Studies on Antiinflammatory Agents. I. Synthesis and Pharmacological Properties of 2′-Phenoxymethanesulfonanilide Derivatives

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Various 2′-phenoxymethanesulfonanilide derivatives were synthesized and evaluated for antiinflammatory and analgesic activities. Some compounds bearing an electron-attracting substituent at the 4′-position strongly inhibited adjuvant-induced arthritis in rats and acetic acid-induced writhing syndrome in mice without causing gastro-intestinal irritation. Among them, 4′-cyano-(FK867) and 4′-acetyl-(FK3311) 2′-(2,4-difluorophenoxy)methanesulfonanilides were selected as the candidates for further development.

Keywords antiinflammatory activity; analgesic activity; gastro-intestinal irritation; 2′-phenoxymethanesulfonanilide; nimesulide; CGP28238; structure–activity relationship

Nonsteroidal antiinflammatory drugs (NSAIDs) represented by indomethacin and asprin have been demonstrated to be useful for relief of the symptoms in a number of arthritic conditions such as rheumatoid arthritis. It has been pointed out, however, that the adverse effects of NSAIDs, namely gastro-intestinal irritation and suppression of the renal function, have to be ameliorated.[1] Many approaches have been tried to obtain a safer NSAID, *e.g.*, a prodrug approach,[2] discovery of a new type of compound having a different mechanism of action,[3] or selectively active agents on the target tissues.[4] Some of the NSAIDs available at present achieve this purpose to some extent but not completely in terms of gastro-intestinal irritation.

Nimesulide and CGP28238, depicted in Fig. 1, which are methanesulfonanilide derivatives, have been reported to exhibit potent antiinflammatory and analgesic activities in various animal models without causing gastro-intestinal irritation.[5] The significant improvement in gastro-intestinal tolerability of CGP28238 has been explained by a cell and tissue selective inhibition of prostaglandin production.[6] From the structural and pharmacological features, nimesulide and CGP28238 can be classified as a novel type of NSAID.

Rufer *et al.*[7] reported that the acidity at the sulfonylamino moiety of CGP28238 played an important role in controlling antiinflammatory activity and ulcerogenicity. On the basis of this finding we designed novel methanesulfonanilide derivatives having an appropriate pK_a at the sulfonylamino moiety. The chemical modification employed in this paper consisted of changing the substituents on the two benzene rings of nimesulide or CGP28238.

We describe in this paper the syntheses and pharmacological activities of these various 2′-phenoxymethanesulfonanilides (**1**, **2**).

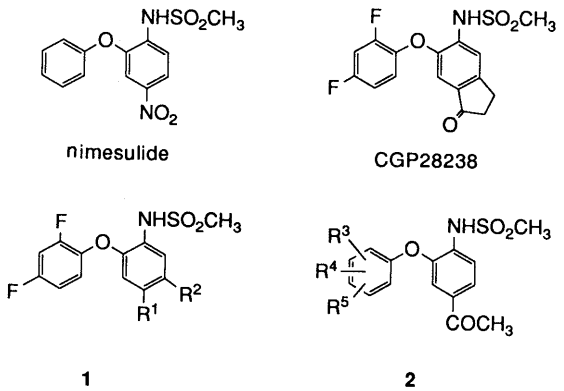


Fig. 1

Chemistry

2′-Phenoxymethanesulfonanilides (**1**, **2**) were prepared along the synthetic route shown in Chart 1. Substituted 2-chloronitrobenzenes (**4**) were synthesized by diazotization of the corresponding 2-chloroanilines (**3**) and subsequent decomposition of the obtained diazonium salt in the presence of sodium nitrite and cuprous oxide. To produce 2-phenoxynitrobenzenes (**5**), Ullmann-type condensation of **4** and substituted phenols in xylene was carried out. Reduction of **5** with iron powder in the presence of ammonium chloride and subsequent methanesulfonylation in pyridine afforded objective **1** and **2**.

Some of 2′-phenoxymethanesulfonanilides (**1**), as shown in Charts 2 and 3, were derived from unsubstituted (**1a**), 4′-cyano-(**1e**), 4′-formyl-(**1f**), or 4′-acetyl-(**1h**) derivative. Nitration of **1a** produced the 4′-nitro derivative (**1b**). The 4′-mercapto derivative (**1aa**) was prepared by the reaction of potassium ethylxanthate with the diazonium salt of the 4′-amino derivative (**6**), which was obtained from **1b** using iron powder. The 4′-formyl, 4′-carboxy, and 4′-tetrazolyl derivatives (**1f**, **1g**, and **1gg**) were derived from **1e** by reduction using Raney nickel in refluxing formic acid, by

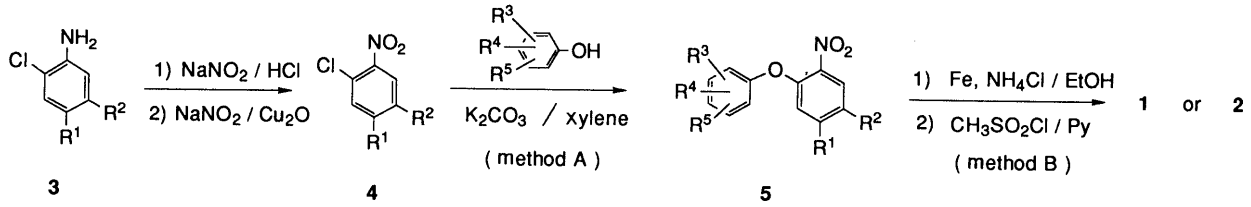


Chart 1

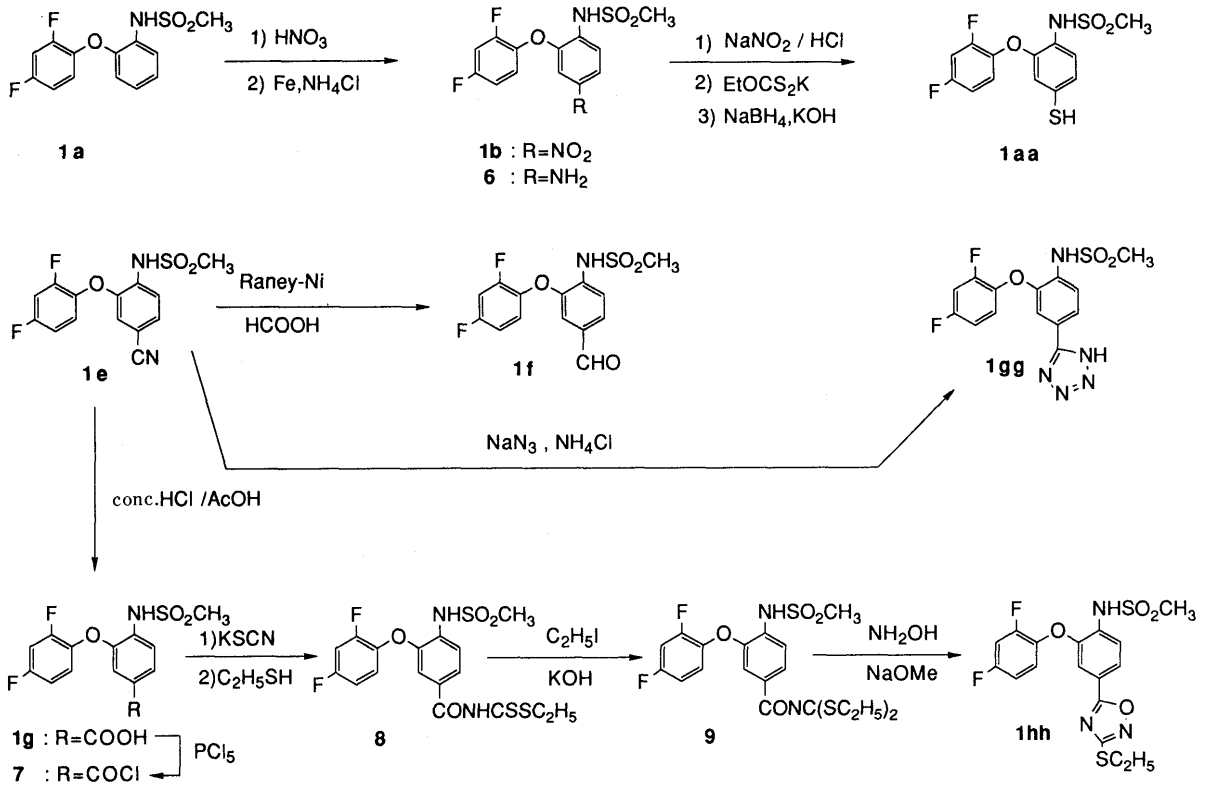


Chart 2

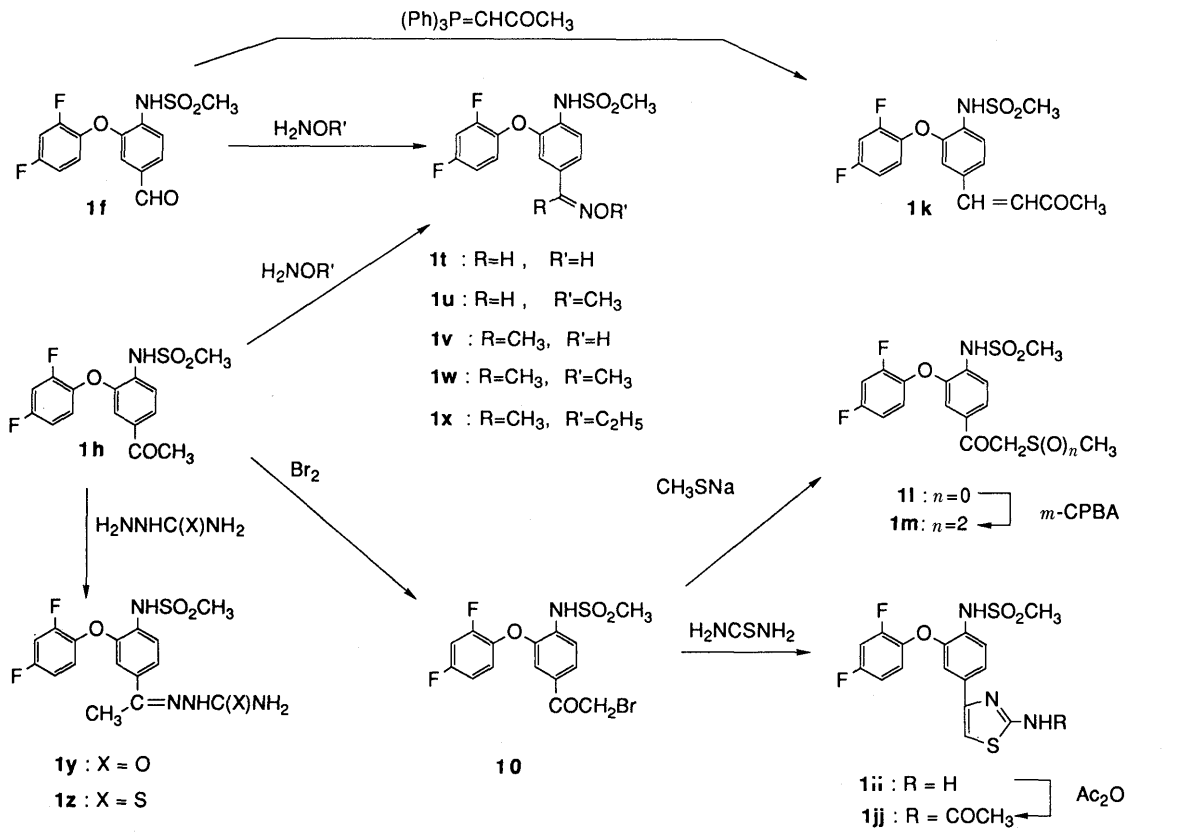


Chart 3

hydrolysis with hydrochloric acid, and by the reaction with sodium azide, respectively. The oxadiazole derivative (**1hh**) was obtained *via* the acid chloride (**7**) by the manner described in the literature.[8] Namely, **7** was converted to the benzoyl dithiocarbamate derivative (**8**), which was subsequently reacted with ethyl iodide to yield **9**. The reaction of **9** with hydroxylamine produced the objective oxadiazole (**1hh**). The oxime derivatives (**1t—x**) were

