Studies on Anti-inflammatory Agents. IV.[1] Synthesis and Pharmacological Properties of 1,5-Diarylpyrazoles and Related Derivatives

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A series of novel 1,5-diarylpyrazole derivatives was synthesized and tested for anti-inflammatory and analgesic activities to develop anti-inflammatory agents with fewer side effects than existing nonsteroidal anti-inflammatory drugs. The structure–activity relationships in this series were extensively studied. Electron-withdrawing substituents such as CN and CF_3 were optimal at the 3-position of the pyrazole ring. Replacement of these substituents with bulky ones gave less active compounds. The 4-(methylsulfonyl)phenyl group seemed to be the optimal group at the 5-position of the pyrazole ring. The most potent compound was 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole-3-carbonitrile (19a), with oral ED_{50} values of 0.030 and 0.47 mg/kg on adjuvant-induced arthritis and collagen-induced arthritis, respectively, and an ED_{30} value of 7.4 mg/kg in the yeast-induced hyperalgesia (Randall–Selitto) assay. Compound 19a also showed potent inducible cyclooxygenase (COX-2)-inhibitory activity (IC_{50} = 0.24 μM) with no COX-1 inhibition even at 100 μM.

Key words anti-inflammatory agent; 1,5-diarylpyrazole; cyclooxygenase; structure–activity relationship; synthesis

Nonsteroidal anti-inflammatory drugs (NSAIDs), represented by indomethacin and aspirin, have been demonstrated to be useful for relief of the symptoms of a number of arthritic conditions, such as rheumatoid arthritis. It has been pointed out, however, that the adverse effects of NSAIDs, namely gastrointestinal (GI) irritation and suppression of renal function, have to be ameliorated.[2] Recently, it has been shown that cyclooxygenase (COX) exists in two isoforms, termed COX-1 and COX-2.[3] It is believed that the anti-inflammatory effects of NSAIDs are mediated by inhibition of COX-2, while the side effects seem to be caused by inhibition of COX-1. A selective COX-2 inhibitor may be able to provide the desired therapeutic profile of an anti-inflammatory drug without the adverse effects commonly associated with COX-1 inhibition in the GI tract and kidney.[4]

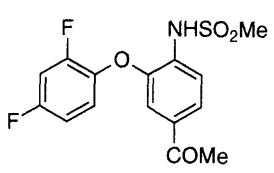
We have already reported on some methanesulfonanilide derivatives such as FK3311, which is a well-balanced anti-inflammatory, analgesic, and antipyretic agent that does not cause GI irritation.[5] Structurally distinct DuP697 (**1**) was also reported to be a potent anti-inflammatory drug which did not cause stomach ulcers or alter renal blood flow.[6] We were interested in the exceptionally strong inhibitory activity of **1** in the rat adjuvant-induced arthritis model. However, the 5-bromothiophene structure in **1** is biologically unstable and might have toxic effects, such as mutagenicity.[7]

From among the isosteric ring systems, the 3-bromo-1,5-diphenylpyrazole skeleton was found to be more stable and to have a steric conformation very similar to that of the 5-bromo-2,3-diphenylthiophene skeleton through a comparison of their frontier orbitals and three-dimensional structures by MO calculation.[8] On the basis of this finding, we designed novel 1,5-diarylpyrazole derivatives, expecting to achieve superior pharmacological and safety profiles. This paper describes the syntheses and pharmacological activities of various 1,5-diarylpyrazoles and related derivatives, and the identification of 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**19a**) as the optimal compound.

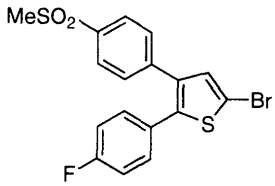
Chemistry

Compounds **7**, **9**, **10** and **11** were synthesized *via* the 3-pyrazolamine derivative **5**, as shown in Chart 1. Compound **5** was prepared from 4-(methylthio)benzaldehyde **2** by Wittig reaction, pyrazoline ring formation with 4-fluorophenylhydrazine, and selective oxidation with MnO_2, according to the method reported by Appleton *et al.*[9] The bromo derivative **6** was obtained by diazotization of **5** and subsequent decomposition of the obtained diazonium salt in the presence of CuBr. A similar reaction using *tert*-BuONO and $CuCl_2$ gave only the reduced product **8**. Oxidation of the sulfides (**6**, **8**, **5**) with peracetic acid or *m*-chloroperbenzoic acid (mCPBA) afforded the sulfones (**7**, **9**, **10**). Compounds **11** were prepared from **10** by treatment with the appropriate acylating agents.

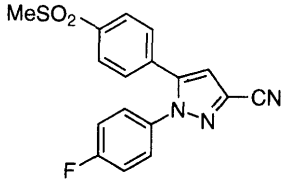
Syntheses of compounds **16**, **18** and **19** are outlined in



FK3311



DuP697 (**1**)



19a

Fig. 1

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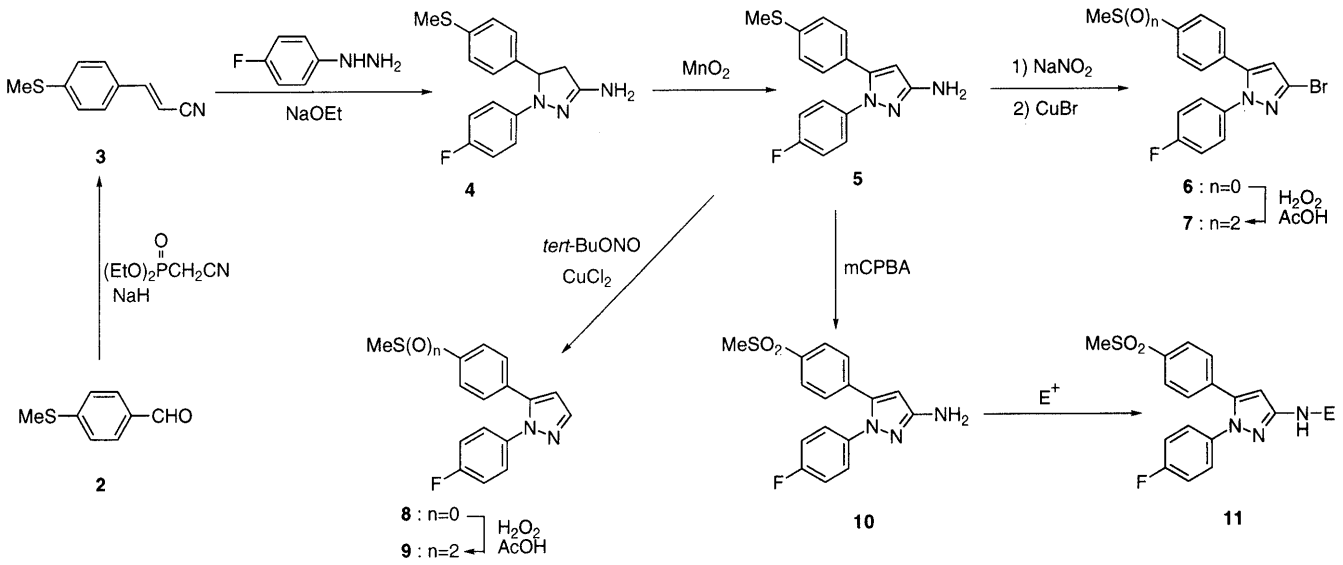


Chart 1

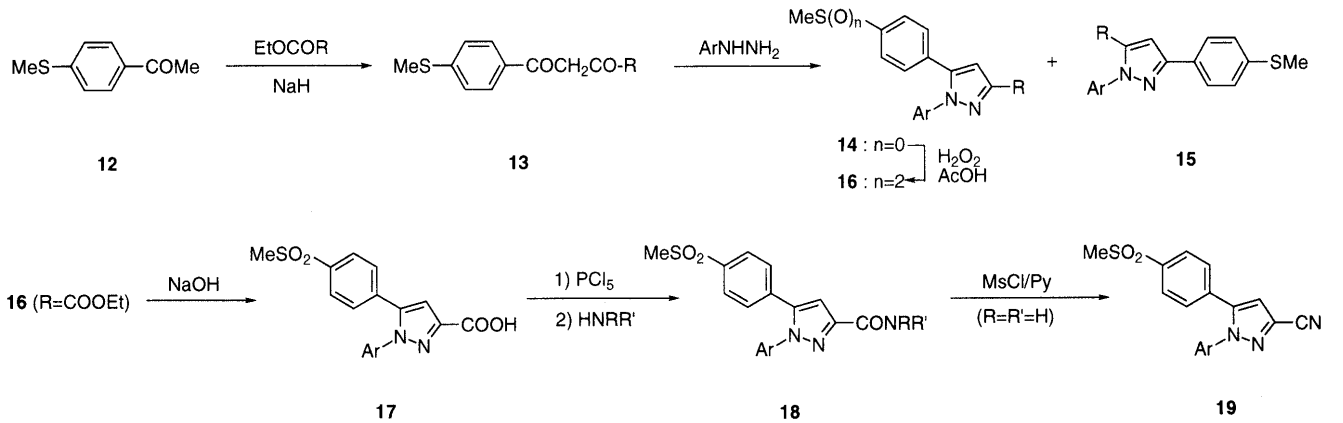


Chart 2

Chart 2. The 1,3-diketones **13** were prepared from the acetophenone **12** and the appropriate esters in the presence of NaH. Compounds **13** and the appropriate hydrazines were heated in EtOH to afford the desired 1,5-diarylpyrazoles **14** as the major products (80—90% yield) and 1,3-diarylpyrazoles **15** as the minor products (5—10% yield).[10] The structural discrimination between **14a** and **15a** (Ar = 4-FPh, R = COOEt) was finally achieved by the derivation of **14a** to **19a** and the X-ray crystallographic analysis of **19a**, as shown in Fig. 2. The treatment of compounds **14** with peracetic acid gave the sulfones **16**. The esters **16** (R = COOEt) were hydrolyzed and treated with PCl_5 to afford the acid chlorides, which were allowed to react with the appropriate amines to give the amides **18**. The nitriles **19** were obtained by dehydration of **18** (R = R′ = H) with methanesulfonyl chloride and pyridine.

