

Preparation and Antiarthritic and Analgesic Activity of 4,5-Diaryl-2-(substituted thio)-1H-imidazoles and Their Sulfoxides and Sulfones¹

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A series of 4,5-diaryl-2-(substituted thio)-1H-imidazoles was synthesized and evaluated as antiinflammatory and analgesic agents in the rat adjuvant induced arthritis assay and the mouse phenyl-*p*-benzoquinone writhing (PQW) assay. Several analogues were found to be more potent than phenylbutazone and indomethacin. Structure-activity relationships are discussed. One of the compounds, 4,5-bis(4-fluorophenyl)-2-[(1,1,2,2-tetrafluoroethyl)sulfonyl]-1H-imidazole (8d, tiplamazole), was found to be 8 times as potent as indomethacin in the rat adjuvant induced arthritis assay and is presently undergoing clinical trial as an antiarthritic drug.

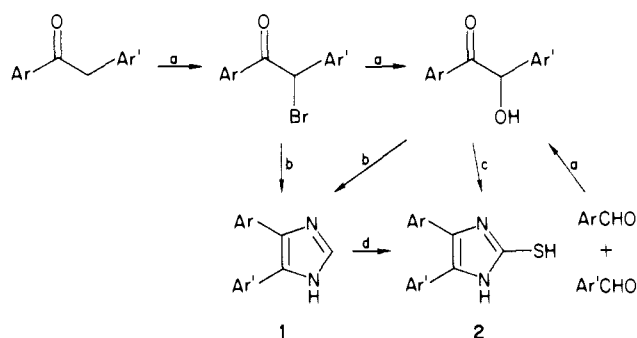
Extensive research efforts in many laboratories have led to compounds of a variety of structural types with demonstrated antiinflammatory activity.² A great majority of these have been arylacetic acids, but compounds acidic by virtue of another functionality, as well as nonacidic compounds, have also been reported.

Work from a number of laboratories has shown that certain diaryl heterocycles have useful antiinflammatory activity. 2-Alkyl-4,5-diarylimidazoles,³ 2-(trifluoromethyl)-4,5-diarylimidazoles,⁴ 2,4,5-triarylimidazoles,⁴ and 2,3-bis(4-methoxyphenyl)indole (indoxole)⁵ have all been reported to have antiinflammatory activity. We now report a series of 4,5-diaryl-2-(substituted thio)imidazoles and their antiinflammatory and analgesic activities.

Chemistry. The sulfides of formulas 3, 6, 9 and 12 were synthesized according to the sequences of Schemes II and III. The 4,5-diarylimidazoles (1) and the 2-mercapto-4,5-diarylimidazoles (2) used as starting materials were either commercially available or were prepared from the appropriate benzoin⁶ by literature methods.⁷ 2-Mercapto-4,5-diarylimidazoles (2) were alkylated with alkyl iodides in the presence of sodium methoxide in methanol to give the sulfides 3 (Table I). To prepare the 2,2,2-trifluoroethyl sulfides 3v, 3w, and 3x, it was found more convenient to treat 2 with (2,2,2-trifluoroethyl)trichloromethanesulfonate in toluene or chloroform in the presence of triethylamine. The vinyl sulfide 3q was prepared by the cuprous chloride catalyzed addition of 4,5-bis(4-methoxyphenyl)-2-mercaptoimidazole to acetylene.

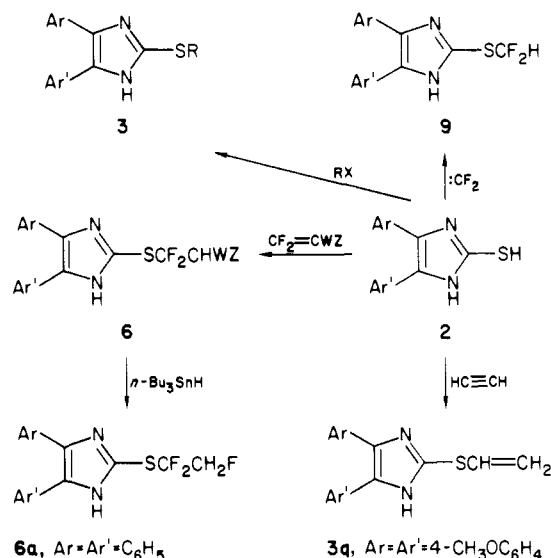
With the exception of 6a, the sulfides 6 (Table II) were prepared by the addition of 2 to tetrafluoroethylene, bromotrifluoroethylene, iodotrifluoroethylene, 1,1-dibromo-2,2-difluoroethylene, or 1,1-dichloro-2,2-difluoroethylene as appropriate. Initially, these reactions were done in dimethylformamide in the presence of methanolic

Scheme I

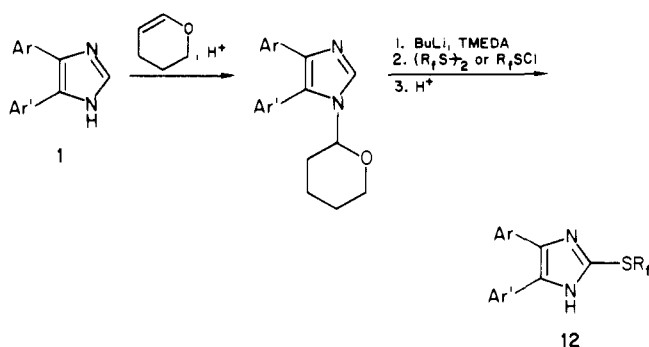


Key: (a) ref 6; (b) ref 7a; (c) ref 7b; (d) ref 7d.

