1.1 g, 77%) as colorless crystals, mp 199—201 °C. IR (Nujol): 3300, 1600, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.63 (3H, s), 3.25 (3H, s), 7.2—8.0 (9H, m). MS $m/z$: 425 ($M^+$). *Anal.* Calcd for $C_{18}H_{16}FNO_4S_3$: C, 50.81; H, 3.79; N, 3.29. Found: C, 50.59; H, 3.78; N, 3.24.

The following compounds were prepared in the same manner as described for **20b**.

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-sulfonamide (**20a**): mp 195—197 °C ($Et_2O$), pale brown crystals. IR (Nujol): 3340, 3250, 1600 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.30 (3H, s), 7.2—8.1 (11H, m). MS $m/z$: 411 ($M^+$). *Anal.* Calcd for $C_{17}H_{14}FNO_4S_3$: C, 49.62; H, 3.43; N, 3.40. Found: C, 50.36; H, 3.53; N, 3.06.

*N,N*-Dimethyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-sulfonamide (**20c**): mp 189—191 °C (EtOH). IR (Nujol): 1600, 1535, 1510 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.79 (6H, s), 3.25 (3H, s), 7.2—8.0 (9H, m). MS $m/z$: 439 ($M^+$). *Anal.* Calcd for $C_{19}H_{18}FNO_4S_3 \cdot 2/3H_2O$: C, 50.54; H, 4.32; N, 3.10. Found: C, 50.25; H, 4.06; N, 3.03.

**4′-[2-(4-Fluorophenyl)-5-(trifluoromethyl)-3-thienyl]methanesulfonanilide (22)** A mixture of **21** (0.49 g, 1.45 mmol)[10] and $MeSO_2Cl$ (0.135 ml, 1.75 mmol) in pyridine (5 ml) was stirred overnight at room temperature. The solvent was evaporated, and the residue was dissolved in THF (5 ml)

and treated with 4 N NaOH (1.5 ml) for 30 min. EtOAc and dilute HCl were added, and the organic layer was separated, washed with brine, dried and evaporated. The residue was chromatographed (toluene–EtOAc, 10 : 1) over silica gel and the product was washed with EtOH to give **22** (0.52 g, 86%) as pale brown crystals, mp 150—152 °C. IR (Nujol): 3320, 1600, 1560, 1510 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.02 (3H, s), 7.1—7.5 (8H, m), 7.85 (1H, s), 9.90 (1H, s). MS *m/z*: 415 ($M^+$), 336. *Anal.* Calcd for $C_{18}H_{13}F_4NO_2S_2$: C, 52.04; H, 3.15; N, 3.37. Found: C, 51.99; H, 3.22; N, 3.20.

**2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene-5-carbonitrile (23)** A mixture of **13a** (4.8 g, 12.8 mmol) and $MeSO_2Cl$ (8.8 g, 76.8 mmol) in pyridine (25 ml) was stirred at 50 °C for 4 h. The mixture was evaporated and the residue was triturated in dilute HCl. The precipitates were collected and recrystallized from EtOH to afford **23** (3.6 g, 79%) as crystals, mp 139—140 °C. IR (Nujol): 2220, 1600, 1510 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.24 (3H, s), 7.1—7.6 (6H, m), 7.91 (2H, d, $J$=8 Hz), 8.24 (1H, s). MS *m/z*: 357 ($M^+$). *Anal.* Calcd for $C_{18}H_{12}FNO_2S_2$: C, 60.56; H, 3.39; N, 3.92. Found: C, 60.68; H, 3.44; N, 3.85.