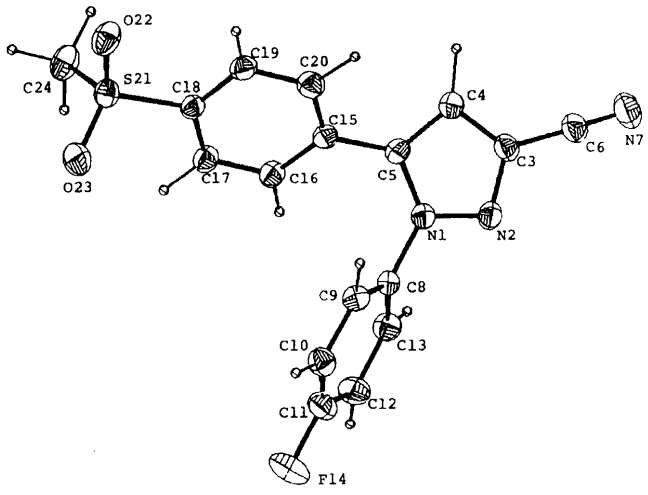


Fig. 2

Compounds **20**, **23**, **24**, **25** and **26a, d** were obtained as shown in Chart 3. The nitrile **19a** was treated with azide salt to give the tetrazole **20**. Treatment of the acetophenone **12** with NaH and CS_2 and subsequent methylation gave the 3,3-bis(methylthio)-2-propen-1-one **21**, which was treated with the hydrazine, followed by oxidation of the methylthio moieties to afford the methylsulfonyl derivative **23**. Compounds **25a—d** were prepared by alkylation of the amino derivative **24**, which was obtained by reduction of the nitro derivative **19j**. The sulfoxide **26a** was synthesized by oxidation of the sulfide **26b** with sodium periodate. The methylamino derivative **26d** was prepared by acidic removal of the formyl group in **27**, which was

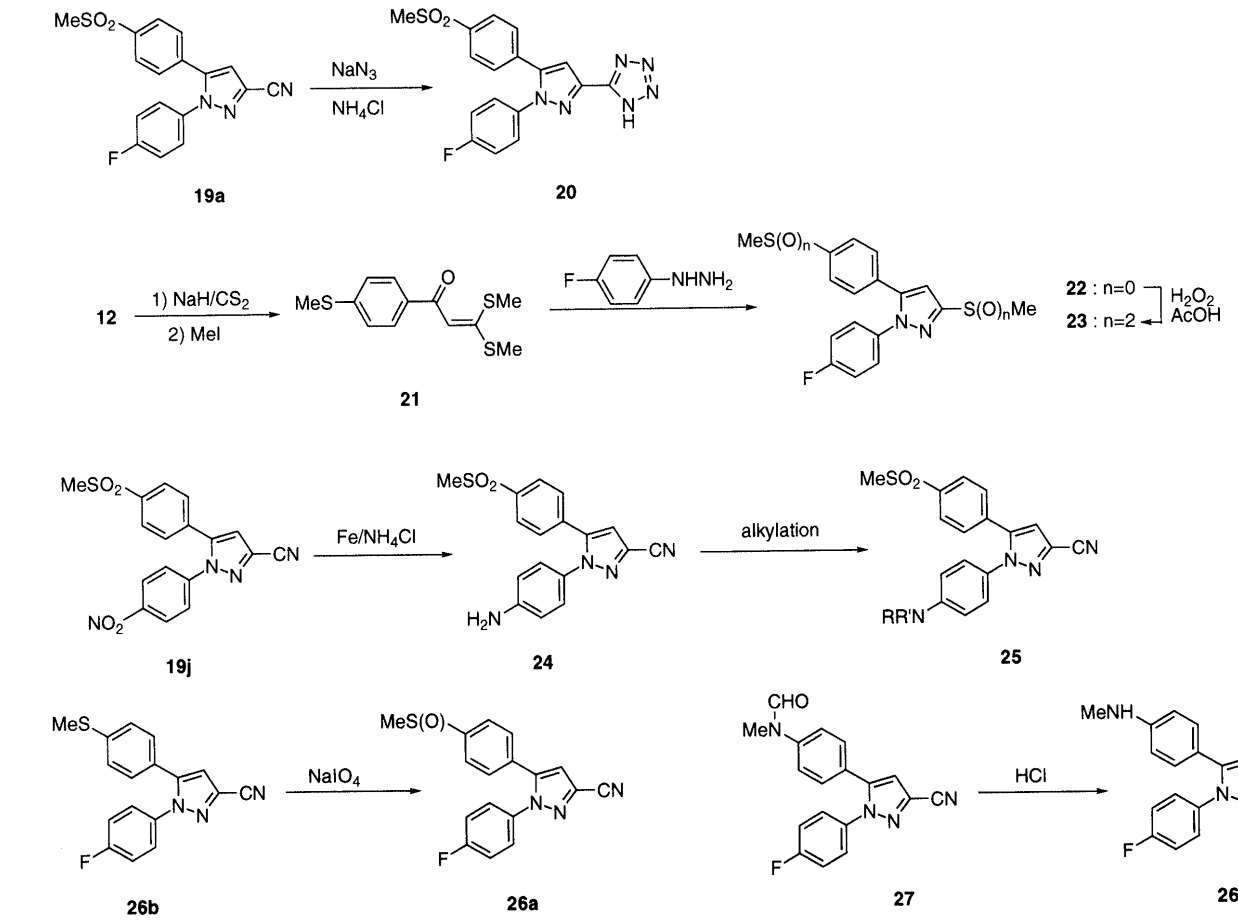


Chart 3

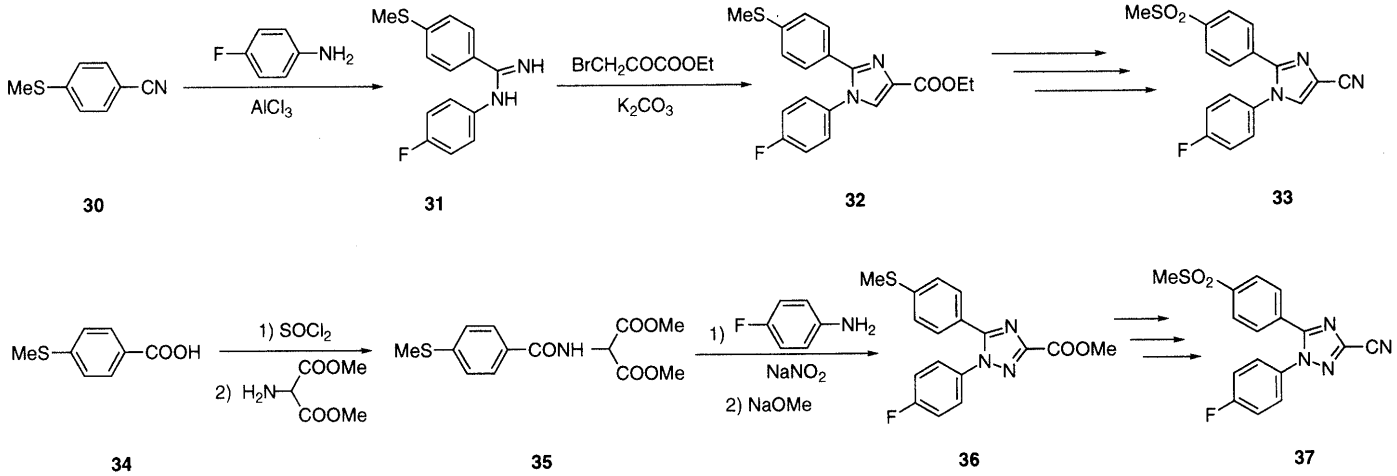


Chart 4

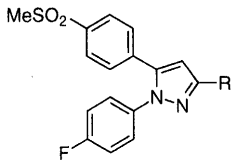
obtained according to the literature.[11] Compounds **26b**, **c**, **e**—**h**, **28** and **29** (Tables 3, 4) were synthesized following the procedure described for **19a** (Chart 2).