Scheme II



Scheme III



- (1) These compounds were initially disclosed in: Cherkofsky, S. C.; Sharpe, T. R. U.S. Patent 4 190 666, 1980.
- (2) For a review and leading references, see: Lombardino, J. G. In "Annual Reports in Medicinal Chemistry"; Hess, H.-J., Ed.; Academic Press: New York, 1981; p 189.
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- (7) (a) Bredereck, H.; Theilig, G. *Chem. Ber.* 1953, 86, 88. (b) Anschutz, R.; Schwickerath, K. *Justus Liebigs Ann. Chem.* 1895, 284, 9. (c) Kochergin, P. M. *J. Gen. Chem. USSR* 1960, 31, 1010. (d) El'tsov, A. V.; Krivozheiko, K. M. *J. Org. Chem. USSR* 1966, 2, 183.

Triton B (benzyltrimethylammonium hydroxide).⁸ However, since the desired sulfide was often accompanied by

the corresponding benzyl and methyl sulfides, it was preferable to use diisopropylamine instead of Triton B. Compound **6a** was prepared by tri-*n*-butyltin hydride reduction of the bromotrifluoroethylene adduct **6v**.

The difluoromethyl sulfides **9** (Table III) were prepared by treating **2** with difluorocarbene generated from chlorodifluoromethane by sodium methoxide induced α elimination.

The perfluoroalkyl sulfides of **12** (Table IV) were prepared by first protecting the diarylimidazoles (**1**) with dihydropyran. Lithiation with *n*-butyllithium/*N,N,N',N'*-tetramethylethylenediamine, treatment with a perfluoroalkyl disulfide or sulfonyl chloride, and finally acidic deprotection gave the desired perfluoroalkyl sulfides **12**.

m-Chloroperbenzoic acid oxidation readily gave the sulfoxides (**4**) and sulfones (**5**) of Table I. The electron-deficient sulfides **6**, **9**, and **12** were more resistant to oxidation, and though the sulfones were readily obtainable, the sulfoxides could only be obtained via chromatographic separation from mixtures containing both sulfoxide and sulfone.

Pharmacological Results and Discussion. The pharmacological activities of the title compounds were determined by the mouse phenyl-*p*-benzoquinone writhing (PQW) assay⁹ and the rat adjuvant induced arthritis model.¹⁰

The structure-activity relationships of these compounds may be conveniently discussed in three parts: (a) the sulfur oxidation state; (b) the aryl substituents; (c) the sulfur substituent. The marked effect of the sulfur oxidation state on analgesic potency may be clearly seen by pairwise comparison of the PQW ED₅₀ of the sulfides and sulfones of Table III. Each sulfone is 20–90 times more potent than the corresponding sulfide. The greater potency of sulfones is further illustrated by consideration of the most active analgesics (PQW ED₅₀ ≤ 1 mg/kg) synthesized (Table V). With the exception of **4o** and **7e** all of these compounds are sulfones. It is noteworthy that the aryl substituents in **4o** and **7e** are *p*-methoxy. *p*-Alkoxy substituents lead to the most active analgesics, with methoxy being slightly more active than ethoxy. The sulfur substituents in the most active compounds are fluorinated alkyl groups.

In parallel with the analgesic potency, antiarthritic potency is highest when the sulfur substituent is fluorinated alkyl. Within the series of very potent tetrafluoroethyl sulfides, greater potency is obtained with para substitution than with meta or ortho substitution. Para substituents with diverse electronic characteristics lead to active antiarthritics, but generally the most potent antiarthritics are halogen substituted. Again in close analogy with analgesic activity, antiarthritic potency is generally greatest for sulfones compared to the other two sulfur oxidation states.

Combining the preferred values for each variable, compound **8d** (tiflamizole) is 8 times more potent than indomethacin in the rat adjuvant induced arthritis assay. On the basis of its high efficacy in rat adjuvant induced arthritis and on other pharmacological,¹¹ pharmacokinetic,¹²

and toxicological¹³ evaluation, tiflamizole was selected for drug development and is currently undergoing clinical trials.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Column chromatography was done on SilicAR CC7 silica gel (Mallinckrodt), using gravity flow. Evaporations were performed on a rotary evaporator under reduced pressure (water aspirator).

2-Mercapto-4,5-bis[3,4-(methylenedioxy)phenyl]imidazole. A mixture of 4,5-bis[3,4-(methylenedioxy)phenyl]imidazole (18.5 g, 54.4 mmol) and sulfur (2 g, 62.5 mmol) in 100 mL of sulfolane was heated to 230 °C, cooled, and then heated at 220 °C for 2 h. The cooled reaction mixture was poured into water, the pH adjusted to 4, and the solid collected and dried. Recrystallization from dimethylformamide (50 mL) gave the product (4.0 g), mp 263–265 °C.