**2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-nitrothiophene (24)** $HNO_3$ (d = 1.42; 2.6 ml, 41.7 mmol) was added dropwise to a stirred solution of **3** (6.0 g, 18.1 mmol) in $Ac_2O$ (98 ml) at 0 °C. The mixture was stirred at 0 °C for 2 h, treated with $NaHCO_3$ (1 g), and evaporated. A solution of the residue in EtOAc was washed with aqueous $NaHCO_3$, dried and evaporated. The residue was chromatographed (toluene–EtOAc, 20 : 1) over silica gel and the product was recrystallized from EtOH to give **24** (4.4 g, 48%) as yellow crystals, mp 155—156 °C. IR (Nujol): 3100, 1600, 1510 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.28 (3H, s), 7.1—8.1 (8H, m), 8.42 (1H, s). MS *m/z*: 377 ($M^+$). *Anal.* Calcd for $C_{17}H_{12}FNO_4S_2$: C, 54.10; H, 3.21; N, 3.71. Found: C, 54.09; H, 3.57; N, 3.63.

**2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thiophenamine (25)** A mixture of **24** (3.6 g, 9.55 mmol), Fe powder (3.6 g) and $NH_4Cl$ (0.36 g) in EtOH (58 ml) and $H_2O$ (22 ml) was stirred under reflux for 1 h. The insoluble material was removed by filtration and washed with DMF (40 ml). The filtrate was evaporated and the residue was triturated with $H_2O$. The precipitates were collected and recrystallized from EtOH to give **25** (2.7 g, 82%) as a pale brown powder, mp 207—209 °C. IR (Nujol): 3450, 3350, 1600, 1510 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.25 (3H, s), 5.8 (2H, s), 6.8—8.0 (9H, m). MS *m/z*: 347 ($M^+$). *Anal.* Calcd for $C_{17}H_{14}FNO_2S_2 \cdot 1/6H_2O$: C, 58.27; H, 4.12; N, 4.00. Found: C, 57.97; H, 4.27; N, 3.97.

***N*-Methyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thiophenamine (26a) and *N*,*N*-Dimethyl-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thiophenamine (26b)** MeI (3 g, 21.3 mmol) was added to an ice-cooled mixture of **25** (1.85 g, 5.33 mmol) and $K_2CO_3$ (2.5 g, 16 mmol) in DMF (20 ml). The whole was stirred at room temperature for 5 h and poured into ice-$H_2O$. The precipitates were collected and chromatographed (toluene–EtOAc, 4 : 1) over silica gel, and the desired, isolated products were independently recrystallized from EtOH to give **26a** (0.9 g, 58%) and **26b** (0.5 g, 31%). **26a**: mp 183—185 °C. IR (Nujol): 1600, 1515 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.93 (3H, s), 3.06 (3H, s), 6.05 (1H, s), 6.8—7.9 (8H, m). MS *m/z*: 361 ($M^+$). *Anal.* Calcd for $C_{18}H_{16}FNO_2S_2 \cdot 5/9H_2O$: C, 58.20; H, 4.64; N, 3.77. Found: C, 57.87; H, 4.20; N, 3.31. **26b**: mp 130—135 °C (dec.). IR (Nujol): 1600, 1555, 1520 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.97 (6H, s), 3.06 (3H, s), 5.94 (1H, s), 6.9—7.9 (8H, m). MS *m/z*: 375 ($M^+$). *Anal.* Calcd for $C_{19}H_{18}FNO_2S_2$: C, 60.80; H, 4.80; N, 3.73. Found: C, 60.84; H, 4.59; N, 3.57.

**Methyl *N*-{2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thienyl}carbamate (27a)** $ClCO_2Me$ (0.23 ml, 3.02 mmol) in MeCN (1 ml) was added dropwise to a stirred solution of **25** (1.1 g, 3.02 mmol) and pyridine (0.24 ml, 3.02 mmol) in MeCN (8 ml) and THF (10 ml) at −20 °C. The mixture was stirred at 5 °C for 1 h, and EtOAc and $H_2O$ were added. The organic layer was dried and evaporated. The residue was chromatographed (toluene–EtOAc, 10 : 1) over silica gel and the product was recrystallized from EtOH to give **27a** (0.84 g, 69%) as pale red crystals, mp 103—108 °C (dec.). IR (Nujol): 3330, 1720, 1600, 1580, 1540 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.28 (3H, s), 3.80 (3H, s), 6.77 (1H, s), 7.2—8.1 (8H, m), 10.94 (1H, s). MS *m/z*: 405 ($M^+$), 373. *Anal.* Calcd for $C_{19}H_{16}FNO_4S_2$: C, 56.28; H, 3.98; N, 3.45. Found: C, 55.73; H, 3.82; N, 3.29.