prepared by the treatment of **1f** or **1h** with an appropriate hydroxylamine. The semicarbazone and the thiosemicarbazone (**1y, z**) were prepared from **1h**. The Wittig reaction of **1f** with 1-triphenylphosphoranylidene-2-propanone afforded the 3-oxo-1-butenyl derivative (**1k**) as *E*-form. The 4′-methylthioacetyl and the 4′-(2-aminothiazol-4-yl) derivatives (**1l** and **1ii**) were prepared through the bromoacetyl derivative (**10**), by the substitution with sodium thiomethoxide, or by the treatment with thiourea in refluxing methanol, respectively. The 4′-methylthioacetyl derivative (**1l**) was converted to the sulfone (**1m**) with *m*-chloroperbenzoic acid, and **1ii** was acylated to **1jj** using acetic anhydride.

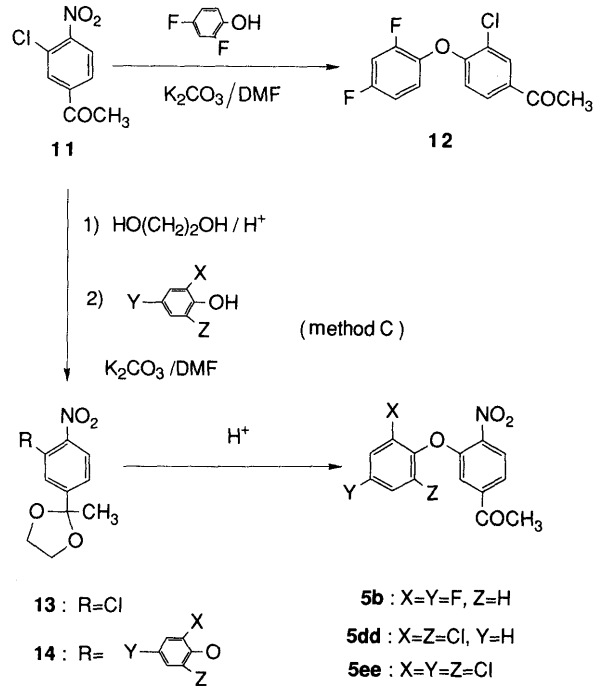


Chart 4

When *N*,*N*-dimethylformamide (DMF) was used as a solvent instead of xylene in the Ullmann-type condensation of 3′-chloro-4′-nitroacetophenone (**11**) and 2,4-difluorophenol, the replacement took place at the position of its nitro group to give 3′-chloro-4′-(2,4-difluorophenoxy)-acetophenone (**12**) as illustrated in Chart 4. In the case of the compound protected with ketal (**13**), however, the chlorine was replaced to afford **14** even if DMF was used as a solvent. Then the desired nitrobenzene derivative (**5**) was produced by hydrolysis of **14**. This method was applied to the synthesis of **5** bearing a sterically hindered phenoxy group like **5dd** and **5ee**, in the case of which no reaction occurred under the condition of method A in Chart 1.

4-Amino- and 4-cyano-2-phenoxynitrobenzene derivatives (**5c, i, s**) were converted to the other 2-phenoxynitrobenzenes as depicted in Chart 5. The 4-alkylthio derivatives (**5d, e, f**) were produced by alkylation of the 4-mercapto derivative (**15**), which was prepared by the reaction of potassium ethylxanthate with the diazonium salt of **5c**. Hydrolysis of **5i** with 50% sulfuric acid afforded the carboxylic acid (**16**), which was converted to the corresponding acid chloride (**17**). The following 2-phenoxynitrobenzenes were prepared through **17**. Friedel–Crafts reaction and amidation with various amines yielded the benzophenone (**5j**) and the amides (**5m—p**), respectively. The ethyl ester (**5l**) and the carboxamide (**5k**) were prepared by esterification of **16** using sulfuric acid as a catalyst, and by partial hydrolysis of **5i** with potassium hydroxide, respectively. 5′-(2,4-Difluorophenoxy)-2′-methyl-4′-nitroacetophenone (**5t**) was synthesized from the cyano derivative (**5s**). The cyano group in **5s** was hydrolyzed with diluted sulfuric acid and then the acid obtained was converted into the corresponding acid chloride (**18**). The objective **5t** was

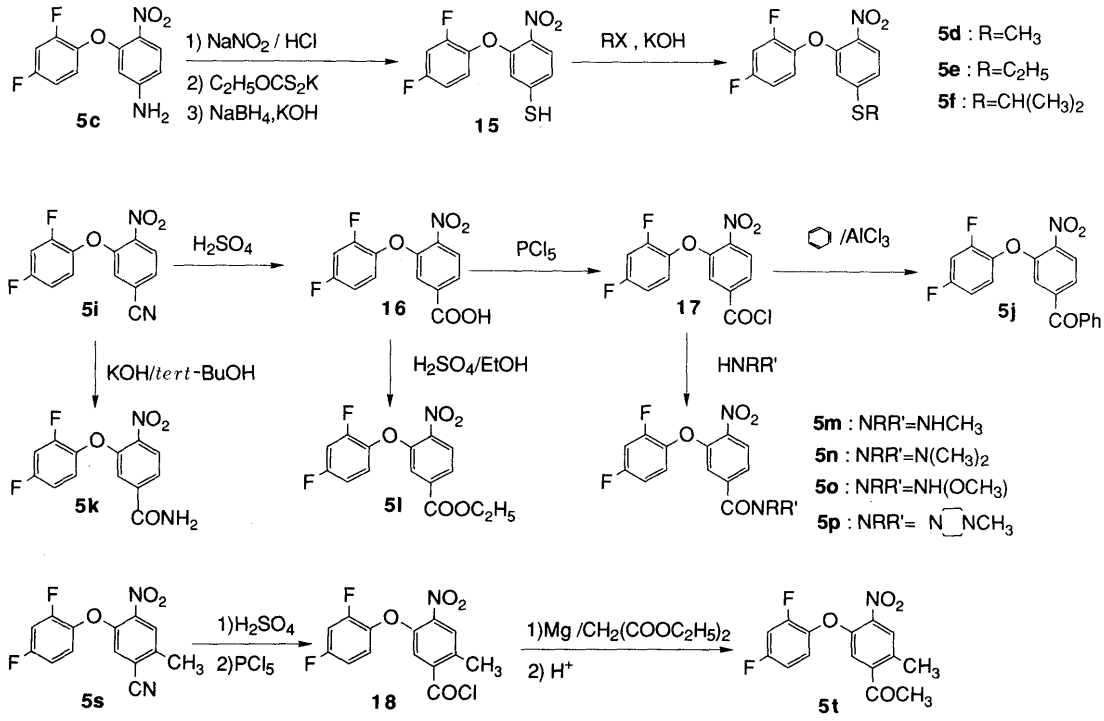
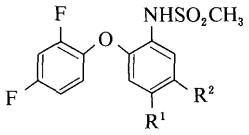
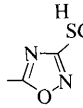
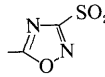


Chart 5

TABLE I. Substituted 2′-(2,4-Difluorophenoxy)methanesulfonanilides (**1**)