2-Mercapto-4,5-bis(4-fluorophenyl)imidazole. A mixture of 4,4'-difluorobenzoin (317 g, 1.29 mol) and thiourea (380 g, 5.00 mol) in 1000 mL of dimethylformamide was heated at reflux for 5 h. Water (100 mL) was then added to the hot solution. Upon cooling, the precipitated product was collected by filtration and washed sequentially with cold dimethylformamide and chloroform. The solid was suspended in ca. 2 L of boiling chloroform for 10 min, collected by filtration, washed again with 1 L of hot chloroform, air-dried, and vacuum-dried (100 °C) to yield the product (194.5 g), mp 312–316 °C. Anal. (C₁₅H₁₀F₂N₂S) C, H, N.

4,5-Bis(4-fluorophenyl)imidazole. A solution of 4,4'-difluorobenzoin (58.7 g, 0.23 mol) in 300 mL of formamide was heated at reflux for 1 h. The cooled reaction mixture was treated with water (50 mL). The resultant solid was collected and washed with water and cold acetonitrile to give the product (37 g), mp 247–250 °C.

2-(Ethylthio)-4,5-bis(4-methoxyphenyl)imidazole (3p). To a suspension of 2-mercapto-4,5-bis(methoxyphenyl)imidazole (31.2 g, 0.100 mol) in methanol (200 mL) was added in one portion sodium methoxide (6.5 g, 0.12 mol) and the mixture then stirred for 15 min. A solution of iodoethane (17.1 g, 0.11 mol) in methanol (50 mL) was added dropwise, and the mixture was heated at reflux for 4.5 h. After stirring overnight at room temperature, the mixture was poured into water and the solid that precipitated was collected, washed with water, and dried to give 33.0 g of crude product. Recrystallization from aqueous ethanol gave 28.8 g (85%) of pure 2-(ethylthio)-4,5-bis(4-methoxyphenyl)imidazole, mp 108–109 °C. Anal. (C₁₉H₂₀N₂O₂S) C, H, N.

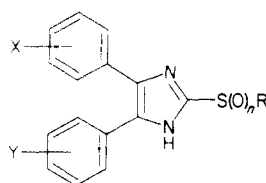
4,5-Diphenyl-2-[(2,2,2-trifluoroethyl)thio]imidazole (3v). A mixture of 4,5-diphenyl-2-mercaptoimidazole (12.6 g, 50 mmol), 2,2,2-trifluoroethyl trichloromethanesulfonate (14.1 g, 50 mmol), and triethylamine (5.1 g, 50 mmol) in 200 mL of toluene was heated at reflux overnight. The reaction mixture was concentrated, dissolved in diethyl ether, washed with water, dried, and concentrated. Chromatography and recrystallization from toluene gave the title compound (9.1 g), mp 188–189 °C.

4,5-Bis(4-methoxyphenyl)-2-(vinylthio)imidazole (3q). To a stainless steel tube was added 4,5-bis(4-methoxyphenyl)-2-mercaptoimidazole (15.0 g, 0.05 mol), cuprous chloride (0.75 g), and 100 mL of dimethylformamide. The tube was cooled, evacuated, and then pressured with 1.3 g of acetylene. The tube was heated at 150 °C with shaking for 8 h, cooled, and vented. The contents were diluted with 500 mL of water, and 25 mL of concentrated ammonium hydroxide was added. The aqueous mixture was extracted with ether (4 × 300 mL). The combined ether extracts were back-washed with water (3 × 300 mL) and then dried and concentrated on a rotary evaporator. The residue was chromatographed on a column containing 600 g of silica gel. The product was eluted with chloroform (cut 6–8, 1-L each) to give after concentration 2.9 g of crystals. A recrystallization from 1-chlorobutane/hexane gave 2.8 g of pure product, mp 114–115