Syntheses of the **19a**-related nitrile compounds **33** and **37** are summarized in Chart 4. The imidazole **32** was synthesized by cyclization of the amidine **31** with bromopyruvate in 60% yield, following the reported synthetic route.[12] The triazole **36** was obtained from 4-(methylthio)benzoic acid **34** by chlorination with $SOCl_2$, amidation with aminomalonate, and cyclization with diazonium salt (*via* **35**). The desired products **33** and **37** were prepared from **32** or **36** by hydrolysis, amidation, dehydration, and oxidation in the usual manner.

Pharmacological Results and Discussion

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

Table 1. 3-Substituted-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazoles



No.	R	Adjuvant arthritis % inhibition[a] (3.2 mg/kg, *p.o.*)	Randall-Selitto relative potency[b] (10 mg/kg, *p.o.*)
7	Br	104[c]	1.03
9	H	81[c]	1.04
10	NH_2	65[c]	1.02
11a	NHCOMe	58[c]	1.04
11b	NHCOOMe	24	1.23[c]
16b	CF_3	96[c,e]	1.17[c]
16c	CHF_2	46[d]	1.07
16d	CH_2F	30	1.09
18a	$CONH_2$	65[c]	1.14[g]
18b	CONHMe	67[c,f]	1.25[c,g]
18c	$CONMe_2$	76[c,f]	1.18[g]
18d		18	1.09
19a	CN	93[c,e]	1.27[c]
20	5-Tet[h]	75[c]	1.04
23	SO_2Me	57[c]	1.12

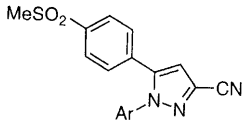
a) Uninjected paw. *b*) Ratio of the pain threshold in the treated *vs.* control animals. *c*) $p<0.01$, *d*) $p<0.05$, significant difference from control. *e*) 1 mg/kg. *f*) 10 mg/kg. *g*) 32 mg/kg. *h*) 5-Tetrazolyl.

results are summarized in Tables 1—4.

From the structure–activity relationships (SARs) of **1** and the related thiophene derivatives, 4-(methylsulfonyl)-phenyl and 4-fluorophenyl groups seemed to play an important role in the strong anti-inflammatory activity of compound **1**.[13] As a first step in the SAR studies, we therefore designed a series of 3-substituted pyrazoles having 4-fluorophenyl and 4-(methylsulfonyl)phenyl groups at the 1 and 5 positions, respectively, as depicted in Table 1. The bromo derivative (**7**) showed very potent anti-inflammatory activity. This suggested the usefulness of the pyrazole ring as a surrogate of the thiophene ring. The sterically small unsubstituted (**9**) and amino (**10**), and electron-withdrawing trifluoromethyl (**16b**), carbamoyl (**18a—c**), cyano (**19a**), tetrazolyl (**20**) and sulfonyl (**23**) derivatives also showed fairly potent anti-inflammatory activities. On the other hand, bulky substituents (*e.g.*, **11b, 18d**) and less electron-attracting or less lipophilic substituents (*e.g.*, **16c, d**) gave less active compounds. Finally, the maximum anti-inflammatory and analgesic activities were achieved with the cyano derivative (**19a**). We chose **19a** as a lead compound for further modification.

The results of the structural modification of the aryl group (Ar) at the 1 position of the pyrazole ring are summarized in Table 2. Removal of the 4-fluoro substituent in **19a** resulted in some loss of the activities (**19b**). The 2- and 3-fluorophenyl (**19c, d**) and 2,4-difluorophenyl (**19e**) analogs showed fairly potent anti-inflammatory activities. Unfortunately, analgesic activities of these analogs were not as favorable as that

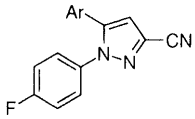
Table 2. 1-Aryl-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitriles



No.	Ar	Adjuvant arthritis % inhibition[a] (3.2 mg/kg, *p.o.*)	Randall-Selitto relative potency[b] (10 mg/kg, *p.o.*)
19b	Ph	64[c]	1.03
19c	2-FPh	80[c]	1.18[c]
19d	3-FPh	70[c]	1.02
19e	2,4-F_2Ph	94[c]	1.09
19f	4-MePh	58[c]	1.05
19g	4-MeOPh	80[c]	1.05
19h	4-MeSPh	67[c]	1.21[c]
19i	4-NCPh	32	NT
19j	4-NO_2Ph	28	NT
24	4-H_2NPh	56	1.16[d]
25a	4-MeNHPh	68[c]	1.27[c]
25b	4-EtNHPh	82[c]	1.05
25c	4-Me_2NPh	67[c]	NT
25d	4-Et_2NPh	74[c]	1.02

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. NT: not tested.

Table 3. 5-Aryl-1-(4-fluorophenyl)pyrazole-3-carbonitriles



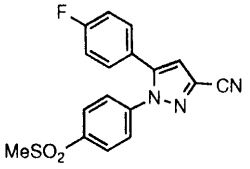
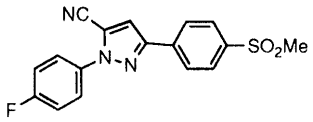
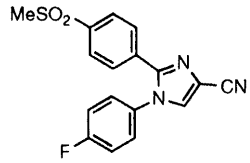
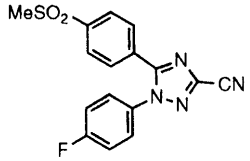
No.	Ar	Adjuvant arthritis % inhibition[a] (3.2 mg/kg, *p.o.*)	Randall-Selitto relative potency[b] (10 mg/kg, *p.o.*)
26a	4-MeS(O)Ph	87[c]	1.44[c]
26b	4-MeSPh	89[c]	1.12[c]
26c	4-MeOPh	56[d]	NT
26d[e]	4-MeNHPh	36	NT
26e	4-MeCONHPh	34	1.02
26f	4-NCPh	38	1.07
26g	4-MeCOPh	25	1.13
26h	5-$MeSO_2$-2-Th[f]	53[c]	1.13

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. *e*) HCl salt. *f*) 5-(methylsulfonyl)-2-thienyl. NT: not tested.

of the lead compound **19a**. We therefore focused our attention on the 4-substituted phenyl analogs. Replacing the 4-fluoro substituent in **19a** with electron-donating moieties such as methyl, methoxy, methylthio or methylamino afforded compounds (**19f—h, 25a—d**) with good potency for inhibition of adjuvant arthritis. On the other hand, electron-withdrawing cyano and nitro substituents gave less active compounds (**19i, j**). The anti-inflammatory activity of compound **25a** was inferior to that of **19a**, but the discovery of a structure with excellent analgesic potency and hydrophilic character was utilized in the following study.[14]

It was suggested that the 4-(methylsufonyl)phenyl group played an essential role in the interaction between **1** and the target enzyme, COX, from the SARs of **1**-related

Table 4. Analogs of Compound **19a**

No.	Structure	Adjuvant arthritis % inhibition[a] (3.2 mg/kg, *p.o.*)	Randall-Selitto relative potency[b] (10 mg/kg, *p.o.*)
28		81[c]	1.12[d]
29		36	1.17[d]
33		5	1.05
37		−14	1.08

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.

derivatives, as mentioned above.[15] We conducted a brief modification study of the 5-aryl part, as depicted in Table 3. Only sulfoxide and sulfide analogs (**26a, b**) showed activities comparable to the parent **19a**. The sulfoxide **26a** was especially attractive in terms of its potent analgesic activity. However, **26a** could be metabolically converted to the sulfone **19a**, existed as a mixture of two optical isomers, and thus was not further evaluated.

Various analogs structurally related to compound **19a** were synthesized and tested, as summarized in Table 4. Among the positional isomers (**28**, **29**), compound **28**, structurally very similar to **19a**, showed moderate activity, which was inferior to that of **19a**. The three-dimensional structures of the imidazole and triazole derivatives (**33**, **37**) maintain a high similarity to that of the pyrazole **19a**, but replacement of pyrazole with these skeletons resulted in loss of anti-inflammatory activity. Compounds **33** and **37** were also shown to be much less active than **19a** in COX inhibitory assay (*in vitro*).[16] These results may be attributable to their unfavorable charge distribution in comparison with **19a**.

Based on the above evaluation, **19a** (FR123826) was selected for further development. The IC_{50} values towards both constitutive (COX-1) and inducible (COX-2) forms of human recombinant COX are compared in Table 5. Compound **19a** showed COX-2-inhibitory activity comparable to that of indomethacin ($IC_{50}=0.24$ and 0.61 μM, respectively) with no COX-1 inhibition even at 100 μM. This finding demonstrates that **19a** is a highly selective COX-2 inhibitor.

