1, 3, 5, and 7 h after treatment. A compound that induced a fall of the basal systolic pressure of less than 10% was considered to be inactive. Each compound was evaluated in three dogs. The significance of before and after treatment differences was calculated by the Dunnett's t test.

Acknowledgment. We thank Dr. P. Ferrari and G. Tuan for IR and mass spectra and Dr. M. Nebuloni and his staff for elemental and thermal analyses.

Registry No. **2a**, 1560-11-8; **2b**, 636-82-8; **2c**, 80969-70-6; **2d**, 23519-90-6; (*cis*)-**3a**, 99343-45-0; (*trans*)-**3a**, 99343-46-1; (*cis*)-**3b**, 99343-47-2; (*trans*)-**3b**, 71551-06-9; (*cis*)-**4a**, 99343-48-3; (*trans*)-**4a**, 99343-49-4; (*cis*)-**4b**, 99343-50-7; (*trans*)-**4b**, 99355-29-0; **5a**, 80969-56-8; **5b**, 99396-52-8; **6a**, 80969-57-9; 6a·DCHA, 99571-76-3; **6b**, 99396-53-9; **7a**, 99343-51-8; **7c**, 99343-52-9; **7d**, 99343-53-0; (*trans*)-**8a**, 99343-54-1; (*trans*)-**8c**, 99343-55-2; **8d**, 99343-56-3; **9a**, 99397-53-2; 9a·DCHA, 99582-29-3; (*cis*)-**9d**, 99343-57-4; **10e**, 80969-61-5; **10f**, 80969-62-6; **10g**, 81024-74-0; **11e**, 81024-72-8; **11f**, 81024-73-9; **11g**, 81024-75-1; **12e**, 81024-76-2; **12f**, 81024-78-4; **12g**, 81024-80-8; **13e**, 80969-64-8; **13f**, 81024-77-3; **13g**, 81024-79-5; **14e**, 80969-66-0; **14f**, 80969-67-1; **14g**, 80969-71-7; **15e**, 81024-81-9; **15f**, 81024-82-0; **15g**, 81024-83-1; **16e**, 99343-58-5; **16f**, 80969-73-9; **16g**, 80969-74-0; **17e**, 99396-54-0; **17f**, 81024-84-2; **17g**, 81024-85-3; **18a**, 10472-24-9; **18c**, 80969-68-2; (*cis*)-**19a**, 933-92-6; (*trans*)-**19a**, 933-93-7; (*cis*)-**19c**, 99343-59-6; (*trans*)-**19c**, 99343-60-9; ACE, 9015-82-1; AcSH, 507-09-5; L-Pro, 147-85-3; L-Pro-OC$(CH_3)_2CH_3$, 2812-46-6; PhCOSH, 98-91-9.

Supplementary Material Available: ^{1}H NMR spectral data of **10–17f,g** and IR and mass spectral data of **10–17e–g** (6 pages). Ordering information is given on any current masthead page.

Synthesis and Antiviral Activity of Sulfonamidobenzophenone Oximes and Sulfonamidobenzamides

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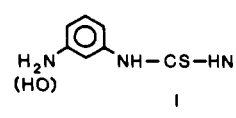
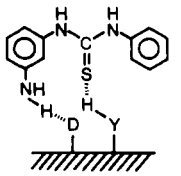
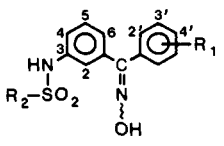
To find antiviral agents, various sulfonamidobenzophenone oximes (II) were synthesized from the appropriate *m*-sulfonamidobenzophenones by hydroxylamine reaction. The reaction products were generally obtained as syn/anti mixtures which were separable by fractional crystallization. The anti isomer had more potent antipoliovirus activity than the syn isomer. Various sulfonamidobenzamides (III) which were structurally related to II were synthesized by the reactions of amino-substituted benzamides with sulfuryl chloride or amines with (aminosulfonyl)benzoyl chloride. Antiviral activity was examined by the plaque-inhibition test. Compounds **5**, **36**, and **69** exhibited strong antipicornavirus activity. The structure–activity relationships are discussed.

m-Amino- and *m*-hydroxy-substituted diphenylthioureas (I) were reported to show antipicornavirus activity by Galabov et al.[1] Analysis of the realtionship between the chemical structure and antiviral activity in I revealed the existence of two active centers which bind the corresponding viral receptors by hydrogen bonds.[1] Our interest was directed to the synthesis of *m*-sulfonamidobenzophenone oximes (II) and *m*-sulfonamidobenzamides (III) with the partial structures of syn and anti isomers of 6-[(hydroxyimino)phenylmethyl]-1-[(1-methylethyl)-sulfonyl]-1*H*-benzimidazole-2-amine (IV),[2] which are virus-specific inhibitors of picornavirus multiplication.

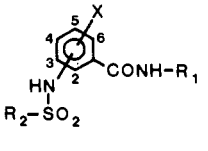


I

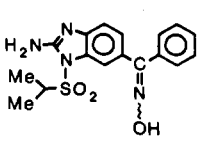




II



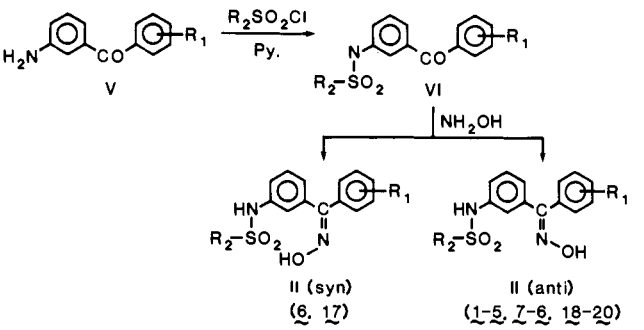
III



IV

In analogy to I, the oxime or the carbamoyl group and the sulfonamido group of II and III were expected to participate in hydrogen-bond formation with the virus-specific target. We thus prepared compounds of these sulfonamide series as shown in Scheme I and II.