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Table I. Alkyl Derivatives



no.	X	Y	n	R	mp, °C	recryst solvent ^a	anal. ^b	rat adjuvant arthritis: ED ₅₀ (po), mg/kg	mouse PQW: ED ₅₀ (po), mg/kg
indomethacin								0.3	0.35 (0.23–0.53)
phenylbutazone								10	65 (49.8–84.8)
aspirin								305	135 (58.8–310)
3a	H	H	0	CH ₃	233–234.5	A/THF	C, H, N	20% at 100 ^g	>100
3b	4-F	4-F	0	CH ₃	221–223.5	I	C, H, N	4	>130
3c	4-Cl	4-Cl	0	CH ₃	241–242	T	C, H, N	4	>135
3d	4-F	4-Cl	0	CH ₃	222–223	T	C, H, N	3.8	>130
3e	4-CH ₃ O	4-CH ₃ O	0	CH ₃	157–158.5	e	C, H, N	4.5	>135
3f	H	4-CH ₃ O	0	CH ₃	187–188.5	I	C, H, N ^h	35% at 25 ^h	>130
3g	4-CH ₃	4-CH ₃	0	CH ₃	221–222	T	C, H, N ⁱ	26% at 25 ^h	>130
3h	4-CF ₃	4-CF ₃	0	CH ₃	212–213	M/W	C, H, N	29% at 9 ^g	>130
3i	H	4-CF ₃	0	CH ₃	176–177	M/W	C, H, N	41% at 9 ^g	>130
3j	4-F	4-CF ₃	0	CH ₃	196–197	M/W	C, H, N	17	>130
3k	4-Cl	4-CF ₃	0	CH ₃	214–215	M/W	C, H, N	3.6	>130
3l	H	3-F	0	CH ₃	202–203	I	C, H, N	75	>130
3m	H	3-Cl	0	CH ₃	170–171	I	C, H, N	43% at 50 ⁱ	>130
3n	H	3,4-Cl ₂	0	CH ₃	183.5–184.5	I	C, H, N	62% at 25 ⁱ	>130
3o	H	H	0	CH ₂ CH ₃	189.5–190.5	MCH/T	C, H, N	100	>130
3p	4-CH ₃ O	4-CH ₃ O	0	CH ₂ CH ₃	108–109	E/W	C, H, N	5	11 (6.8–17.7)
3q	4-CH ₃ O	4-CH ₃ O	0	CH=CH ₂	114–115	B/H	C, H, N	12	34 (14.9–77.8)
3r	4-CH ₃ O	4-CH ₃ O	0	CH ₂ CH ₂ CH ₃	152–153	H ^d	C, H, N	9	40 (15.5–103)
3s	4-CH ₃ O	4-CH ₃ O	0	CH ₂ CH=CH ₂	167–167.5	E/W	C, H, N	20	26 (11.4–59.4)
3t	4-CH ₃ O	4-CH ₃ O	0	CH(CH ₃) ₂	127–128	DE/H ^d	C, H, N	38% at 30 ⁱ	>130
3u	H	H	0	CH ₂ CH ₂ CH ₂ CH ₃	161–162	MCH	C, H, N	>75	>130
3v	H	H	0	CH ₂ CF ₃	188–189	T	C, H, N	54% at 150 ⁱ	>130
3w	4-Cl	4-Cl	0	CH ₂ CF ₃	212–213	T	C, H, N	4	>130
3x	4-CH ₃ O	4-CH ₃ O	0	CH ₂ CF ₃	219–220	MCH	C, H, N	35	>135
3y	H	H	0	CH ₂ CF ₂ CF ₃	183–184	MCH	C, H, N		>135
3z	4-CH ₃ O	4-CH ₃ O	0	CH ₂ COCH ₃	115–117.5	H ^d	C, H, N	10	45 (14.3–141.9)
3aa	H	H	0	CH ₂ SCH ₃	172–173.5	E/W	C, H, N ^m	>50	>130
3bb	4-CH ₃ O	4-CH ₃ O	0	CH ₂ SCH ₃	171–172	E/W	C, H, N	46% at 30 ^h	>130
3cc	4-CH ₃ O	4-CH ₃ O	0	CH ₂ SOCH ₃	84.5–86.5	DE ^d	C, H, N	52	78 (35.9–169.6)
4a	H	H	1	CH ₃	199.5–201	c	C, H, N	33% at 100 ^g	>100
4b	4-F	4-F	1	CH ₃	185–187	I	C, H, N	4	>130
4c	4-Cl	4-Cl	1	CH ₃	202 dec	DE ^d	C, H, N	2.5	49 (21.9–110)
4d	4-CH ₃ O	4-CH ₃ O	1	CH ₃	166–167	e	C, H, N	6.5	>135
4e	H	3-F	1	CH ₃	163.5–164.5	T/MCH	C, H, N	67% at 100 ⁱ	>130
4f	H	3-Cl	1	CH ₃	150–151.5	I	C, H, N	77% at 75 ⁱ	>130
4g	H	3,4-Cl ₂	1	CH ₃	188–189	I	C, H, N	46% at 50 ⁱ	>130
4h	H	H	1	CH ₂ CH ₃	172–173	E	C, H, N	44% at 75 ^h	>130
4i	4-CH ₃ O	4-CH ₃ O	1	CH ₂ CH ₃	161–162	B	C, H, N	10	36 (18.6–69.6)
4j	4-CH ₃ O	4-CH ₃ O	1	CH ₂ CH ₂ CH ₃	143–144.5	DE ^d	C, H, N	15	40 (16.2–99)
4k	4-CH ₃ O	4-CH ₃ O	1	CH(CH ₃) ₂	169–170	DE/H ^d	C, H, N	36% at 30 ^h	>130
4l	H	H	1	CH ₂ CH ₂ CH ₂ CH ₃	157–158	E	C, H, N	>100	>130
4m	H	H	1	CH ₂ CF ₃	204–205	c	C, H, N	75	54 (15.9–183)
4n	4-Cl	4-Cl	1	CH ₂ CF ₃	214 dec	A	C, H, N	2.3	5.3 (2.6–10.7)
4o	4-CH ₃ O	4-CH ₃ O	1	CH ₂ CF ₃	193.5 dec	E	C, H, N	11	0.86 (0.33–2.23)
4p	H	H	1	CH ₂ CH ₂ CF ₃	180–181	E	C, H, N	>75	>130
4q	H	H	1	CH ₂ CF ₂ CF ₃	186.5–187.5	E	C, H, N	>75	>130
4r	H	H	1	CH ₂ CH ₂ CF ₂ CF ₃	134–135	E	C, H, N	>75	>130
4s	4-CH ₃ O	4-CH ₃ O	1	CH ₂ COCH ₃	138–140	DE ^d	C, H, N	35	135 ⁱ
4t	4-CH ₃ O	4-CH ₃ O	1	CH ₂ SCH ₃	142.5–143.5	DE ^d	C, H, N	28	34 (15.0–77.0)
5a	4-F	4-F	2	CH ₃	239–240	T/EA	C, H, N	4.5	>130
5b	4-Cl	4-Cl	2	CH ₃	254–255	DE ^d	C, H, N	2	3.7 (1.9–7.2)
5c	H	4-F	2	CH ₃	215–216	I	C, H, N	>9	135 ⁱ
5d	H	4-Cl	2	CH ₃	169–170	T	C, H, N	30	>130
5e	4-F	4-Cl	2	CH ₃	226–227	DE ^d	C, H, N	2.8	>130
5f	4-CH ₃ O	4-CH ₃ O	2	CH ₃	143–144.5	DE ^d	C, H, N	10	34 (18.9–61.1)
5g	H	4-CH ₃ O	2	CH ₃	98 dec	B/T	C, H, N	33% at 25 ^h	26 (8.4–80.4)
5h	H	4-C ₂ H ₅ O	2	CH ₃	172.5–173.5	I	C, H, N	41% at 50 ⁱ	>130
5i	H	4-CH ₃	2	CH ₃	137–140	T	C, H, N	45% at 100 ⁱ	>130
5j	H	4-CF ₃	2	CH ₃	198–199	T	C, H, N	32% at 50 ^h	>130
5k	4-F	4-CF ₃	2	CH ₃	189–190	MCH/T	C, H, N	3.7	>130
5l	4-Cl	4-CF ₃	2	CH ₃	224–225	T	C, H, N	2.2	>135
5m	2-Cl	2-Cl	2	CH ₃	171–172	B	C, H, N	>50	108 (57.4–203.2)
5n	H	3-F	2	CH ₃	215–216	I	C, H, N	32% at 75 ⁱ	>130
5o	H	3-Cl	2	CH ₃	171–172	I	C, H, N	55% at 10 ⁱ	>130
5p	H	3,4-Cl ₂	2	CH ₃	199–200	I	C, H, N	59% at 50 ⁱ	>130