Ethyl *N*-{2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thienyl}carbamate (**27b**): This compound was prepared in the same manner as described for **27a**: mp 70—75 °C (hexane–EtOAc), pale brown powder. IR (Nujol): 3330, 1720, 1580, 1530 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.27 (3H, t, $J$=7 Hz), 3.22 (3H, s), 4.19 (2H, q, $J$=7 Hz), 6.67 (1H, s), 7.1—7.9 (8H, m), 10.91 (1H, s). MS *m/z*: 419 ($M^+$), 373. *Anal.* Calcd for $C_{20}H_{18}FNO_4S_2$: C, 57.27; H, 4.32; N, 3.36. Found: C, 57.55; H, 4.65; N, 3.06.

*N*-{2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-thienyl}methanesulfonamide (**27c**): This compound was prepared in the same manner as described for **22**: mp 87—90 °C (toluene–EtOAc), pale brown powder. IR (Nujol): 3200, 1600, 1510 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.17 (3H, s), 3.26 (3H, s), 6.98 (1H, s), 7.1—8.0 (8H, m), 10.4 (1H, br s). MS *m/z*: 425 ($M^+$), 346. *Anal.* Calcd for $C_{18}H_{16}FNO_4S_3$: C, 50.81; H, 3.79; N, 3.29. Found: C, 50.55; H, 3.95; N, 3.21.

**3-[4-(Methylthio)phenyl]-2-(4-nitrophenyl)acrylic Acid (29)** A mixture of **28** (2.0 g, 13.2 mmol), 4-nitrophenylacetic acid (2.4 g, 13.2 mmol) and NaOMe (0.8 g, 14.8 mmol) in $Ac_2O$ (10 ml) was refluxed for 24 h. $CHCl_3$ and aqueous $NaHCO_3$ were added, and the aqueous layer was separated, acidified with HCl and extracted with EtOAc. The extract was washed with $H_2O$, dried and evaporated, and the residue was washed with EtOH to afford **29** (1.6 g, 42%), mp 217—219 °C (dec.).[14] IR (Nujol): 1690, 1670, 1610, 1590, 1515 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.42 (3H, s), 6.98 (2H, d, $J$=8 Hz), 7.10 (2H, d, $J$=8 Hz), 7.42 (2H, d, $J$=8 Hz), 7.83 (1H, s), 8.25 (2H, d, $J$=8 Hz), 12.8 (1H, s). MS *m/z*: 315 ($M^+$).

**2-[4-(Methylthio)phenyl]-1-(4-nitrophenyl)ethanone (30)** A mixture of **29** (1.6 g, 5.08 mmol) and $PCl_5$ (1.1 g, 5.59 mmol) in $CH_2Cl_2$ (20 ml) was stirred at room temperature for 1 h. The solvent was evaporated to give the acryloyl chloride as a solid.

A solution of the above chloride in $Me_2CO$ was added dropwise to an ice-cooled mixture of $NaN_3$ (0.5 g, 7.62 mmol), $H_2O$ (10 ml) and $Me_2CO$ (10 ml); the pH of the reaction mixture was kept at 7.5 by addition of aqueous $Na_2CO_3$. The whole was stirred at room temperature for 2 h and extracted with EtOAc. The extract was washed with brine, dried and evaporated to afford the acryloyl azide as a solid.