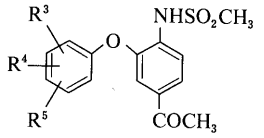


1

No.	R^1	R^2	Method	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1a	H	H	B	83	121—123	E	$C_{13}H_{11}F_2NO_3S$	52.17	3.71	4.68	52.08	3.55	4.86
1b	NO_2	H	[b]	81	162—164	E	$C_{13}H_{10}F_2N_2O_5S$	45.35	2.93	8.14	45.33	2.83	8.19
1c	CH_3	H	B	71	88—89	EA–H	$C_{14}H_{13}F_2NO_3S$	53.67	4.18	4.47	53.89	4.05	4.45
1d	CF_3	H	B	63	115—117	E–H	$C_{14}H_{10}F_5NO_3S$	45.78	2.74	3.81	46.26	3.01	4.09
1e	CN	H	B	86	185—187	E	$C_{14}H_{10}F_2N_2O_3S$	51.85	3.11	8.64	51.81	3.12	8.92
1f	CHO	H	[c]	92	156—157	E	$C_{14}H_{11}F_2NO_4S$	51.37	3.39	4.28	51.26	3.75	4.43
1g	COOH	H	[c]	52	167—169	EA–H	$C_{14}H_{11}F_2NO_5S$	48.98	3.23	4.08	48.50	3.25	4.05
1h	$COCH_3$	H	B	79	117—118	E	$C_{15}H_{13}F_2NO_4S$	52.78	3.84	4.10	52.86	3.78	4.17
1i	COC_2H_5	H	B	66	107—109	E	$C_{16}H_{15}F_2NO_4S$	54.08	4.25	3.94	54.56	4.51	4.00
1j	COPh	H	B	53	160—170 (dec.)	E	$C_{20}H_{14}F_2NNaO_4S \cdot H_2O$	54.17	3.64	3.16	54.10	3.73	3.12
1k	$CH=CHCOCH_3$	H	[d]	39	130—132	E	$C_{17}H_{15}F_2NO_4S$	55.58	4.12	3.81	55.54	4.27	3.81
1l	$COCH_2SCH_3$	H	[d]	46	74—76	E	$C_{16}H_{15}F_2NO_4S_2$	49.60	3.90	3.62	49.59	3.88	3.62
1m	$COCH_2SO_2CH_3$	H	[d]	44	162—163	EA	$C_{16}H_{15}F_2NO_6S_2$	45.82	3.60	3.34	46.01	3.75	3.31
1n	$COOC_2H_5$	H	B	65	111—113	E	$C_{16}H_{15}F_2NO_5S$	51.75	4.07	3.77	51.57	4.21	3.80
1o	$CONH_2$	H	B	64	147—150	EA–H	$C_{14}H_{12}F_2N_2O_4S$	49.12	3.53	8.18	49.37	3.53	8.40
1p	$CONHCH_3$	H	B	81	137—139	EA–H	$C_{15}H_{14}F_2N_2O_4S$	50.56	3.96	7.86	50.63	3.72	7.85
1q	$CON(CH_3)_2$	H	B	84	165—167	E	$C_{16}H_{16}F_2N_2O_4S$	51.89	4.35	7.56	51.88	4.38	7.57
1r	$CONH(OCH_3)$	H	B	49	125—127	EA–H	$C_{15}H_{14}F_2N_2O_5S$	48.39	3.79	7.52	48.80	3.43	7.49
1s		H	B	89	159—160	E	$C_{19}H_{21}F_2N_3O_4S$	53.64	4.98	9.88	53.22	5.00	9.71
1t	$CH=NOH$	H	[d]	72	155—157	E–W	$C_{14}H_{12}F_2N_2O_4S$	49.12	3.53	8.18	49.23	3.21	8.27
1u	$CH=NOCH_3$	H	[d]	75	110—112	E	$C_{15}H_{14}F_2N_2O_4S$	50.56	3.96	7.86	50.53	3.77	8.00
1v	$C(CH_3)=NOH$	H	[d]	90	150—151	E–W	$C_{15}H_{14}F_2N_2O_4S$	50.56	3.96	7.86	50.36	3.52	7.90
1w	$C(CH_3)=NOCH_3$	H	[d]	86	118—120	E	$C_{16}H_{16}F_2N_2O_4S$	51.89	4.35	7.56	51.69	4.27	7.40
1x	$C(CH_3)=NOC_2H_5$	H	[d]	95	114—116	E	$C_{17}H_{18}F_2N_2O_4S$	53.12	4.72	7.29	53.24	4.73	7.25
1y	$C(CH_3)=NNHCONH_2$	H	[d]	63	187—189	M	$C_{16}H_{16}F_2N_4O_4S$	48.24	4.05	14.06	48.06	4.19	13.72
1z	$C(CH_3)=NNHCSNH_2$	H	[d]	58	219—220 (dec.)	EA	$C_{16}H_{16}F_2N_4O_3S_2$	46.37	3.89	13.52	46.46	3.71	13.52
1aa	SH	H	[b]	56	103—105	EA–H	$C_{13}H_{11}F_2NO_3S_2$	47.12	3.35	4.23	47.30	2.96	4.26
1bb	SCH_3	H	B	74	76—78	E–H	$C_{14}H_{13}F_2NO_3S_2$	48.69	3.79	4.06	48.40	3.94	4.34
1cc	SC_2H_5	H	B	92	Oil		$C_{15}H_{15}F_2NO_3S_2 \cdot 1/2H_2O$	48.90	4.37	3.80	48.93	4.20	3.88
1dd	$SCH(CH_3)_2$	H	B	81	Oil		$C_{16}H_{17}F_2NO_3S_2 \cdot 1/2H_2O$	50.25	4.74	3.66	50.22	4.67	3.71
1ee	$SOCH_3$	H	[e]	81	164—166	E	$C_{14}H_{13}F_2NO_4S_2$	46.53	3.62	3.88	46.94	3.55	4.22
1ff	SO_2CH_3	H	[f]	92	182—184	E	$C_{14}H_{13}F_2NO_5S_2$	44.56	3.47	3.71	44.90	3.66	3.94
1gg		H	[c]	83	222—223 (dec.)	E	$C_{14}H_{11}F_2N_5O_3S$	45.78	3.02	19.06	46.25	2.91	19.21
1hh		H	[c]	49	116—119	E	$C_{17}H_{15}F_2N_3O_4S_2$	47.77	3.54	9.83	47.94	3.50	9.54
1ii		H	[d]	64	182—183	E	$C_{16}H_{13}F_2N_3O_3S_2$	48.36	3.30	10.57	48.21	2.77	10.52
1jj		H	[d]	62	192—193	E	$C_{18}H_{15}F_2N_3O_4S_2$	49.20	3.44	9.56	49.52	3.50	9.60
1kk		H	[f]	62	168—169	E	$C_{17}H_{15}F_2N_3O_6S_2$	44.44	3.29	9.15	44.70	3.26	9.49
1ll	H	$COCH_3$	B	85	142—143	E	$C_{15}H_{13}F_2NO_4S$	52.78	3.84	4.10	52.82	3.53	4.12
1mm	$COCH_3$	CH_3	B	76	116—117	E	$C_{16}H_{15}F_2NO_4S$	54.08	4.25	3.94	54.26	4.19	4.07
1nn	CN	CH_3	B	76	193—194	E	$C_{15}H_{12}F_2N_2O_3S \cdot 1/2H_2O$	51.87	3.77	8.06	51.61	3.35	7.99

a) E = ethanol, EA = ethyl acetate, E–H = ethanol–hexane, EA–H = ethyl acetate–hexane, E–W = ethanol–water, M = methanol. *b*) Obtained from **1a** according to the synthetic route as shown in Chart 2. *c*) Obtained from **1e** according to the synthetic route as shown in Chart 2. *d*) Obtained from **1f** or **1h** according to the synthetic route as shown in Chart 3. *e*) Obtained from **1bb** using 1.1 eq of *m*-CPBA. *f*) Obtained from **1bb** or **1hh** using 2.2 eq of *m*-CPBA.

TABLE II. 4′-Acetyl-2′-(substituted phenoxy)methanesulfonanilides (**2**)



2

No.	R^3–R^5	Method	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
2a	H	B	60	113—114	E–W	$C_{15}H_{15}NO_4S$	59.00	4.95	4.59	59.31	4.85	4.56
2b	2-F	B	32	92—94	E	$C_{15}H_{14}FNO_4S$	55.72	4.36	4.33	56.08	4.34	4.37
2c	4-F	B	48	95—96	E–W	$C_{15}H_{14}FNO_4S$	55.72	4.36	4.33	56.13	4.32	4.38
2d	2-Cl	B	36	102—103	E–W	$C_{15}H_{14}ClNO_4S$	53.02	4.14	4.12	53.39	4.13	4.09
2e	3-Cl	B	80	290—300 (dec.)	W	$C_{15}H_{13}ClNNaO_4S$	49.80	3.62	3.87	50.00	3.68	3.91
2f	4-Cl	B	53	103—104	E–W	$C_{15}H_{14}ClNO_4S$	53.02	4.14	4.12	53.35	4.12	4.07
2g	2-Cl, 3-Cl	B	51	162—170 (dec.)	W	$C_{15}H_{12}Cl_2NNaO_4S\cdot 1/2H_2O$	44.46	3.23	3.46	44.02	3.22	3.51
2h	2-Cl, 4-Cl	B	46	119—121	E–W	$C_{15}H_{13}Cl_2NO_4S$	48.14	3.50	3.74	48.35	3.44	3.78
2i	2-Cl, 5-Cl	B	65	175—177	E–EA	$C_{15}H_{13}Cl_2NO_4S$	48.14	3.50	3.74	48.31	3.40	3.70
2j	2-Cl, 6-Cl	B	62	155—156	E	$C_{15}H_{13}Cl_2NO_4S$	48.14	3.50	3.74	48.24	3.47	3.80
2k	2-Cl, 4-Cl, 6-Cl	B	37	199—201	E	$C_{15}H_{12}Cl_3NO_4S$	44.08	2.96	3.43	44.00	2.72	3.30
2l	2-Cl, 4-F	B	56	96—98	E	$C_{15}H_{13}ClFNO_4S$	50.36	3.66	3.91	50.51	3.67	3.88
2m	2-Br	B	66	95—96	E	$C_{15}H_{14}BrNO_4S$	46.89	3.67	3.65	47.48	3.67	3.61
2n	2-CH_3	B	73	150—160 (dec.)	W	$C_{16}H_{16}NNaO_4S\cdot 2H_2O$	50.92	5.34	3.71	50.46	4.82	3.75
2o	2-OCH_3	B	80	160—161	E	$C_{16}H_{17}NO_5S$	57.30	5.11	4.18	57.31	5.02	4.16
2p	2-SCH_3	B	73	122—125	E	$C_{16}H_{17}NO_4S_2$	54.68	4.88	3.99	54.71	4.64	3.92
2q	2-$SOCH_3$	b)	61	113—116	E	$C_{16}H_{17}NO_5S_2$	52.30	4.66	3.81	51.97	4.42	3.80
2r	2-SO_2CH_3	b)	82	189—191	E	$C_{16}H_{17}NO_6S_2$	50.12	4.47	3.65	49.90	4.00	3.59

a) E=ethanol, E–W=ethanol–water, W=water. *b*) Obtained from **2p** using 1.1 or 2.2 eq *m*-CPBA.

obtained by the reaction of **18** with ethoxy magnesium diethyl malonate, followed by hydrolysis and decarboxylation under an acidic condition.

Pharmacological Results and Discussion

The methanesulfonanilide derivatives (**1** and **2**) were tested for antiinflammatory and analgesic activities through oral administration, which were assessed as inhibition of adjuvant-induced arthritis in rats, and of acetic acid-induced writhing in mice, respectively. The test results are summarized in Tables III and IV. The structure activity relationship on these compounds may be discussed in the two parts: (**1**) the substituents (R^1 and R^2) on the right hand benzene ring, (**2**) the substituents (R^3, R^4, and R^5) in the phenoxy part.

Concerning the substituent R^1, maximum activity was achieved with a nitro group (**1b**), but **1b** showed severe toxicity (9 out of 10 rats died in the adjuvant-induced arthritis experiment). The electron-attracting groups, *e.g.*, cyano (**1e**), acetyl (**1h**), amide (**1o**), were comparatively potent. On the other hand, the compound bearing an electron-donating methyl group (**1c**) was less active than the above compounds. Therefore our synthesic efforts were directed mainly toward the compounds having an electron-attracting group.

Surprisingly, formyl (**1f**), carboxy (**1g**), and other acyl groups (**1i—n**) were inactive or weak, while some amide (**1p, q**), oxime (**1u—w**), or semicarbazone (**1y**) derivatives showed moderate activities. Introduction of a sulfur-containing group (**1aa—ff**) or a hetero aromatic ring such as tetrazole (**1gg**), thiazole (**1ii, jj**), or oxadiazole (**1hh, kk**) also resulted in exhibiting only a marginal effect. These observations suggest that the structural requirement in

TABLE III. Antiinflammatory and Analgesic Activities of Substituted 2′-(2,4-Difluorophenoxy)methanesulfonanilides (**1**)

No.	Adjuvant arthritis % inhibition[a] (10 mg/kg)	Writhing syndrome % inhibition (100 mg/kg)	No.	Adjuvant arthritis % inhibition[a] (10 mg/kg)	Writhing syndrome % inhibition (100 mg/kg)
1a	3	NT	**1u**	48	50[c]
1b	100[b,c]	93[c]	**1v**	61[d]	12[d]
1c	11	33[d]	**1w**	81[c]	5
1d	58[c]	1	**1x**	17	22
1e	85[c]	89[c]	**1y**	70[d]	65[c]
1f	−16	−2	**1z**	−3	30[d]
1g	−13	10[d]	**1aa**	20	NT
1h	79[c]	81[c]	**1bb**	49[c]	53[c]
1i	20	33[c]	**1cc**	14	NT
1j[e]	−30	3	**1dd**	23	NT
1k	55[c]	45[c]	**1ee**	21	NT
1l	13	59[c]	**1ff**	58[c]	47[c]
1m	36[d]	33[c]	**1gg**	−19	3
1n	28	NT	**1hh**	31	18
1o	59[c]	43[c,f]	**1ii**	22	39[c]
1p	65[d]	28[c]	**1jj**	−36	40[d]
1q	59[c]	13[d]	**1kk**	45[d]	62[c]
1r	−9	43[c]	**1ll**	4	30[c]
1s	9	29[d]	**1mm**	25	10
1t	22	20	**1nn**	91[c]	45[c]

a) Uninjected paw. *b*) 9/10 rats died. *c*) $p<0.05$, *d*) $p<0.01$, significant difference from control. *e*) Evaluated as sodium salt. *f*) 32 mg/kg. NT: not tested.

