Studies on Antiinflammatory Agents. II.[1] Synthesis and Pharmacological Properties of 2′-(Phenylthio)methanesulfonanilides and Related Derivatives

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The structure of the previously reported new antiinflammatory agent (1, FK3311) was chemically modified in an attempt to find novel compounds with more potent and broader-spectrum activities. Some 2′-(phenylthio) and 2′-(phenylamino)methanesulfonanilides (2 and 3), in particular those bearing an electron-attracting substituent at the 4′-position, potently inhibited adjuvant arthritis in rats as well as collagen-induced arthritis in mice when administered orally. 4′-Carbamoyl-2′-(2,4-difluorophenylthio)methanesulfonanilide (3b), which was selected as a candidate for further development from among the compounds synthesized herein, exhibited activity in reducing arthritis in a spontaneous autoimmune disease model (MRL/lpr mice) within the dose range of 10—100 mg/kg (*p.o.*).

Keywords antiinflammatory activity; antirheumatic activity; immunoregulatory activity; FK 3311; methanesulfonanilide; structure–activity relationship

Rheumatoid arthritis (RA) is a systemic disease characterized by inflammation and progressive joint destruction. This disease is also associated with immunological abnormalities including excess immunoglobulin production, the presence of autoantibodies, and an impairment of lymphocyte function.[2] A number of therapeutic agents such as non-steroidal antiinflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), steroids, and immunosuppressants are being used for the treatment of RA.[3] Among them, steroid therapy has been shown to produce significant clinical improvement, which is ascribed to dual actions to modulate inflammation and immunoregulation.[4] Therefore, another type of drug which exerts such dual activities should be therapeutically useful.

We previously reported[1] the antiinflammatory activity of 2′-phenoxymethanesulfonanilide derivatives and showed that FK3311 (**1**), depicted in Fig. 1, had well-balanced antiinflammatory and analgesic activities without any ulcerogenicity. We continued chemical modification studies of **1** to discover novel compounds exerting potent and broad activities in a variety of RA models, particularly models in which the immune system participates. During the studies, some 2′-(phenylthio) and 2′-(phenylamino)methanesulfonanilide derivatives (**2** and **3**) were found to inhibit not only adjuvant arthritis in rats but also collagen-induced arthritis in mice. This paper describes the synthesis of novel methanesulfonanilide derivatives (**2**—**4**) and their pharmacological activities.

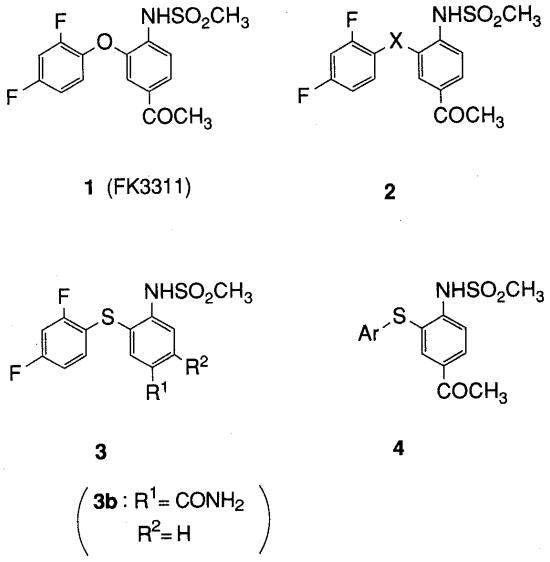


Fig. 1

Chemistry

4′-Acetylmethanesulfonanilide derivatives **2a**—**h** were prepared *via* the by synthetic routes illustrated in Charts 1 and 2. Most of the derivatives (**2a**—**e** and **2g**) were derived from 3′-chloro-4′-nitroacetophenone **5a**[1] as shown in Chart 1. Condensation of **5a** with potassium 2,4-difluorothiophenoxide in xylene yielded 3′-(2,4-difluorophenylthio)-4′-nitroacetophenone (**6a**). Reduction of **6a** with iron powder in the presence of ammonium chloride and subsequent sulfonylation in pyridine afforded 4′-acetyl-2′-(2,4-difluorophenylthio)methanesulfonanilide (**2a**). Sulfinyl (**2b**) and sulfonyl (**2c**) derivatives were obtained by the oxidation of **2a** with *m*-chloroperbenzoic acid or hydrogen peroxide.

2′-(Phenylamino)methanesulfonanilides (**2d** and **2e**) were prepared *via* **7**, which was obtained by Ullmann-type reaction of the ketal **5b**[1] and 2,4-difluoroaniline in the presence of potassium carbonate and cupric oxide, because the nucleophilicity of aniline was weaker than that of thiophenoxide. Compound **7** was hydrolyzed with hydrochloric acid, reduced with iron powder, and sulfonylated to give **2d**. Compound **7** was methylated followed by the same procedure as described for **2d**, affording **2e**.

The 2′-carbamoyl derivative (**2g**) was obtained from the ketal derivative (**5c**), which was prepared from **5b** by using cuprous cyanide. Compound **5c** was reduced with iron powder, sulfonylated, and deprotected with hydrochloric acid. The obtained nitrile was hydrolyzed to give the carboxylic acid (**9**). The acid chloride of **9** was reacted with 2,4-difluoroaniline to afford **2g**.

The 2′-benzoyl (**2f**) and benzamido (**2h**) derivatives were prepared from commercially available aniline derivatives **10** and **14**, respectively, as shown in Chart 2. Friedel–Crafts

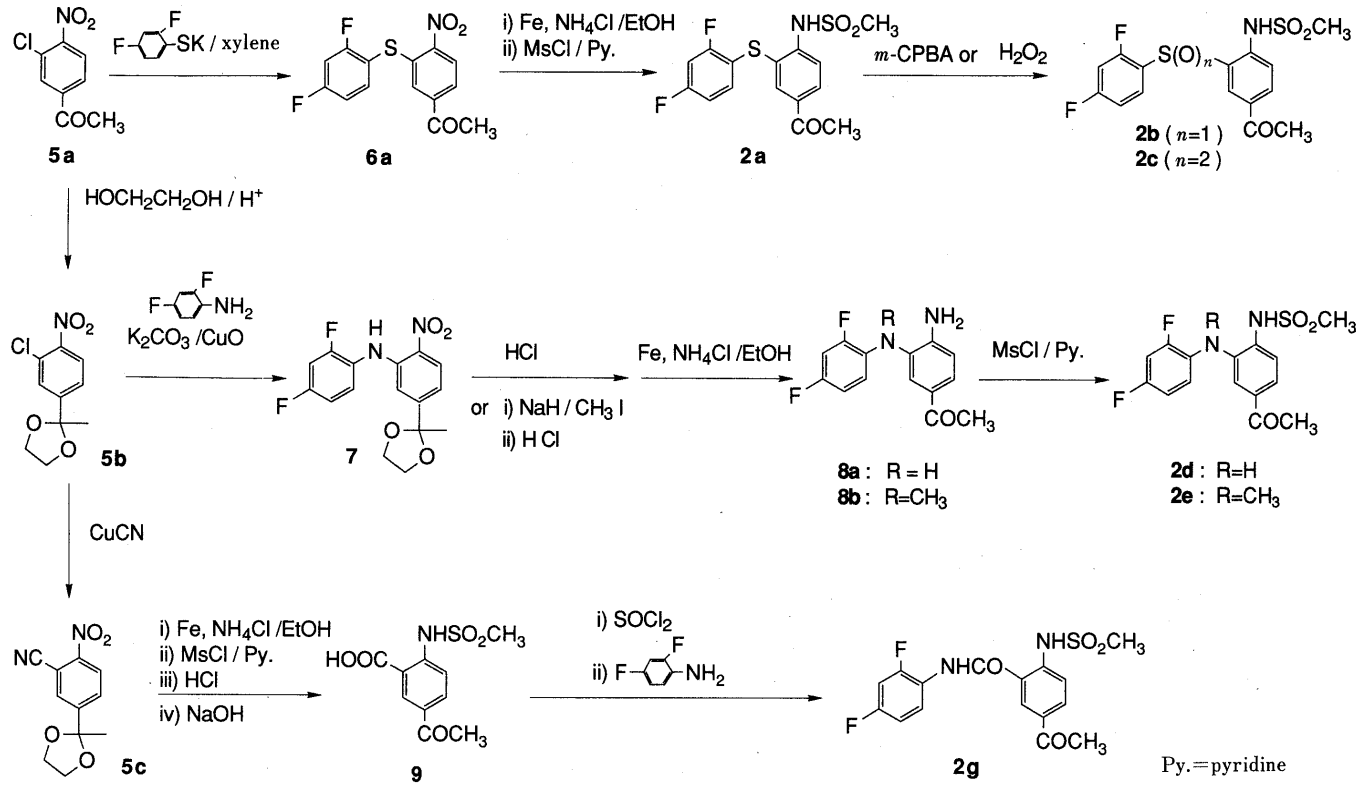


Chart 1

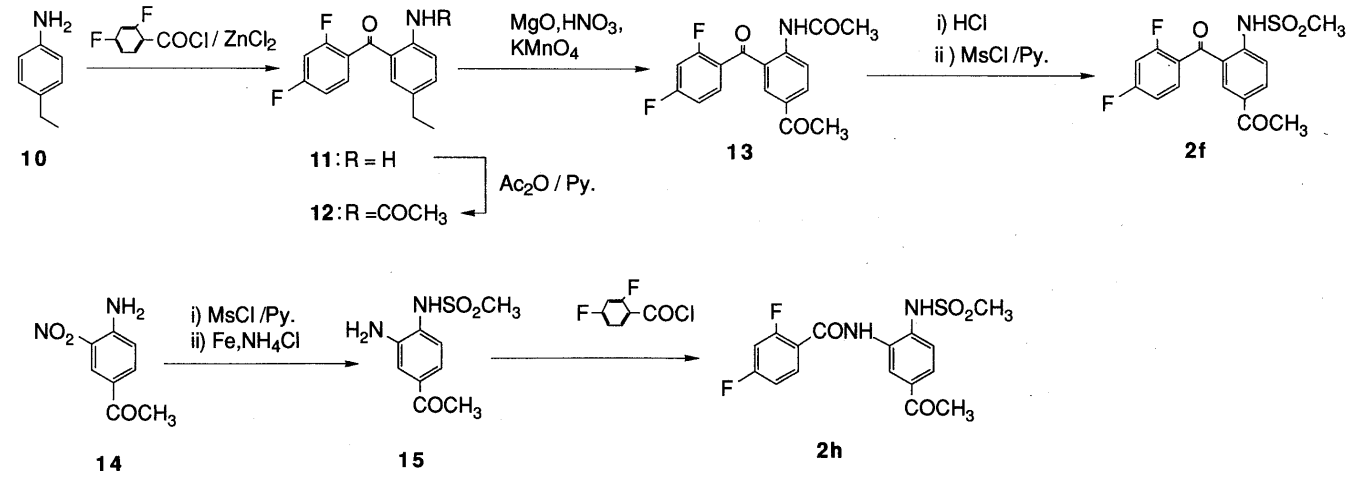


Chart 2

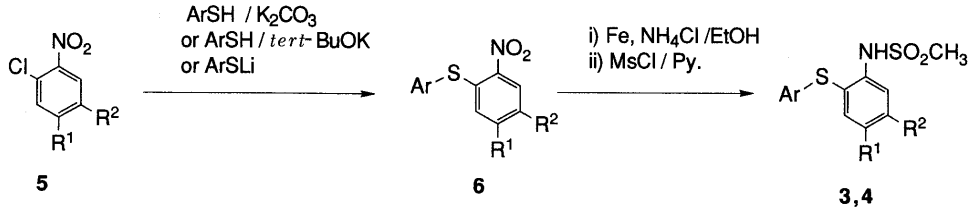
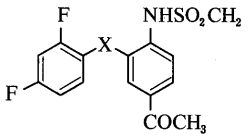


Chart 3

reaction of **10** with 2,4-difluorobenzoyl chloride in the presence of zinc chloride yielded the 2-aminobenzophenone derivative (**11**), which was subsequently acylated with acetic anhydride to afford acetanilide (**12**). Oxidation of the ethyl group of **12** was performed as described in the literature.[5] The acetophenone (**13**) was hydrolyzed with hydrochloric acid and sulfonylated to afford **2f**. The benzamido derivative (**2h**) was prepared by condensation of 2,4-difluorobenzoyl chloride and the sulfonanilide (**15**), which was obtained from **14** in the usual manner.