A mixture of the above azide (2.0 g), AcOH (20 ml) and $H_2O$ (10 ml) was refluxed for 3 h and poured into ice-$H_2O$. The precipitates were collected and washed with $H_2O$ to give **30** (1.1 g, 75%), mp 105—107 °C.[14] IR (Nujol): 1695, 1600, 1520 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.47 (3H, s), 4.28 (2H, s), 7.1—7.3 (4H, m), 8.13 (2H, d, $J$=8 Hz), 8.27 (2H, d, $J$=8 Hz). MS *m/z*: 287 ($M^+$).

Ethyl 3-[4-(Methylthio)phenyl]-2-(4-nitrophenyl)thiophene-5-carboxylate (**31**): This compound was prepared from **30** in the same manner as described for **10**: Oil.[14] IR (Nujol): 1710, 1600, 1520 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.30 (3H, t, $J$=7 Hz), 2.48 (3H, s), 4.20 (2H, q, $J$=7 Hz), 7.1—7.3 (4H, m), 7.47 (2H, d, $J$=8 Hz), 7.82 (1H, s), 8.18 (2H, d, $J$=8 Hz). MS *m/z*: 399 ($M^+$).

3-[4-(Methylthio)phenyl]-2-(4-nitrophenyl)thiophene-5-carboxylic Acid (**32**): This compound was prepared from **31** in the same manner as described for **19**: mp 190—195 °C (dec.) ($H_2O$).[14] IR (Nujol): 1690, 1595, 1515 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.47 (3H, s), 6.6—8.3 (9H, m). MS *m/z*: 371 ($M^+$).

3-[4-(Methylthio)phenyl]-2-(4-nitrophenyl)thiophene (**33**): This compound was prepared from **32** in the same manner as described for **9**: mp 135—140 °C (EtOAc), pale brown solid.[14] $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.47 (3H, s), 6.8—8.2 (10H, m).

**5-Bromo-3-[4-(methylthio)phenyl]-2-(4-nitrophenyl)thiophene (34)** Following the procedure reported previously,[8] **33** was treated with $Br_2$ to give **34** (90% yield) as a pale brown powder, mp 230 °C (dec.) (EtOAc).[14] IR (Nujol): 1600, 1515 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.50 (3H, s), 7.1—8.2 (9H, m). MS *m/z*: 407, 405.

**5-Bromo-2-[4-(formylamino)phenyl]-3-[4-(methylthio)phenyl]thiophene (35)** A mixture of $Ac_2O$ (3.3 g, 32.3 mmol) and $HCO_2H$ (1.5 g, 32.6 mmol) was stirred at 50 °C for 30 min. 2-(4-Aminophenyl)-5-bromo-3-[4-(methylthio)phenyl]thiophene (4.0 g, 10.6 mmol), which was obtained from **34** in the same manner as described for **25**,[10] was added to the mixture and the whole was stirred at room temperature for 2 h, then poured into ice-$H_2O$. The precipitates were collected and washed with $H_2O$ to give **35** (3.8 g, 88%), mp 150—160 °C (dec.).[14] IR (Nujol): 1690, 1600 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.48 (3H, s), 6.8—7.7 (9H, m), 8.29 (1H, s), 9.40 (1H, s). MS *m/z*: 405, 403.

**5-Bromo-2-[4-(*N*-methylformylamino)phenyl]-3-[4-(methylthio)phenyl]thiophene (36)** NaH (60%; 0.45 g, 11.3 mmol) was added to an ice-cooled solution of **35** (3.8 g, 9.41 mmol) in DMF (50 ml). The mixture was stirred at 5 °C for 30 min, and then MeI (3 g, 26.8 mmol) was added. The whole was stirred for 2 h and evaporated. Ice-$H_2O$ was

added to the residue, and the precipitates were collected and washed with $H_2O$ to give **36** (3.8 g, 97%), mp 150—155 °C (dec.).[14] IR (Nujol): 1685, 1600 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.48 (6H, s), 6.9—7.6 (9H, m), 8.52 (1H, s). MS *m/z*: 419, 417.