Scheme I



Chemistry. The general synthetic routes for the preparation of II are illustrated in Scheme I. The starting *m*-aminobenzophenones (V) were prepared according to methods described in the literature.[3-11] *m*-Sulfonamidobenzophenone VI, prepared by the reaction of V with dimethylsulfamoyl chloride or isopropylsulfuryl chloride, was treated with hydroxylamine to obtain the desired *m*-sulfonamidobenzophenone oximes (II) (Scheme I). The

(1) Galabov, A. S.; Galabov, B. S.; Neykova, N. A. *J. Med. Chem.* **1980**, *23*, 1048.
(2) Wikel, J. H.; Paget, C. J.; Delong, D. C.; Nelson, J. D.; Wu, C. Y. E.; Paschal, J. W.; Dinner, A.; Templeton, R. J.; Chaney, M. O.; Jones, N. D.; Chamberlin, J. W. *J. Med. Chem.* **1980**, *23*, 368.
(3) Oelschläger, H. *Arch. Pharm. (Weinheim, Ger.)* **1957**, *290*, 587.
(4) Newman, M. S.; Smith, A. S. *J. Org. Chem.* **1948**, *13*, 592.
(5) Geigy, R.; Koenigs, W. *Chem. Ber.* **1885**, *18*, 2400.
(6) Robertson, J. E. U.S. Reissue 29032, U.S. Reissue 3576866; *Chem. Abstr.* **1977**, *86*, 139625.
(7) Yuldashev, Kh, Yu. *Sb. Nauchn. Tr.-Tashk. Gos. Univ. im V.I. Lenina* **1977**, *539*, 112; *Chem. Abstr.* **1979**, *91*, 174959.
(8) Majoie, B. Ger. Offen. 2637098; *Chem. Abstr.* **1977**, *86*, 189537.
(9) Limpricht, H.; Lenz, M. *Liebigs Ann. Chem.* **1895**, *286*, 307.
(10) Auwers, K. *Chem. Ber.* **1904**, 3890.
(11) Yamashita, M. *Bull. Chem. Soc. Jpn.* **1928**, *3*, 108.

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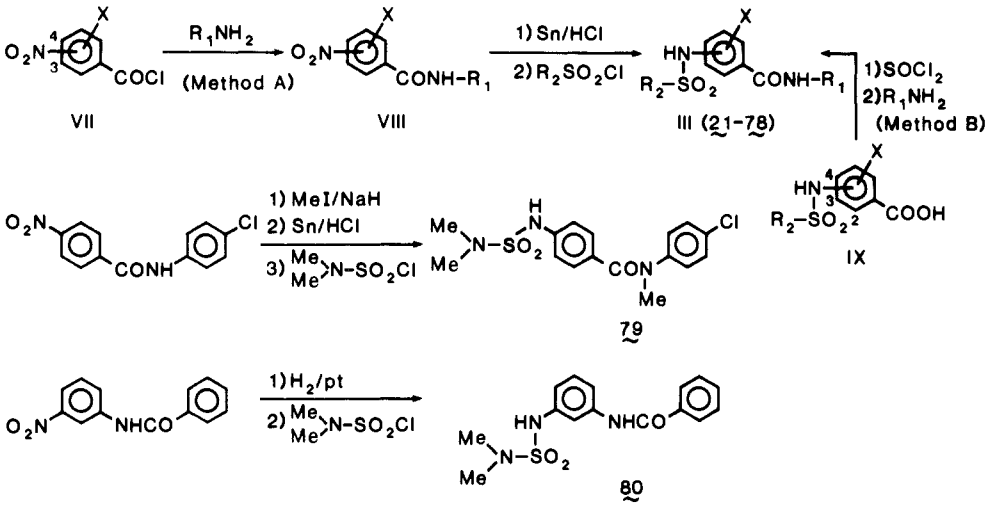
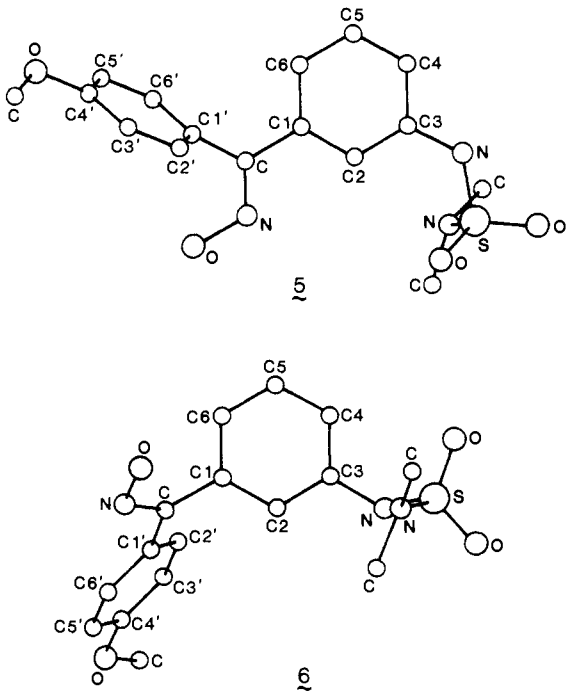
Scheme II





5

6

Figure 1. Molecular structures of **5** and **6**. Hydrogen atoms have been omitted for clarity.

reaction products were generally obtained as syn/anti mixtures which were separable by fractional crystallization. Syn and anti isomers were detected by high-performance liquid chromatography and ^1H NMR spectroscopy,[12] with the differences in the ^1H NMR spectra being conclusive for distinguishing the isomers. Comparison of the NMR spectra of compounds **5** (anti) and **6** (syn) in II showed that the signal from the methyl proton on the dimethylsulfamoyl group was shifted to lower field in the spectra of **6** (syn) (Experimental Section). Their structures were identified from the crystal structures of *anti*- and *syn*-3-[(dimethylsulfamoyl)amino]-4′-methoxybenzophenone oxime (**5** and **6**) by X-ray diffraction (Figure 1).

The appropriate 3-sulfonamido-3′- or 4′-(methoxycarbonyl)benzophenone oximes (II) (mixture of anti and syn forms) were reduced with lithium aluminum hydride in THF to the desired (hydroxymethyl)benzophenone oxime and subsequently recrystallized to give the anti form **11**, **12**, and **13**, respectively.

3′-Amino-3-[(dimethylsulfamoyl)amino]benzophenone oxime (**20**) was prepared by catalytic hydrogenation on platinum catalyst in methanol from 3′-nitro-3-[(dimethylsulfamoyl)amino]benzophenone oxime (II, R_1 = 3-NH_2, R_2 = $SO_2N(Me)Me$, a mixture of anti and syn forms) and followed by fractional recrystallization of the resulting aminobenzophenone oxime. Various sulfonamidobenzamides (III), structurally related to II, were synthesized by method A or B from the nitrobenzoyl chlorides (VII) with amines. The amides obtained (VIII) were treated with tin/hydrochloric acid or catalytic hydrogenation on platinum catalyst and reduced to the amino-substituted benzmides. Treatment of the above amides with dimethylsulfamoyl chloride or alkylsulfuryl chloride gave the desired sulfonamidobenzamides (III) (method A, Scheme II). Compounds III were also obtained by the reaction of amines with the sulfonamidobenzoic acid IX through the corresponding acid chlorides (method B, Scheme II).

4′-Chloro-4-nitrobenzanilide, which was prepared from 4-nitrobenzoyl chloride and 4-chloroaniline, was methylated with methyl iodide in the presence of sodium hydride in dimethylformamide to the *N*-methyl-4′-chloro-4-nitrobenzanilide. The desired *N*-methyl-4′-chloro-4-[(dimethylsulfamoyl)amino]benzanilide (**79**) was prepared by reaction of the above product with catalytic hydrogenation on platinum catalyst followed by treatment of the resulting *N*-methyl-4′-chloro-4-aminobenzanilide with dimethylsulfamoyl chloride in pyridine.