TABLE I. Physical and Pharmacological Properties of 2′-Substituted-4′-acetylmethanesulfonanilides



2

No.	X	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	N	Adjuvant arthritis % inhibition[d]
2a[b]	S	49	114—117	E	$C_{15}H_{13}F_2NO_3S_2$	50.41 (50.61)	3.67 3.54	3.92 3.89)	81[f]
2b[b]	SO	58	151—152	E	$C_{15}H_{13}F_2NO_4S_2$	48.25 (48.29	3.51 3.11	3.75 3.70)	53
2c[b]	SO_2	83	183—184	E	$C_{15}H_{13}F_2NO_5S_2$	46.27 (46.99	3.36 2.80	3.60 3.56)	23
2d[b]	NH	85	130—132	E	$C_{15}H_{14}F_2N_2O_3S$	52.94 (52.98	4.15 4.13	8.23 8.20)	74[e]
2e[b]	NCH_3	32	152—154	E	$C_{16}H_{16}F_2N_2O_3S$	54.23 (54.29	4.55 4.36	7.91 7.88)	−42
2f[c]	CO	35	114—117	E–EA	$C_{16}H_{13}F_2NO_4S$	54.39 (54.50	3.71 3.91	3.96 3.94)	56[f]
2g[b]	NHCO	45	202—204	E	$C_{16}H_{14}F_2N_2O_4S$	52.17 (52.06	3.83 3.79	7.61 7.49)	−12
2h[c]	CONH	51	153—155	EA–A	$C_{16}H_{14}F_2N_2O_4S$	52.17 (52.02	3.83 4.02	7.61 7.64)	17
1	O								79[f]

a) E=ethanol, EA=ethyl acetate, A=acetone. *b*) Synthetic methods are shown in Chart 1 and Experimental. *c*) Synthetic methods are shown in Chart 2 and Experimental. *d*) 10 mg/kg *p.o.* (uninjected paw). *e*) $p<0.05$. *f*) $p<0.01$.

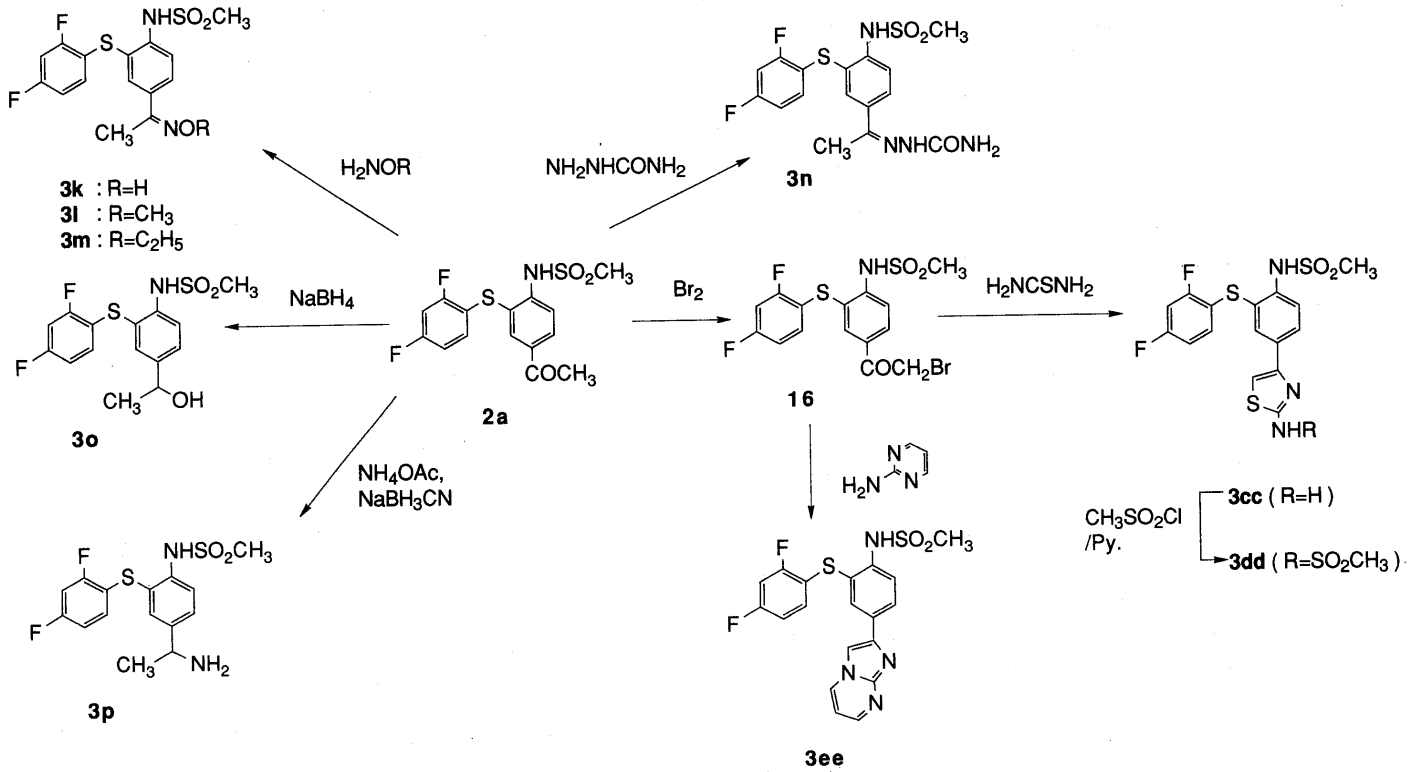
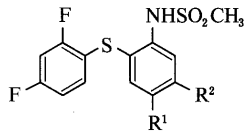


Chart 4

Most of the 2′-(arylthio)methanesulfonanilides (**3** and **4**) listed in Tables II and III were prepared *via* the synthetic route shown in Chart 3. Condensation of **5** with thiols gave 2-(arylthio)nitrobenzene derivatives (**6**). Reduction and sulfonylation of **6** in a manner similar to that described for **2a** afforded compounds **3** and **4**.

Some of the 2′-(phenylthio)methanesulfonanilide derivatives (**3**) were obtained from the 4′-acetyl, 4′-propionyl, and

TABLE II. Physical and Pharmacological Properties of 2′-(2,4-Difluorophenylthio)-4′,5′-disubstituted Methanesulfonanilides (**3**)



3

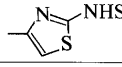
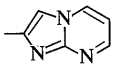
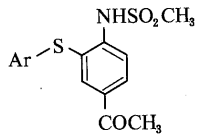
No.	R^1	R^2	Yield (%)	mp (°C)	Recrystn.[a] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Adjuvant arthritis % inhibition[g]
3a[b]	COOH	H	52	154–155	E	$C_{14}H_{11}F_2NO_4S_2$	46.79 (46.82)	3.09 3.09	3.90 3.97)	40
3b[c]	$CONH_2$	H	54	176—178	E	$C_{14}H_{12}F_2N_2O_3S_2$	46.92 (46.89)	3.37 3.34	7.82 7.75)	70[i]
3c[c]	$CONHCH_3$	H	76	154—155	E	$C_{15}H_{14}F_2N_2O_3S_2$	48.38 (48.15)	3.79 3.83	7.52 7.50)	74[i]
3d[c]	$CONHC_2H_5$	H	71	174—176	E	$C_{16}H_{16}F_2N_2O_3S_2$	49.73 (49.70)	4.17 4.17	7.25 7.17)	66[i]
3e[c]	$CON(CH_3)_2$	H	75	145—146	E	$C_{16}H_{16}F_2N_2O_3S_2$	49.73 (49.56)	4.17 4.27	7.25 7.21)	52[i]
3f[c]	$CONHCH(CH_3)_2$	H	75	200—201	E	$C_{17}H_{18}F_2N_2O_3S_2$	50.99 (51.04)	4.53 4.74	6.99 6.85)	17
3g[c]	CONHPh	H	84	187—188	E	$C_{20}H_{16}F_2N_2O_3S_2 \cdot 1/2H_2O$	54.16 (54.29)	3.86 3.89	6.31 6.19)	−1
3h[c]	$CONHCH_2Ph$	H	71	166—168	E	$C_{21}H_{18}F_2N_2O_3S_2$	56.24 (55.86)	4.04 3.85	6.25 6.21)	−30
3i[c]	$CONH(CH_2)_2N(C_2H_5)_2 \cdot HCl$	H	32	155—157	[f]	$C_{20}H_{25}F_2N_2O_3S_2 \cdot HCl \cdot 3/2H_2O$	46.10 (45.90)	5.41 5.21	8.06 8.11)	−51
3j[b]	$CONHCH_2COOH$	H	67	210—211	E	$C_{16}H_{14}F_2N_2O_5S_2$	46.15 (46.27)	3.39 3.48	6.73 6.70)	−26
3k[d]	$C(CH_3)=NOH$	H	87	196—197	E	$C_{15}H_{14}F_2N_2O_3S_2$	48.38 (48.38)	3.79 3.86	7.52 7.43)	15
3l[d]	$C(CH_3)=NOCH_3$	H	83	110—111	E	$C_{16}H_{16}F_2N_2O_3S_2$	49.73 (49.92)	4.17 4.33	7.25 7.19)	69[i]
3m[d]	$C(CH_3)=NOC_2H_5$	H	89	100—101	E	$C_{17}H_{18}F_2N_2O_3S_2$	50.99 (50.92)	4.53 4.57	6.99 6.95)	51[h]
3n[d]	$C(CH_3)=NNHCONH_2$	H	86	201—203 (dec.)	M	$C_{16}H_{15}F_2N_4O_3S_2$	46.37 (46.59)	3.89 3.79	13.52 13.40)	−1
3o[d]	$CH(OH)CH_3$	H	66	118—120	E–W	$C_{15}H_{15}F_2NO_3S_2$	50.13 (50.14)	4.21 4.22	3.90 4.04)	90[i]
3p[d]	$CH(NH_2)CH_3$	H	34	165—166	E	$C_{15}H_{16}F_2N_2O_2S_2$	50.27 (49.81)	4.50 4.46	7.82 7.75)	68[i]
3q[c]	COC_2H_5	H	70	95—97	E	$C_{16}H_{13}F_2NO_3S_2$	51.74 (51.73)	4.07 3.87	3.77 3.78)	42[i]
3r[e]	$CH(OH)C_2H_5$	H	56	57—58	E	$C_{16}H_{17}F_2NO_3S_2$	51.46 (51.50)	4.59 4.52	3.75 3.70)	30
3s[e]	$CH(NH_2)C_2H_5$	H	23	163—164	E	$C_{16}H_{18}F_2N_2O_2S_2$	51.60 (51.61)	4.87 4.88	7.52 7.54)	62[i]
3t[e]	$COC(=NOH)CH_3$	H	90	140—143	E	$C_{16}H_{14}F_2N_2O_4S_2$	47.99 (47.97)	3.52 3.46	7.00 6.90)	−17
3u[e]	$COCOCH_3$	H	37	108—109	E	$C_{16}H_{13}F_2NO_4S_2$	49.86 (49.84)	3.40 3.27	3.64 3.71)	21
3v[c]	CN	H	51	134—135	E	$C_{14}H_{10}F_2N_2O_2S_2$	49.40 (49.60)	2.96 2.94	8.23 8.52)	49[i]
3w[e]	$COCH_2Ph$	H	41	120—122	E	$C_{21}H_{17}F_2NO_3S_2$	58.18 (58.52)	3.95 4.29	3.23 3.27)	−2
3x[e]	$CH(OH)CH_2Ph$	H	74	83—84	E–H	$C_{21}H_{19}F_2N_2O_3S_2$	57.91 (58.30)	4.40 4.39	3.22 3.19)	41[h]
3y[e]	CHO	H	87	109—110	E	$C_{14}H_{11}F_2NO_3S_2$	48.97 (49.37)	3.23 3.33	4.08 4.62)	−26
3z[e]	CH_2OH	H	74	119—120	E	$C_{14}H_{13}F_2NO_3S_2$	48.69 (49.03)	3.79 3.90	4.06 4.59)	34
3aa[c]	SCH_3	H	56	86—88	E	$C_{14}H_{13}F_2NO_2S_3$	46.52 (46.40)	3.62 3.57	3.88 3.89)	47[h]
3bb[c]	SO_2CH_3	H	64	179—180	E	$C_{19}H_{13}F_2NO_4S_3$	42.74 (42.69)	3.33 3.26	3.88 3.89)	4
3cc[d]	 ·HBr	H	92	134—137	[f]	$C_{16}H_{13}F_2N_3O_2S_3 \cdot HBr \cdot H_2O$	37.51 (37.64)	3.15 3.24	8.20 8.18)	8
3dd[d]		H	24	159—161	M	$C_{17}H_{15}F_2N_3O_4S_4 \cdot H_2O$	40.06 (40.08)	3.36 3.11	8.24 8.25)	−1