**5-Bromo-2-[4-(formylamino)phenyl]-3-[4-(methylsulfinyl)phenyl]thiophene (37)** A mixture of **35** (1.0 g, 2.48 mmol) and mCPBA (0.5 g, 2.32 mmol) in $CH_2Cl_2$ (80 ml) was stirred at 0 °C for 1 h. The mixture was washed successively with aqueous $NaHCO_3$ and $H_2O$, dried and evaporated. The residue was chromatographed ($CH_2Cl_2$–$Me_2CO$, 5 : 1) over silica gel to give **37** (1.0 g, 96%) as a pale yellow powder, mp 130—133 °C (dec.). IR (Nujol): 3250, 1690, 1600, 1515 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.76 (3H, s), 6.9—8.1 (10H, m), 8.36 (1H, s). MS *m/z*: 421, 419. *Anal.* Calcd for $C_{18}H_{14}BrNO_2S_2$: C, 51.43; H, 3.33; N, 3.33. Found: C, 51.56; H, 3.70; N, 3.15.

**5-Bromo-2-[4-(methylamino)phenyl]-3-[4-(methylsulfinyl)phenyl]thiophene (38)** A mixture of 5-bromo-2-[4-(*N*-methylformylamino)phenyl]-3-[4-(methylsulfinyl)phenyl]thiophene (2.0 g, 4.61 mmol), which was obtained from **36** in the same manner as described for **37**,[10] and concentrated HCl (10 ml) in MeOH (100 ml) and THF (20 ml) was stirred at room temperature for 2 h. The mixture was evaporated and the residue was triturated in aqueous $NaHCO_3$ to give a powder. The crude powder was chromatographed ($CHCl_3$–MeOH, 25 : 1) over silica gel to afford **38** (0.5 g, 29%), mp 160—164 °C (dec.). IR (Nujol): 3350, 1610, 1520 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.74 (3H, s), 2.76 (3H, s), 6.4—7.7 (9H, m). MS *m/z*: 407, 405. *Anal.* Calcd for $C_{18}H_{16}BrNOS_2 \cdot H_2O$: C, 50.94; H, 4.28; N, 3.30. Found: C, 50.66; H, 3.82; N, 3.14.

**Biological Methods. AA, CIA, Randall-Selitto and COX Assays** These experiments were carried out according to the procedures described in previous reports.[3,11]

**Effects on the DTH Response to Bovine Type II Collagen in Mice** Seven male DBA/1 mice were used per group. The mice were sensitized at the tail base with 125 $\mu$g of type II collagen emulsified in complete Freund's adjuvant containing *Mycobacterium tuberculosis* strain H37Rv (Wako Pure Chemical Industries Ltd., Osaka, Japan). Two weeks later, a 0.04 ml challenge dose of 2.5 mg/ml type II collagen in phosphate-buffered saline(PBS) was injected into the plantar region of the right hind foot, and 0.04 ml of PBS into the left hind foot to act as a control. Twenty-four hours after challenge, the volumes of the two hind feet were measured with a volume meter (Muromachi MK-550). The drug was administered orally on consecutive days (except holidays), starting from the sensitization. Data were expressed as % inhibition compared with the vehicle control for each study.

**Effects on the Production of TNF-$\alpha$ (*in Vitro*)** Human PBMC were isolated from heparinized venous blood from 2 healthy adult male volunteers. PBMC ($1.0 \times 10^6$ cells in 1.0 ml culture medium/well) were stimulated with LPS (Sigma, St. Louis, MO) 10 $\mu$g/ml for 24 h at 37 °C in the presence or absence of a drug. The PBMC culture supernatants were assayed for TNF-$\alpha$ levels by enzyme-linked immunosorbent assay (ELISA). The effects of the drug on TNF-$\alpha$ production were expressed as % inhibition compared with values obtained in the absence of the drug.

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