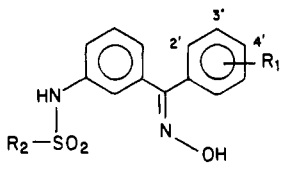
3′-Nitrobenzanilide, prepared from 3-nitroaniline and benzoyl chloride, was reduced with catalytic hydrogenation on platinum to 3′-aminobenzanilide. This was treated with dimethylsulfamoyl chloride in pyridine to obtain the desired 3′-[(dimethylsulfamoyl)amino]benzanilide (**80**).

Results and Discussion

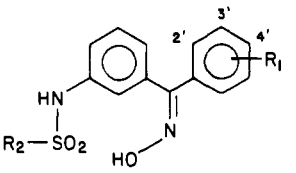
The compounds in Tables I and II were subjected to biological evaluation in plaque-inhibition test against polio- and rhinoviruses. The procedures used for examining are described in the Experimental Section and the results are summarized in Table III. The antiviral activity of II, which exists as *syn*- and *anti*-oxime groups, was more potent in anti isomers **5** and **16** than syn isomers **6** and **17**, respectively. This was similar to the case with IV. The similar molecular geometry of these compounds suggests that active centers of these compounds which bind the corresponding viral receptors are common features.

(12) (a) Poziomek, E. J.; Kramer, D. N.; Mosher, W. A.; Michel, H. O. *J. Med. Chem.* **1961**, *83*, 3916. (b) Ogata, M. *Chem. Pharm. Bull.* **1963**, *11*, 1517.

Table I. *m*-Sulfonamidobenzophenone Oximes (II)



anti



syn

compd no.	R_1	R_2	recrystn solvent	mp, °C	conformation	yield,[a] %	formula	anal.
1	H	N(Me)Me	AcOEt	179–182	anti	2	$C_{15}H_{17}N_3O_3S$	C, H, N, S
2	4'-Cl	N(Me)Me	AcOEt	146–148	anti	10	$C_{15}H_{16}ClN_3O_3S$	C, H, Cl, N, S
3	4'-Me	N(Me)Me	AcOEt	175–177	anti	20	$C_{16}H_{19}N_3O_3S$	C, H, N, S
4	3'-OMe	N(Me)Me	AcOEt/*i*-Pr_2O	134–136	anti	3	$C_{16}H_{19}N_3O_4S$	C, H, N, S
5	4'-OMe	N(Me)Me	AcOEt	162–164	anti	13	$C_{16}H_{19}N_3O_4S$	C, H, N, S
6	4'-OMe	N(Me)Me	benzene	157–158	syn	10	$C_{16}H_{19}N_3O_4S$	C, H, N, S
7	4'-OMe	pyrrolidinyl	AcOEt	161.5–163	anti	14	$C_{18}H_{21}N_3O_4S$	C, H, N, S
8	4'-OMe	isopropyl	AcOEt	176–178.5	anti	8	$C_{17}H_{20}N_2O_4S$	C, H, N, S
9	4'-OEt	N(Me)Me	AcOEt	158–159	anti	3	$C_{17}H_{21}N_3O_4S$	C, H, N, S
10	4'-SMe	N(Me)Me	AcOEt	154–155	anti	1	$C_{16}H_{19}N_3O_3S_2$	C, H, N, S
11	3'-CH_2OH	N(Me)Me	AcOEt	150–151	anti	4	$C_{16}H_{19}N_3O_4S$	C, H, N, S
12	4'-CH_2OH	N(Me)Me	MeOH	194–195	anti	16	$C_{16}H_{19}N_3O_4S$	C, H, N, S
13	4'-CH_2OH	isopropyl	MeOH	220–223	anti	8	$C_{17}H_{20}N_2O_4S$	C, H, N, S
14	4'-CH_2OMe	isopropyl	AcOEt/*i*-Pr_2O	104–106	anti	4	$C_{18}H_{22}N_2O_4S$	C, H, N, S
15	4'-CH_2OMe	N(Me)Me	AcOEt	136–137	anti	11	$C_{17}H_{21}N_3O_4S$	C, H, N, S
16	2',4'-$(MeO)_2$	N(Me)Me	Et_2O	140.5–141.5	anti	18	$C_{17}H_{21}N_3O_5S$	C, H, N, S
17	2',4'-$(MeO)_2$	N(Me)Me	AcOEt/*i*-Pr_2O	100–102	syn	28	$C_{17}H_{21}N_3O_5S$	C, H, N, S
18	3',4'-$(MeO)_2$	N(Me)Me	AcOEt/Et_2O	128–129	anti	1	$C_{17}H_{21}N_3O_5S$	C, H, N, S
19	3',4'-OCH_2O-	N(Me)Me	AcOEt	182–185	anti	12	$C_{16}H_{17}N_3O_5S$	C, H, N, S
20	3'-NH_2	N(Me)Me	AcOEt	177–178	anti	3	$C_{15}H_{18}N_4O_3S$	C, H, N, S

[a] Yield from V to II.

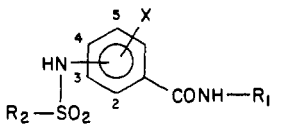
From the geometrical analogy in the interaction between the benzophenone oximes (II) or the benzamides (III) and the viral target, it is speculated that the distance between the SO_2NH group and the CONH group in the benzamide series (III) is important to the antiviral potency. As was the case with the position of the sulfonamido group in the benzanilide moiety, the introduction of a sulfonamido group in the 2-position (**32**) and the 3'-position (**80**) led to reduction of activity. The 3- (**33**) and the 4-position (**31**) showed the high antiviral activity, although the former was somewhat less active than the latter; compare **37** and **71**, and also **38** and **69**.

Methyl substitution to the carbamoyl group considerably decreased the antiviral activity; compare **68** and **79**. This demonostrated the importance of the CONH group in the antiviral effect in this moiety. Substitution on the benzoyl group decreased potency; **35**, **77**, and **78** were less potent. Interestingly, as in the case with the alkyl substitution, introduction to the 4'-position resulted in high potency, and maximum effects by varying the length of the alkyl bridge were found with C_4 alkyl; compare **31**, **36**, **60**, **61**, **64–67**, **70**, **73**, **74–76**, maximum activity being found with **36**. In contrast, introducing of an alkyl (methyl) group to the 3'-position (**52**) resulted in inefficacious antiviral activity. The potency of **52** was comparable to that of the parent compound (**31**); compare **31**, **52**, and **70**.