TABLE II. (continued)

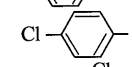
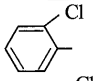
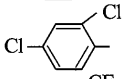
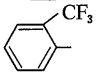
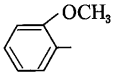
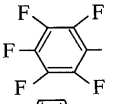
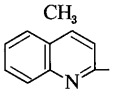
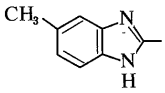
No.	R^1	R^2	Yield (%)	mp (°C)	Recrystn.[a] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Adjuvant arthritis % inhibition[g]
3ee[d]		H	25	216—218	EA	$C_{19}H_{14}F_2N_4O_2S_2$	52.77 (52.92	3.26 3.45	12.96 12.64)	54[h]
3ff[e]	$CH=CHCOCH_3$	H	76	119—120	E	$C_{17}H_{15}F_2NO_3S_2$	53.25 (53.04	3.94 3.88	3.65 3.76)	19
3gg[c]	H	$COCH_3$	73	131—132	E	$C_{15}H_{13}F_2NO_3S_2$	50.41 (50.29	3.67 3.67	3.92 3.92)	52[h]
3hh[c]	CN	CH_3	51	137—139	E	$C_{15}H_{12}F_2N_2O_2S_2$	50.84 (50.11	3.41 3.49	7.90 7.75)	75[i]

a) E=ethanol, W=water, H=hexane, M=methanol, EA=ethyl acetate. *b*) Obtained by hydrolysis of the corresponding ester. See Experimental. *c*) Compounds were prepared according to the route shown in Chart 3. *d*) Synthetic routes are shown in Chart 4. *e*) Synthetic routes are shown in Chart 5. *f*) Not recrystallized (washed with EtOH). *g*) 10 mg/kg *p.o.* (uninjected paw). *h*) $p<0.05$. *i*) $p<0.01$.

TABLE III. Physical and Pharmacological Properties of 2′-(Arylthio)-4′-acetylmethanesulfonanilides (**4**)[a]



4

No.	Ar	Yield (%)	mp (°C)	Recrystn.[b] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Adjuvant arthritis % inhibition[c]
4a		60	76—78	E	$C_{15}H_{15}NO_3S_2$	56.05 (56.58	4.70 4.73	4.36 4.39)	32[d]
4b		44	120—121	E	$C_{15}H_{14}ClNO_3S_2$	50.64 (50.85	3.94 3.78	3.94 4.01)	38
4c		39	139—142	E	$C_{15}H_{14}ClNO_3S_2$	50.63 (50.17	3.97 4.03	3.94 3.91)	72[e]
4d		52	190—193	EA–E–D	$C_{15}H_{13}Cl_2NO_3S_2$	46.16 (46.14	3.36 3.37	3.59 3.57)	45
4e		32	155—157	E	$C_{16}H_{14}F_3NO_3S_2$	49.35 (49.31	3.62 3.60	3.62 3.59)	−35
4f		39	107—109	E	$C_{16}H_{17}NO_4S_2$	54.68 (54.77	4.88 4.97	3.99 4.02)	12
4g		41	122—123	E	$C_{15}H_{10}F_5NO_3S_2$	43.79 (43.99	2.45 2.49	3.41 3.37)	1
4h		52	98—99	E	$C_{16}H_{13}NO_3S_3$	47.68 (47.47	4.00 4.05	4.28 4.26)	−30
4i		29	115—116	E	$C_{14}H_{14}N_2O_3S_2$	52.15 (52.10	4.36 3.68	8.69 8.67)	51[d]
4j		57	126—128	E	$C_{12}H_{12}N_2O_3S_3$	43.88 (43.56	3.68 3.64	8.53 8.53)	35
4k		32	167—168	E–EA	$C_{11}H_{13}N_5O_3S_2$	40.35 (40.50	4.00 3.99	21.39 21.25)	−57[e]
4l		15	158—159	E	$C_{18}H_{16}N_2O_3S_2 \cdot 1/4H_2O$	57.37 (57.20	4.34 4.41	7.43 7.19)	13
4m		18	187—189	E	$C_{17}H_{17}N_3O_3S_2$	54.38 (53.98	4.57 4.70	11.19 10.97)	13

a) All compounds were prepared according to the route shown in Chart 3. *b*) E=ethanol, EA=ethyl acetate, D=*N*,*N*-dimethylformamide. *c*) 10 mg/kg *p.o.* (uninjected paw). *d*) $p<0.05$. *e*) $p<0.01$.

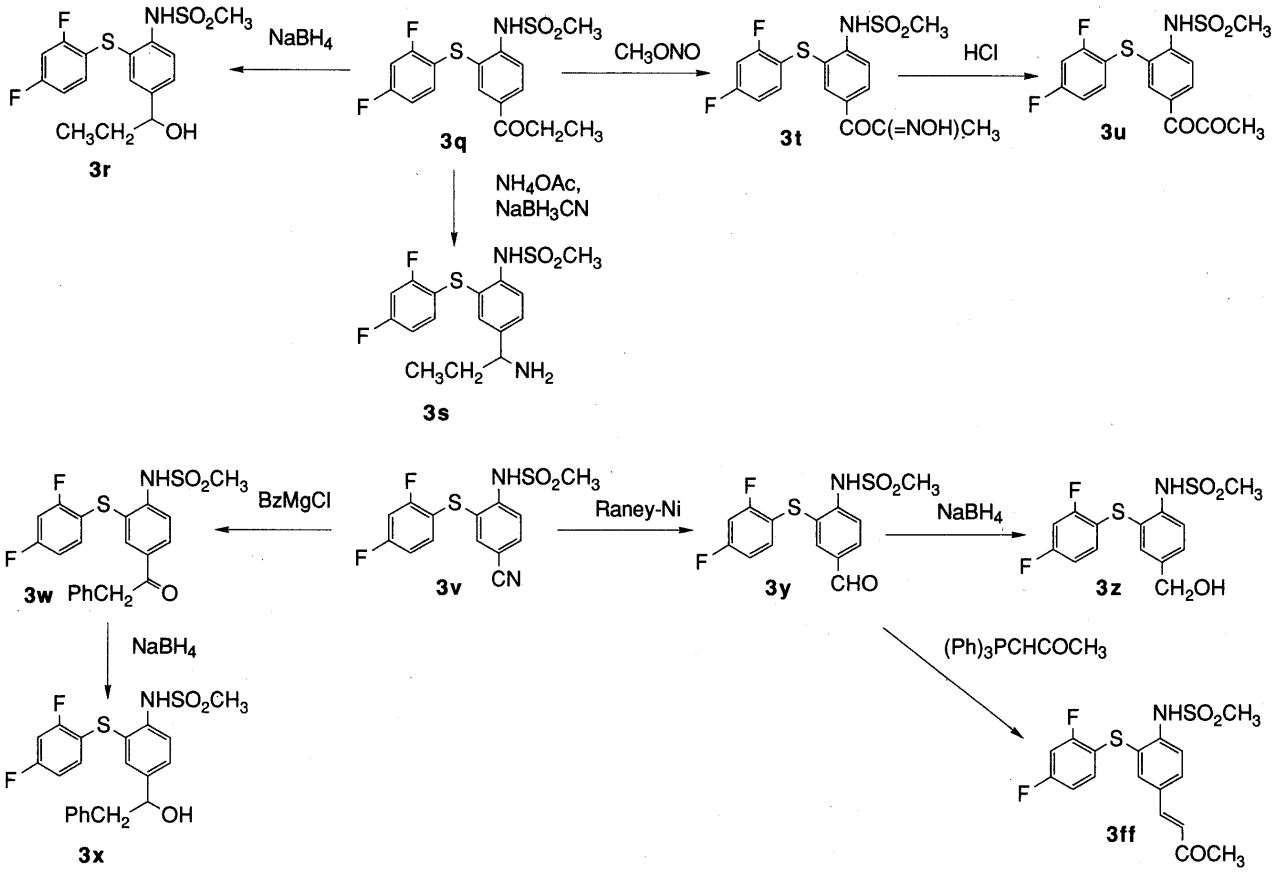


Chart 5

4′-cyano derivatives (**2a**, **3q** and **3v**) as shown in Charts 4 and 5. Oxime derivatives (**3k**—**m**) were prepared by the treatment of **2a** with appropriate hydroxylamines. The semicarbazone (**3n**) was prepared from **2a** and semicarbazide in refluxing ethanol. Reduction of **2a** with sodium borohydride afforded the 4′-(1-hydroxyethyl) derivative (**3o**). Similarly, the 4′-(1-aminoethyl) derivative (**3p**) was prepared by reductive amination of **2a** with sodium cyanoborohydride and ammonium acetate. 4′-(2-Amino-4-thiazolyl) and 4′-(imidazo[1,2-*a*]pyrimidin-2-yl) derivatives (**3cc** and **3ee**) were prepared through the bromoacetyl derivative (**16**) by treatment with thiourea or 2- aminopyrimidine. Compound **3cc** was converted to the methylsulfonyl derivative (**3dd**) by using methanesulfonyl chloride in pyridine. The 4′-propionyl derivative (**3q**) was converted to 4′-(1-hydroxypropyl) and 4′-(1-aminopropyl) derivatives (**3r** and **3s**) by methods similar to those used for **3o** and **3p**. The 4′-pyruvoyl derivative (**3u**) was obtained by hydrolysis of the oxime (**3t**), which was prepared by oxidation of **3q** with freshly prepared methyl nitrite. The 4′-cyano derivative (**3v**) was treated with Grignard reagent to afford the 4′-phenylacetyl derivative (**3w**), which was subsequently converted to the 4′-(1-hydroxy-2-phenylethyl) derivative (**3x**). The 4′-formyl derivative (**3y**), which was prepared from **3v** and Raney nickel, was converted to the 4′-hydroxymethyl derivative (**3z**) by reduction with sodium borohydride and to the 3-oxo-1-butenyl derivative (**3ff**) by reaction with 1-triphenylphosphoranylidene-2-propanone.