The *in vivo* data are summarized in Table 6. Compound

Table 5. Comparison of Compound **19a** with Reference Compounds (*in Vitro*)

Compound	IC_{50}, μM		Selectivity[a]
	COX-1	COX-2	
19a	>100	0.24	>416
DuP697	11	0.020	550
Indomethacin	0.23	0.61	0.38

a) Selectivity = IC_{50}(COX-1)/IC_{50}(COX-2).

Table 6. Comparison of Compound **19a** with Reference Compounds (*in Vivo*)

	19a	DuP697	Indomethacin
Adjuvant arthritis[a]			
ED_{50} (mg/kg, *p.o.*)[b]	0.030	0.085	0.15
UD_{50} (mg/kg, *p.o.*)[c]	>10	>3.2	0.069
Safety index[d]	>333	>38	0.46
Collagen arthritis[e]			
ED_{50} (mg/kg, *p.o.*)	0.47	4.0	0.68
Randall-Selitto[a]			
ED_{30} (mg/kg, *p.o.*)	7.4	1.3	3.4

a) In rats. *b*) Uninjected paw. *c*) The median dose for production of GI lesions. *d*) UD_{50}/ED_{50}. *e*) Type II collagen-induced arthritis in mice.

19a was more potent than the reference compounds (DuP697 and indomethacin) in two representative chronic arthritis models, namely adjuvant arthritis and collagen-induced arthritis ($ED_{50}=0.030$ and 0.47 mg/kg, respectively). Compound **19a** also showed good analgesic activity and no ulcerogenicity, as expected from the *in vitro* COX-2 selectivity. These data suggest that selective COX-2 inhibitors such as **19a** may represent a new generation of NSAIDs useful for the treatment of various inflammatory diseases such as rheumatoid arthritis.

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 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).

3-[4-(Methylthio)phenyl]acrylonitrile (3) A solution of diethyl cyanomethylphosphonate (5.3 ml, 32.9 mmol) in tetrahydrofuran (THF) (10 ml) was added dropwise to an ice-cooled mixture of NaH (60% in mineral oil; 1.3 g, 32.9 mmol) in THF (40 ml). The mixture was stirred at 5 °C for 15 min, then a solution of **2** (5 g, 32.9 mmol) in THF (10 ml) was added to it at 5 °C. The whole was stirred at room temperature for 5 h, diluted with EtOAc, and washed with H_2O. The organic layer was dried and concentrated *in vacuo*. The residue was washed with a small amount of Et_2O to give **3** (4.7 g, 82%) as a pale brown powder.[17] IR (Nujol): 2220, 1615, 1590, 1490 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.51 (3H, s), 6.40 (1H, d, $J=17$ Hz), 7.2—7.7 (5H, m). MS *m/z*: 175 (M^+).

1-(4-Fluorophenyl)-4,5-dihydro-5-[4-(methylthio)phenyl]-3-pyrazolamine (4) 4-Fluorophenylhydrazine hydrochloride (4 g, 24.6 mmol) was added to a solution of Na (1.13 g, 49.2 mmol) in EtOH (50 ml) and the mixture was refluxed for 1 h. It was cooled, then **3** (4.3 g, 24.6 mmol) was added and the resulting mixture was refluxed overnight. EtOAc and H_2O were added and the organic layer was separated, dried, and concentrated. The oily residue (7.6 g) was chromatographed (toluene–EtOAc, 2:1) over silica gel (76 g) to afford **4** (5 g, 68%) as a brown solid.[17] ^{1}H-NMR (DMSO-d_6) δ: 2.44 (3H, s), 4.8—5.0 (1H, m), 5.74

(2H, s), 6.6—7.5 (10H, m). MS *m/z*: 301 (M^+).

1-(4-Fluorophenyl)-5-[4-(methylthio)phenyl]-3-pyrazolamine (5) A mixture of **4** (1 g, 3.3 mmol) and MnO_2 (1.16 g, 13.3 mmol) in CH_2Cl_2 (100 ml) was stirred at room temperature for 2 h. The insoluble material was removed by filtration and the filtrate was concentrated to dryness. The residue (1g) was chromatographed ($CHCl_3$–EtOAc, 5 : 1) over silica gel (16 g) to afford **5** (0.64 g, 65%) as a pale brown powder.[17] IR (Nujol): 3400, 1600, 1565, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.46 (3H, s), 4.97 (2H, s), 5.82 (1H, s), 7.0—7.3 (8H, m). MS *m/z* : 299 (M^+).

3-Bromo-1-(4-fluorophenyl)-5-[4-(methylthio)phenyl]pyrazole (6) A solution of $NaNO_2$ (0.26 g, 4.33 mmol) in H_2O (0.3 ml) was added to an ice-salt-cooled mixture of **5** (1 g, 3.34 mmol), MeCN (1 ml), concentrated H_2SO_4 (0.6 ml), and H_2O (1.6 ml). The resultant mixture was stirred at 0 °C for 30 min and added portionwise to a mixture of CuBr (645 mg, 4.50 mmol), NaBr (582 mg, 5.65 mmol), concentrated HBr (1.7 ml), and H_2O (3 ml) at 80 °C. The whole was stirred at 80 °C for 30 min and extracted with toluene. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was chromatographed (toluene) over silica gel (10 g) and the product was recrystallized from hexane–EtOH to give **6** (0.35 g, 29%), mp 98—99 °C. IR (Nujol): 1600, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 6.49 (1H, s), 6.9—7.3 (8H, m). MS *m/z*: 364 (M^+). *Anal.* Calcd for $C_{16}H_{12}BrFN_2S$: C, 52.89; H, 3.33; N, 7.71. Found: C, 52.90; H, 3.31; N, 7.61.

3-Bromo-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (7) A mixture of **6** (30 mg, 0.0826 mmol) and 30% H_2O_2 (0.1 ml, 0.833 mmol) in AcOH (2 ml) was stirred at 60 °C for 2 h. The solvent was evaporated and the residue was recrystallized from EtOH to afford **7** (25 mg, 77%) as crystals, mp 185—186 °C. IR (Nujol): 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.24 (3H, s), 7.03 (1H, s), 7.2—8.0 (8H, m). MS *m/z*: 396 (M^+). *Anal.* Calcd for $C_{16}H_{12}BrFN_2O_2S$: C, 48.61; H, 3.06; N, 7.09. Found: C, 48.87; H, 3.06; N, 6.73.

1-(4-Fluorophenyl)-5-[4-(methylthio)phenyl]pyrazole (8) A mixture of **5** (3 g, 10 mmol), $CuCl_2$ (1.6 g, 12 mmol), and *tert*-butyl nitrile (1.14 g, 11.1 mmol) in MeCN (50 ml) and dioxane (20 ml) was stirred at room temperature for 4 h. The insoluble material was removed by filtration and the filtrate was diluted with EtOAc, washed with dilute HCl, dried, and evaporated *in vacuo*. The residue (3.8 g) was chromatographed (toluene–EtOAc, 10 : 1) over silica gel to afford **8** (1.4 g, 48%) as a brown oil.[17] IR (Film): 1600, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 6.48 (1H, d, J=1.8 Hz), 6.9—7.4 (8H, m), 7.70 (1H, d, J=1.8 Hz). MS *m/z*: 284 (M^+).

1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (9) Following the procedure described for compound **7**, the sulfide **8** was oxidized to the sulfone **9**, mp 110—112 °C (EtOH–isopropyl ether). IR (Nujol): 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (3H, s), 6.83 (1H, d, J=1.9 Hz), 7.2—8.0 (9H, m). MS *m/z*: 316 (M^+). *Anal.* Calcd for $C_{16}H_{13}FN_2O_2S$: C, 60.74; H, 4.14; N, 8.86. Found: C, 60.59; H, 4.33; N, 8.71.

1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-pyrazolamine (10) mCPBA (18.1 g, 83.6 mmol) was added portionwise to an ice-cooled solution of **5** (10 g, 33.4 mmol) in CH_2Cl_2 (240 ml). The mixture was stirred at 5 °C for 1 h, and EtOAc and aqueous $NaHCO_3$ were added. The organic layer was separated, washed with aqueous $NaHCO_3$, dried, and evaporated. The residue was chromatographed (toluene–EtOAc, 2 : 1) over silica gel and the product was recrystallized from EtOH to give **10** (4.3 g, 39%) as off-white crystals, mp 178—181 °C. IR (Nujol): 3450, 3320, 3200, 1640, 1600, 1575, 1560, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.23 (3H, s), 5.08 (2H, s), 5.99 (1H, s), 7.1—7.5 (6H, m), 7.88 (2H, d, J=8 Hz). MS *m/z*: 331 (M^+). *Anal.* Calcd for $C_{16}H_{14}FN_3O_2S \cdot 1/5EtOH$: C, 57.84; H, 4.50; N, 12.34. Found: C, 58.45; H, 4.57; N, 11.97.