Table I (Continued)

no.	X	Y	n	R	mp, °C	recryst solvent ^a	anal. ^b	rat adjuvant arthritis: ED ₅₀ (po), mg/kg	mouse PQW: ED ₅₀ (po), mg/kg
5q	H	H	2	CH ₂ CH ₃	213–214	E	C, H, N	32% at 100 ^c	>135
5r	4-CH ₃ O	4-CH ₃ O	2	CH ₂ CH ₃	136–137	B	C, H, N	6	10 (4.6–21.7)
5s	H	H	2	CH ₂ CH ₂ CH ₃	211–213	E/W	C, H, N	26% at 100 ^b	>130
5t	4-CH ₃ O	4-CH ₃ O	2	CH ₂ CH ₂ CH ₃	152–153	DE ^d	C, H, N	9.5	40 (15.7–101.9)
5u	4-CH ₃ O	4-CH ₃ O	2	CH ₂ CH=CH ₂	162–163	B	C, H, N	10	>130
5v	4-CH ₃ O	4-CH ₃ O	2	CH ₂ (CH ₃) ₂	175–176	DE ^d	C, H, N	30	>130
5w	H	H	2	CH ₂ CH ₂ CH ₂ CH ₃	203–204	E	C, H, N	>100	>130
5x	H	H	2	CH ₂ CF ₃	228 dec	A	C, H, N	15	10.4 (6.0–18.0)
5y	4-F	4-F	2	CH ₂ CF ₃	247 dec	E	C, H, N	3.5	20 (9.2–43.6)
5z	4-Cl	4-Cl	2	CH ₂ CF ₃	241 dec	N	C, H, N	10	10 (5.9–17.1)
5aa	4-CH ₃ O	4-CH ₃ O	2	CH ₂ CF ₃	173.5–174.5	B	C, H, N		0.58 (0.31–1.10)
5bb	H	H	2	CH ₂ CH ₂ CF ₃	228–229	E	C, H, N	>75	>135
5cc	H	H	2	CH ₂ CF ₂ CF ₃	197–198	E	C, H, N	>100	>130
5dd	H	H	2	CH ₂ CH ₂ CF ₂ CF ₃	183–184	E	C, H, N	>75	>130
5ee	4-CH ₃ O	4-CH ₃ O	2	CH ₂ COCH ₃	134–135	DE ^d	C, H, N	20	26 (8.6–78.6)
5ff	4-CH ₃ O	4-CH ₃ O	2	CH ₂ SO ₂ CH ₃	202–203 dec	I	C, H, N	43% at 80 ⁱ	>130