The benzonitrile **6c** was converted to ester and amide derivatives as depicted in Chart 6. The ester **6e** was prepared by esterification of the carboxylic acid **6d**, which was

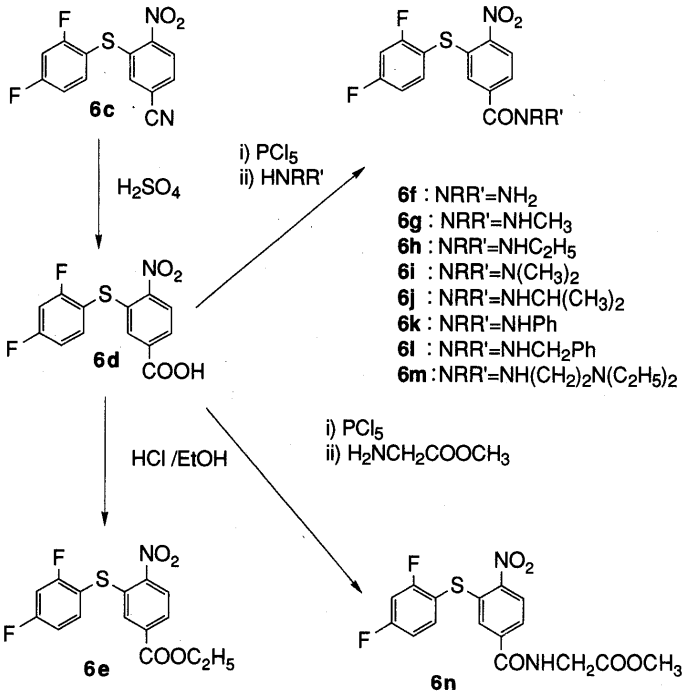


Chart 6

obtained by hydrolysis of **6c** with sulfuric acid. Compound **6d** was converted to the acid chloride by using phosphorus pentachloride. Various amide derivatives (**6f**—**m**) were obtained by reaction of the acid chloride and appropriate amines. The acid chloride was also treated with glycine

methylester to afford **6n**.

Pharmacological Results and Discussion

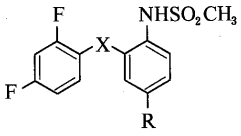
The methanesulfonanilide derivatives (**2**—**4**) were first tested for antiinflammatory activity, which was assessed in terms of inhibition of adjuvant arthritis in rats. The results are summarized in Tables I—III. The structure–activity relationship for these compounds may be discussed in three parts: (i) the connecting group (X) between the two benzene rings in **2**, (ii) the substituents (R^1, R^2) on the right hand benzene ring in **3**, (iii) the left hand aromatic part (Ar) in **4**.

As a first step in the chemical modification of **1** (FK3311), we designed a series of compounds (**2a**—**h**), which had various connecting groups (X) as a surrogate of the oxygen atom in **1**. This modification of X could change the physicochemical properties of the whole molecule and the acidity as well as the steric environment of the methylsulfonylamino moiety, which was proposed to be one of the essential pharmacophores in the molecule. As shown in Table I, the maximum activity was achieved with the thio derivative (**2a**). The amino (**2d**) and carbonyl (**2f**) derivatives also showed fairly potent activity. On the other hand, the compounds that had bulky connecting groups such as sulfinyl (**2b**), sulfonyl (**2c**), methylamino (**2e**) and amido (**2g** and **2h**) were weak or inactive. As a further evaluation, antirheumatic activities of **2a** and **2d** were investigated in comparison with **1** using the type II collagen-induced arthritis model in mice (Table IV). Among the three compounds, **2a** showed the most potent activity, especially in terms of inhibition of anti type II collagen antibody production. Therefore, we selected **2a** as a lead compound for further modification.

In Table II, the results of the structural modification of R^1 and R^2 in **3** are summarized. On the basis of structure–activity relationship of FK3311,[1] electron-attracting groups were selected as substituents R^1. As expected, amide (**3b**—**e**) derivatives showed good activity. Introduction of bulky substituents such as isopropyl (**3f**), phenyl (**3g**) and benzyl (**3h**) on the amide group resulted in loss of activity. Hydrophilic amide derivatives (**3i** and **3j**) were also inactive. Oxime (**3l** and **3m**), 1-hydroxyethyl (**3o**) and 1-aminoethyl (**3p**) derivatives showed moderate to excellent activity. These derivatives are probably metabolically equivalent to the acetyl derivative (**2a**). In contrast, propionyl (**3q**), 1-hydroxypropyl (**3r**) and 1-aminopropyl (**3s**) derivatives were less active than the corresponding C_2 derivatives (**2a**, **3o** and **3p**). Introduction of other electron-attracting groups (**3a**, **3t**—**w** and **3y**), sulfur-containing groups (**3aa** and **3bb**) and heteroaromatic rings (**3cc**—**3ee**) also resulted in compounds exhibiting weak or marginal effects. With regard to the influence of substitution at R^1 or R^2, the 5′-acetyl derivative (**3gg**) was shown to be significantly less active than its 4′-acetyl analog (**2a**). Compound **3hh**, having an additional methyl group in the R^2 position, was superior to the corresponding unsubstituted **3v**, but this compound was excluded from further evaluation due to a side effect (vomiting) in mice at 100 mg/kg. The five most potent compounds (**3b**, **3c**, **3l**, **3o** and **3p**) were subsequently examined in the collagen-induced arthritis model.

Concerning the derivatives modified in the aryl part, all compounds (**4a**—**m**) except **4c** were weakly active or inactive as shown in Table III. The 2-chlorophenyl derivative **4c** showed potent activity but also severe toxicity (8 out of 10 mice died in the collagen-induced arthritis experiment at 100 mg/kg).

TABLE IV. Effects of Selected Compounds on Type II Collagen-Induced Arthritis in Mice



No.	X	R	Collagen arthritis % inhibition			
			100 mg/kg		10 mg/kg	
			Arthritic score	Anti CIIAb[a)]	Arthritic score	Anti CIIAb[a)]
2a	S	$COCH_3$	47[b)]	69[d)]	4	NT
2d	NH	$COCH_3$	43[c)]	45[c)]	15	1
3b	S	$CONH_2$	43[d)]	61[d)]	41[c)]	51[c)]
3c	S	$CONHCH_3$	71[d)]	53[d)]	2	17
3l	S	$C(CH_3)=NOCH_3$	53[d)]	51[c)]	34[c)]	41[c)]
3o	S	$CO(OH)CH_3$	37	73[d)]	31	23
3p	S	$CO(NH_2)CH_3$	57[b)]	48[b)]	15	30
1	O	$COCH_3$	NE	NE	NT	NT

NE: no effect. NT: not tested. *a*) Anti type II collagen antibody. *b*) $p<0.05$. *c*) $p<0.01$. *d*) $p<0.001$.

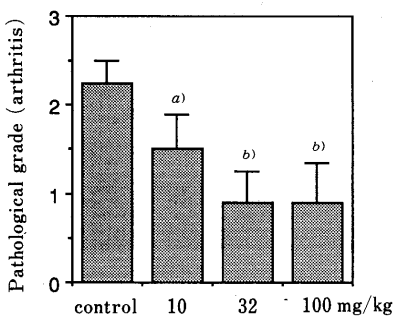


Fig. 2. Effect of **3b** on MRL/lpr Mice

3b was orally administered for 13 weeks. *a*) $p<0.05$. *b*) $p<0.01$.

Table IV summarizes the effects of the selected compounds on collagen-induced arthritis. Two compounds (**3b** and **3l**) significantly inhibited both arthritic score and anti collagen antibody production even at 10 mg/kg. Antiarthritic activity of these compounds was further evaluated in a spontaneous autoimmune disease model, MRL/lpr mouse. Compound **3b** inhibited arthritic syndrome in this model in a dose-dependent manner from 10 mg/kg, as depicted in Fig. 2.

In conclusion, the chemical modification of **1** has led to a novel compound **3b** (FR115068), which possesses a broad spectrum of both antiinflammatory and immunoregulatory activities as shown in the adjuvant arthritis, collagen-induced arthritis, and MRL/lpr mouse assays. Compound **3b** should be able not only to reduce arthritic inflammation but also to ameliorate immunological abnormalities of RA in the clinic. Compound **3b** was thus selected as a candidate for further development. Its detailed pharmacological activities and mechanism of action will be reported elsewhere in due course.

Experimental

Melting points were measured on a Mitamura capillary melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-408 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a Varian EM-390 instrument using tetramethylsilane as an internal standard. Organic extracts were dried over anhydrous $MgSO_4$. Column chromatography was performed using Kieselgel 60 (70—230 mesh, E. Merck).

Synthetic methods, yields, melting points, recrystallization solvents and analysis data of **2**—**4** are summarized in Tables I—III and spectral data are given in Table VII. Synthetic methods, yields, melting points, and spectral data of **6** are summarized in Tables V and VI.

Potassium 2,4-Difluorothiophenoxide 2,4-Difluorothiophenol, which was prepared from 2,4-difluoroaniline (50 g, 0.38 mol) as described in the literature,[6] was dissolved in a solution of potassium hydroxide (22 g, 0.39 mol) in MeOH (300 ml). The solvent was evaporated off, and the residue was washed with Et_2O to afford the title product (58 g, 82%) as a powder, mp >250 °C. IR (Nujol): 3300, 1640, 1595 cm^{-1}.

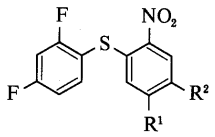
3′-(2,4-Difluorophenylthio)-4′-nitroacetophenone (6a) A mixture of **5a** (2.4 g, 12 mmol),[1] potassium 2,4-difluorothiophenoxide (2.7 g, 14.7 mmol), and *N*,*N*-dimethylformamide (DMF) (5 ml) in xylene (50 ml) was stirred at room temperature for 8 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated under reduced pressure. The residual solid was recrystallized from EtOH to afford **6a** (2.3 g, 57%).

4′-Acetyl-2′-(2,4-difluorophenythio)methanesulfonanilide (2a) Iron powder (2.0 g, 36 mmol) and ammonium chloride (200 mg, 3.7 mmol) were added to a solution of **6a** (2.3 g, 7.4 mmol) in EtOH (20 ml) and H_2O (10 ml) and then the reaction mixture was refluxed for 1 h. The hot reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue obtained was dissolved in a mixture of EtOAc and H_2O. The organic layer was washed with brine, dried, and evaporated to afford 4′-amino-3′-(2,4-difluorophenylthio)acetophenone (2.0 g). Methanesulfonyl chloride (1.0 g, 8.7 mmol) was added to a solution of the above aminoacetophenone derivative in pyridine (20 ml) at 0 °C, and the reaction mixture was stirred overnight. The mixture was poured into cold diluted HCl and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated under reduced pressure. The residue was recrystallized from EtOH to afford **2a** (1.3 g, 49%).

4′-Acetyl-2′-(2,4-difluorophenylsulfinyl)methanesulfonanilide (2b) *m*-Chloroperbenzoic acid (80%, 0.76 g, 3.5 mmol) was added to a solution of **2a** (1.2 g, 3.4 mmol) in CH_2Cl_2 (12 ml) at 0—5 °C, and the mixture was stirred for 1 h, then washed successively with a saturated $NaHCO_3$ solution, H_2O, and brine, and dried. After removal of the solvent, the residue was recrystallized from EtOH to afford **2b** (730 mg, 58%).