***N*-{1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-pyrazolyl}acetamide (11a)** A mixture of **10** (0.7 g, 2.11 mmol) and Ac_2O (0.22 ml, 2.33 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 3 h and then concentrated *in vacuo*. The residue was chromatographed (toluene–EtOAc, 2 : 1) over silica gel and the product was recrystallized from EtOH to give **11a** (0.52 g, 66%) as pale brown crystals, mp 203—205 °C. IR (Nujol): 3350, 1690, 1580, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.05 (3H, s), 3.21 (3H, s), 6.98 (1H, s), 7.2—7.6 (6H, m), 7.89 (2H, d, J=8 Hz), 10.72 (1H, s). MS *m/z*: 373 (M^+). *Anal.* Calcd for $C_{18}H_{16}FN_3O_3S$: C, 57.90; H, 4.32; N, 11.25. Found: C, 57.46; H, 4.31; N, 11.10.

Methyl *N*-{1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-pyrazolyl}carbamate (11b) Methyl chloroformate (0.163 ml, 2.11 mmol) in MeCN (0.7 ml) was added dropwise to a stirred solution of **10** (0.7 g, 2.11 mmol) and pyridine (0.171 ml, 2.11 mmol) in MeCN (6 ml) and THF (7 ml) at −20 °C. The mixture was stirred at 5 °C for 1 h, diluted with EtOAc, washed with H_2O, dried, and evaporated. The residue was recrystallized from $CHCl_3$–EtOH to give **11b** (0.51 g, 62%) as pale brown crystals, mp 225—227 °C. IR (Nujol): 3320, 1730, 1585, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.16 (3H, s), 3.62 (3H, s), 6.73 (1H, s), 7.1—7.5 (6H, m), 7.84 (2H, d, J=8 Hz), 10.22 (1H, s). MS *m/z*: 389 (M^+), 357. *Anal.* Calcd for $C_{18}H_{16}FN_3O_4S \cdot 1/4H_2O$: C, 54.88; H, 4.22; N, 10.67. Found: C, 54.79; H, 4.15; N, 10.47.

Ethyl 4-[4-(Methylthio)phenyl]-2,4-dioxobutanoate (13a) A mixture of **12** (1 g, 6.02 mmol) and NaH (60%; 288 mg, 7.2 mmol) in *N*,*N*-dimethylformamide (DMF) (7 ml) was stirred at room temperature for 30 min,[18] then cooled to 0 °C, and diethyl oxalate (0.98 ml, 7.2 mmol) was added dropwise to it. The reaction mixture was stirred at room temperature for 3 h, poured into ice–H_2O, and acidified with dilute HCl. The precipitates were collected and washed with H_2O to afford **13a** (1.6 g, 100%) as a pale brown powder,[17] mp 91—97 °C. IR (Nujol): 3420, 1735, 1620, 1595, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (3H, t, J=7 Hz), 2.54 (3H, s), 4.25 (2H, q, J=7 Hz), 6.78 (1H, s), 7.35 (2H, d, J=8.5 Hz), 7.91(2H, d, J=8.5 Hz). MS *m/z*: 266 (M^+), 193.

Ethyl 1-(4-Fluorophenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxylate (14a) and Ethyl 1-(4-Fluorophenyl)-3-[4-(methylthio)phenyl]pyrazole-5-carboxylate (15a) A mixture of **13a** (21 g, 79.3 mmol) and 4-fluorophenylhydrazine hydrochloride (14 g, 87.1 mmol) in EtOH (180 ml) and dioxane (180 ml) was refluxed for 4 h. The insoluble material was removed by filtration and the filtrate was evaporated. The residue was chromatographed (toluene–EtOAc, 20 : 1) over silica gel to afford **14a** (24 g, 86%) as a pale brown powder,[17] mp 100—102 °C. IR (Nujol): 1710, 1600, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 2.48 (3H, s), 4.45 (2H, q, J=7 Hz), 7.0—7.4 (9H, m). MS *m/z* : 356 (M^+).

15a (2.3 g, 8.1%)[17] was obtained as a minor product in the eluate prior to **14a**. mp 100—104 °C. IR (Nujol): 1730, 1600, 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz), 2.51 (3H, s), 4.27 (2H, q, J=7 Hz), 7.1—7.9 (9H, m). MS *m/z*: 356 (M^+).

Ethyl 1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylate (16a) A solution of **14a** (0.95 g, 2.67 mmol) and 30% H_2O_2 (0.79 ml, 6.91 mmol) in AcOH (9.5 ml) was stirred at 70 °C for 3 h. The mixture was cooled in an ice–H_2O bath and the precipitates were collected and washed with EtOH to afford **16a** (0.94 g, 91%) as colorless crystals, mp 210—212 °C. IR (Nujol): 1715, 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.32 (3H, t, J=7 Hz), 3.25 (3H, s), 4.35 (2H, q, J=7 Hz), 7.3—7.6 (7H, m), 7.92 (2H, d, J=8.5 Hz). MS *m/z*: 388 (M^+). *Anal.* Calcd for $C_{19}H_{17}FN_2O_4S$: C, 58.75; H, 4.41; N, 7.21. Found: C, 58.39; H, 4.43; N, 7.14.

Following the same procedure as described for compound **16a**, the following compounds were obtained from the appropriate **14**.[11]

1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-pyrazole (**16b**): mp 210—212 °C (EtOH–EtOAc), colorless crystals. IR (Nujol): 3150, 1605, 1520, 1505 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.26 (3H, s), 7.3—7.6 (7H, m), 7.96 (2H, d, J=8 Hz). MS *m/z*: 384 (M^+). *Anal.* Calcd for $C_{17}H_{12}F_4N_2O_2S$: C, 53.12; H, 3.15; N, 7.29. Found: C, 52.89; H, 3.07; N, 7.25.

3-(Difluoromethyl)-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole (**16c**): mp 190—191 °C (EtOH), off-white solid. IR (Nujol): 1600, 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.08 (3H, s), 6.5—8.0 (10H, m). MS *m/z*: 366 (M^+). *Anal.* Calcd for $C_{17}H_{13}F_3N_2O_2S$: C, 55.73; H, 3.58; N, 7.65. Found: C, 55.72; H, 3.45; N, 7.60.

3-(Fluoromethyl)-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole (**16d**): mp 166—167 °C (EtOH), off-white solid. IR (Nujol): 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (3H, s), 5.35 (1H, s), 5.59 (1H, s), 6.9—8.0 (9H, m). MS *m/z*: 348 (M^+). *Anal.* Calcd for $C_{17}H_{14}F_2N_2O_2S$: C, 58.61; H, 4.05; N, 8.04. Found: C, 58.27; H, 4.08; N, 7.85.

1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylic Acid (17a) A mixture of **16a** (4.4 g, 11.4 mmol) and 4 N NaOH (5.7 ml, 22.8 mmol) in THF (20 ml), EtOH (10 ml), and dioxane (20 ml) was stirred at room temperature overnight. H_2O (50 ml) was added and the mixture was acidified with HCl. The precipitates were collected and washed with H_2O to afford **17a** (4.1 g, 100%),[17] mp 232—234 °C. IR (Nujol): 1695, 1600, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (3H, s), 7.2—7.6 (7H, m), 7.92 (2H, d, J=8 Hz), 13.1 (1H, s). MS *m/z*: 360 (M^+).

***N*-Methyl-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxamide (18b)** A mixture of **17a** (1.1 g, 3.05 mmol) and PCl_5 (0.67 g,

3.21 mmol) in toluene (16 ml) and THF (9 ml) was stirred at room temperature for 2 h. The insoluble material was removed by filtration and the filtrate was evaporated to give the acid chloride (1.37 g) as an oil.

A mixture of 25% $MeNH_2$ (2 ml), ice–H_2O (5 ml), and THF (10 ml) was added to the above chloride, and the whole was stirred overnight. The precipitates were collected and the filtrate was extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated. The residue and the former precipitates were combined and recrystallized from EtOAc–EtOH to afford **18b** (1 g, 88%) as colorless crystals, mp 271—273 °C. IR (Nujol): 3400, 1660, 1605, 1550, 1535, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.78 (3H, d, J=5 Hz), 3.25 (3H, s), 7.16 (1H, s), 7.3—7.6 (6H, m), 7.91 (2H, d, J=8 Hz), 8.35 (1H, q, J=5 Hz). MS m/z: 373 (M^+). *Anal.* Calcd for $C_{18}H_{16}FN_3O_3S$: C, 57.90; H, 4.32; N, 11.25. Found: C, 57.86; H, 4.53; N, 10.83.

Following the same procedure as described for compound **18b**, the following compounds were obtained from **17a**.

1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxamide (**18a**): mp 215—217 °C (EtOAc–EtOH). IR (Nujol): 3470, 3200, 1680, 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (3H, s), 7.16 (1H, s), 7.2—7.6 (7H, m), 7.77 (1H, s), 7.91 (2H, d, J=8.5 Hz). MS m/z: 359 (M^+), 341. *Anal.* Calcd for $C_{17}H_{14}FN_3O_3S$: C, 56.81; H, 3.93; N, 11.69. Found: C, 56.82; H, 4.00; N, 11.35.