^a Key: A = acetonitrile; B = *n*-butyl chloride; C = chloroform; CT = carbon tetrachloride; DE = diethyl ether; E = ethanol; EA = ethyl acetate; G = glyme; H = hexanes; I = 2-propanol; M = methanol; MC = methylene chloride; MCH = methylcyclohexane; N = nitromethane; T = toluene; TB = *t*-butyl alcohol; W = water. ^b NMR (proton and fluorine where appropriate), IR, and mass spectra for all compounds were consistent with assigned structures. Except where indicated, C, H, N denotes satisfactory analyses ($\pm 0.4\%$) for these elements. ^c Concentration of the worked-up reaction mixture directly gave pure product. ^d Triturated with solvent indicated. ^e Concentration of appropriate chromatographic fractions directly gave pure product. ^f Chromatographed material was triturated with solvent indicated. ^g Decrease in paw volume at indicated dose; $p < 0.05$ as compared to control by student's *t*-test. ^h Decrease in paw volume at indicated dose; $p < 0.01$ as compared to control by student's *t*-test. ⁱ Decrease in paw volume at indicated dose; $p < 0.001$ as compared to control by student's *t*-test. ^j Highest dose tested. ^k N: calcd, 9.45; found, 8.80. ^l N: calcd, 9.52; found, 8.82. ^m C: calcd, 65.35; found, 65.95. ⁿ H: calcd, 5.92; found, 5.45.

°C. Anal. (C₁₉H₁₈N₂O₂S) C, H, N.

4,5-Bis(3-chlorophenyl)-2-[(1,1,2,2-tetrafluoroethyl)thio]imidazole (6s). A stainless-steel tube was charged with 2-mercapto-4,5-bis(3-chlorophenyl)imidazole (6.4 g, 19.9 mmol), diisopropylamine (0.4 g, 39.6 mmol), and dimethylformamide (75 mL). The tube was sealed, cooled, and evacuated, and charged with tetrafluoroethylene (4.0 g, 40 mmol). The tube was shaken for 20 h, and the contents were then poured into ice water. This was stirred until crystals formed which were collected and recrystallized from 2-propanol/water to give the product (4.8 g), mp 208–209 °C. Anal. (C₁₇H₁₀Cl₂F₄N₂S) C, H, N.

4,5-Diphenyl-2-[(2-bromo-1,1,2-trifluoroethyl)thio]imidazole (6v). A stainless-steel tube was charged with 4,5-diphenyl-2-mercaptoimidazole (25.2 g, 0.1 mol), diisopropylamine (2 g, 0.02 mol), and dimethylformamide (200 mL), purged with nitrogen, and charged with bromotrifluoroethylene (32.2 g, 0.2 mol). The sealed tube was shaken for 20 h, and the contents were poured into ice water. The crude solid was collected, washed with water and hexane, and then recrystallized from methylcyclohexane/toluene to give the product (35 g), mp 184–186 °C. Anal. (C₁₇H₁₂BrF₃N₂S) C, H, N.

4,5-Diphenyl-2-[(1,1,2-trifluoroethyl)thio]imidazole (6a). To a solution of 4,5-diphenyl-2-[2-bromo-1,1,2-trifluoroethyl)thio]imidazole (20.7 g, 0.05 mol) in 250 mL of toluene was added tri-*n*-butyltin hydride (15 g, 0.05 mol). The mixture was heated at reflux overnight. Another 15 g (0.05 mol) of tri-*n*-butyltin hydride was added, and heating continued for 4 h. The mixture was then added directly to a column of 2.5 lb of silica gel. Elution with toluene followed by recrystallization from toluene gave the product (5.9 g), mp 225–226.5 °C. Anal. (C₁₇H₁₃F₃N₂S) C, H, N.

4,5-Bis(4-chlorophenyl)-2-[(difluoromethyl)thio]imidazole (9c). A stainless-steel bomb was charged with 2-mercapto-4,5-bis(4-chlorophenyl)imidazole (16 g, 50 mmol), sodium methoxide (8.1 g, 150 mmol), and methanol (200 mL). The bomb was sealed, cooled, evacuated, and charged with chlorodifluoromethane (13 g, 150 mmol). The bomb was heated at 70 °C for 8 h, and the contents were poured into ice water. The crude solid was collected, washed with water, dried, and then chromatographed on silica gel. Recrystallization from toluene gave the product (8.3 g), mp 222–223 °C. Anal. (C₁₆H₁₀Cl₂F₂N₂S) C, H, N.