Among the various benzophenone oximes (II) and benzanilide moieties (III), three compounds, **5**, **36** and **69**, were selected for further evaluation of their antiviral effects against different type of rhinovirus and other picornaviruses. They showed potent activity against every picornavirus examined (Table IV). Among viruses tested, rhinoviruses were inhibited in higher degree than that of coxsackie- and enteroviruses. However, they had no effect on vesicular stomatis, vaccinia, herpes, and influenza A_0 viruses ($ED_{50} > 25$ μg/mL). Finally, the chemotherapeutic indices of these compounds were compared. Although **36** showed very high potency, it had a smaller chemotherapeutic index than **5** and **69**. The index of **69** was markedly superior to that of **5** and **36**. Antiviral activity of zinviroxime[2] and enviroxime[2] used for reference compound was tested in a parallel experimental study. As shown Table III antiviral activity against rhinovirus of **69** was comparable to zinviroxime, and chemotherapeutic indices of the compound in either polio- or rhinoviruses were superior to that of zinviroxime and enviroxime. Studies on the mode of action of selected compounds were carried out with use of poliovirus. The first experiment was made to test virucidal effect. Poliovirus was mixed with an equal volume of medium containing compound to make a final concentration of 50, 5, and 0.5 μ/mL. After incubation for 30 min at 37 °C, the samples were diluted and assayed on CV-1 cell monolayer. The titration results are shown in Table V. No significant virucidal effect by **36** and **69** was detected at concentrations as high as 50 μg/mL. Since the compounds do not inactivate poliovirus on contact, it is suggested that the inhibition occurs after virus has entered the cell. Therefore, the next experiment was performed to find the stage of virus replication senstivie to the compound. One microgram/milliliter of **36** was added to Hela cell monolayers infected with poliovirus at hourly intervals and incubated at 37 °C until 7-h postinfection (PI) when all cultures were frozen and harvested. Samples were then subjected to the plaque assay method to determine the virus titer. Table VI shows that when the compound was added to the infected cells before or at 2-h PI, remarkable inhibition can be observed. But if the compound was added 4-h PI or later, there was no inhibition. This finding suggests that between 0- and 4-h PI is the period sensitive to the compound and adsorption and penentration of the virus are not target sites of inhibition. The time between 2 and 4 h after adsorption was the period when viral RNAs and viral proteins were being synthesized most vigorously.[13] The fact that the compound showed pronounced activity during this period of the virus growth cycle suggests that viral macromolecule synthesis could be the target of its action.

(13) Baltimore, D.; Girard, M. *Proc. Natl. Acad. Sci. U.S.A.* **1966**, *56*, 741.

Table II. Sulfonamidobenzamides (III)