N,*N*-Dimethyl-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxamide (**18c**): mp 171—173 °C (EtOAc–Et_2O), off-white crystals. IR (Nujol): 1620, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.02 (3H, s), 3.25 (3H, s), 3.32 (3H, s), 7.08 (1H, s), 7.2—8.0 (8H, m). MS m/z: 387 (M^+). *Anal.* Calcd for $C_{19}H_{18}FN_3O_3S$: C, 58.90; H, 4.68; N, 10.85. Found: C, 58.41; H, 4.66; N, 10.06.

1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(1-pyrrolidinylcarbonyl)pyrazole (**18d**): mp 229—230 °C (EtOH–THF), colorless crystals. IR (Nujol): 1615, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77—2.07 (4H, m), 3.00 (3H, s), 3.67 (2H, t, J=6 Hz), 3.97 (2H, t, J=6 Hz), 6.9—7.5 (7H, m), 7.78 (2H, d, J=8 Hz). MS m/z: 413 (M^+). *Anal.* Calcd for $C_{21}H_{20}FN_3O_3S$: C, 61.02; H, 4.84; N, 10.17. Found: C, 61.17; H, 4.96; N, 10.07.

1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (19a) A mixture of **18a** (2.7 g, 7.51 mmol) and methanesulfonyl chloride (3.4 ml, 43.4 mmol) in pyridine (25 ml) was stirred at 50 °C for 6 h. The solvent was evaporated, and EtOAc and H_2O were added to the residue. The precipitates were collected and washed with H_2O. The filtrate was separated and the organic layer was washed with dilute HCl, dried, and concentrated to dryness. The residue and the former precipitates were recrystallized from EtOH–EtOAc to afford **19a** (2.4 g, 95%) as colorless crystals, mp 194—196 °C. IR (Nujol): 2240, 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (3H, s), 7.3—7.6 (7H, m), 7.95 (2H, d, J=7 Hz). MS m/z: 341 (M^+). *Anal.* Calcd for $C_{17}H_{12}FN_3O_2S$: C, 59.81; H, 3.54; N, 12.31. Found: C, 59.56; H, 3.51; N, 12.15.

Following the same procedure as described for compound **19a**, the following compounds were obtained from the appropriate **18**.[11]

5-[4-(Methylsulfonyl)phenyl]-1-phenylpyrazole-3-carbonitrile (**19b**): mp 179—180 °C (EtOAc). IR (Nujol): 2250, 1600, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (3H, s), 7.3—8.0 (10H, m). MS m/z: 323 (M^+). *Anal.* Calcd for $C_{17}H_{13}N_3O_2S \cdot 1/6H_2O$: C, 62.56; H, 4.11; N, 12.87. Found: C, 62.30; H, 4.12; N, 12.67.

1-(2-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**19c**): mp 147—148 °C (EtOH). IR (Nujol): 2250, 1600, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.07 (3H, s), 7.00 (1H, s), 7.2—8.0 (8H, m). MS m/z: 341 (M^+). *Anal.* Calcd for $C_{17}H_{12}FN_3O_2S$: C, 59.81; H, 3.54; N, 12.31. Found: C, 59.50; H, 3.72; N, 12.19.

1-(3-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**19d**): mp 167—168 °C (EtOH). IR (Nujol): 2250, 1600, 1495 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.26 (3H, s), 7.2—8.0 (9H, m). MS m/z: 341 (M^+). *Anal.* Calcd for $C_{17}H_{12}FN_3O_2S$: C, 59.81; H, 3.54; N, 12.31. Found: C, 59.82; H, 3.70; N, 12.28.

1-(2,4-Difluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**19e**): mp 129—130 °C (EtOH). IR (Nujol): 2250, 1610, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.08 (3H,s), 6.8—8.0 (8H, m). MS m/z: 359 (M^+). *Anal.* Calcd for $C_{17}H_{11}F_2N_3O_2S$: C, 56.82; H, 3.09; N, 11.69. Found: C, 57.07; H, 3.10; N, 11.61.

1-(4-Methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**19f**): mp 210—211 °C (EtOH). IR (Nujol): 2250, 1600, 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 3.08 (3H, s), 6.96 (1H, s), 7.1—8.0 (8H, m). MS m/z: 337 (M^+). *Anal.* Calcd for $C_{18}H_{15}N_3O_2S \cdot 1/5H_2O$: C, 63.40; H, 4.55; N, 12.32. Found: C, 63.42; H, 4.45; N, 11.98.

1-(4-Methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**19g**): mp 153—154 °C (EtOH). IR (Nujol): 2250, 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (3H, s), 3.80 (3H, s), 7.0—8.0 (9H, m). MS m/z: 353 (M^+). *Anal.* Calcd for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89. Found: C, 60.79; H, 4.24; N, 11.71.

5-[4-(Methylsulfonyl)phenyl]-1-[4-(methylthio)phenyl]pyrazole-3-carbonitrile (**19h**): mp 181—182 °C (THF–EtOH). IR (Nujol): 2250, 1610, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (3H, s), 3.09 (3H, s), 6.96 (1H, s), 7.1—7.5 (6H, m), 7.93 (2H, d, J=8 Hz). MS m/z: 369 (M^+). *Anal.* Calcd for $C_{18}H_{15}N_3O_2S_2$: C, 58.54; H, 4.65; N, 11.38. Found: C, 58.05; H, 4.08; N, 11.15.

1-(4-Cyanophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**19i**):[19] mp 159—160 °C (EtOH). IR (Nujol): 2250, 2240, 1610, 1550, 1505 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.11 (3H, s), 7.01 (1H, s), 7.4—8.0 (8H, m). MS m/z: 348 (M^+). *Anal.* Calcd for $C_{18}H_{12}N_4O_2S$: C, 62.07; H, 3.45; N, 16.09. Found: C, 61.53; H, 3.39; N, 15.89.

5-[4-(Methylsulfonyl)phenyl]-1-(4-nitrophenyl)pyrazole-3-carbonitrile (**19j**): mp 199—200 °C (EtOH), off-white crystals. IR (Nujol): 2250, 1600, 1530, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.26 (3H, s), 7.5—7.7 (4H, m), 7.63(1H, s), 7.97 (2H, d, J=8 Hz), 8.34 (2H, d, J=8 Hz). MS m/z: 368 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_4O_4S$: C, 55.43; H, 3.28; N, 15.21. Found: C, 55.08; H, 3.23; N, 14.91.

5-{1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-pyrazolyl}-1*H*-tetrazole (20) A mixture of **19a** (1 g, 2.93 mmol), NH_4Cl (0.25 g, 4.67 mmol), and NaN_3 (0.24 g, 3.69 mmol) in DMF (10 ml) was stirred at 105 °C for 10 h. It was then poured into ice–H_2O and the precipitates were collected, washed with H_2O, and recrystallized from EtOH–THF to afford **20** (0.71 g, 63%) as colorless crystals, mp 278—279 °C (dec.). IR (Nujol): 3150, 1655, 1620, 1600, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.27 (3H, s), 7.3—7.6 (7H, m), 7.95 (2H, d, J=8 Hz). MS m/z: 384 (M^+). *Anal.* Calcd for $C_{17}H_{13}FN_6O_2S \cdot 1/3THF$: C, 53.91; H, 3.87; N, 20.58. Found: C, 54.04; H, 3.76; N, 20.51.

3,3-Bis(methylthio)-1-[4-(methylthio)phenyl]-2-propen-1-one (21) A solution of CS_2 (4.6 g, 60.4 mmol) in THF (60 ml) was added dropwise to a mixture of **12** (10 g, 60.2 mmol) and 60% NaH (4.8 g, 120 mmol) in THF (100 ml) at room temperature over a 1 h period. The resultant mixture was stirred at 40 °C for 2 h. A solution of MeI (17.1 g, 120 mmol) in THF (60 ml) was then added and the whole was stirred at 40 °C for 1 h and under reflux for 1 h. H_2O and $CHCl_3$ were added and the organic layer was separated, washed with H_2O, dried, and evaporated. The residue was washed with MeOH to give **21** (10.5 g, 65%),[17] mp 119—122 °C. IR (Nujol): 1620, 1590, 1550, 1495 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 2.53 (3H, s), 2.56 (3H, s), 6.74 (1H, s), 7.26 (2H, d, J=7 Hz), 7.83 (2H, d, J=7 Hz). MS m/z: 270 (M^+).

1-(4-Fluorophenyl)-3-(methylthio)-5-[4-(methylthio)phenyl]pyrazole (22) A mixture of **21** (2.7 g, 10 mmol) and 4-fluorophenylhydrazine hydrochloride (1.8 g, 11 mmol) in AcOH (15 ml) was stirred at 100 °C for 7 h. The solvent was evaporated and the residue was chromatographed ($CHCl_3$) over silica gel to afford **22** (0.73 g, 22%) as an oil.[17] IR (Nujol): 1590, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 2.59 (3H, s), 6.40 (1H, s), 6.9—7.4 (8H, m).