4,5-Bis(4-fluorophenyl)-2-[(trifluoromethyl)thio]imidazole (12b). To a slurry of 1-(tetrahydropyran-2-yl)-4,5-bis(4-fluorophenyl)imidazole (1.7 g, 5 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.7 g, 6 mmol) in 40 mL of diethyl ether at –78 °C was added dropwise 1.6 M *n*-butyllithium (4 mL, 6.4 mmol)

in 10 mL of diethyl ether. The resultant solution was stirred 10 min and then treated dropwise with a solution of bis(trifluoromethyl) disulfide (toxic) (1.3 g, 6.4 mmol) in 10 mL of diethyl ether. The reaction mixture was stirred at –78 °C for 0.5 h, allowed to warm to room temperature, and then poured into aqueous NaHCO₃. The aqueous layer was extracted with diethyl ether, and the combined organics were dried and concentrated. The crude protected product was dissolved in 25 mL of ethanol, treated with 25 mL of 1 N HCl, and heated at reflux for 1 h. The cooled reaction mixture was poured into saturated aqueous NaHCO₃ and extracted with methylene chloride. The combined organics were dried and concentrated to give a semisolid that was triturated with methylcyclohexane/hexane. The resultant solid was chromatographed to give the product (0.9 g), mp 227–229 °C. Anal. (C₁₆H₉F₅N₂S) C, H, N.

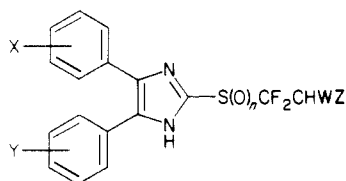
4,5-Diphenyl-2-[(2,2,2-trifluoroethyl)sulfonyl]imidazole (5x). To a mixture of 4,5-diphenyl-2-[(2,2,2-trifluoroethyl)thio]imidazole (15.7 g, 0.0470 mol) and chloroform (100 mL) cooled in an ice bath was added dropwise 86.4% *m*-chloroperbenzoic acid (19.0 g, 0.0952 mol) in chloroform (200 mL). After the mixture was stirred for 4 days at room temperature, tetrahydrofuran was added, and the mixture was washed with saturated sodium bicarbonate, dried with magnesium sulfate, and stripped of solvent to give 16.9 g of crude product. Two crystallizations from acetonitrile gave the product (8.8 g) as colorless needles, mp 228 °C dec. Anal. (C₁₇H₁₃F₃N₂O₂S) C, H, F, N.

Pharmaceutical Methods. PQW Assay. A test compound suspended in 1% methylcellulose was given orally to fasted (17–21 h) female white mice, 5–20 animals per double blind test. Aqueous 0.01% phenyl-*p*-benzoquinone, 0.20 mL per mouse, was injected intraperitoneally 6 min before observations were begun. At an appropriate time after the oral administration of the test compound, the mice were observed for 10 min for a characteristic stretching or writhing syndrome, which is indicative of pain induced by phenylquinone. The effective analgesic dose for 50% of the mice (ED₅₀) was calculated by the moving average method.¹⁴

Adjuvant-Induced Arthritis. Male Charles River Lewis rats (130–150 g) were injected subcutaneously in the plantar area of the right hind paw with 0.1 mL of adjuvant (Difco heat-killed, lyophilized *Mycobacterium butyricum* suspended in mineral oil 5 mg/mL). A total of 20 nonarthritic controls were injected with mineral oil. The animals were held for 2 weeks to allow development of arthritis. Paw volumes (uninjected, left hind paw) were

(14) Thompson, W. R. *Bact. Rev.* 1947, 11, 115.