4′-Acetyl-2′-(2,4-difluorophenylsulfonyl)methanesulfonanilide (2c) Hydrogen peroxide (30%, 1 ml) was added dropwise to a stirred solution of **2a** (1.2 g, 3.4 mmol) in AcOH (7 ml). The mixture was stirred at 70 °C for 1 h, then cooled, and poured into an aqueous $NaHCO_3$ solution (50 ml). The precipitates were collected by filtration and recrystallized from a

TABLE V. 2-(Phenylthio)nitrobenzene Derivatives (**6**)

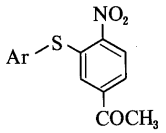


6

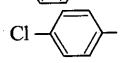
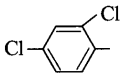
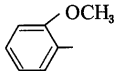
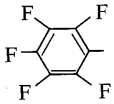
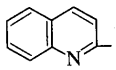
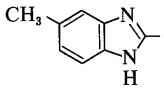
No.	R^1	R^2	Yield (%)	mp (°C)	IR ν_{max}^{Nujol} (cm^{-1})	NMR ($CDCl_3$) δ (ppm)
6a[a]	$COCH_3$	H	57	141—143	1695, 1595, 1575, 1510	2.45 (3H, s), 6.90—8.40 (6H, m)
6b[a]	COC_2H_5	H	50	128—130	1700, 1600, 1575, 1515	1.00 (3H, t, J=7 Hz), 2.96 (2H, q, J=7 Hz), 7.20—8.10 (5H, m), 8.44 (1H, d, J=8 Hz)[d]
6c[a]	CN	H	84	145—147	2240, 1600, 1515	7.20—8.10 (5H, m), 8.40 (1H, d, J=8 Hz)[d]
6d[b]	COOH	H	95	215—217	1700, 1600, 1515	6.90—8.01 (5H, m), 8.32 (1H, d, J=8 Hz)
6e[c]	$COOC_2H_5$	H	84	66—68	1725, 1600, 1515	1.31 (3H, t, J=7 Hz), 2.30 (2H, q, J=8 Hz), 6.90—8.00 (5H, m), 8.30 (1H, d, J=8 Hz)
6f[c]	$CONH_2$	H	69	170—172	3500, 3200, 1690, 1590, 1580, 1510	7.32—8.10 (5H, m), 8.40 (1H, d, J=8 Hz)[d]
6g[c]	$CONHCH_3$	H	68	142—143	3350, 1645, 1580, 1550, 1510	2.97 (3H, d, J=6 Hz), 6.17 (1H, br s), 6.87—7.80 (5H, m), 8.25 (1H, d, J=8 Hz)
6h[c]	$CONHC_2H_5$	H	91	144—147	3300, 1630, 1595, 1570, 1510	1.23 (3H, t, J=6 Hz), 3.23—3.73 (2H, m), 6.20 (1H, br s), 6.98—7.88 (5H, m), 8.30 (1H, d, J=8 Hz)
6i[c]	$CON(CH_3)_2$	H	91	105—108	1640, 1595, 1570, 1510	2.85 (3H, s), 3.06 (3H, s), 6.80—7.87 (5H, m), 8.32 (1H, d, J=8 Hz)
6j[c]	$CONHCH(CH_3)_2$	H	92	147—149	3300, 1635, 1600, 1570, 1550	1.23 (6H, d, J=6 Hz), 3.87—4.47 (1H, m), 5.87 (1H, br s), 6.90—8.00 (5H, m), 8.32 (1H, d, J=8 Hz)
6k[c]	CONHPh	H	91	175—177	3350, 1660, 1640, 1535	6.89—7.80 (10H, m), 8.33 (1H, d, J=8 Hz)
6l[c]	$CONHCH_2Ph$	H	93	130—132	3300, 1650, 1600, 1550, 1510	4.54 (2H, d, J=6 Hz), 6.37 (1H, br s), 6.87—7.87 (10H, m), 8.27 (1H, d, J=8 Hz)
6m[c]	$CON(CH_2)_2N(C_2H_5)_2$	H	100	Oil	3350, 1660, 1640, 1600, 1570, 1510[e]	1.10 (6H, t, J=7 Hz), 2.67 (4H, q, J=7 Hz), 2.75 (2H, t, J=7 Hz), 3.42—3.61 (2H, m), 6.53—7.02 (3H, m), 7.35 (1H, t, J=7 Hz), 7.65 (1H, dd, J=7, 2 Hz), 7.90 (1H, d, J=2 Hz)
6n[c]	$CONHCH_2COOCH_3$	H	95	139—140	3360, 1730, 1660, 1600, 1580, 1535	3.67 (3H, s), 4.00 (2H, d, J=6 Hz), 7.27—8.52 (6H, m), 9.27 (1H, t, J=6 Hz)
6o[a]	SCH_3	H	82	124—125	1600, 1570, 1560, 1480	2.25 (3H, s), 6.42—7.90 (5H, m), 8.12 (1H, d, J=8 Hz)
6p[a]	SO_2CH_3	H	59	152—153	1600, 1510	2.98 (3H, s), 7.00—7.80 (5H, m), 8.42 (1H, d, J=8 Hz)
6q[a]	H	$COCH_3$	95	118—119	1690, 1600, 1520	2.67 (3H, s), 6.87—8.05 (5H, m), 8.80 (1H, d, J=8 Hz)
6r[a]	CN	CH_3	64	168—174	2230, 1595, 1555, 1520	2.60 (3H, s), 6.90—7.90 (4H, m), 8.20 (1H, s)

a) Synthetic methods are shown in Chart 3. *b*) Obtained from **6c** according to the synthetic route shown in Chart 6. *c*) Obtained from **6d** according to the synthetic route shown in Chart 6. *d*) Measured in DMSO-d_6. *e*) Taken as a liquid film.

TABLE VI. 2-(Arylthio)nitrobenzene Derivatives (6)[a]



6

No.	Ar	Yield (%)	mp (°C)	IR ν_{max}^{Nujol} (cm^{-1})	NMR ($CDCl_3$) δ (ppm)
6s		78	144—145	1690, 1595, 1575, 1510	2.35 (3H, s), 7.35—7.80 (7H, m), 8.28 (1H, d, J=8 Hz)
6t		81	120—122	1695, 1590, 1575, 1510	2.45 (3H, s), 7.40—7.85 (6H, m), 8.30 (1H, d, J=8 Hz)
6u		71	136—139	1695, 1595, 1575, 1510	2.40 (3H, s), 7.25—7.80 (6H, m), 8.32 (1H, d, J=8 Hz)
6v		62	90—92	1690, 1575, 1510, 1450	2.48 (3H, s), 7.30—7.90 (5H, m), 8.33 (1H, d, J=8 Hz)
6w		31	Oil	1695, 1590, 1575, 1520	2.40 (3H, s), 7.20—8.20 (6H, m), 8.35 (1H, d, J=8 Hz)
6x		103	90—100	1695, 1590, 1580, 1510	2.37 (3H, s), 3.90 (3H, s), 7.00—7.80 (6H, m), 8.29 (1H, d, J=8 Hz)
6y		62	Oil	1700, 1645, 1590, 1575, 1515, 1490	2.56 (3H, s), 7.20 (1H, dd, J=8, 2 Hz), 7.40 (1H, d, J=2 Hz), 7.90 (1H, d, J=8 Hz)
6z		72	133—136	3100, 1695, 1595, 1575, 1510	2.50 (3H, s), 7.30—8.20 (5H, m), 8.42 (1H, d, J=8 Hz)[c]
6aa		54	Oil	1690, 1570, 1510[b]	2.34 (3H, s), 7.00—8.60 (7H, m)
6bb		59	92—94	1695, 1595, 1575, 1505	2.48 (3H, s), 7.60—8.40 (5H, m)
6cc		35	111—115	1695, 1615, 1570, 1500	2.56 (3H, s), 4.11 (3H, s), 7.89 (1H, d, J=2 Hz), 7.97 (1H, dd, J=8, 2 Hz), 8.35 (1H, d, J=8 Hz)
6dd		34	91—94	1690, 1615, 1570, 1500	2.64 (3H, s), 7.20—8.50 (9H, m)[c]
6ee		58	182—185	3120, 1695, 1590, 1520	2.35 (3H, s), 2.50 (3H, s), 6.90—8.00 (5H, m), 8.25 (1H, d, J=8 Hz)

a) All compounds were prepared according to the route shown in Chart 3. Synthesis of each compound is described in Experimental. *b*) Taken as a liquid film. *c*) Measured in DMSO-d_6.

mixture of EtOH and EtOAc to afford **2c** (1.1 g, 83%).

2-[3-(2,4-Difluorophenylamino)-4-nitrophenyl]-2-methyl-1,3-dioxolane (7) A mixture of **5b**[1] (7.9 g, 32 mmol), 2,4-difluoroaniline (20.9 g, 162 mmol), cupric oxide (800 mg, 10 mmol) and potassium carbonate (5.4 g, 39 mmol) was heated with vigorous stirring at 200 °C for 2 h, then allowed to cool, and H_2O (50 ml) and EtOAc (80 ml) were added. The resulting mixture was stirred for 30 min and filtered. The organic layer was separated, washed with H_2O, dried and evaporated under reduced pressure. The oily residue was chromatographed on a column of silica gel with toluene to afford **7** (10 g, 92%) as an oil. IR (Nujol): 3500, 3400, 1620, 1580 cm^{-1}.

4′-Amino-3′-(2,4-difluorophenylamino)acetophenone (8a) A mixture of **7** (10 g, 29.7 mmol) and 3 N HCl (20 ml) in acetone (40 ml) was stirred overnight at room temperature. After removal of the solvent, the residue obtained was dissolved in a mixture of EtOAc and saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried and evaporated to afford an oil (8.5 g). A mixture of the above oil (8.5 g), iron powder (8.0 g, 143 mmol), and ammonium chloride (800 mg, 15 mmol) in EtOH (100 ml) and H_2O (50 ml) was refluxed for 1 h. The hot reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue obtained was dissolved in a mixture of EtOAc and H_2O. The organic layer was washed with brine, dried, and evaporated under reduced pressure. The oily residue was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (20 : 1) to afford **8a** (1.74 g, 22%) as crystals, mp 121—123 °C. IR (Nujol): 3500, 3400, 3320, 1650, 1610, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.45 (3H, s), 4.00—4.60 (2H, br s), 5.00—5.50 (1H, br s), 6.40—7.00 (4H, m), 7.60—7.80 (2H, m).

4′-Amino-3′-(*N*-methyl-2,4-difluorophenylamino)acetophenone (8b) Sodium hydride (60% dispersion in mineral oil, 0.14 g, 3.6 mmol) was added portionwise to a solution of **7** (1.0 g, 3.0 mmol) in DMF (10 ml) at 0—5 °C and the reaction mixture was stirred for an additional 15 min. Methyl iodide (1.7 g, 12 mmol) was added to the resulting mixture at the same temperature. After stirring for 30 min, the reaction mixture was poured into ice-water (50 ml) and extracted with EtOAc. The organic layer was washed with H_2O, dried and evaporated under reduced pressure. The oily residue was chromatographed on a column of silica gel with toluene to afford an oil (0.88 g). This oil was treated with HCl and then with iron powder in a similar manner to that described for **8a** to give **8b** (147 mg, 18%) as crystals, mp 130—134 °C. IR (Nujol): 3450, 3350, 1645, 1615, 1560, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.30 (3H, s), 2.90 (3H, s), 5.60—8.50 (6H, m).

Compounds **2d** and **2e** were prepared by the same method as that used for **2a**.