21-78

compd no.	R_1	R_2 (position)	X	recrystn solvent	mp, °C	method	yield,[a] %	formula	anal.
21	4-OMePh	N(Me)Me (3)	H	AcOEt	123-124	A	16	$C_{16}H_{19}N_3O_4S$	C, H, N, S
22	4-CNPh	N(Me)Me (3)	H	AcOEt/*i*-Pr_2O	133-134	A	20	$C_{16}H_{16}N_4O_3S$	C, H, N, S
23	Ph	1-pyrrolidinyl (3)	H	AcOEt	146-147	A	28	$C_{17}H_{19}N_3O_3S$	C, H, N, S
24	Ph	1-piperidinyl (3)	H	AcOEt/Et_2O	110-111	A	25	$C_{18}H_{21}N_3O_3S$	C, H, N, S
25	Ph	Me (3)	H	MeOH	177-178	A	23	$C_{14}H_{14}N_2O_3S$	C, H, N, S
26	Ph	Ph (3)	H	AcOEt/Et_2O	159-160	A	30	$C_{19}H_{16}N_2O_3S$	C, H, N, S
27	2-pyridyl	N(Me)Me (3)	H	AcOEt/*i*-Pr_2O	143-145	A	10	$C_{14}H_{16}N_4O_3S$	C, H, N, S
28	cyclohexyl	N(Me)Me (3)	H	MeOH	184-185	A	26	$C_{15}H_{23}N_3O_3S$	C, H, N, S
29	3-ClPh	N(Me)Me (3)	H	AcOEt/*i*-Pr_2O	127-128	A	41	$C_{15}H_{16}ClN_3O_3S$	C, H, Cl, N, S
30	Ph	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	142-143	A	43	$C_{16}H_{18}N_2O_3S$	C, H, N, S
31	Ph	N(Me)Me (4)	H	MeOH	213-215	A	47	$C_{15}H_{17}N_3O_3S$	C, H, N, S
32	Ph	N(Me)Me (2)	H	AcOEt/*i*-Pr_2O	123-125	A	22	$C_{15}H_{17}N_3O_3S$	C, H, N, S
33	Ph	N(Me)Me (3)	H	AcOEt	140-141.5	A	22	$C_{15}H_{17}N_3O_3S$	C, H, N, S
34	3-COOMePh	N(Me)Me (4)	H	AcOEt/*i*-Pr_2O	150-151	A	13	$C_{17}H_{19}N_3O_5S$	C, H, N, S
35	4-ClPh	*i*-Pr (3)	6-CH_3	AcOEt/*i*-Pr_2O	149-150	A	20	$C_{17}H_{19}ClN_2O_3S$	C, H, Cl, N, S
36	*n*-BuPh	N(Me)Me (4)	H	AcOEt/*i*-Pr_2O	173.5-174	A	36	$C_{19}H_{25}N_3O_3S$	C, H, N, S
37	4-CF_3Ph	N(Me)Me (3)	H	MeOH/AcOEt	175-176	A	40	$C_{16}H_{16}F_3N_3O_3S\cdot{}^1/_2H_2O$	C, H, F, N, S
38	4-BrPh	N(Me)Me (3)	H	MeOH/*i*-Pr_2O	164-166	A	21	$C_{15}H_{16}BrN_3O_3S$	C, H, Br, N, S
39	3-OHPh	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	171.5-172	B	42	$C_{16}H_{18}N_2O_4S$	C, H, N, S
40	3,4-Cl_2Ph	*i*-Pr (3)	H	AcOEt	184-185.5	B	50	$C_{16}H_{16}Cl_2N_2O_3S$	C, H, Cl, N
41	2-thiazolyl	*i*-Pr (3)	H	MeOH/AcOEt	216-217	B	55	$C_{13}H_{15}N_3O_3S_2$	C, H, N, S
42	2-MeCOPh	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	163-164	B	32	$C_{18}H_{20}N_2O_4S$	C, H, N, S
43	3-NO_2Ph	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	173-173.5	B	29	$C_{16}H_{17}N_3O_5S$	C, H, N, S
44	2-NH_2Ph	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	130-131	B	21	$C_{16}H_{19}N_3O_3\cdot{}^1/_{10}C_6H_{14}O$[b]	C, H, N, S
45	*t*-Bu	*i*-Pr (3)	H		oil	B	72	$C_{14}H_{22}N_2O_3S$	C, H, N, S
46	3-CH_2OHPh	*i*-Pr (3)	H		oil	B	41	$C_{17}H_{20}N_2O_4S\cdot{}^1/_3Et_2O$	C, H, N, S
47	3-Cl	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	146-147	B	59	$C_{16}H_{17}ClN_2O_3S$	C, H, Cl, N, S
48	4-COOMePh	*i*-Pr (3)	H	AcOEt/Et_2O	157-158	B	29	$C_{18}H_{20}N_2O_5S$	C, H, N, S
49	4-ClPh	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	151-152	B	71	$C_{16}H_{17}ClN_2O_3S$	C, H, Cl, N, S
50	2-ClPh	N(Me)Me (4)	H	AcOEt	190-192	B	21	$C_{15}H_{16}ClN_3O_3S$	C, H, Cl, N, S
51	3-ClPh	N(Me)Me (4)	H	MeOH/AcOEt	223-224	B	22	$C_{15}H_{16}ClN_3O_3S$	C, H, Cl, N, S
52	3-MePh	N(Me)Me (4)	H	AcOEt/*i*-Pr_2O	177-178	B	41	$C_{17}H_{20}N_2O_3S$	C, H, N, S
53	$CH(Ph)_2$	*i*-Pr (3)	H	AcOEt	225-227	B	72	$C_{23}H_{24}N_2O_3S$	C, H, N, S
54	-CH_2-2-furyl	*i*-Pr (3)	H	AcOEt	135.5-136.5	B	78	$C_{18}H_{18}N_2O_4S$	C, H, N, S
55	benzyl	*i*-Pr (3)	H	MeOH/AcOEt	158-5-159.5	B	81	$C_{17}H_{20}N_2O_3S$	C, H, N, S
56	2-CF_3Ph	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	116	B	45	$C_{17}H_{17}F_3N_2O_3S$	C, H, F, N, S
57	4-BrPh	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	147.5-148.5	B	53	$C_{16}H_{17}BrN_2O_3S$	C, H, Br, N, S
58	4-FPh	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	146-147	B	72	$C_{16}H_{17}FN_2O_3S$	C, H, F, N, S
59	3-BrPh	N(Me)Me (4)	H	DMF/MeOH	232-233	B	34	$C_{15}H_{16}BrN_3O_3S$	C, H, Br, N, S
60	4-EtPh	N(Me)Me (4)	H	MeOH	207-208	B	22	$C_{17}H_{21}N_3O_3S$	C, H, N, S
61	4-*i*-PrPh	N(Me)Me (4)	H	MeOH/AcOEt	194-195	B	44	$C_{18}H_{23}N_3O_3S\cdot{}^1/_5H_2O$	C, H, N, S
62	4-IPh	N(Me)Me (4)	H	MeOH/AcOEt	215-216	B	44	$C_{15}H_{16}IN_3O_3S$	C, H, I, N, S
63	4-*n*-PrOPh	N(Me)Me (4)	H	CH_3CN	195-196	B	28	$C_{18}H_{23}N_3O_4S$	C, H, N, S
64	4-*t*-BuPh	N(Me)Me (4)	H	AcOEt	201-202	B	11	$C_{19}H_{25}N_3O_3S$	C, H, N, S
65	4-*n*-BuPh	*i*-Pr (4)	H	MeOH	181-182	B	16	$C_{20}H_{26}N_2O_3S$	C, H, N, S
66	4-*sec*-amyl-Ph	N(Me)Me (4)	H	AcOEt/*i*-Pr_2O	138-139	B	13	$C_{20}H_{27}N_3O_3S$	C, H, N, S
67	4-*n*-BuPh	*i*-Pr (3)	H	AcOEt/*i*-Pr_2O	122-123	B	48	$C_{20}H_{26}N_2O_3S$	C, H, N, S
68	4-ClPh	N(Me)Me (4)	H	DMF/Et_2O	219-221	B	42	$C_{15}H_{16}ClN_3O_3S\cdot{}^1/_6H_2O$	C, H, Cl, N, S
69	4-BrPh	N(Me)Me (4)	H	MeOH/*i*-Pr_2O	219-220	A	8	$C_{15}H_{16}BrN_3O_3S$	C, H, Br, N, S
70	4-MePh	N(Me)Me (4)	H	MeOH/AcOEt	199-200	A	18	$C_{16}H_{19}N_3O_3S$	C, H, N, S
71	4-CF_3Ph	N(Me)Me (4)	H	MeOH	227-228	B	7	$C_{16}H_{16}F_3N_3O_3S\cdot{}^1/_3H_2O$	C, H, F, N, S
72	4-CF_3Ph	*i*-Pr (4)	H	AcOEt/*i*-Pr_2O	226.5-227.5	A	12	$C_{17}H_{16}F_3N_2O_3S$	C, H, F, N, S
73	4-*n*-amyl-Ph	N(Me)Me (4)	H	AcOEt/*i*-Pr_2O	148-149	B	3	$C_{20}H_{27}N_3O_3S\cdot{}^1/_3H_2O$	C, H, N, S
74	4-*n*-PrPh	N(Me)Me (4)	H	AcOEt/*i*-Pr_2O	184-186	B	6	$C_{18}H_{23}N_3O_3S$	C, H, N, S
75	4-*n*-hexyl-Ph	N(Me)Me (4)	H	AcOEt/*i*-Pr_2O	155-156	B	6	$C_{21}H_{29}N_3O_3S$	C, H, N, S
76	4-*i*-BuPh	N(Me)Me (4)	H	AcOEt/*i*-Pr_2O	188-190	B	3	$C_{19}H_{25}N_3O_3S$	C, H, N, S
77	Ph	N(Me)Me (3)	4-Cl	AcOEt/*i*-Pr_2O	147-149	B	12	$C_{15}H_{16}ClN_3O_3S$	C, H, Cl, N, S
78	4-ClPh	N(Me)Me (3)	6-Cl	AcOEt/*i*-Pr_2O	157-158	A	9	$C_{15}H_{16}Cl_2N_3O_3S$	C, H, Cl, N, S

[a] Method A: overall yield from VII to III. Method B: overall yield from IX to III. [b] (*i*-$Pr)_2O$.