1-(4-Fluorophenyl)-3-(methylsulfonyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole (23) A mixture of **22** (0.73 g, 2.21 mmol), 30% H_2O_2 (1.5 ml, 13.3 mmol), and concentrated H_2SO_4 (2 drops) in AcOH (10 ml) was stirred at 60 °C for 4 h. The solvent was evaporated and the residue was dissolved in EtOAc. This solution was washed with aqueous $NaHCO_3$ and H_2O successively, dried, and concentrated to dryness. The residue was recrystallized from EtOAc–EtOH to give **23** (0.54 g, 49%) as crystals, mp 209—210 °C. IR (Nujol): 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.26 (3H, s), 3.38 (3H, s), 7.3—8.0 (9H, m). MS m/z: 394 (M^+). *Anal.* Calcd for $C_{17}H_{15}FN_2O_4S_2$: C, 51.77; H, 3.83; N, 7.10. Found: C, 51.43; H, 3.82; N, 6.84.

1-(4-Aminophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (24) A mixture of **19j** (1.1 g, 2.99 mmol), Fe powder (1.1 g), and NH_4Cl (0.11 g) in EtOH (20 ml) and H_2O (7 ml) was refluxed for 1 h. EtOAc was added and the mixture was filtered. The filtrate was evaporated and the residue was recrystallized from EtOAc to afford **24** (0.83 g, 82%) as crystals, mp 228—229 °C. IR (Nujol): 3480, 3400, 3150, 2250, 1645, 1605, 1520 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (3H, s), 5.57 (2H, s), 6.5—8.0 (9H, m). MS m/z: 338 (M^+). *Anal.* Calcd for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.21; H, 4.16; N, 16.44.

1-[4-(Methylamino)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (25a) A mixture of **24** (1 g, 2.96 mmol), MeI (0.42 g, 2.96 mmol), and K_2CO_3 (0.6 g, 4.35 mmol) in DMF (10 ml) was stirred

at room temperature for 1 h. The mixture was poured into H_2O and extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated. The residue was chromatographed ($CHCl_3$) over silica gel to afford **25a** (0.31 g, 30%) as crystals, mp 166—168 °C. IR (Nujol): 3450, 2240, 1610, 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.51 (3H, d, J=5 Hz), 3.25 (3H, s), 6.17 (1H, q, J=5 Hz), 6.5—8.0 (9H, m). *Anal.* Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.09; H, 4.57; N, 15.81.

Following the same procedure as described for compound **25a**, the following compounds were obtained from **24**.

1-[4-(Ethylamino)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**25b**): mp 167—168 °C (EtOH). IR (Nujol): 3400, 2240, 1610, 1525 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7Hz), 3.07 (3H, s), 3.13 (2H, q, J=7 Hz), 6.5—8.0 (9H, m). MS m/z: 366 (M^+). *Anal.* Calcd for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.95; N, 15.29. Found: C, 61.82; H, 4.88; N, 15.00.

1-[4-(Diethylamino)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**25d**): mp 155—156 °C (EtOH). IR (Nujol): 2240, 1610, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (6H, t, J=7 Hz), 3.07 (3H, s), 3.37 (4H, q, J=7 Hz), 6.5—8.0 (9H, m). MS m/z: 394 (M^+), 379. *Anal.* Calcd for $C_{21}H_{22}N_4O_2S$: C, 63.94; H, 5.62; N, 14.20. Found: C, 63.57; H, 5.45; N, 14.04.

1-[4-(Dimethylamino)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (25c) A mixture of **24** (0.7 g, 2.07 mmol) and HCOOH (1 ml) in formalin (37%; 5 ml) was refluxed for 30 min. $CHCl_3$ was added and the mixture was washed with H_2O, dried, and evaporated. The residue was chromatographed (EtOAc–toluene, 2:1) over silica gel and the product was recrystallized from EtOAc to afford **25c** (0.46 g, 55%) as crystals, mp 171—172 °C. IR (Nujol): 2240, 1610, 1530 cm^{-1}. MS m/z: 366 (M^+). *Anal.* Calcd for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.95; N, 15.29. Found: C, 62.10; H, 4.95; N, 15.02.

1-(4-Fluorophenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole-3-carbonitrile (26a) A solution of $NaIO_4$ (0.7 g, 3.30 mmol) in H_2O (5 ml) was added to an ice-cooled solution of **26b** (0.6 g, 1.94 mmol) in MeOH (50 ml). The resulting solution was stirred at room temperature for 8 h and the insoluble material was filtered off. The filtrate was evaporated and the residue was dissolved in EtOAc. This solution was washed with aqueous $NaHSO_3$ and H_2O successively, dried, and concentrated. The residue was chromatographed ($CHCl_3$–MeOH, 50:1) over silica gel and the product was crystallized from hexane–EtOH to afford **26a** (0.45 g, 71%) as crystals, mp 104—105 °C. IR (Nujol): 2250, 1600, 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s), 6.94 (1H, s), 7.0—7.7 (8H, m). MS m/z: 325 (M^+), 310. *Anal.* Calcd for $C_{17}H_{12}FN_3OS$: C, 62.76; H, 3.72; N, 12.91. Found: C, 62.73; H, 3.74; N, 12.70.

1-(4-Fluorophenyl)-5-[4-(methylamino)phenyl]pyrazole-3-carbonitrile hydrochloride (26d) A mixture of **27** (0.7 g, 2.19 mmol) and 10% HCl (3 ml) in MeOH (15 ml) was stirred at 60 °C for 2 h. The solvent was evaporated and the residue was washed with EtOH to afford **26d** (0.43 g, 60%), mp 189—191 °C. IR (Nujol): 2650, 2450, 2250, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.73 (3H, s), 6.8—7.5 (9H, m). MS m/z: 292 (M^+). *Anal.* Calcd for $C_{17}H_{13}FN_4 \cdot HCl$: C, 62.11; H, 4.29; N, 17.04. Found: C, 61.95; H, 4.31; N, 17.03.

Following the same procedure as described for **19a**, the following compounds were prepared from the appropriate substituted acetophenones or acetylthiophene.[11]

1-(4-Fluorophenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carbonitrile (**26b**): mp 106—107 °C (EtOH), yellow needles. IR (Nujol): 2250, 1600, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 6.84 (1H, s), 7.0—7.4 (8H, m). MS m/z: 309 (M^+). *Anal.* Calcd for $C_{17}H_{12}FN_3S$: C, 66.00; H, 3.91; N, 13.58. Found: C, 65.68; H, 4.04; N, 13.34.

1-(4-Fluorophenyl)-5-(4-methoxyphenyl)pyrazole-3-carbonitrile (**26c**): mp 122—123 °C (EtOH). IR (Nujol): 2250, 1610, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s), 6.8—7.4 (9H, m). MS m/z: 293 (M^+). *Anal.* Calcd for $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.58; H, 4.18; N, 14.24.

5-[4-(Acetylamino)phenyl]-1-(4-fluorophenyl)pyrazole-3-carbonitrile (**26e**): mp 96—98 °C (EtOH). IR (Nujol): 3340, 2250, 1670, 1600, 1535, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.04 (3H, s), 7.1—7.6 (9H, m), 10.10 (1H, s). MS m/z: 320 (M^+). *Anal.* Calcd for $C_{18}H_{13}FN_4O \cdot 2/3EtOH$: C, 66.15; H, 4.88; N, 15.96. Found: C, 65.82; H, 4.55; N, 16.13.

5-(4-Cyanophenyl)-1-(4-fluorophenyl)pyrazole-3-carbonitrile (**26f**): mp 154—156 °C (EtOH). IR (Nujol): 2250, 2230, 1615, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.96 (1H, s), 7.0—7.7 (8H, m). MS m/z: 288 (M^+). *Anal.* Calcd for $C_{17}H_9FN_4$: C, 70.83; H, 3.15; N, 19.44. Found: C, 70.34; H, 3.23; N, 19.15.

5-(4-Acetylphenyl)-1-(4-fluorophenyl)pyrazole-3-carbonitrile (**26g**): mp 170—172 °C (EtOAc–EtOH). IR (Nujol): 2250, 1680, 1610, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.61 (3H, s), 6.95 (1H, s), 7.0—7.4 (6H, m), 7.93 (2H, d, J=9 Hz). MS m/z: 305 (M^+). *Anal.* Calcd for $C_{18}H_{12}FN_3O \cdot 1/6H_2O$: C, 70.12; H, 4.04; N, 13.63. Found: C, 70.13; H, 4.04; N, 13.60.

1-(4-Fluorophenyl)-5-[5-(methylsulfonyl)-2-thienyl]pyrazole-3-carbonitrile (**26h**): mp 131—132 °C (EtOH). IR (Nujol): 2250, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.35 (3H, s), 7.3—7.8 (7H, m). MS m/z: 347 (M^+). *Anal.* Calcd for $C_{15}H_{10}FN_3O_2S_2$: C, 51.86; H, 2.90; N, 12.10. Found: C, 52.00; H, 2.89; N, 11.82.