2-(3-Cyano-4-nitrophenyl)-2-methyl-1,3-dioxolane (5c) A mixture of **5b**[1] (9.8 g, 40 mmol) and cuprous cyanide (4.0 g, 45 mmol) in DMF (20 ml)

TABLE VII. Spectral Data for **2**, **3** and **4**

No.	IR ν_{max}^{Nujol} (cm^{-1})	NMR δ (ppm)
2a	3250, 1680, 1595, 1490	($CDCl_3$): 2.55 (3H, s), 3.02 (3H, s), 6.70—8.30 (7H, m)
2b	3100, 1685, 1600, 1500	(DMSO-d_6): 2.60 (3H, s), 3.08 (3H, s), 7.10—8.30 (7H, m)
2c	3280, 1690, 1600	(DMSO-d_6): 2.60 (3H, s), 3.25 (3H, s), 7.20—8.50 (7H, m)
2d	3420, 3150, 1670, 1610, 1570, 1520	($CDCl_3$): 2.51 (3H, s), 3.08 (3H, s), 5.84 (1H, br s), 6.60—7.10 (3H, m), 7.32 (1H, br s), 7.57 (1H, d, J=8 Hz), 7.65—7.80 (2H, m)
2e	3270, 1680, 1600, 1505	(DMSO-d_6): 2.51 (3H, s), 3.03 (3H, s), 3.06 (3H, s), 6.60—7.20 (3H, m), 7.60—7.90 (4H, m)
2f	3100, 1690, 1640, 1615, 1600	($CDCl_3$): 2.55 (3H, s), 3.21 (3H, s), 6.70—8.30 (6H, m), 10.95 (1H, br s)
2g	3350, 1670, 1650, 1610, 1540, 1505	(DMSO-d_6): 2.62 (3H, s), 3.23 (3H, s), 6.90—7.70 (4H, m), 8.10 (1H, dd, J=8, 2 Hz), 8.48 (1H, d, J=2 Hz), 10.60 (1H, s), 10.85 (1H, s)
2h	3440, 3240, 1690, 1615, 1610	(DMSO-d_6): 2.55 (3H, s), 3.05 (3H, s), 7.10—8.10 (5H, m), 8.30 (1H, d, J=2 Hz), 9.45 (1H, br s), 9.80 (1H, br s)
3a	3240, 1690, 1600, 1485	(DMSO-d_6): 3.17 (3H, s), 7.15—7.97 (6H, m)
3b	3420, 3250, 3200, 1660, 1615	(DMSO-d_6): 3.13 (3H, s), 7.07—8.03 (7H, m), 9.50 (1H, s)
3c	3400, 3325, 1630, 1600	($CDCl_3$): 3.00 (3H, d, J=6 Hz), 3.00 (3H, s), 6.30 (1H, d, J=6 Hz), 6.70—8.03 (7H, m)
3d	3300, 1630, 1600, 1480	($CDCl_3$): 1.25 (3H, t, J=7 Hz), 3.00 (3H, s), 3.23—3.70 (2H, m), 6.22 (1H, br s), 6.75—8.03 (7H, m)
3e	3240, 1630, 1600	($CDCl_3$): 3.00 (3H, s), 3.04 (6H, s), 6.76—7.81 (7H, m)
3f	3280, 1630, 1600, 1480	(DMSO-d_6): 1.13 (6H, d, J=6 Hz), 3.13 (3H, s), 3.77—4.21 (1H, m), 7.00—8.30 (7H, m), 9.47 (1H, s)
3g	3325, 3275, 1650, 1600	(DMSO-d_6): 3.17 (3H, s), 7.04—8.07 (11H, m), 9.57 (1H, br s), 10.27 (1H, br s)
3h	3360, 3300, 1630, 1650	(DMSO-d_6): 3.13 (3H, s), 4.43 (2H, d, J=6 Hz), 7.00—7.97 (11H, m), 9.03 (1H, t, J=6 Hz), 9.00 (1H, br s)
3i	3300, 2625, 2470, 1640, 1600	($CDCl_3$ + CD_3OD): 1.32 (6H, t, J=6 Hz), 3.03 (3H, s), 3.17 (4H, q, J=6 Hz), 3.22 (2H, t, J=6 Hz), 3.56—3.78 (2H, m), 6.75—7.92 (6H, m)
3j	3450, 3250, 1750, 1625, 1600	(DMSO-d_6): 3.17 (3H, s), 3.90 (2H, d, J=6 Hz), 7.70—7.97 (6H, m), 8.87 (1H, t, J=6 Hz)
3k	3250, 1595, 1485, 1450	(DMSO-d_6): 2.07 (3H, s), 3.12 (3H, s), 7.03—7.73 (6H, m), 9.43 (1H, br s)
3l	3300, 1600	(DMSO-d_6): 2.07 (3H, s), 3.13 (3H, s), 3.87 (3H, s), 7.03—7.74 (6H, m), 9.42 (1H, br s)
3m	3250, 1600, 1485	(DMSO-d_6): 1.18 (3H, t, J=7 Hz), 2.03 (3H, s), 3.07 (3H, s), 4.10 (2H, q, J=7 Hz), 7.03—7.06 (6H, m), 9.04 (1H, s)
3n	3520, 3400, 1675, 1570	(DMSO-d_6): 2.05 (3H, s), 3.05 (3H, s), 6.33 (2H, br s), 7.00—8.00 (6H, m), 9.39 (2H, br s)
3o	3450, 3100, 1595, 1485	($CDCl_3$): 1.43 (3H, d, J=6 Hz), 1.87 (1H, s), 2.92 (3H, s), 4.85 (1H, q, J=6 Hz), 6.70—7.80 (7H, m)
3p	3120, 1595, 1485	(DMSO-d_6): 1.23 (3H, t, J=7 Hz), 2.73 (3H, s), 3.98 (1H, q, J=7 Hz), 5.88 (3H, br s), 6.78 (1H, s), 6.90—7.50 (5H, m)
3q	3310, 3240, 1685, 1595, 1490	(DMSO-d_6): 1.03 (3H, t, J=7 Hz), 2.97 (2H, q, J=7 Hz), 3.18 (3H, s), 7.00—8.10 (6H, m), 9.62 (1H, s)
3r	3500, 3300, 1600, 1480	($CDCl_3$):0.93 (3H, t, J=7 Hz), 1.50—2.10 (3H, m), 2.98 (3H, s), 4.40—4.80 (1H, m), 6.70—7.90 (7H, m)
3s	3150, 1600, 1465	(DMSO-d_6): 0.70 (3H, t, J=6 Hz), 1.37—1.74 (2H, m), 2.77 (3H, s), 3.70 (1H, t, J=6 Hz), 5.37 (2H, br s), 6.77 (1H, s), 6.97—7.48 (6H, m)
3t	3360, 3250, 1675, 1600	($CDCl_3$): 2.20 (3H, s), 3.00 (3H, s), 6.77—8.07 (7H, m), 8.65 (1H, s)
3u	3300, 1715, 1670, 1590	($CDCl_3$): 2.53 (3H, s), 3.07 (3H, s), 6.77—8.33 (7H, m)
3v	3240, 2240, 1595, 1485	($CDCl_3$): 3.05 (3H, s), 6.90—8.00 (7H, m)
3w	3300, 1680, 1595, 1560, 1485	($CDCl_3$): 2.97 (3H, s), 4.15 (2H, s), 6.70—8.20 (12H, m)
3x	3450, 3270, 1595, 1485	(DMSO-d_6): 2.80 (2H, d, J=6 Hz), 3.03 (3H, s), 4.50—4.90 (1H, m), 5.31 (1H, d, J=5 Hz), 6.90—7.60 (11H, m), 9.23 (1H, br s)
3y	3250, 1700, 1600, 1485	($CDCl_3$): 3.08 (3H, s), 6.77—8.10 (7H, m), 9.94 (1H, s)
3z	3250, 1600, 1485, 1460	($CDCl_3$): 1.82 (1H, br s), 2.97 (3H, s), 4.69 (2H, s), 6.75—7.80 (7H, m)
3aa	3250, 1600, 1485, 1470	($CDCl_3$): 2.47 (3H, s), 2.95 (3H, s), 6.77—7.72 (7H, m)
3bb	3250, 1590, 1480, 1460	(DMSO-d_6): 3.20 (6H, s), 7.05—8.00 (6H, m), 9,82 (1H, s)
3cc	3460, 3400, 3300, 3100, 1625	(DMSO-d_6): 3.13 (3H, s), 7.14—7.70 (9H, m), 9.50 (1H, br s)
3dd	3550, 3250, 1535, 1490	(DMSO-d_6): 3.00 (3H, s), 3.13 (3H, s), 7.10—7.81 (8H, m), 9.50 (1H, br s)
3ee	3300, 1620, 1470	(DMSO-d_6): 3.13 (3H, s), 6.95—9.00 (9H, m), 8.30 (1H, s), 9.47 (1H, s)
3ff	3300, 1660, 1500, 1460	($CDCl_3$): 2.37 (3H, s), 3.00 (3H, s), 6.49—7.84 (9H, m)
3gg	3250, 1675, 1595	($CDCl_3$): 2.60 (3H, s), 3.07 (3H, s), 6.83—8.20 (7H, m)
3hh	3230, 2220, 1600, 1550	($CDCl_3$): 2.52 (3H, s), 3.01 (3H, s), 6.70—7.50 (3H, m), 7.58 (1H, s), 7.73 (1H, s), 7.83 (1H, br s)
4a	3360, 1685, 1595, 1485	(DMSO-d_6): 2.52 (3H, s), 3.13 (3H, s), 7.40—8.10 (8H, m), 9.42 (1H, br s)
4b	3250, 1680, 1595, 1560, 1490	(DMSO-d_6): 2.60 (3H, s), 2.93 (3H, s), 7.00—8.30 (8H, m)
4c	3280, 1675, 1590, 1560	(DMSO-d_6): 2.53 (3H, s), 3.16 (3H, s), 6.70—8.20 (7H, m), 9.52 (1H, br s)
4d	3250, 1672, 1580, 1560	(DMSO-d_6): 2.47 (3H, s), 3.06 (3H, s), 6.75—8.10 (6H, m), 9.48 (1H, br s)
4e	3280, 1680, 1590, 1560	(DMSO-d_6): 2.50 (3H, s), 3.15 (3H, s), 7.00—8.20 (7H, m), 9.45 (1H, br s)
4f	3260, 1670, 1590, 1560	(DMSO-d_6): 2.45 (3H, s), 3.06 (3H, s), 3.79 (3H, s), 6.70—8.00 (7H, m), 9.17 (1H, br s)
4g	3280, 1685, 1640, 1590, 1510, 1495	(DMSO-d_6): 2.53 (3H, s), 3.20 (3H, s), 7.50—8.10 (3H, m), 9.80 (1H, br s)
4h	3300, 1675, 1590, 1490	(DMSO-d_6): 2.47 (3H, s), 3.17 (3H, s), 7.10—8.00 (6H, m), 9.66 (1H, br s)
4i	3240, 1680, 1600, 1580	(DMSO-d_6): 2.54 (3H, s), 3.00 (3H, s), 7.00—8.40 (7H, m), 8.87 (1H, br s)
4j	3260, 1680, 1600, 1560	(DMSO-d_6): 2.57 (3H, s), 3.15 (3H, s), 7.60—8.20 (5H, m), 9.77 (1H, br s)
4k	3270, 1685, 1595, 1565	(DMSO-d_6): 2.51 (3H, s), 3.09 (3H, s), 3.98 (3H, s), 7.90—8.10 (3H, m), 9.70 (1H, br s)
4l	3250, 1675, 1595, 1560, 1495	(DMSO-d_6): 2.60 (3H, s), 3.02 (3H, s), 7.20—8.30 (9H, m), 9.14 (1H, br s)
4m	3300, 1685, 1595, 1490	(DMSO-d_6): 2.39 (3H, s), 2.52 (3H, s), 3.13 (3H, s), 6.90—8.10 (6H, m)

was refluxed for 11 h. An aqueous solution of sodium bicarbonate (200 ml) and EtOAc (100 ml) were added to the reaction mixture. After stirring for several minutes, the mixture was filtered. The organic layer was dried and evaporated under reduced pressure. The residue obtained was chromatographed on a column of silica gel with a mixture of toluene and EtOAc to afford the title compound (4.6 g, 49%) as crystals, mp 65—66 °C. IR (Nujol): 2230, 1590, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.70 (3H, s), 3.70—4.40 (4H, M), 7.80—8.20 (2H, m), 8.35 (1H, d, J=8 Hz).

5-Acetyl-2-(methylsulfonylamino)benzoic Acid (9) A mixture of **5c** (3.90 g, 16.7 mmol), iron powder (3.9 g, 70 mmol) and ammonium chloride (400 mg, 7.5 mmol) in EtOH (50 ml) and H_2O (25 ml) was treated in a manner similar to that described for **2a** to afford a solid (3.09 g). Methanesulfonyl chloride (3.8 g, 33 mmol) was added to the solution of the above solid in pyridine (20 ml) at 0 °C, and the reaction mixture was stirred overnight, then evaporated under reduced pressure. The residue was dissolved in a 5% NaOH solution and the solution was washed with toluene. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc. The organic layer was washed with H_2O and dried to afford 4′-acetyl-3′-cyanomethanesulfonanilide (1.64 g, 41%) as crystals, mp 173—176 °C. IR (Nujol): 3120, 2230, 1680, 1610, 1570, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.58 (3H, s), 3.20 (3H, s), 7.60 (1H, d, J=9 Hz), 8.17 (1H, dd, J=9, 2 Hz), 8.35 (1H, d, J=2 Hz), 9.60—11.2 (1H, br s). A mixture of the above cyano derivative (1.49 g, 6.25 mmol), a 24% NaOH aqueous solution (15 ml) and EtOH (10 ml) was refluxed for 6 h. The reaction mixture was acidified with concentrated HCl. The precipitates were collected by filtration and dried to afford **9** (2.2 g, 95%) as crystals, mp 196—201 °C. IR (Nujol): 3600, 3450, 1690, 1670, 1600, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.60 (3H, s), 3.32 (3H, s), 7.70 (1H, d, J=8 Hz), 8.22 (1H, dd, J=8, 2 Hz), 8.55 (1H, d, J=2 Hz).