TABLE IV. Antiinflammatory and Analgesic Activities of 4′-Acetyl-2′-(substituted phenoxy)methanesulfonanilides (**2**)

No.	Adjuvant arthritis % inhibition[a] (10 mg/kg)	Writhing syndrome % inhibition (100 mg/kg)	No.	Adjuvant arthritis % inhibition[a] (10 mg/kg)	Writhing syndrome % inhibition (100 mg/kg)
2a	38	1	**2j**	−91[b]	50[c]
2b	58[b]	−1	**2k**	−51	NT
2c	−29	2	**2l**	82[c]	65[c]
2d	56[b]	44[c]	**2m**	−46	62[c]
2e[d]	2	41[c]	**2n**[d]	−17	63[c]
2f	51[b]	3	**2o**	−52[c]	24
2g[d]	28	50[c]	**2p**	−35	52[c]
2h	68[c]	47[c]	**2q**	−8	67[c]
2i	22	40[c]	**2r**	−44	17

a) Uninjected paw. *b*) $p<0.01$, *c*) $p<0.05$, significant difference from control. *d*) Evaluated as sodium salt. NT: not tested.

TABLE V. Pharmacological Properties of **1e** (FK867) and **1h** (FK3311) in Comparison with the Reference Compounds

Compound	Antiinflammatory[a] ED_{50} (mg/kg)		Ulcerogenic[a] UD_{50} (mg/kg) stomach	Analgesic[b] ED_{30} (mg/kg)	Antipyretic[c] ED_{50} (mg/kg)
	Injected paw	Uninjected paw			
1e (FK867)[d]	1.2	0.31	>10	4.4	5.0
1h (FK3311)	4.2	3.2	>10	3.6	6.8
CGP28238	0.29	0.27	>1	79	NT
Indomethacin	0.17	0.17	0.016	3.1	2.6

a) Adjuvant-induced arthritis in rats (*p.o.*). *b*) Randall-Selitto's method in rats (*p.o.*). *c*) Yeast-induced pyrexia in rats (*p.o.*). *d*) Sodium salt. NT: not tested.

exhibiting the potent antiinflammatory and analgesic activities might be rather strict. Consequently, it was shown that a cyano or an acetyl was the appropriate substituent for R^1.

With regard to the influence of substitution at R^1 or R^2, 5′-acety derivative (**1ll**) was shown to be significantly less active than its 4′-acetyl analog (**1h**). The compounds having an additional methyl group in the R^2 position exhibited the interesting pharmacological results, namely, a drastic decrease of potency in 4′-acetyl (**1mm**) and nearly equal activities in 4′-cyano (**1nn**), compared to the corresponding unsubstituted compounds (**1h**, **e**).

Concerning the substituents in the phenoxy part, 2,4-dichloro (**2h**) and 2-chloro-4-fluoro (**2l**) seemed to be the best among the compounds prepared, but a remarkable improvement over 2,4-difluoro (**1h**) could not be observed. A structure activity relationship on the substituents in the phenoxy part might be difficult to discuss. Indeed, some compounds such as **2j**, **2k**, and **2o** stimulated the inflammation in adjuvant arthritis test.

Based on detailed pharmacological and toxicological evaluation, sodium salts of **1e** (FK867) and **1h** (FK3311) were selected as candidates for further development. As can be seen in Table V, these two compounds showed not only well-balanced antiinflammatory, analgesic, and antipyretic activities, but also no ulcerogenicity. These properties appear to be superior to those of CGP28238 or indomethacin.

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. Mass spectra (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).

The commercially unavailable 2-chloroaniline derivatives (**3**), 4-amino-3-chloro-α,α,α-trifluorotoluene,[9] 4-amino-3-chlorobenzonitrile,[9] 4′-amino-3′-chloroacetophenone,[10] and 1-(4-amino-3-chlorophenyl)-1-propanone,[10] were prepared by the method described in the cited literature.

3-Chloro-4-nitrobenzonitrile (4: $R^1=CN$, $R^2=H$) A solution of sodium nitrite (8.1 g, 117 mmol) in H_2O (40 ml) was added to a suspension of 4-amino-3-chlorobenzonitrile[9] (11.0 g, 72 mmol) in concentrated HCl (28 ml) and H_2O (28 ml) at 0 to 5 °C, and the reaction mixture was stirred for 10 min. The mixture was then added to a suspension of sodium nitrite (36 g, 0.52 mol) and cuprous oxide (3.8 g, 26.6 mmol) in H_2O (160 ml) at −5 to 0 °C, and stirred at the same temperature for 30 min and at room temperature for 30 min. The reaction mixture was extracted with CH_2Cl_2 and the extract was washed with brine, dried, and evaporated under reduced pressure. The residue obtained was chromatographed on a column of silica gel eluting with $CHCl_3$ to afford the titled compound (11.5 g, 87%) as a yellow oil. IR (Nujol): 2250, 1570, 1535 cm^{-1}.

The following 2-chloro-nitrobenzene derivatives (**4**) were prepared according to the above method.

3-Chloro-4-nitrotoluene (4: $R^1=CH_3$, $R^2=H$) 37% yield as an oil. IR (film): 1600, 1530, 1410, 1350 cm^{-1}.

3′-Chloro-4′-nitroacetophenone (4: $R^1=COCH_3$, $R^2=H$) 75% yield as crystals, mp 47—49 °C. IR (Nujol): 1695, 1580, 1530, 1360, 1215 cm^{-1}.

3-Chloro-4-nitro-α,α,α-trifluorotoluene (4: $R^1=CF_3$, $R^2=H$) 47% yield as an oil. IR (film): 1590, 1540, 1400, 1325, 1180, 1140 cm^{-1}.

1-(3-Chloro-4-nitrophenyl)-1-propanone (4: $R^1=COC_2H_5$, $R^2=H$) 58% yield as an oil. IR (Nujol): 1700, 1610, 1525, 1505, 1350, 1215 cm^{-1}.

5-Chloro-2-methyl-4-nitrobenzonitrile (4: $R^1=CN$, $R^2=CH_3$) A solution of sodium nitrite (2.0 g, 29 mmol) in H_2O (3 ml) was added to a suspension of 2-amino-4-chloro-5-nitrotoluene (5.0 g, 27 mmol) in tetrahydrofuran (THF) (13 ml), concentrated HCl (5.1 ml), and H_2O (27 ml) at 0 to 5 °C and the resulting mixture was stirred for 1.0 h. Then the mixture was added slowly to a suspension of cupric sulfate pentahydrate (9.7 g, 39 mmol) and potassium cyanide (7.3 g, 112 mmol) in H_2O (80 ml) at 0 to 5 °C, and stirred for 20 min. The reaction mixture was extracted with EtOAc, and the extract was washed with brine, dried, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with $CHCl_3$ as an eluent to afford the titled compound (1.20 g, 23%) as an oil. IR (Nujol): 2240, 1565, 1530, 1460, 1380, 1355 cm^{-1}.

3-(2,4-Difluorophenoxy)-4-nitrobenzonitrile (5i) (Method A) A mixture of 3-chloro-4-nitrobenzonitrile (5.0 g, 27 mmol), 2,4-difluorophenol (4.0 g, 30 mmol), and potassium carbonate (4.0 g, 30 mmol) in xylene (70 ml) was refluxed for 5.5 h. After cooling, the insoluble materials were filtered, and the filtrate was evaporated under reduced pressure. The residue obtained was recrystallized from EtOH to afford **5i** (5.9 g, 78%) as crystals, mp 109—110 °C.

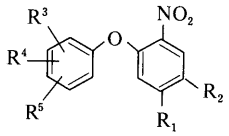
The 2-phenoxynitrobenzene derivatives (**5**) prepared by this method are listed in Table VI along with their physical data.

4′-Cyano-2′-(2,4-difluorophenoxy)methanesulfonanilide (1e) (Method B) Iron powder (1.0 g, 17.6 mmol) and ammonium chloride (100 mg, 1.9 mmol) was added to a solution of **5i** (1.0 g, 3.6 mmol) in EtOH (20 ml) and H_2O (10 ml) and then the reaction mixture was refluxed for 30 min. 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, and the organic layer was separated, washed with brine, dried, and evaporated to afford 4-amino-3-(2,4-difluorophenoxy)-benzonitrile (0.9 g), which was used for the next reaction without purification. Methanesulfonyl chloride (450 mg, 3.9 mmol) was added to the solution of the above aminobenzonitrile derivative in pyridine (5 ml) at 0 °C, and the reaction mixture was stirred overnight. After removal of the solvent, 1 N HCl was added to form precipitates, which were recrystallized from EtOH to afford **1e** (1.02 g, 86%) as crystals, mp 185—187 °C.

Most of the methanesulfonanilide derivatives (**1** and **2**) shown in Tables I and II were prepared by this method. The spectral data of the compounds (**1** and **2**) are listed in Table VII.