5-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (**28**): mp 162—163 °C (EtOH). IR (Nujol): 3140, 2250, 1610, 1595, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.09 (3H, s), 6.89 (1H, s), 7.0—8.0 (8H, m). MS m/z: 341 (M^+). *Anal.* Calcd for $C_{17}H_{12}FN_3O_2S$: C, 59.81; H, 3.54; N, 12.31. Found: C, 59.65; H, 3.53; N, 12.13.

1-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]pyrazole-5-carbonitrile (**29**): Compound **29** was prepared from **15a**. mp 200—202 °C (EtOH–EtOAc), pale brown crystals. IR (Nujol): 2240, 1600, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.28 (3H, s), 7.4—8.3 (9H, m). MS m/z: 341 (M^+). *Anal.* Calcd for $C_{17}H_{12}FN_3O_2S$: C, 59.81; H, 3.54; N, 12.31. Found: C, 59.89; H, 3.68; N, 12.20.

***N*-(4-Fluorophenyl)-4-(methylthio)benzamidine (31)** A mixture of **30** (10 g, 67 mmol), 4-fluoroaniline (7.44 g, 67 mmol), and $AlCl_3$ (8.92 g, 67 mmol) was heated at 150 °C for 30 min, then poured into dilute HCl and extracted with THF. The extract was evaporated and the residue was washed with H_2O to afford **31** (13 g, 74%) as a gray powder.[17] ^{1}H-NMR (DMSO-d_6) δ: 2.52 (3H, s), 6.9—7.3 (6H, m), 7.90 (2H, d, J=8 Hz).

Ethyl 1-(4-Fluorophenyl)-2-[4-(methylthio)phenyl]imidazole-4-carboxylate (32) A mixture of **31** (10 g, 38 mmol), ethyl bromopyruvate (15 g, 76 mmol), and K_2CO_3 (5.3 g, 38 mmol) in EtOH (100 ml) was refluxed for 2 h. Ethyl bromopyruvate (10 g) and K_2CO_3 (5.3 g) were added and the mixture was refluxed for an additional 2 h. The mixture was filtered through celite and the filtrate was evaporated. A solution of the residue in AcOH (150 ml) was refluxed for 1 h and evaporated. The residue was chromatographed (toluene–EtOAc, 5:1) over silica gel to afford **32** (8.2 g, 60%) as a yellow oil.[17] ^{1}H-NMR (DMSO-d_6) δ: 1.30 (3H, t, J=7 Hz), 2.46 (3H, s), 4.28 (2H, q, J=7 Hz), 7.1—7.5 (8H, m), 8.16 (1H, s).

Dimethyl 4-(Methylthio)benzamidomalonate (35) A solution of **34** (5.7 g, 33.9 mmol) in $SOCl_2$ (10 ml) was refluxed for 1 h and evaporated *in vacuo*. A mixture of the residue and dimethyl aminomalonate hydrochloride (6.2 g, 33.9 mmol) in CH_2Cl_2 (50 ml) was refluxed for 42 h. The insoluble material was removed by filtration and the filtrate was washed with H_2O and aqueous $NaHCO_3$ successively, dried, and evaporated. The residue was washed with isopropanol to give **35** (5.2 g, 51%),[17] mp 89—92 °C. IR (Nujol): 3350, 1750, 1640, 1600, 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.53 (3H, s), 3.73 (6H, s), 5.36 (1H, d, J=8 Hz), 7.35 (2H, d, J=8 Hz), 7.86 (2H, d, J=8 Hz), 9.31 (1H, d, J=8 Hz). MS m/z: 297 (M^+).

Methyl 1-(4-Fluorophenyl)-5-[4-(methylthio)phenyl]-1H-1,2,4-triazole-3-carboxylate (36) A solution of $NaNO_2$ (1.42 g, 20.6 mmol) in H_2O (10 ml) was added dropwise to a mixture of 4-fluoroaniline (2.3 g, 20.5 mmol) and concentrated HCl (5 ml) in AcOH (15 ml) at 0 °C. The mixture was stirred at 0 °C for 15 min, then a solution of **35** (5.1 g, 17.2 mmol) in acetone (60 ml) and a solution of K_2CO_3 (23.6 g) in H_2O (40 ml) were added successively at −10 °C. The resulting red mixture was stirred at 0 °C for 30 min and then extracted with EtOAc. The extract was washed with H_2O, aqueous $NaHCO_3$, and H_2O successively, dried, and evaporated.

A mixture of the residue (9.7 g) and NaOMe (189 mg, 3.5 mmol) in MeOH (100 ml) was stirred at room temperature for 3 h, then cooled to 0 °C, and the precipitates were collected to afford **36** (4.1 g, 70%),[17] mp 189—190 °C. IR (Nujol): 1740, 1600, 1515, 1495 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 4.05 (3H, s), 7.0—7.5 (8H, m). MS m/z: 343 (M^+).

Following the same procedure as described for **19a**, the following compounds were obtained from **32** or **36**.

1-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]imidazole-4-carbonitrile (**33**): mp 210—211 °C (AcOH–H_2O), white powder. IR (Nujol): 2240, 1600, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.24 (3H, s), 7.3—8.0 (8H, m), 8.61 (1H, s). MS m/z: 341 (M^+). *Anal.* Calcd for $C_{17}H_{12}FN_3O_2S$: C, 59.81; H, 3.54; N, 12.31. Found: C, 59.93; H, 3.65; N, 12.29.

1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-1,2,4-triazole-3-

Table 7. Crystallographic Data for **19a**

Formula	$C_{17}H_{12}FN_3O_2S$
Molecular weight	341.37
Crystal color, habit	Colorless, prismatic
Crystal dimensions (mm)	$0.25 \times 0.25 \times 0.15$
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Lattice parameters: a (Å)	14.544 (1)
b (Å)	11.515 (1)
c (Å)	9.720 (1)
V (Å^3)	1627.7 (2)
Z	4
Dx (g/cm^3)	1.393
Total reflections	1626
R	0.053
Rw	0.052

carbonitrile (**37**): mp 263—264 °C (AcOH–H_2O). IR (Nujol): 2250, 1600, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.27 (3H, s), 7.4—8.1 (8H, m). MS m/z: 342 (M^+). *Anal.* Calcd for $C_{16}H_{11}FN_4O_2S$: C, 56.14; H, 3.24; N, 16.36. Found: C, 55.89; H, 3.17; N, 16.16.

X-Ray Crystallographic Analysis of 19a Diffraction measurements were performed on a Rigaku AFC-5UD diffractometer using graphite-monochromated CuKα radiation ($\lambda = 1.54178$ Å). Crystallographic data are listed in Table 7.

Biological Methods. Adjuvant Arthritis and Collagen-Induced Arthritis These experiments were carried out according to the procedures described in the previous report.[5b]

Inflammatory Hyperalgesia Induced by Brewer's Yeast in Rats (Randall–Selitto Assay) Ten male Sprague Dawley rats were used per group. A suspension, 0.1 ml, of 5% brewer's yeast in 0.5% methyl cellulose was injected into the right hind paw. The pain threshold was determined 3 h after yeast injection, by applying pressure to the foot and reading the pressure at which the rat withdrew the foot. The drugs were given orally 2 h after yeast injection. The pain threshold in the treated rats was compared with that in the control rats.

hCOX-1 and hCOX-2 Enzyme Assays (*in Vitro*) CHO cells expressing either recombinant human COX-1 or COX-2 were used as the enzyme source.[20] COX activity was assayed as prostaglandin (PG) E_2 formation using radioimmunoassay (RIA). hCOX-1(1 μg/150 μl) or hCOX-2 (3 μg/150 μl) was preincubated with an inhibitor in 0.1 M Tris–HCl buffer (pH 7.3) containing 2 μM hematin and 5 mM L-tryptophan at 30 °C for 5 min, followed by a 5 min incubation with arachidonic acid (10 μM) at 30 °C. The enzyme reaction was stopped by the addition of 1 N HCl. The PGE_2 formed was extracted with EtOAc and measured by RIA (Amersham).

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7) Compound **1** was metabolized to a 5-(methylsulfonyl)thiophene derivative in rats. Compound **1** also showed mutagenicity in a chromosome aberration test conducted by Toxicology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. (unpublished results).
8) The energy levels and the orbital distributions of HOMO and LUMO, and the torsion angles of the benzene rings of the most stable conformer of 5-bromo-3-(4-acetylphenyl)-2-(4-fluorophenyl)thiophene (**38**) and that of 3-bromo-5-(4-acetylphenyl)-1-(4-fluorophenyl)pyrazole (**39**) were calculated by the MNDO method: *e.g.*, the torsion angle of the 4-acetylphenyl ring was +77.7° (**38**) and +79.1° (**39**) and that of the 4-fluorophenyl ring was +77.4° (**38**) and +77.3° (**39**), respectively.
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