***N*-(2,4-Difluorophenyl)-5-acetyl-2-(methylsulfonylamino)benzamide (2g)** A mixture of **9** (1.5 g, 5.8 mmol) and thionyl chloride (15 ml) was refluxed for 40 min. Excess thionyl chloride was evaporated off under reduced pressure to afford a solid residue (1.9 g). A solution of the above solid in tetrahydrofuran (THF) (10 ml) was added dropwise to a stirred solution of 2,4-difluoroaniline (2.3 g, 17.5 mmol) in H_2O (5 ml) at 0—5 °C. The reaction mixture was stirred at room temperature for 3 h and extracted with EtOAc. The combined organic layer was washed with 3 N HCl and H_2O, dried and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (4 : 1) to afford **2g** (970 mg, 45%).

2-Amino-5-ethyl-2′,4′-difluorobenzophenone (11) Zinc chloride (7.2 g, 53 mmol) was added to a stirred mixture of 2,4-difluorobenzoyl chloride [prepared from 2,4-difluorobenzoic acid (15 g, 0.96 mmol) and thionyl chloride (50 ml)] and 4-ethylaniline (5.3 g, 44 mmol) at 180 °C. The mixture was stirred for 2.5 h at 200 °C and then cooled to 120 °C. To the mixture was added 3 N HCl (50 ml), and the resulting mixture was refluxed for 1.5 h. After cooling, the supernatant was decanted. Reflux and decantation were repeated three times. Then 75% sulfuric acid (40 ml) was added to the residue. The mixture was stirred at 140 °C for 2 h, poured onto ice (500 g), and extracted with CH_2Cl_2. The organic layer was washed with 3 N HCl (200 ml), 3 N NaOH (200 ml) and H_2O, dried and evaporated under reduced pressure. The oily residue was chromatographed on a column of silica gel with toluene to afford **11** (3.5 g, 31%) as crystals, mp 42—46 °C. IR (Nujol): 3470, 3360, 1630, 1590, 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.10 (3H, t, J=7 Hz), 2.45 (2H, q, J=7 Hz), 6.20 (2H, s), 6.68 (1H, d, J=8 Hz), 6.80—7.60 (5H, m).

2-(2,4-Difluorobenzoyl)-4-ethylacetanilide (12) A mixture of **11** (3.4 g, 13.1 mmol) and acetic anhydride (1.6 g, 15.8 mmol) in pyridine (20 ml) was stirred overnight at room temperature. H_2O (5 ml) was added and the mixture was then evaporated under reduced pressure. The residue was dissolved in a mixture of H_2O and EtOAc. The organic layer was washed with 2 N HCl and aqueous $NaHCO_3$ solution, dried and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (40 : 1) to afford **12** (3.3 g, 82%) as crystals, mp 97—99 °C. IR (Nujol): 3300, 1690, 1640, 1590, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.16 (3H, t, J=7 Hz), 2.25 (3H, s), 2.58 (2H, q, J=7 Hz), 6.80—7.70 (5H, m), 8.68 (1H, d, J=9 Hz), 11.1 (1H, s).

4-Acetyl-2-(2,4-difluorobenzoyl)acetanilide (13) A mixture of **12** (3.1 g, 10 mmol), HNO_3 (3.4 ml, 54 mmol), $KMnO_4$ (4.0 g, 25 mmol), and magnesium oxide (1.0 g, 2.5 mmol) in H_2O (300 ml) was stirred at 60 °C for 9 h. After cooling, EtOAc (150 ml) and $NaHCO_3$ (15 g) were added. The resulting mixture was stirred for 1 h and filtered, and the organic layer was dried and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (20 : 1) to afford **13** (2.3 g, 71%) as crystals, mp 132—134 °C. IR (Nujol): 3270, 1710, 1670, 1650, 1610, 1590, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.29 (3H, s), 2.52 (3H, s), 6.80—7.70 (3H, m), 8.10—8.30 (2H, m), 8.89 (1H, d, J=9 Hz), 11.3 (1H, s).

4′-Acetyl-2′-(2,4-difluorobenzoyl)methanesulfonanilide (2f) A mixture of **13** (4.2 g, 13 mmol) and concentrated HCl (10 ml) in EtOH (30 ml) was refluxed for 5 h. After cooling, the mixture was evaporated under reduced pressure. The residue was dissolved in a mixture of a saturated $NaHCO_3$ solution and EtOAc. The organic layer was dried, and evaporated to afford the amine (3.6 g, 12 mmol). A mixture of the above amine, methanesulfonyl chloride (5.5 ml, 48 mmol) and pyridine (1.0 ml, 12 mmol) in benzene (10 ml) was refluxed for 4 h. The mixture was poured into ice-water and extracted with EtOAc. The extract was washed with a saturated $NaHCO_3$ solution, dried and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with toluene and EtOAc (20 : 1) to afford **2f** (1.6 g, 35%).

4′-Acetyl-2′-aminomethanesulfonanilide (15) Methanesulfonyl chloride (3.81 g, 33 mmol) was added to a solution of **14** (3.0 g, 17 mmol) in pyridine (20 ml) at 0 °C, and the mixture was stirred overnight. The mixture was poured into cold diluted HCl and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated under reduced pressure to afford an oil (3.0 g). A mixture of this oil, iron powder (3.0 g, 53.7 mmol) and ammonium chloride (0.3 g, 5.6 mmol) in EtOH (40 ml) and H_2O (20 ml) was refluxed for 1 h. The hot reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in a mixture of EtOAc and H_2O. The organic layer was dried and evaporated to afford **15** (1.62 g, 42%) as crystals, mp 130—135 °C. IR (Nujol): 3500, 3400, 3320, 1675, 1645, 1600, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.60 (3H, s), 3.00 (3H, s), 7.20—7.50 (3H, m).

***N*-[5-Acetyl-2-(methylsulfonylamino)phenyl)]-2,4-difluorobenzamide (2h)** A mixture of **15** (1.58 g, 6.9 mmol) and 2,4-difluorobenzoyl chloride [prepared from 2,4-difluorobenzoic acid (1.3 g, 8.3 mmol) and thionyl chloride (10 ml)] in pyridine (15 ml) was stirred at 0 °C for 3 h. The reaction mixture was evaporated under reduced pressure, and the residue was stirred with a 5% NaOH solution (40 ml) at room temperature for 1 h. The resulting solution was washed with toluene and acidified with concentrated HCl. The precipitates were collected by filtration and recrystallized from a mixture of acetone and EtOAc to afford **2h** (1.3 g, 51%).

3-Chloro-4-nitrothioanisole (5: R^1=SCH_3, R^2=H) A solution of 3-chloro-4-nitrothiophenol (3.3 g, 17.4 mmol) in DMF (5 ml) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.7 g, 17.5 mmol) in DMF (10 ml) at 0 to 5 °C and the resulting mixture was stirred for 1 h. Methyl iodide (3.7 g, 26 mmol) was added dropwise to the above mixture at 5 °C. After stirring at the same temperature for 1 h, the reaction mixture was poured into ice-water (80 ml) and extracted with toluene. The extract was dried and evaporated under reduced pressure. The oily residue was crystallized from a mixture of hexane and EtOH to afford the title compound (2.8 g, 79%) as crystals, mp 89—92 °C. IR (Nujol): 1570, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.53 (3H, s), 7.00—7.30 (2H, m), 7.84 (1H, d, J=9 Hz).

2-Chloro-4-(methylsulfonyl)nitrobenzene (5: R^1=SO_2CH_3, R^2=H) A mixture of 3-chloro-4-nitrothioanisole (1.3 g, 6.38 mmol), AcOH (3 ml) and 30% hydrogen peroxide (1.5 ml) was stirred at 80 °C for 2 h. The reaction mixture was evaporated under reduced pressure. The residue was triturated with EtOH to afford the title compound (1.2 g, 79%) as crystals, mp 116—118 °C. IR (Nujol): 1590, 1530 cm^{-1}.

4′-Nitro-3′-(phenylthio)acetophenone (6s) A mixture of **5a** (1.50 g, 7.51 mmol), thiophenol (1.63 g, 11.3 mmol) and potassium carbonate (1.56 g, 11.3 mmol) in toluene was stirred at 70 °C for 5 h. Water and EtOAc were added to the reaction mixture and the organic layer was washed with H_2O, dried and evaporated under reduced pressure. The residue was washed with toluene to afford **6s** (1.60 g, 78%).

Some other derivatives (**6t—v** and **6x—z**) were also prepared by this method.

4′-Nitro-3′-[2-(trifluoromethyl)phenylthio]acetophenone (6w) A solution of **5a** (2.7 g, 10 mmol) in toluene (50 ml) was added to a stirred solution of lithium 2-(trifluoromethyl)benzenethioxide (4.4 g)[7] [prepared from 2-(trifluoromethyl)bromobenzene (3.27 ml, 24 mmol), sulfur (0.77 g, 24 mmol) and *n*-BuLi (1.6 N; 15 ml, 24 mmol)] in ether (142 ml) at 0 °C. The mixture was stirred at room temperature for 2 h and refluxed for 20 min. The resulting mixture was poured into a mixture of EtOAc and H_2O. The organic layer was washed with brine, dried and evaporated under reduced pressure. The oily residue was chromatographed on a column of silica gel with toluene to afford **6w** (1.3 g, 31%).

4′-Nitro-3′-(2-pyridylthio)acetophenone (6aa) A mixture of 2-mercaptopyridine (1.7 g, 15 mmol), potassium *tert*-butoxide (1.7 g, 15 mmol) and

DMF (3 ml) in toluene (30 ml) was stirred at room temperature for 30 min. Then **5a** (1.5 g, 7.5 mmol) was added to the above mixture followed by stirring for an additional 18 h. The reaction mixture was poured into water and the precipitates were collected by filtration and washed with toluene to afford **6aa** (1.1 g, 54%).

Most of the heteroaromatic derivatives (**6bb**—**ee**) were also prepared by this method.

3-(2,4-Difluorophenylthio)-4-(methylsulfonylamino)benzoic Acid (3a) The crude ethyl 3-(2,4-difluorophenylthio)-4-(methylsulfonylamino)benzoate, which was prepared from **6e** (1.1 g, 3.2 mmol) was dissolved in MeOH (20 ml). Potassium hydroxide (2.0 g) was added to the above solution and the mixture was stirred at room temperature for 30 min. The resulting mixture was evaporated under reduced pressure and the residue was dissolved in a mixture of $CHCl_3$ and H_2O. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated under reduced pressure. The obtained residue was recrystallized from EtOH to afford **3a** (660 mg, yield from **6e**: 52%).

***N*-[3-(2,4-Difluorophenylthio)-4-(methylsulfonylamino)benzoyl]glycine (3j)** The crude *N*-[3-(2,4-difluorophenylthio)-4-nitrobenzoyl]glycine methyl ester, which was prepared from **6n** (2.3 g, 6.1 mmol) was dissolved in MeOH (20 ml). Potassium hydroxide (3.0 g) was added to the above solution and the mixture was stirred at room temperature for 1.0 h. The resulting mixture was evaporated under reduced pressure and the residue was dissolved in a mixture of $CHCl_3$ and H_2O. The aqueous layer was acidified with concentrated HCl to afford precipitates. The precipitates were collected and recrystallized from EtOH to afford **3j** (1.69 g, yield from **6n**: 67%).