Preparation of Sodium Salt of 1e The compound **1e** (15.0 g, 46 mmol) was dissolved in a solution of sodium hydroxide (2.0 g, 50 mmol) in water (70 ml). The insoluble material was filtered off and the filtrate was

TABLE VI. 2-Phenoxynitrobenzene Derivatives (**5**)



5

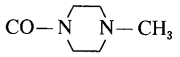
No.	R^1	R^2	R^3–R^5	Method	Yield (%)	mp (°C)	IR (Nujol) ν_{max} (cm^{-1})	NMR ($CDCl_3$) δ (ppm)
5a	H	H	2-F, 4-F	A	86	[a]	1610, 1530, 1505, 1480, 1350	6.70—8.00 (7H, m)
5b	$COCH_3$	H	2-F, 4-F	A C	60 65[b]	96—98	1695, 1610, 1520, 1505	2.57 (3H, s), 6.80—8.20 (6H, m)
5c	NH_2	H	2-F, 4-F	[c]	85	140—142	3500, 3400, 1635, 1580	5.96 (1H, d, J=2 Hz), 6.30—7.40 (4H, m), 8.00 (1H, d, J=8 Hz)
5d	SCH_3	H	2-F, 4-F	[c]	54	56—58	1580, 1520, 1505, 1440, 1340	2.40 (3H, s), 6.50—8.00 (6H, m)
5e	SCH_2CH_3	H	2-F, 4-F	[c]	34	57—58	1595, 1580, 1500, 1460, 1400, 1340	1.30 (3H, t, J=8 Hz), 2.90 (2H, q, J=8 Hz), 6.70—8.00 (6H, m)
5f	$SCH(CH_3)_2$	H	2-F, 4-F	[c]	52	Oil	1680, 1590, 1500, 1480, 1340	1.25 (6H, d, J=8 Hz), 3.40 (1H, m), 6.70—8.00 (6H, m)
5g	CH_3	H	2-F, 4-F	A	48	93—96	1610, 1505, 1440	2.34 (3H, s), 6.50—7.20 (5H, m), 7.91 (1H, d, J=8 Hz)
5h	CF_3	H	2-F, 4-F	A	60	Oil	1620, 1530, 1500, 1430, 1330	6.86—7.70 (5H, m), 8.05 (1H, d, J=8 Hz)
5i	CN	H	2-F, 4-F	A	78	109—110	2250, 1615, 1590, 1530, 1510	6.80—7.50 (5H, m), 8.02 (1H, d, J=8 Hz)
5j	COPh	H	2-F, 4-F	[c]	68	72—73	1660, 1600, 1525, 1510, 1415, 1355, 1310	7.70—8.00 (11H, m)
5k	$CONH_2$	H	2-F, 4-F	[c]	94	159—163	3550, 3400, 3200, 1680, 1505, 1460, 1380, 1350	6.84—8.04 (6H, m)[d]
5l	$COOC_2H_5$	H	2-F, 4-F	[c]	94	83—85	1720, 1620, 1530, 1510, 1320, 1290	1.37 (3H, t, J=7 Hz), 4.43 (2H, q, J=7 Hz), 6.80—8.12 (6H, m)
5m	$CONHCH_3$	H	2-F, 4-F	[c]	85	186—188	3350, 1650, 1590, 1560, 1500, 1350	2.91 (3H, s), 6.86—8.03 (6H, m)
5n	$CON(CH_3)_2$	H	2-F, 4-F	[c]	89	81—83	1630, 1610, 1530, 1505, 1420, 1355	2.90 (3H, s), 3.03 (3H, s), 6.75—7.97 (6H, m)
5o	$CONH(OCH_3)$	H	2-F, 4-F	[c]	71	103—105	3250, 1660, 1590, 1530, 1505, 1355	3.76 (3H, s), 6.75—7.97 (6H, m), 9.49 (1H, s)
5p		H	2-F, 4-F	[c]	80	75—78	1635, 1525, 1505, 1460, 1445, 1355	2.23—2.57 (4H, m), 2.30 (3H, s), 3.23—3.87 (4H, m), 6.84—8.10 (6H, m)
5q	COC_2H_5	H	2-F, 4-F	A	42	86—88	1700, 1610, 1525, 1505	1.20 (3H, t, J=8 Hz), 2.92 (2H, q, J=8 Hz), 6.80—8.00 (6H, m)
5r	H	$COCH_3$	2-F, 4-F	A	84	84—85	1690, 1620, 1540, 1505, 1345, 1300	2.60 (3H, s), 6.80—7.40 (4H, m), 8.10 (1H, dd, J=9, 2 Hz), 8.55 (1H, d, J=2 Hz)
5s	CN	CH_3	2-F, 4-F	A	55	95—97	2240, 1535, 1500, 1270, 1200, 1145	2.56 (3H, s), 6.78—7.28 (4H, m), 7.80 (1H, s)
5t	$COCH_3$	CH_3	2-F, 4-F	[c]	44	110—113	1710, 1620, 1500, 1480, 1340	2.46 (3H, s), 2.49 (3H, s), 6.75—7.26 (4H, m), 7.78 (1H, s)
5u	$COCH_3$	H	H	A	43	40—47	1690, 1610, 1580, 1520, 1415, 1310	2.55 (3H, s), 6.80—8.10 (8H, m)
5v	$COCH_3$	H	2-F	A	62	79—81	1700, 1610, 1520, 1500, 1420, 1350	2.57 (3H, s), 7.10—7.40 (4H, m), 7.48 (1H, d, J=2 Hz), 7.70 (1H, dd, J=8, 2 Hz), 8.10 (1H, d, J=8 Hz)
5w	$COCH_3$	H	4-F	A	78	68—72	1700, 1610, 1590, 1510, 1500, 1415	2.57 (3H, s), 6.90—7.30 (4H, m), 7.53 (1H, d, J=2 Hz), 7.72 (1H, dd, J=8, 2 Hz), 8.00 (1H, d, J=8 Hz)
5x	$COCH_3$	H	2-Cl	A	67	68—69	1690, 1610, 1580, 1530, 1410, 1340, 1270	2.55 (3H, s), 7.00—7.60 (5H, m), 7.70 (1H, dd, J=8, 2 Hz), 8.03 (1H, d, J=8 Hz)
5y	$COCH_3$	H	3-Cl	A	55	Oil	1695, 1580, 1530, 1470, 1410, 1350	2.58 (3H, s), 6.80—8.20 (7H, m)
5z	$COCH_3$	H	4-Cl	A	80	72—74	1690, 1610, 1580, 1520, 1415, 1345, 1310	2.58 (3H, s), 6.99—7.60 (5H, m), 7.88 (1H, dd, J=8, 2 Hz), 8.02 (1H, d, J=8 Hz)
5aa	$COCH_3$	H	2-Cl, 3-Cl	A	52	74—78	1700, 1610, 1530, 1415, 1350, 1310	2.58 (3H, s), 7.00—7.40 (3H, m), 7.52 (1H, d, J=2 Hz), 7.74 (1H, dd, J=8, 2 Hz), 8.06 (1H, d, J=8 Hz)
5bb	$COCH_3$	H	2-Cl, 4-Cl	A	45	101—103	1700, 1610, 1520, 1410, 1345, 1310	2.58 (3H, s), 7.02 (1H, d, J=8 Hz), 7.28 (1H, dd, J=8, 2 Hz), 7.35 (1H, d, J=2 Hz), 7.51 (1H, d, J=2 Hz), 7.72 (1H, dd, J=8, 2 Hz), 8.02 (1H, d, J=8 Hz)

TABLE VI. (continued)

No.	R^1	R^2	R^3–R^5	Method	Yield (%)	mp (°C)	IR (Nujol) ν_{max} (cm^{-1})	NMR ($CDCl_3$) δ (ppm)
5cc	$COCH_3$	H	2-Cl, 5-Cl	A	49	90—94	1700, 1580, 1530, 1410, 1390	2.60 (3H, s), 7.08 (1H, d, J=2 Hz), 7.20 (1H, dd, J=8, 2 Hz), 7.48 (1H, d, J=2 Hz), 7.50 (1H, d, J=8 Hz), 7.80 (1H, dd, J=8, 2 Hz), 8.10 (1H, d, J=8 Hz)
5dd	$COCH_3$	H	2-Cl, 6-Cl	C	62[b]	131—133	1700, 1610, 1530, 1450, 1420	2.55 (3H, s), 7.10—7.50 (4H, m), 7.70 (1H, dd, J=8, 2 Hz), 8.05 (1H, d, J=8 Hz)
5ee	$COCH_3$	H	2-Cl, 4-Cl, 6-Cl	C	17[b]	135—138	1695, 1600, 1540, 1445	2.60 (3H, s), 7.19 (1H, d, J=2 Hz), 7.50 (2H, s), 7.73 (1H, dd, J=8, 2 Hz), 8.08 (1H, d, J=8 Hz)
5ff	$COCH_3$	H	2-Cl, 4-F	A	41	Oil	1695, 1605, 1530, 1480, 1415, 1350, 1280	2.58 (3H, s), 6.90—7.40 (4H, m), 7.73 (1H, dd, J=8, 2 Hz), 8.05 (1H, d, J=8 Hz)
5gg	$COCH_3$	H	2-Br	A	58	Oil	1695, 1610, 1580, 1530, 1470, 1415, 1350	2.57 (3H, s), 7.00—8.02 (7H, m)
5hh	$COCH_3$	H	2-CH_3	A	48	Oil	1695, 1605, 1580, 1530, 1490, 1415, 1355	2.25 (3H, s), 2.52 (3H, s), 6.80—7.40 (5H, m), 7.67 (1H, dd, J=8, 2 Hz), 8.00 (1H, d, J=8 Hz)
5ii	$COCH_3$	H	2-OCH_3	A	60	94—96	1695, 1610, 1520, 1345, 1280	2.52 (3H, s), 3.77 (3H, s), 6.90—7.40 (5H, m), 7.65 (1H, dd, J=8, 2 Hz), 8.00 (1H, d, J=8 Hz)
5jj	$COCH_3$	H	2-SCH_3	A	25	84—86	1695, 1610, 1540, 1380, 1360	2.43 (3H, s), 2.52 (3H, s), 6.80—7.40 (5H, m), 7.70 (1H, dd, J=8, 2 Hz), 8.32 (1H, d, J=8 Hz)

a) bp 143—147 °C/0.7 mmHg. *b*) Yield based on the ketal derivative (**13**). *c*) See Experimental. *d*) $CDCl_3$–CD_3OD.

concentrated under reduced pressure. The residue obtained was dissolved in EtOAc (100 ml) at room temperature and the solution was immediately filtered. The filtrate was then stirred at room temperature for 0.5 h to form precipitates, which were filtered and washed with EtOAc to afford sodium salt of **1e** (14.5 g, 93%) as powder, mp 267—268 °C.

The other sodium salts of **1j**, **2e**, **2g**, and **2n** were prepared by the similar method as that used for **1e**.

2′-(2,4-Difluorophenoxy)-4′-nitromethanesulfonanilide (1b) 2′-(2,4-Difluorophenoxy)methanesulfonanilide (**1a**, 8.0 g, 27 mmol) was added portionwise to 71% nitric acid (40 ml, 53 mmol) at room temperature. The mixture was stirred for 2 h and then poured into water. The precipitates formed were collected by filtration and recrystallized from EtOH to afford **1b** (7.4 g, 81%) as crystals, mp 162—164 °C.

2′-(2,4-Difluorophenoxy)-4′-mercaptomethanesulfonanilide (1aa) Iron powder (8.3 g, 148 mmol) and ammonium chloride (830 mg, 15.3 mmol) was added to a solution of **1b** (8.2 g, 24 mmol) in EtOH (80 ml) and H_2O (40 ml) and then the reaction mixture was refluxed for 30 min. 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, and the organic layer was separated, washed with brine, dried, and evaporated to afford crude **6** as pale yellow crystals (6.2 g), mp 145—148 °C. IR (Nujol): 3450, 3350, 1620, 1500 cm^{-1}. A solution of sodium nitrite (1.56 g, 18 mmol) in H_2O (3 ml) was added dropwise to a suspension of **6** (6.2 g, 19 mmol) in H_2O (50 ml) and concentrated HCl (6 ml) at 5 to 10 °C, and the mixture was stirred for 15 min. The resulting solution was added dropwise to a solution of potassium ethyl xanthate (10 g, 62 mmol) in H_2O (40 ml) at 65 °C, and the reaction mixture was stirred for 15 min. The reaction mixture was extracted with toluene, and the organic layer was separated, washed with H_2O, dried, and evaporated under reduced pressure. The residue obtained was dissolved in MeOH (100 ml), and the solution was stirred with sodium borohydride (0.54 g, 14 mmol) and potassium hydroxide (3.0 g, 53 mmol) at room temperature for 1 h. The reaction mixture was acidified with 10% H_2SO_4 (5 ml) and concentrated under reduced pressure. The residue obtained was dissolved in a mixture of EtOAc and H_2O, and the organic layer was separated, washed with H_2O, dried, and evaporated under reduced pressure to afford an oily residue which was chromatographed on a column of silica gel eluting with $CHCl_3$ to give a pale yellow solid. This solid was recrystallized from a mixture of EtOAc and hexane to afford **1aa** (4.4 g, 56%) as crystals, mp 103—105 °C.