Table III. Antipoliovirus and Antirhinovirus Activities of Sulfonamidobenzophenone Oximes (II) and Sulfonamidobenzamides (III)

compd no.	50% effective dose: ED_{50},[a] μg/mL polio 1	rhino (10 or 1A)	50% effective dose: ED_{50},[a] μg/mL CV-1	Hela	chemotherapeutic index CV-1	Hela	compd no.	50% effective dose: ED_{50},[a] μg/mL polio 1	rhino (10 or 1A)	50% effective dose: ED_{50},[a] μg/mL CV-1	Hela	chemotherapeutic index CV-1	Hela
1	0.79	0.54	19.0	22.0	24	41	**42**	5					
2	0.46	0.53	12.0	21.0	26	40	**43**	>25					
3	0.44	0.41	38.0	32.0	86	78	**44**	>50					
4	0.34	0.41	25.0	36.0	74	88	**45**	>50					
5	0.26	0.29	14.5	13.0	56	45	**46**	>50					
6	7.6	5.4	26.0	36.0	3.4	6.7	**47**	1.5					
7	1.1						**48**	4.0					
8	0.36	0.62	11.5	9.1	32	15	**49**	1.2					
9	5.5						**50**	6.2					
10	0.32	0.26	2.9	8.6	9	33	**51**	1.6					
11	0.50	1.6	10.0	>100	20	>62	**52**	2.3					
12	0.40	0.37	22.0	50.0	55	135	**53**	>50					
13	0.20	0.39	46.0	34.0	23	87	**54**	>50					
14	0.22	0.98	15.0	62.0	68	63	**55**	>50					
15	0.25	0.36	7.0	31.5	28	88	**56**	0.6					
16	1.0	0.89	28.0	≥50	28	≥56	**57**	0.7					
17	19.5	4.0	36	36	1.8	9	**58**	4.2					
18	0.55						**59**	5.0					
19	3.4						**60**	0.36	0.20	3.6	1.6	10	8
20	0.70		46.0		66		**61**	0.21	0.10	2.2	1.2	10	12
21	4.0						**62**	0.30	0.30	1.6	3.0	5	10
22	5.0						**63**	0.7					
23	6.4						**64**	0.12					
24	11.0						**65**	0.16					
25	>50						**66**	0.18	0.11	2.7	1.6	15	15
26	17.0						**67**	0.42					
27	44						**68**	0.50	0.32	110	70	220	220
28	28						**69**	0.30	0.26	200	130	600	500
29	1.5						**70**	0.54	0.38	200	4.2	370	11
30	7						**71**	0.18	0.17	3.5	1.2	19	7
31	3						**72**	0.25					
32	25						**73**	0.32	0.51	1.2	1.1	4	2
33	4.0						**74**	0.16	0.15	1.0	0.56	6	4
34	1.2						**75**	0.16	0.24	1.7	0.96	11	4
35	12						**76**	0.16	0.13	1.2	0.46	7	4
36	0.09	0.13	1.6	0.68	18	5	**77**	10					
37	0.46						**78**	>50					
38	1.7						**79**	>25					
39	25.0						**80**	20					
40	>25						zinviroxime[2]	0.14	0.24	8.6	15.7	61	65
41	25						enviroxime[2]	0.032	0.024	8.8	5.1	275	213

[a] Evaluation of **1**–**20**, zinviroxime, and enviroxime were conducted against rhinovirus 10 and **21**–**80** were conducted against rhinovirus 1A. [b] Chemotherapeutic index = 50% cytotoxic dose/50% effective dose.

Table IV. Antiviral Spectrum of **5**, **36**, and **69** (ED_{50}, μg/mL)

compd. no.	rhino[a] 1A	10	19	26	coxsackie B4	A9	entero 70
5	0.29	0.26	0.44	ND[b]	0.64	ND[b]	0.75
36	0.12	0.09	0.12	0.13	0.42	0.40	0.70
69	0.68	0.42	0.60	0.68	4.0	5.2	ND[b]

[a] Hela cell (Ohio) monolayers were infected with 500 $TCID_{50}$ of rhinovirus, and then the medium containing a serial dilution of the test compound was added. After incubation at 33 °C for 3 days the infected cells were stained with crystal violet and observed for cytopathic effect (CPE) under a microscope. End points were read as 50% inhibition. [b] Not done.

Table V. Effect of Time of Addition[a]

time	virus titer	inhibn, %	time	virus titer	inhibn, %
0	4.8×10^8	88.3	4	3.1×10^9	24.4
1	3.6×10^8	91.2	5	4.3×10^9	0
2	5.0×10^8	87.8	virus control	4.1×10^9	
3	1.6×10^9	61.0			

[a] Infected cells were treated with 1.0 μg/mL of **36** in hourly intervals. Virus titration was made at 7-h PI.

Table VI. Failure of Virucidal Activity of **36** and **69**

compd no.	concn, μg/mL	virus titer, PFU/mL	inhibn, %
36	50	7.4×10^7	0
	5	7.6×10^7	3
	0.5	6.4×10^7	10
69	50	7.4×10^7	0
	5	7.1×10^7	0
	0.5	6.6×10^7	12
	virus control	7.3×10^7	

Experimental Section

Melting points were determined in a "Büchi" capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian T-60 spectrometer. Elemental analyses were perfomed by the analytical department of Shionogi Research Laboratories and are within ±0.4% of the calculated values.

3-[(Dimethylsulfamoyl)amino]-4′-methoxybenzophenone

Oxime (II, anti-5 and syn-6). To a stirred solution of dry pyridine (25 mL) and 3-amino-4′-methoxybenzophenone (V; 5.0 g, 22 mmol) was added portionwise dimethylsulfamoyl chloride (4.74 g, 33 mmol) at room temperature. After 4 h, the mixture was diluted with ice water and acidified with dilute HCl and extracted with CH_2Cl_2. The organic layer was extracted with dilute NaOH and the alkaline extract was acidified with dilute HCl. The resulting precipitate was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to obtain the residue. Recrystallization of this crystalline residue from AcOEt/$(i\text{-Pr})_2O$ gave 3-[(dimethylsulfamoyl)amino]-4′-methoxybenzophenone (VI; 5.5 g, 75%, mp 130–131 °C). This product was used without further purification for the next step.

A solution of the above compound VI (9 g, 26.9 mmol) and hydroxylamine hydrochloride (11.22 g, 161.5 mmol) in EtOH (180 mL) was refluxed for 7 h. The residue was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on silica gel. The fractions eluted with 2% MeOH/CH_2Cl_2 gave a mixture of **5** and **6** (8.5 g, mp 132–144.5 °C, 90%) after washing with $(i\text{-Pr})_2O$. Recrystallization of this mixture from AcOEt gave 1.63 g (**5**, mp 162–164 °C, 13% overall yield from V, >98.5% purity by HPLC). Anal. ($C_{16}H_{19}N_3O_4S$) C, H, N, S.

The above filtrate was evaporated to remove the solvent. Repeated recrystallization of the residue from benzene gave 1.23 g (**6**, mp 157–158 °C, 10% overall yield from V, >99.9% purity by HPLC). Anal. ($C_{16}H_{19}N_3O_4S$) C, H, N, S.

HPLC Conditions. Analytical high-pressure liquid chromatography separation was performed with a Waters Model 6000A solvent delivery system with a JASCO UVIDEC-100-II detector. Column: Cosmosil 5Ph, 4.6 mm × 150 mm. Mobile phase: MeOH-H_2O (2:3). Flow rate: 1.0 mL/min. Monitored at 240 nm. Retention time: 43 min (anti, **5**), 40 min (syn, **6**).

^{1}H NMR Chemical Shifts. **5** (Me_2SO-d_6): δ 2.56 [6 H, s, N(Me)Me], 3.67 (3 H, s, OMe), 6.63–7.40 (8 H, m, aromatics), 9.68 (1 H, s, NH), 11.05 (1 H, s, OH).