2′-(2,4-Difluorophenylthio)-4′-[1-(hydroxyimino)ethyl]methanesulfonanilide (3k) A mixture of **2a** (1.00 g, 2.8 mmol), hydroxylamine hydrochloride (200 mg, 2.9 mmol) and pyridine (225 mg, 2.8 mmol) in EtOH (15 ml) was refluxed for 4 h. The reaction mixture was evaporated under reduced pressure. The residue was triturated with H_2O to afford a powder, which was recrystallized from EtOH giving **3k** (900 mg, 87%).

3′-(2,4-Difluorophenylthio)-4′-(methylsulfonylamino)acetophenone Semicarbazone (3n) A mixture of **2a** (1.16 g, 3.6 mmol), semicarbazide hydrochloride (400 mg, 3.6 mmol), and pyridine (290 mg, 3.6 mmol) in EtOH (15 ml) was refluxed for 2 h. After cooling, the reaction mixture was evaporated under reduced pressure, and the residue was recrystallized from MeOH to afford **3n** (0.92 g, 86%).

2′-(2,4-Difluorophenylthio)-4′-(1-hydroxyethyl)methanesulfonanilide (3o) Sodium borohydride (0.2 g, 5.3 mmol) was added portionwise to a stirred solution of **2a** (1.55 g, 4.34 mmol) in methanol (30 ml) at 15 °C. After stirring at room temperature overnight, the resulting mixture was treated with acetic acid and then evaporated under reduced pressure. The residue was dissolved in a mixture of EtOAc and H_2O. The organic layer was washed with a saturated $NaHCO_3$ solution, dried and evaporated under reduced pressure. The residual oil was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (4 : 1), followed by recrystallization from EtOH and water to afford **3o** (1.03 g, 66%).

The other alcohol derivatives (**3r**, **x** and **z**) were prepared by a similar method to that described for **3o**.

4′-(1-Aminoethyl)-2′-(2,4-difluorophenylthio)methanesulfonanilide (3p) A mixture of **2a** (2.5 g, 7.0 mmol), ammonium acetate (5.4 g, 70 mmol) and sodium cyanoborohydride (0.96 g, 15.2 mmol) in MeOH (50 ml) was refluxed for 5 h. The reaction mixture was evaporated to dryness under reduced pressure. The obtained residue was dissolved in a mixture of EtOAc and H_2O. The organic layer was washed with H_2O, dried and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with a mixture of $CHCl_3$ and MeOH (9 : 1) to afford **3p** (0.84 g, 34%).

Compound **3s** was prepared by a similar method to that described for **3p**.

4′-(2-Amino-4-thiazolyl)-2′-(2,4-difluorophenylthio)methanesulfonanilide hydrobromide (3cc) A solution of bromine (0.81 g, 5.0 mmol) in $CHCl_3$ (5 ml) was added slowly to a solution of **2a** (1.8 g, 5.0 mmol) and benzoyl peroxide (8 mg) in $CHCl_3$ (20 ml) at room temperature and the mixture was stirred for 1 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give the bromoacetyl derivative (**16**). Crude **16** was dissolved in MeOH (10 ml) and then thiourea (0.58 g, 7.6 mmol) was added. The mixture was stirred at room temperature for 1 h. The precipitates were collected by filtration and washed with EtOH to afford **3cc** (1.9 g, 92%).

2′-(2,4-Difluorophenylthio)-4′-[2-(methylsulfonylamino)-4-thiazolyl]-methanesulfonanilide (3dd) A solution of **3cc** (1.2 g, 2.3 mmol) and methanesulfonyl chloride (0.56 g, 4.9 mmol) in pyridine (5 ml) was stirred at room temperature overnight. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in a mixture of EtOAc and H_2O. The organic layer was washed with diluted HCl, dried, and evaporated under reduced pressure. The obtained residue was acidified with diluted HCl and extracted with $CHCl_3$. The combined extract was washed with H_2O, dried and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (1 : 1) followed by recrystallization from MeOH to afford **3dd** (0.26 g, 24%).

2′-(2,4-Difluorophenylthio)-4′-(imidazo[1,2-*a*]pyrimidin-2-yl)methanesulfonanilide (3ee) The bromoacetyl derivative (**16**), prepared from **2a** (2.0 g, 5.6 mmol), was dissolved in EtOH (30 ml) and 2-aminopyrimidine (0.8 g, 8.5 mmol) was added to the solution. The mixture was refluxed for 4 h and then the solvent was evaporated off under reduced pressure. The residue was dissolved in a mixture of EtOH and aqueous $NaHCO_3$ solution. The organic layer was washed with H_2O, dried and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with a mixture of $CHCl_3$ and MeOH (20 : 1) followed by recrystallization from EtOAc to afford **3ee** (0.6 g, 25%).

2′-(2,4-Difluorophenylthio)-4′-[2-(hydroxyimino)-1-oxopropyl]methanesulfonanilide (3t) Methyl nitrite [prepared from sodium nitrite (1.4 g, 20 mmol), MeOH (0.9 ml) and sulfuric acid (0.7 ml) in H_2O (2.3 ml)] was introduced into a mixture of **3q** (2.54 g, 6.9 mmol) in THF (10 ml) and 12% hydrogen chloride in Et_2O (10 ml). The mixture was stirred at 3 °C for 5 h and evaporated under reduced pressure. The residual solid was recrystallized from EtOH to afford **3t** (2.5 g, 90%).

2′-(2,4-Difluorophenylthio)-4′-pyruvoylmethanesulfonanilide (3u) A suspension of **3t** (1.7 g, 4.25 mmol) in concentrated HCl (8 ml) was refluxed for 2 h. The mixture was extracted with EtOAc, and the extract was washed with H_2O and saturated $NaHCO_3$, dried and evaporated under reduced pressure. The residual oil was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (5 : 1) followed by recrystallization from EtOH to afford **3u** (0.6 g, 37%).

2′-(2,4-Difluorophenylthio)-4′-(phenylacetyl)methanesulfonanilide (3w) Benzyl chloride (1.92 ml, 16.7 mmol) was added dropwise to a suspension of magnesium (357 mg, 14.7 mmol) in THF (15 ml) at 40 °C. The reaction mixture was stirred at room temperature for 40 min. A solution of **3v** (1.0 g, 2.94 mmol) in THF (15 ml) was added to the above mixture and the resulting mixture was stirred for 1 h. The mixture was quenched with a saturated ammonium chloride solution and extracted with EtOAc. The organic layer was washed with diluted HCl, dried, and evaporated under reduced pressure. The residual oil was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (40 : 1) followed by recrystallization from EtOH to afford **3w** (0.52 g, 41%).

2′-(2,4-Difluorophenylthio)-4′-formylmethanesulfonanilide (3y) A mixture of **3v** (4.8 g, 14.1 mmol) and Raney nickel (4.8 g) in formic acid (130 ml) was refluxed for 2 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$, and the solution was washed with saturated $NaHCO_3$ solution, dried, and evaporated under reduced pressure. The residual oil was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (5 : 1) to afford **3y** (3.0 g, 87%).

2′-(2,4-Difluorophenylthio)-4′-(3-oxo-1-butenyl)methanesulfonanilide (3ff) A mixture of **3y** (1.0 g, 2.9 mmol) and 1-triphenylphosphoranylidene-2-propanone (1.4 g, 4.3 mmol) in DMSO (5 ml) was stirred at 80 °C for 10 h. After cooling, the reaction mixture was diluted with a mixture of AcOEt and H_2O, and the organic layer was washed with H_2O and brine, dried, and evaporated under reduced pressure. The residue obtained was chromatographed on a column of silica gel with a mixture of toluene and EtOAc (1 : 1) to give a solid, which was recrystallized from EtOH to afford **3ff** (850 mg, 76%).

3-(2,4-Difluorophenylthio)-4-nitrobenzoic Acid (6d) A mixture of **6c** (3.6 g, 12.3 mmol), concentrated H_2SO_4 (5 ml) and H_2O (3 ml) was refluxed for 15 min. After cooling, the reaction mixture was poured into ice-water and extracted with EtOAc. The extract was washed with H_2O, dried and evaporated under reduced pressure to afford **6d** (3.6 g, 95%).

Ethyl 3-(2,4-Difluorophenylthio)-4-nitrobenzoate (6e) A mixture of **6d** (1.2 g, 3.9 mmol) and an EtOH solution of HCl (20%, 3 ml) was refluxed for 2 h. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in a mixture of EtOAc and H_2O. The organic layer was washed with a saturated $NaHCO_3$ solution and H_2O, dried and evaporated under reduced pressure. The residue was recrystallized from a mixture of hexane and EtOH to afford **6e** (1.1 g, 84%).

3-(2,4-Difluorophenylthio)-4-nitrobenzamide (6f) PCl_5 (0.9 g, 4.32

mmol) was added to a suspension of **6d** (1.3 g, 4.18 mmol) in benzene (10 ml) at room temperature. The mixture was stirred for 30 min and the solvent was evaporated off under reduced pressure. The obtained acid chloride was dissolved in benzene (10 ml) and added to a mixture of ammonia water (3 ml), H_2O (7 ml) and ether (5 ml) at room temperature, and the reaction mixture was stirred for 2 h. The mixture was extracted with EtOAc and the organic layer was washed with saturated $NaHCO_3$ and brine and dried. After removal of the solvent, the residue was recrystallized from a mixture of EtOH and hexane to afford **6f** (0.9 g, 69%).

***N*-[3-(2,4-Difluorophenylthio)-4-nitrobenzoyl]glycine Methyl Ester (6n)** The crude acid chloride of **6d** (2.0 g, 6.4 mmol) was dissolved in acetone (5 ml) and the solution was added to a solution of glycine methyl ester hydrochloride (0.89 g, 7.1 mmol) and $NaHCO_3$ (1.62 g, 19.3 mmol) in H_2O (30 ml) and acetone (10 ml) at 0 °C. The mixture was stirred for 10 min then concentrated under reduced pressure, and the residue was collected by filtration and washed with H_2O to afford **6n** (2.33 g, 95%).

Biological Activities. Adjuvant Arthritis in Rats Ten female Sprague Dawley rats were used per group. A dose of 0.5 mg of *Mycobacterium tuberculosis* (strain Aoyama B) suspended in 0.05 ml of liquid paraffin was injected subcutaneously into the right hind paw. The injection of mycobacterial adjuvant produced a local inflammatory lesion (primary lesion) and 10 d later, secondary lesions in both the injected and uninjected paws. The difference in volumes of both paws before and after adjuvant injection was taken as a measure of the severity of arthritis. The test compound was given orally once a day for 23 consecutive days from day 1.

Collagen-Induced Arthritis in Mice Eight male DBA/1 mice were used per group. Type II bovine collagen was solubilized in complete Freund's adjuvant (CFA). Mice were primed with 200 μg of type II collagen in CFA intradermally at the base of the tail, and challenged after 21 d with the same procedure. From the day of the second challenge, a tested drug was administered orally once a day for 3 weeks and mice were inspected weekly for signs of arthritis. Anti type II collagen antibody was measured 2 weeks after the second challenge. Blood was obtained by retro-orbital bleeding and quantitated by enzyme-linked immunosorbent assay. An arthritis index was used to score the severity of disease, as follows grade 0, no overt sign; grade 1, joint swelling and erythema; grade 2, visible joint disorder; grade 3, joint ankyosis.

MRL/lpr Mouse Assay MRL/lpr mice (6 weeks of age) were purchased from Charles River Co. and ten mice were used per group. The drug was administered orally once a day for 13 weeks. Hind joints were removed, fixed in formalin, processed, and stained with hematoxylin and eosin. The lesion was graded on a scale of 0—3, where 0 = normal and 3 = pronounced abnormalities.

Acknowledgements The authors are grateful to the members of the Pharmacological Division for biological assays. We are also indebted to the Analytical Division for elemental analyses and spectral mesurements.

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