2′-(2,4-Difluorophenoxy)-4′-formylmethanesulfonanilide (1f) A mixture of **1e** (1.5 g, 4.6 mmol) and Raney–Ni (1.5 g) in 75% formic acid (40 ml) was refluxed for 2 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue obtained was recrystallized from EtOH to afford **1f** (1.40 g, 92%) as crystals, mp 156—157 °C.

3-(2,4-Difluorophenoxy)-4-(methanesulfonamido)benzoic Acid (1g) A mixture of **1e** (1.2 g, 3.7 mmol) and concentrated HCl (5 ml) in acetic acid (5 ml) was refluxed for 8 h. After cooling, the resulting precipitates were collected by filtration, and washed with H_2O. The crude product was recrystallized from a mixture of EtOAc and hexane to afford **1g** (0.66 g, 52%) as crystals, mp 167—169 °C.

2′-(2,4-Difluorophenoxy)-4′-(5-tetrazolyl)methanesulfonanilide (1gg) A mixture of **1e** (2.1 g, 6.5 mmol), sodium azide (0.5 g, 7.7 mmol), and ammonium chloride (0.43 g, 8.0 mmol) in DMF (10 ml) was heated at 110 °C for 6 h. The reaction mixture was poured into ice-diluted HCl and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated under reduced pressure. The residue obtained was recrystallized from EtOH to afford **1gg** (2.0 g, 83%) as crystals, mp 222—223 °C (dec.).

5-[3-(2,4-Difluorophenoxy)-4-methanesulfonamidophenyl]-3-ethylthio-1,2,4-oxadiazole (1hh) PCl_5 (410 mg, 1.8 mmol) was added to a suspension of **1g** (0.60 g, 1.9 mmol) in benzene (6 ml) at room temperature. The mixture was stirred for 30 min, and the solvent was evaporated under reduced pressure. The residue obtained was dissolved in toluene (6 ml) and potassium thiocyanate (730 mg, 7.5 mmol) was added to the solution. The mixture was refluxed for 18 h, and then ethyl mercaptan (0.7 ml) was added to the cooled reaction mixture. The resulting mixture was stirred at 60 °C for 4 h. After removal of the solvent, the residue was dissolved in a mixture of EtOAc and H_2O, and the organic layer was separated, washed with H_2O, dried, and evaporated under reduced pressure to afford powder of **8** (0.83 g). IR (Nujol): 3260, 1695, 1610, 1585, 1500 cm^{-1}. A solution of ethyl iodide (0.17 ml, 2.1 mmol) in THF (5.0 ml) was added dropwise to a stirred mixture of **8** (0.83 g, 1.9 mmol) and potassium hydroxide (140 mg, 2.5 mmol) in THF (15 ml). The mixture was stirred overnight at room temperature. After removal of the solvent, the residue was dissolved in a mixture of $CHCl_3$ and H_2O, the organic layer was separated, washed with H_2O, dried, and evaporated under reduced pressure to afford brown crystals of **9** (0.84 mg). A mixture of **9** (0.84 g, 1.7 mmol) and hydroxylamine hydrochloride (150 mg, 2.2 mmol) was added to a solution of sodium (50 mg, 2.2 mmol) in MeOH (5 ml). The mixture was refluxed for 5 h, and the solvent was evaporated under reduced pressure. The residue obtained was dissolved in a mixture of $CHCl_3$ and H_2O, and the organic layer was separated, washed with H_2O, dried, and evaporated. The residue was chromatographed on a column of silica gel eluting with toluene and EtOAc (20 : 1) to afford **1hh** (0.38 g, 49%) as crystals, mp 116—119 °C.

2′-(2,4-Difluorophenoxy)-4′-(hydroxyiminomethyl)methanesulfonanilide (1t) A mixture of **1f** (1.2 g, 3.7 mmol), hydroxylamine hydrochloride

TABLE VII. Spectral Data of 2′-Phenoxymethanesulfonanilides (**1** and **2**)

No.	IR (Nujol) ν_{max} (cm^{-1})	NMR δ (ppm)
1a	3300, 1620, 1500, 1330	($CDCl_3$): 3.10 (3H, s), 6.60—7.80 (8H, m)
1b	3450, 3350, 1605, 1520, 1500	($CDCl_3$): 3.00 (3H, s), 5.52 (2H, br s), 6.00—7.70 (7H, m)
1c	3270, 1620, 1510	($CDCl_3$): 2.25 (3H, s), 3.00 (3H, s), 6.50—7.53 (7H, m)
1d	3260, 1510, 1335, 1250, 1160, 1120	($CDCl_3$): 3.13 (3H, s), 6.83—7.87 (7H, m)
1e	3330, 2250, 1610, 1585, 1510	($CDCl_3+CD_3OD$): 3.14 (3H, s), 6.90—7.80 (6H, m)
1f	3300, 1690, 1605, 1505, 1345, 1160	($CDCl_3$): 3.17 (3H, s),6.80—7.92 (7H, m), 9.84 (1H, s)
1g	3300, 1710, 1615, 1510	($CDCl_3+CD_3OD$): 3.17 (3H, s), 6.90—8.00 (6H, m)
1h	3200, 1685, 1605, 1590, 1505, 1345	($CDCl_3$): 2.50 (3H, s), 3.11 (3H, s), 6.70—7.80 (7H, m)
1i	3240, 1675, 1610, 1505, 1445, 1350	($CDCl_3$): 1.17 (3H, t, J=7 Hz), 2.89 (2H, q, J=7 Hz), 3.12 (3H, s), 6.80—7.80 (7H, m)
1j	3450, 1640, 1590, 1500	(D_2O): 2.94 (3H, s), 6.60—7.80 (11H, m)
1k	3230, 1645, 1575, 1510	($CDCl_3$): 2.33 (3H, s), 3.10 (3H, s), 6.50—7.80 (9H, m)
1l	3300, 1665, 1605, 1585, 1505	($CDCl_3$): 2.10 (3H, s), 3.17 (3H, s), 3.67 (2H, s), 6.80—7.80 (7H, m)
1m	3400, 1670, 1610, 1505	(DMSO-d_6): 3.13 (3H, s), 3.23 (3H, s), 5.03 (2H, s), 7.10—8.10 (6H, m), 10.02 (1H, s)
1n	3250, 1715, 1610, 1590, 1505	($CDCl_3$): 1.33 (3H, t, J=7 Hz), 3.10 (3H, s), 4.32 (2H, q, J=7 Hz), 6.70—8.00 (7H, m)
1o	3460, 3280, 3170, 1680, 1615, 1585, 1505	($CDCl_3$): 3.10 (3H, s), 5.94 (2H, br s), 6.80—7.90 (7H, m)
1p	3460, 3270, 1650, 1615, 1550, 1505	($CDCl_3$): 2.92 (3H, d, J=5 Hz), 3.06 (3H, s), 6.05 (1H, br s), 6.70—7.00 (7H, m)
1q	3100, 1630, 1580, 1505, 1490	($CDCl_3$): 3.00 (6H, s), 3.12 (3H, s), 6.70—7.80 (7H, m)
1r	3150, 1635, 1580, 1500	($CDCl_3$): 3.12 (3H, s), 3.84 (3H, s), 6.80—7.80 (8H, m)
1s	1625, 1575, 1500	($CDCl_3+CD_3OD$): 2.35 (3H, s), 2.30—2.60 (4H, m), 3.10 (3H, s), 3.40—3.80 (4H, m), 6.70—7.80 (6H, m)
1t	3300, 1610, 1505	($CDCl_3$): 3.10 (3H, s), 5.70 (1H, br s), 6.80—7.80 (7H, m), 8.00 (1H, s)
1u	3400, 1620, 1510	($CDCl_3$): 3.07 (3H, s), 3.93 (3H, s), 6.80—7.70 (8H, m)
1v	3300, 1610, 1580, 1510	($CDCl_3+CD_3OD$): 2.17 (3H, s), 3.07 (3H, s), 6.60—7.70 (6H, m)
1w	3300, 1615, 1510	($CDCl_3$): 2.12 (3H, s), 3.07 (3H, s), 3.93 (3H, s), 6.80—7.80 (7H, m)
1x	3250, 1610, 1505	($CDCl_3$): 1.24 (3H, t, J=7 Hz), 2.11 (3H, s), 3.03 (3H, s), 4.17 (2H, q, J=7 Hz). 6.80—7.80 (7H, m)
1y	3500, 3200, 1710, 1580, 1505	(DMSO-d_6): 2.10 (3H, s), 3.04 (3H, s), 6.33 (2H, s), 6.90—7.70 (6H, m), 9.26 (1H, s), 9.43 (1H, s)
1z	3480, 3360, 3200, 1590, 1500	(DMSO-d_6): 2.22 (3H, s), 3.07 (3H, s), 7.00—8.40 (8H, m), 9.57 (1H, s), 10.20 (1H, s)
1aa	3280, 2600, 1620, 1580, 1500	($CDCl_3$): 3.00 (3H, s), 6.54 (1H, s), 6.40—7.60 (7H, m)
1bb	3300, 1610, 1580, 1500	($CDCl_3$): 2.35 (3H, s), 3.00 (3H, s), 6.40—7.60 (7H, m)
1cc	3260, 1615, 1580, 1500	($CDCl_3$): 1.24 (3H, t, J=7 Hz), 2.83 (2H, q, J=7 Hz), 3.02 (3H, s), 6.60—7.60 (7H, m)
1dd	3260, 1620, 1580, 1500	($CDCl_3$): 1.22 (6H, d, J=7 Hz), 3.03 (3H, s), 2.93—3.50 (1H, m), 6.70—7.65 (7H, m)
1ee	1615, 1500	($CDCl_3+CD_3OD$): 2.70 (3H, s), 3.10 (3H, s), 6.80—8.00 (6H, m)
1ff	3260, 1620, 1595, 1505	($CDCl_3+CD_3OD$): 3.00 (3H, s), 3.13 (3H, s), 6.80—8.00 (6H, m)
1gg	3250, 1620, 1590, 1505	($CDCl_3+CD_3OD$): 3.14 (3H, s), 6.80—7.80 (6H, m)
1hh	3480, 3340, 3130, 1620, 1540, 1500	(CD_3OD): 3.07 (3H, s), 6.77 (1H, s), 7.00—7.60 (6H, m)
1ii	3200, 1660, 1550, 1500	($CDCl_3$): 2.00 (3H, s), 3.07 (3H, s), 6.70—7.80 (8H, m), 10.1 (1H, br s)
1jj	3400, 1620, 1550, 1500	(DMSO-d_6): 1.38 (3H, t, J=7 Hz), 3.23 (3H, s), 3.30 (2H, q, J=7 Hz), 7.20—7.90 (6H, m), 10.04 (1H, s)
1kk	3310, 1615, 1565, 1510	(DMSO-d_6): 1.30 (3H, t, J=7 Hz), 3.30 (3H, s), 3.68 (2H, q, J=7 Hz), 7.20—8.00 (6H, m), 10.15 (1H, s)
1ll	3240, 1680, 1610, 1590, 1500	($CDCl_3$): 2.56 (3H, s), 3.10 (3H, s), 6.72 (1H, d, J=9 Hz), 6.70—7.40 (4H, m), 7.73 (1H, dd, J=9, 2 Hz), 8.30 (1H, d, J=2 Hz)
1mm	3260, 1680, 1670, 1610, 1575, 1505	($CDCl_3$): 2.40 (3H, s), 2.51 (3H, s), 3.10 (3H, s), 6.80—7.40 (5H, m), 7.56 (1H, s)
1nn	3250, 2230, 1615, 1580, 1505	($CDCl_3$): 2.53 (3H, s), 3.16 (3H, s), 6.80—7.70 (6H, m)
2a	3250, 1690, 1610, 1505	($CDCl_3$): 2.49 (3H, s), 3.07 (3H, s), 6.90—7.80 (9H, m)
2b	3220, 1680, 1600, 1585, 1520, 1500	($CDCl_3$): 2.50 (3H, s), 3.11 (3H, s), 7.10—7.50 (6H, m), 7.70 (1H, dd, J=9, 2 Hz), 7.76 (1H, d, J=9 Hz)
2c	3250, 1680, 1500	($CDCl_3$): 2.49 (3H, s), 3.10 (3H, s), 6.90—7.30 (5H, m), 7.40 (1H, s), 7.70 (2H, s)
2d	3350, 1675, 1605, 1580, 1500	($CDCl_3$): 2.50 (3H, s), 3.12 (3H, s), 7.00—7.70 (6H, m), 7.75 (2H, s)
2e	1660, 1590, 1550	(DMSO-d_6): 2.34 (3H, s), 2.52 (3H, s), 6.70—7.80 (7H, m)
2f	3150, 1675, 1605, 1575, 1510, 1485	($CDCl_3$): 2.50 (3H, s), 3.08 (3H, s), 6.97 (2H, d, J=9 Hz), 7.30—7.50 (4H, m), 7.73 (2H, s)
2g	1665, 1590, 1550, 1500	(DMSO-d_6): 2.40 (3H, s), 2.55 (3H, s), 6.55 (1H, dd, J=6, 5 Hz), 7.10—7.50 (4H, m), 7.65 (1H, dd, J=8, 2 Hz)
2h	3300, 1680, 1610, 1580, 1500	($CDCl_3$): 2.50 (3H, s), 3.11 (3H, s), 7.08 (1H, d, J=8 Hz), 7.20—7.40 (3H, m), 7.54 (1H, d, J=2 Hz), 8.73 (2H, s)
2i	3230, 1670, 1605, 1580, 1500	($CDCl_3$): 2.52 (3H, s), 3.12 (3H, s), 7.00—7.60 (5H, m), 7.77 (2H, s)
2j	3220, 1675, 1605, 1500	($CDCl_3$): 2.49 (3H, s), 3.12 (3H, s), 7.07 (1H, d, J=2 Hz), 7.10—7.60 (4H, m), 7.70 (1H, dd, J=8, 2 Hz), 7.80 (1H, d, J=8 Hz)
2k	3370, 1680, 1610, 1510	($CDCl_3$): 2.50 (3H, s), 3.12 (3H, s), 7.00—7.90 (4H, m), 7.43 (2H, s)
2l	3230, 1680, 1605, 1580, 1515	($CDCl_3$): 2.50 (3H, s), 3.13 (3H, s), 7.00—7.80 (7H, m)
2m	3200, 1670, 1610, 1580, 1500	($CDCl_3$): 2.50 (3H, s), 3.12 (3H, s), 7.00—7.90 (8H, m)
2n	3450, 1650, 1590, 1550, 1495	(D_2O): 2.00 (3H, s), 2.38 (3H, s), 3.00 (3H, s), 6.80—7.80 (7H, m)
2o	3280, 1675, 1605, 1500	($CDCl_3$): 2.48 (3H, s), 3.02 (3H, s), 3.78 (3H, s), 6.80—7.40 (4H, m), 7.42 (1H, s), 7.58 (1H, br s), 7.70 (2H, s)
2p	3280, 1670, 1600	($CDCl_3$): 2.43 (3H, s), 2.50 (3H, s), 3.02 (3H, s), 6.90—7.90 (8H, m)
2q	1690, 1610, 1580, 1505	($CDCl_3$): 2.57 (3H, s), 2.98 (3H, s), 3.00 (3H, s), 6.80—7.90 (7H, m), 8.98 (1H, s)
2r	3290, 1680, 1610, 1580, 1510	(DMSO-d_6): 2.50 (3H, s), 3.15 (3H, s), 3.43 (3H, s), 7.00—8.10 (6H, m), 9.90 (1H, s)