6 (Me_2SO-d_6): δ 2.62 [6 H, s, N(Me)Me], 3.64 (3 H, s, OMe), 6.62–7.37 (8 H, m, aromatics), 9.66 (1 H, s, NH), 10.87 (1 H, s, OH).

The other benzophenone oximes (**1–4, 7–10, 12–19**) were prepared in a similar manner.

***anti*-3-[(Dimethylsulfamoyl)amino]-3′-(hydroxymethyl)benzophenone Oxime (11).** To a stirred solution of dry THF (40 mL) and 3-[(dimethylsulfamoyl)amino]-3′-(methoxycarbonyl)benzophenone oxime (25 g, 6.6 mmol, syn and anti mixture), which was prepared by a method similar to that described for **5** and **6**, was added portionwise $LiAlH_4$ (50 mg, 13.2 mmol) with ice cooling. After 10 min, the mixture was diluted with H_2O, acidified with dilute HCl, and extracted with H_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 3% MeOH/CH_2Cl_2 were collected to obtain II [R_1 = 3′-CH_2OH, R_2 = N(Me)Me, a mixture of syn and anti forms]. Repeated recrystallization of this material from AcOEt gave **11** (anti form, 119 mg, mp 150–157 °C, 5%). The overall yield of **11** from 3-amino-3′-(methoxycarbonyl)benzophenone (V) was 4%.

^{1}H NMR Chemical Shifts. **11** (Me_2SO-d_6): δ 2.67 [6 H, s, N(Me)Me], 4.53 (2 H, s, CH_2), 5.17 (1 H, s, COH), 6.83–7.42 (8 H, m, aromatics), 9.83 (1 H, s, NH), 11.27 (1 H, s, NOH). Anal. ($C_{16}H_{19}N_3O_4S$) C, H, N, S.

***anti*-3′-Amino-3-[(dimethylsulfamoyl)amino]benzophenone Oxime (20).** 3-[(Dimethylsulfamoyl)amino]-3′-nitrobenzophenone oxime (1.8 g, 4.9 mmol, syn and anti mixture), prepared by a method similar to that described for **5** and **6**, was combined with PtO_2 (360 mg) and MeOH (50 mL) and subjected to hydrogenation. The catalyst was removed by filtration and the filtrate was evaporated. The residue was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silic gel. The fractions eluted with 5% MeOH/CH_2Cl_2 were collected to obtain II [R_1 = 3′-NH_2, R_2 = N(Me)Me, a mixture of syn and anti forms]. Repeated recrystallization of this material from AcOEt gave **20** (antl form, 140 mg, mp 177–178 °C, 9%) in an overall yield from 3-amino-3′-nitrobenzophenone (V) of 3%.

^{1}H NMR Chemical Shifts. **20** (Me_2SO-d_6): δ 2.68 [6 H, s, N(Me)Me], 5.07 (2 H, br s, NH_2), 6.30–7.33 (8 H, m, aromatics), 9.83 (1 H, br s, NH), 11.12 (1 H, s, NOH). Anal. ($C_{15}H_{18}N_4O_3S$) C, H, N, S.

4′-Bromo-3-[(dimethylsulfamoyl)amino]benzanilide (38) (Method A). To a stirred solution of 4-bromoaniline (2.03 g, 11.8 mmol) and Et_3N (1.31 g, 13 mmol) in dry CH_2Cl_2 (20 mL) was added portionwise 3-nitrobenzoyl chloride (2.0 g, 10.8 mmol) with ice cooling. After 5 min at room temperature, the mixture was diluted with aqueous $NaHCO_3$ and the resulting precipitate was filtered and dried to obtain 4′-bromo-3-nitrobenzanilide (3 g).

A mixture of the above product (3 g, 9.4 mmol), tin (2.22 g, 18.7 mmol), and 6 N HCl (15 mL) in THF (30 mL) was heated at 50 °C for 1 h and then concentrated under reduced pressure. NaOH (10%) was added to the residue, and the resulting crystals were collected by filtration. They were then dissolved in THF and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was washed with $i\text{-Pr}_2O$ to obtain 4′-bromo-3-aminobenzanilide (1.92 g). To a stirred solution of dry pyridine (10 mL) and this product (1.92 g, 6.6 mmol) was added portionwise dimethylsulfamoyl chloride (1.42 g, 9.9 mmol) at room temperature. After 1.5 h at 60 °C, the reaction mixture was diluted with ice water, acidified with dilute HCl, and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over Na_2SO_4, and then the solvent was evaporated. The residue was chromatographed on silica gel, and the fractions eluted with 3% MeOH/CH_2Cl_2 were collected to obtain **38** (920 mg, mp 164–166 °C, from MeOH/$i\text{-Pr}_2O$, overall yield 21%).

^{1}H NMR Chemical Shifts. **38** (Me_2SO-d_6): δ 2.73 [6 H, s, N(Me)Me], 7.37–7.83 (8 H, m, aromatics), 10.13 (1 H, s, SO_2NH), 10.40 (1 H, s, CONH). Anal. ($C_{15}H_{16}BrN_3O_3S$) C, H, Br, N, S.

The other benzamides (**21–37, 69, 70, 72, 78**) were prepared in a similar manner.

***N*-Methyl-4′-Chloro-4-[(dimethylsulfamoyl)amino]benzanilide (79).** To a solution of 4-chloroaniline (8.04 g, 63 mmol) and triethylamine (6.4 g, 63 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise 4-nitrobenzoyl chloride (11.7 g, 63 mmol) in dry CH_iCl_2 (30 mL) at room temperature. After 10 min, aqueous $NaHCO_3$ was added to the reaction mixture. The resultant precipitates were filtered and recrystallized from MeOH/AcOEt to obtain 4′-chloro-4-nitrobenzanilide (15.4 g). The product was used without further purification for the next step.

To a solution of the above product (2 g, 7.2 mmol) and 50% NaH (408 mg, 8.5 mmol) in DMF (20 mL) was added dropwise methyl iodide (1.21 g, 8.5 mmol) at room temperature. After 30 min, the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave *N*-methyl-4′-chloro-4-nitrobenzanilide (1.35 g), which was used without further purification for the next step.

A mixture of the above product (1.3 g, 4.5 mmol), tin (0.84 g, 7 mmol), and 6 N HCl (65 mL) in THF (13 mL) was heated at 50 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was combined with 10% NaOH and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent left a residue which was washed with AcOEt/$i\text{-Pr}_2O$ to obtain *N*-methyl-4-amino-4′-chlorobenzanilide (1.05 g). This product was used without further purification for the next step.

To a stirred solution of dry pyridine (4 mL) and the above product (800 mg, 3.1 mmol) was added portionwise dimethylsulfamoyl chloride (660 mg, 4.6 mmol) at 50 °C. After 2 h, the reaction mixture was diluted with 6 N HCl and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed on silica gel. The fraction eluted with 3% MeOH/CH_2Cl_2 was collected to obtain *N*-methyl-4′-chloro-4-[(dimethylsulfamoyl)amino]benzanilide (**79**) (760 mg, mp 188–189 °C from AcOEt, overall yield 34%).