(261 mg, 3.8 mmol), and pyridine (245 mg, 3.7 mmol) in EtOH (20 ml) was refluxed for 1 h. The reaction mixture was evaporated under reduced pressure, and a small amount of H_2O was added to form precipitates, which were collected by filtration and recrystallized from an aqueous EtOH to afford **1t** (970 mg, 72%) as crystals, mp 155—157 °C.

The methoxyiminomethyl (**1u**) and some iminoethyl derivatives (**1v—x**) were prepared by the similar method as that used for **1t**.

3′-(2,4-Difluorophenoxy)-4′-(methanesulfonamido)acetophenone Semicarbazone (1y) A mixture of **1h** (1.5 g, 4.4 mmol), semicarbazide hydrochloride (500 mg, 4.5 mmol), and pyridine (350 mg, 4.4 mmol) in EtOH (20 ml) was refluxed for 2 h. After cooling, the reaction mixture was evaporated under reduced pressure, and the residue obtained was recrystallized from MeOH to afford **1y** (1.1 g, 63%) as crystals, mp 187—189 °C.

3′-(2,4-Difluorophenoxy)-4′-(methanesulfonamido)acetophenone Thiosemicarbazone (1z) A mixture of **1h** (1.5 g, 4.4 mmol) and thiosemicarbazide (440 mg, 4.8 mmol) in EtOH (20 ml) was refluxed for 32 h. After cooling, the reaction mixture was evaporated under reduced pressure, and the residue obtained was recrystallized from AcOEt to afford **1z** (1.05 g, 58%) as crystals, mp 219—220 °C (dec.).

2′-(2,4-Difluorophenoxy)-4′-(3-oxo-1-butenyl)methanesulfonanilide (1k) A mixture of **1f** (2.3 g, 7.0 mmol) and 1-triphenylphosphoranylidene-2-propanone (2.3 g, 7.2 mmol) in dimethyl sulfoxide (DMSO) (10 ml) was stirred at 80 °C for 13 h. After cooling, the reaction mixture was diluted with a mixture of AcOEt and H_2O, and the organic layer was separated, washed with H_2O and brine, dried, and evaporated under reduced pressure. The residue obtained was chromatographed on a column of silica gel eluting with a mixture of $CHCl_3$ and MeOH (200 : 1) to give a solid. This solid was recrystallized from EtOH to afford **1k** (1.0 g, 39%) as crystals, mp 130—132 °C.

2′-(2,4-Difluorophenoxy)-4′-(methylthioacetyl)methanesulfonanilide (1l) A solution of bromine (1.4 g, 8.8 mmol) in $CHCl_3$ (15 ml) was added slowly to a solution of **1h** (3.0 g, 8.8 mmol) and benzoylperoxide (11 mg) in $CHCl_3$ (30 ml) at room temperature, and the mixture was stirred for 1 h. The reaction mixture was washed successively with H_2O, saturated $NaHCO_3$, brine, dried, and evaporated under reduced pressure to give crude bromoacetyl derivative (**10**) which was used for the next reaction without purification. Crude **10** was dissolved in $CHCl_3$ (30 ml), and aqueous 20% sodium thiomethoxide (5 ml) was added to the solution. The mixture was stirred at room temperature for 2 h. The reaction mixture was acidified with 10% HCl, and the organic layer was separated, washed with brine, dried, and evaporated under reduced pressure. The residue obtained was chromatographed on a column of silica gel eluting with a mixture of toluene and EtOAc (5 : 1) to give a yellow amorphous solid. This solid was recrystallized from EtOH to afford **1l** (1.6 g, 46%) as crystals, mp 74—76 °C.

2′-(2,4-Difluorophenoxy)-4′-(methylsulfonylacetyl)methanesulfonanilide (1m) *m*-Chloroperbenzoic acid (1.38 g, 6.4 mmol) was added to a solution of **1l** (1.38 g, 3.56 mmol) in CH_2Cl_2 (35 ml) at room temperature, and the mixture was stirred for 1 h. The reaction mixture was washed successively with saturated $NaHCO_3$, H_2O, and brine and dried. After removal of the solvent, the residue was recrystallized from AcOEt to afford **1m** (660 mg, 44%) as crystals, mp 162—163 °C.

The other sulfone derivatives (**1ff**, **1kk**, and **2r**) were respectively prepared from **1bb**, **1hh**, or **2p** by the similar method described for **1m**.

2′-(2,4-Difluorophenoxy)-4′-(methylsulfinyl)methanesulfonanilide (1ee) *m*-Chloroperbenzoic acid (0.18 g, 0.83 mmol) was added to a solution of **1bb** (0.26 g, 0.75 mmol) in CH_2Cl_2 (7 ml) at room temperature, and the mixture was stirred for 1 h. The reaction mixture was washed successively with saturated $NaHCO_3$, H_2O, and brine and dried. After removal of the solvent, the residue was recrystallized from EtOH to afford **1ee** (220 mg, 81%) as crystals, mp 164—166 °C.

The other sulfinyl derivative (**2q**) was prepared from **2p** by the similar method as that described for **1ee**.

4′-(2-Amino-4-thiazolyl)-2′-(2,4-difluorophenoxy)methanesulfonanilide (1ii) The bromoacetyl derivative (**10**) which was prepared from **1h** (1.0 g) according to the method described for **1l** was dissolved in MeOH (10 ml), and thiourea (334 mg, 4.4 mmol) was added to the solution. The mixture was refluxed for 1 h, and then the solvent was evaporated under reduced pressure. The oily residue obtained was treated with saturated $NaHCO_3$ to form precipitates, which were collected by filtration, and recrystallized from EtOH to afford **1ii** (740 mg, 64%) as crystals, mp 182—183 °C.

4′-(2-Acetamido-4-thiazolyl)-2′-(2,4-difluorophenoxy)methanesulfonanilide (1jj) A solution of **1ii** (1.2 g, 3.0 mmol) in acetic anhydride (5 ml) was stirred at 80 °C for 30 min. After removal of the excess acetic anhydride, the residue was chromatographed on a column of silica gel eluting with a mixture of toluene and EtOAc (1 : 1) to afford a yellow amorphous solid. This solid was recrystallized from EtOH to afford **1jj** (823 mg, 62%) as crystals, mp 192—193 °C.

3′-Chloro-4′-(2,4-difluorophenoxy)acetophenone (12) A mixture of **11** (1.00 g, 5.0 mmol), 2,4-difluorophenol (780 mg, 6.0 mmol), and potassium carbonate (830 mg, 6.0 mmol) in DMF (10 ml) was heated at 120 °C for 2.5 h. The reaction mixture was poured into ice-H_2O, and extracted with EtOAc. The combined extracts were washed with H_2O and dried, and the solvent was evaporated under reduced pressure, The residue was chromatographed on a column of silica gel eluting with toluene to afford a pale yellow oil **12** (1.2 g, 86%). IR (film). 1690, 1675, 1600, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.56 (3H, s), 6.70—8.05 (6H, m). MS *m/z*: 283 (M^+), 267 (base).

3′-(2,6-Dichlorophenoxy)-4′-nitroacetophenone (5dd) (Method C) A mixture of **11** (3.0 g, 15 mmol), ethylene glycol (9.3 g, 145 mmol), and *p*-toluenesulfonic acid (500 mg) in toluene (30 ml) was refluxed for 6 h under an azeotropic condition. After cooling, the reaction mixture was washed with saturated $NaHCO_3$, H_2O, and brine. The organic layer was separated, dried, and evaporated under reduced pressure to afford the ketal **13** (3.9 g). A mixture of **13** (3.9 g, 16 mmol) and potassium 2,6-dichlorophenoxide (4.0 g, 20 mmol) in DMF (40 ml) was heated at 150 °C for 10 h. The reaction mixture was poured into ice-H_2O, and extracted with EtOAc. The extract was washed with brine and dried. After removal of the solvent, the residue was chromatographed on a column of silica gel with toluene to afford an oil (4.1 g). A mixture of this oil (4.1 g) and 3N HCl (15 ml) in acetone (30 ml) was refluxed for 2.5 h. The reaction mixture was evaporated under reduced pressure. The residue obtained was dissolved in mixture of EtOAc and H_2O, and the organic layer was separated, washed with brine, dried, and evaporated under reduced pressure to afford **5dd** (3.4 g, 62% based on **13**) as crystals, mp 131—133 °C.

5b and **5ee** were also prepared by this method. The spectral data of 2-phenoxynitrobenzene derivatives (**5**) are listed in Table VI.

3-(2,4-Difluorophenoxy)-4-nitroaniline (5c) Fuming nitric acid (51 ml) was added to a solution of 3-chloroacetanilide (84 g, 0.49 mol) in AcOH (75 ml) and concentrated H_2SO_4 (126 ml) at 10—15 °C, and then mixture was stirred for 1 h. The reaction mixture was poured into ice-H_2O and extracted with EtOAc. The extract was washed with brine and dried. After removal of the solvent, the residue was recrystallized from toluene to afford 3-chloro-4-nitroacetanilide (55.5 g, 52%) as crystals, mp 132—135 °C. IR (Nujol): 3600, 1690, 1630, 1570 cm^{-1}. This compound (55.5 g) was converted to 3-(2,4-difluorophenoxy)-4-nitroacetanilide according to method A. The crude product (72.0 g) obtained was refluxed for 40 min in a mixture of AcOH (50 ml) and concentrated HCl (300 ml). After cooling, the precipitates formed were collected by filtration and washed with H_2O to afford **5c** (59.0 g, 85%) as crystals, mp 140—142 °C.

2′,4′-Difluoro-5-methylthio-2-nitrodiphenylether (5d) A solution of sodium nitrite (2.03 g, 29 mmol) in H_2O (4 ml) was added dropwise to a stirred solution of **5c** (7.0 g, 28 mmol) in a mixture of concentrated HCl (7.6 ml), H_2O (16 ml), and EtOH (16 ml) at 5—7 °C. The reaction mixture was stirred for 20 min. The mixture was then added portionwise to a stirred solution of potassium ethyl xanthate (5.9 g, 37 mmol) in H_2O (60 ml) at 65 °C. After stirring for 20 min, the reaction mixture was extracted with toluene. The extract was washed with H_2O, dried, and evaporated under reduced pressure to afford an oil (8.6 g). A mixture of this oil (8.6 g), sodium borohydride (0.7 g, 38 mmol), and potassium hydroxide (1.8 g, 32 mmol) in MeOH (50 ml) was stirred at 5 to 10 °C for 15 min. The reaction mixture was acidified with 10% H_2SO_4, and then evaporated under reduced pressure. The residue obtained was dissolved in a mixture of EtOAc and H_2O and the organic layer was separated, washed with H_2O, and dried, After removal of the solvent, the residue was recrystallized from a mixture of EtOH and hexane to afford crystals of **15**, mp 77—78 °C. IR (Nujol): 2570, 1610, 1595, 1575, 1510 cm^{-1}. Methyl iodide (4.1 g, 29 mmol) was added to a stirred solution of **15** (4.1 g, 15.4 mmol) and potassium hydroxide (1.05 g, 18.7 mmol) in MeOH (20 ml) and H_2O (20 ml). The reaction mixture was stirred for 20 min. The precipitates formed were filtered washed with 50% MeOH, and dried to afford **5d** (4.5 g, 54%) as crystals, mp 56—58 °C.

5e and **5f** were also prepared from **15** by this method.

3-(2,4-Difluorophenoxy)-4-nitrobenzophenone (5j) A mixture of **5i** (5.0 g, 18.1 mmol) and concentrated H_2SO_4 (5 ml) in H_2O (5 ml) was refluxed for 30 min. After cooling, the reaction mixture was poured into ice-H_2O. The precipitates formed were collected by filtration, and washed with H_2O to afford **16** (4.0 g), mp 184—186 °C. IR (Nujol): 1700, 1620, 1600, 1540, 1500 cm^{-1}. PCl_5 (2.9 g, 13.5 mmol) was added to a suspension of **16** (4.0 g, 13.4 mmol) in benzene (80 ml) at room temperature. The

mixture was stirred for 30 min and the solvent was evaporated under reduced pressure to give crude acid chloride **17**. The obtained **17** was dissolved in benzene (40 ml), and the solution was added to a suspension of $AlCl_3$ (4.5 g, 34 mmol) in benzene (400 ml) at room temperature, and then the reaction mixture was allowed to stand overnight. The resulting mixture was treated with 6 N HCl, and extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$, brine, and dried. After removal of the solvent, the residue was recrystallized from a mixture of EtOH and hexane to afford **5j** (4.4 g, 68%) as crystals, mp 72—73 °C.

3-(2,4-Difluorophenoxy)-4-nitrobenzenecarboxamide (5k) A mixture of **5i** (1.0 g, 3.6 mmol) and potassium hydroxide (260 mg, 4.0 mmol) in *tert*-BuOH (10 ml) was heated at 80 °C for 2 min. The reaction mixture was evaporated under reduced pressure, and the residue was recrystallized from a mixture of diluted HCl and a small amount of EtOH to afford **5k** (1.0 g, 94%) as crystals, mp 159—163 °C.

Ethyl 3-(2,4-Difluorophenoxy)-4-nitrobenzoate (5l) A mixture of **16** (1.0 g, 3.4 mmol) and concentrated H_2SO_4 (3 drops) in dry EtOH (10 ml) was refluxed for 8 h. After cooling, the reaction mixture was evaporated under reduced pressure. The residue was diluted with H_2O and extracted with EtOAc. The combined extracts were washed successively with saturated $NaHCO_3$ and brine, dried, and evaporated to afford **5l** (1.03 g, 94%) as crystals, mp 83—85 °C.

***N*-Methyl-3-(2,4-difluorophenoxy)-4-nitrobenzamide (5m)** The crude **17**, which was prepared from **16** (1.0 g) according to the method described for **5j** was dissolved in THF (10 ml). An aqueous 40% methylamine (2 ml, 26 mmol) was added to the above solution at 0 to 5 °C and the mixture was stirred for 1 h. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in EtOAc and H_2O. The organic layer was separated, washed with brine, dried, and evaporated under reduced pressure to afford **5m** (880 mg, 85%) as crystals, mp 186—188 °C.

The other benzamide derivatives (**5n**—**p**) were similarly prepared.

5′-(2,4-Difluorophenoxy)-2′-methyl-4′-nitroacetophenone (5t) A mixture of **5s** (1.5 g, 5.2 mmol) and concentrated H_2SO_4 (2 ml) in H_2O (2 ml) was stirred at 150 °C for 3 h. The reaction mixture was dissolved in a mixture of EtOAc and H_2O, and the organic layer was separated, washed with H_2O, dried, and evaporated to afford 5-(2,4-difluorophenoxy)-2-methyl-4-nitrobenzoic acid (1.4 g), mp 166—167 °C. IR (Nujol): 1715, 1620, 1525, 1510 cm^{-1}. A mixture of this benzoic acid (1.4 g, 4.5 mmol) and PCl_5 (1.0 g, 4.8 mmol) in benzene (10 ml) was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure to afford **18** (1.6 g). A solution of diethyl malonate (0.88 g, 55 mmol) and EtOH (0.5 ml) in Et_2O (5 ml) was added dropwise to stirred mixture of magnesium (132 mg, 5.5 mmol), EtOH (0.5 ml), and CCl_4 (0.3 ml) in Et_2O (5 ml) at room temperature. The mixture was stirred at room temperature for 1 h, and refluxed for 30 min. To the resulting mixture was added dropwise a solution of **18** (1.6 g) in Et_2O (3 ml) at 5 °C. The mixture was stirred at room temperature for 2 h, and refluxed for 1 h. The reaction mixture was poured into 10% H_2SO_4 and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated under reduced pressure to afford an oil (2.1 g). A mixture of this oil and concentrated H_2SO_4 (1 ml) in acetic acid (6 ml) and H_2O (5 ml) was refluxed for 3 h. The reaction mixture was neutralized with an aqueous sodium hydroxide, and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated under reduced pressure. The oily residue was chromatographed on a column of silica gel eluting with toluene and EtOAc (10 : 1) to afford **5t** (0.69 g, 44%) as crystals, mp 110—113 °C.

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 in 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 the adjuvant injection was a measure of arthritis. The tested compound was given orally once a day for 23 consecutive days from day 1.

Writhing Syndrome Induced by Acetic Acid in Mice: Ten male DDY mice were used per group. Writhing syndrome was produced by an intraperitoneal injection of 20 ml/kg of 0.6% acetic acid in mice. The animals were observed from 3 to 13 min after acetic acid injection, and the total number of writhing episodes was recorded. The tested compound was given orally 1 h before acetic acid injection. The frequency of writhing in the treated animals was compared with that in the control animals.

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