^{1}H NMR Chemical Shifts. **79** (Me_2SO-d_6): δ 2.73 [6 H, s, N(Me)Me], 7.20–8.00 (8 H, m, aromatics), 10.00 (1 H, s, SO_2NH), 10.23 (1 H, s, CONH). Anal. ($C_{16}H_{18}ClN_3O_3S$) C, H, Cl, N, S.

3′-[(Dimethylsulfamoyl)amino]benzanilide (80). To a solution of 3-nitroaniline (2 g, 16.3 mmol) and triethylamine (1.99 g, 19.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise benzoyl chloride (2.76 g, 19.6 mmol) in CH_2Cl_2 (10 mL) at room tem-

perature. After 30 min, the reaction mixture was diluted with dilute HCl. The resultant precipitates were filtered and recrystallized from MeOH to obtain 3'-nitrobenzanilide (2.55 g, mp 154–155 °C). A mixture of the above product, 3'-nitrobenzanilide (2.55 g, 10.5 mmol), PtO_2 (255 mg), and MeOH (40 mL) was subjected to hydrogenation. The catalyst was filtered and the filtrate was evaporated. The residue was washed with $(i\text{-Pr})_2O$ to obtain 3'-aminobenzanilide (2.22 g, mp 120–122 °C).

To a solution of the 3'-aminobenzanilide (2.2 g, 10.4 mmol) in dry pyridine (11 mL) was added dropwise dimethylsulfamoyl chloride (2.23 g, 15.5 mmol) at room temperature. After 3 h, the reaction mixture was acidified with 6 N HCl, extracted with CH_2Cl_2, and washed with H_2O. Evaporation of the solvent gave the residue which was chromatographed on silica gel. The fractions eluted with 3% $MeOH/CH_2Cl_2$ were collected to obtain **80** [1.65 g, mp 137–138.5 °C, from $AcOEt/(i\text{-Pr})_2O$, overall yield 32%].

^{1}H NMR Chemical Shifts. **80** (Me_2SO-d_6): δ 2.77 [6 H, s, N(Me)Me], 6.87–8.07 (9 H, m, aromatics), 9.90 (1 H, s, SO_2NH), 10.32 (1 H, s, CONH). Anal. ($C_{15}H_{17}N_3O_3S$) C, H, N, S.

4-[(Dimethylsulfamoyl)amino]-4'-ethylbenzanilide (60) (Method B). To a stirred solution of dry pyridine (100 mL) and ethyl 4-aminobenzoate (20 g, 121 mmol) was added portionwise dimethylsulfamoyl chloride (20.9 g, 146 mmol) at room temperature. After 16 h, the pyridine was allowed to evaporate and the residue was heated at 70 °C for 15 min in 10% NaOH. After cooling, the reaction mixture was acidified with 6 N HCl and extracted with $MeOH/CH_2Cl_2$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was washed with $AcOEt/Et_2O$ and filtered. The crystalline residue was recrystallized from $AcOEt/Et_2O$ to obtain 4-[(dimethylsulfamoyl)amino]benzoic acid (7.1 g), which was used without further purification for the next step.

A mixture of the above acid (1 g, 4.1 mmol) and $SOCl_2$ (5 mL) was refluxed for 10 min, and the resultant mixture was evaporated to remove $SOCl_2$. The residue was mixed with benzene and evaporated to remove excess $SOCl_2$. The residue was mixed with 4-ethylaniline (550 mg, 4.5 mmol) and dry CH_2Cl_2 (10 mL), and a solution of triethylamine (500 mg, 4.9 mmol) and CH_2Cl_2 (10 mL) was added dropwise with ice cooling and stirring. The resultant mixture was stirred at room temperature for 10 min. The reaction mixture was mixed with aqueous $NaHCO_3$ and shaken with CH_2Cl_2. The organic layer was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent left a residue which was chromatographed on silica gel. The fractions eluted with 2% $MeOH/CH_2Cl_2$ were collected to obtain **60** (312 mg, mp 207–208 °C from MeOH, 22% overall yield).

^{1}H NMR Chemical Shifts. **60** (Me_2SO-d_6): δ 1.71 (3 H, t, J = 12 Hz, CCH_3), 2.57 (2 H, q, J = 12 Hz, CH_2C), 2.73 [6 H, s, N(Me)Me], 7.08–7.97 (8 H, m, aromatics), 10.00 (1 H, s, SO_2NH), 10.23 (1 H, s, CONH). Anal. ($C_{17}H_{21}N_3O_3S$) C, H, N, S.

The other benzamides (**39–68**, **71**, **73–77**) were prepared in a similar manner.

X-ray Results. Crystal Data. **5**: $C_{16}H_{19}N_3O_4S$, triclinic, space group $P\bar{1}$, a = 10.924 (1) Å, b = 11.082 (1) Å, c = 7.246 (1) Å, α = 101.67 (1)°, β = 91.81 (1)°, γ = 95.64 (1)°, z = 2. **6**: $C_{16}H_{19}N_3O_4S$, triclinic, space group $P\bar{1}$, a = 11.019 (2), Å, b = 12.447 (1) Å, c = 6.688 (1) Å, α = 103.53 (1)°, β = 103.56 (1)°, γ = 91.63 (1)°, z = 2. The structures were solved by direct methods and refined by a block-diagonal least-squares technique to R = 0.041 for **5** (including all the hydrogen atoms) and R = 0.046 for **6** (excluding the methyl hydrogen atoms).

Plaque-Inhibition Test. For the assay of rhinovirus (types 10, 1A) and coxsackievirus (types B4, A9), Hela cell (Ohio) monolayers were used. CV-1 cells were used for poliovirus (type 1 Mahoney), and LLC-MK2 cells were used for enterovirus 70. A confluent monolayer of these cells in a flask was infected with 100–200 plaque-forming unit (PFU) and then overlaid with agar medium (2.0% agar in MEM with 4% fetal bovine serum) containing different concentrations of the compound to be tested and incubated at 37 °C for polio- and coxsackieviruses and at 33 °C for rhino- and enteroviruses, respectively. On the day plaques appeared, the second overlay was added with the same medium plus neutral red (0.004%). The plaques were counted, and the 50% plaque-inhibition concentration of the compound (ED_{50}) was calculated from the dose–response curve.

Cytotoxicity Test. Two hundred cells/milliliter of the cells in suspension to be tested were mixed with the medium (10% fetal bovine serum in MEM) containing a serial diluion of the test compound. After incubation for 7 days at 37 °C in 5% CO_2 atmosphere, the cell colony that formed was stained with 1% crystal violet and counted, and the 50% cytotoxic dose was calculated from the dose–response curve.

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