Table II. Fluoro Olefin Adducts



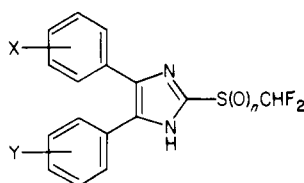
no.	X	Y	n	W	Z	mp, °C	recryst solvent ^a	anal. ^b	rat adjuvant arthritis: ED ₅₀ (po), mg/kg	mouse PQW: ED ₅₀ (po), mg/kg
6a	H	H	0	F	H	225–226.5	T	C, H, N	2	>135
6b	H	H	0	F	F	212–213	H ^d	C, H, N	1.2	81 ^j
6c	4-F	4-F	0	F	F	220–221.5	B	C, H, N	0.05	>81
6d	4-Cl	4-Cl	0	F	F	223–224	T	C, H, N	0.33	>135
6e	H	4-F	0	F	F	196–197.5	T	C, H, N	0.18	>130
6f	H	4-Cl	0	F	F	205–206	I/W	C, H, N	0.3	>130
6g	H	3,4-Cl ₂	0	F	F	209–211	T	C, H, N	3	>130
6h	4-F	4-Cl	0	F	F	206.5–207.5	E/W	C, H, N	0.18	>130
6i	H	4-(CH ₃) ₂ N	0	F	F	189–192.5	TB		3	34 (16.6–69.5)
6j	4-CH ₃ O	4-CH ₃ O	0	F	F	134–136	DE/H	C, H, N	4.5	45 (16.7–121.5)
6k	H	4-CH ₃ O	0	F	F	175–175.5	E/W	C, H, N ^k	30	>130
6l	H	4-C ₂ H ₅ O	0	F	F	185–186	MCH/T	C, H, N	32% at 10 ^h	>130
6m	4-F	4-CH ₃ O	0	F	F	170–171.5	B	C, H, N	14	>130
6n	4-F	4-CH ₃ S	0	F	F	155.5–157	MCH	C, H, N ^l	1.6	>108
6o	4-CH ₃	4-CH ₃	0	F	F	204–205	E/W	C, H, N	27	>130
6p	H	4-CF ₃	0	F	F	202–204	DMF/W	C, H, N	4.5	>130
6q	4-F	4-CF ₃	0	F	F	182.5–183.5	e	C, H, N	1.5	>130
6r	4-Cl	4-CF ₃	0	F	F	202–204	DMF/W	C, H, N	35% at 1 ^h	>130
6s	3-Cl	3-Cl	0	F	F	208–209	I/W	C, H, N	1.2	>130
6t	H	3-Cl	0	F	F	212–213	T	C, H, N	0.6	>130
6u	H	3-F	0	F	F	205.5–207	T	C, H, N ^m	2.5	>130
6v	H	H	0	F	Br	184–186	MCH/T	C, H, N	11	>130
6w	4-CH ₃ O	4-CH ₃ O	0	F	Br	151–153	H ^d	C, H, N	10	59 (26.7–130.0)
6x	4-CH ₃ O	4-CH ₃ O	0	Br	Br	172–174	B	C, H, N	2.3	>135
7a	H	H	1	F	F	181–182	H ^d	C, H, N	0.18	4.7 (2.5–8.9)
7b	4-F	4-F	1	F	F	192.5–193	T	C, H, N	0.055	
7c	4-Cl	4-Cl	1	F	F	198–199 dec	T	C, H, N	0.22	11 (3.1–39.5)
7d	H	3,4-Cl ₂	1	F	F	135–138	MCH	C, H, N	0.45	52 (22.9–118)
7e	4-CH ₃ O	4-CH ₃ O	1	F	F	162.5–163.5	DE/H	C, H, N	2.4	0.8 (0.23–2.73)
8a	H	H	2	F	H	239–240	T	C, H, N	0.14	5.6 (2.7–11.8)
8b	4-CH ₃ O	4-CH ₃ O	2	F	H	162–164	T/MCH	C, H, N	5	0.53 (0.23–1.22)
8c	H	H	2	F	F	234–235	H ^d	C, H, N	0.095	0.48 (0.28–0.81)
8d	4-F	4-F	2	F	F	239–240	T	C, H, N	0.03	0.67 (0.37–1.22)
8e	4-Cl	4-Cl	2	F	F	235–236.5	T	C, H, N	0.18	11 (4.8–25.4)
8f	H	4-F	2	F	F	228–229	T	C, H, N	0.03	0.86 (0.48–1.53)
8g	H	3,4-Cl ₂	2	F	F	197–198	T/H	C, H, N	0.02	6.5 (4.9–8.7)
8h	4-F	4-Cl	2	F	F	220–221	T	C, H, N	0.09	6.3 (3.2–12.3)
8i	4-NO ₂	4-NO ₂	2	F	F	240–240.5	EA		8.5	
8j	4-F	4-NO ₂	2	F	F	208–211	MC		0.37	21.6 (10.2–45.9)
8k	4-F	4-NH ₂ -HCl	2	F	F	238–241 dec	DE	C, H, N	>3	
8l	4-CH ₃ O	4-CH ₃ O	2	F	F	156–157	DE/H	C, H, N	1.4	0.11 (0.05–0.23)
8m	H	4-CH ₃ O	2	F	F	169–170	T	C, H, N	1.1	0.33 (0.20–0.53)
8n	H	4-C ₂ H ₅ O	2	F	F	162–163	T/MCH	C, H, N	1.5	0.95 (0.49–1.84)
8o	4-F	4-CH ₃ O	2	F	F	189–190	B	C, H, N	1.7	0.28 (0.09–0.86)
8p	4-CH ₃	4-CH ₃	2	F	F	225–226	T	C, H, N ⁿ	0.35	11 (4.8–25.4)
8q	H	4-CH ₃	2	F	F	202–203	T	C, H, N	0.8	5.5 (2.8–10.9)
8r	H	4-CF ₃	2	F	F	188–189	T/MCH	C, H, N	2.4	40 (28.6–55.9)
8s	4-F	4-CF ₃	2	F	F	166–167	T/MCH	C, H, N	>1	18 (8.8–36.8)
8t	4-Cl	4-CF ₃	2	F	F	208–209	T/MCH	C, H, N	1.8	45 (20.0–101.0)
8u	2-Cl	2-Cl	2	F	F	183–184	T	C, H, N	0.8	4.4 (1.9–10.1)
8v	2-CH ₃ O	2-CH ₃ O	2	F	F	155–157	MCH/T	C, H, N	>9	40 (20.2–79.4)
8w	3-Cl	3-Cl	2	F	F	208–209	T	C, H, N	0.16	20.9 (10.9–40.0)
8x	H	3-Cl	2	F	F	193–194	T/MCH	C, H, N	0.04	19.8 (7.5–51.9)
8y	4-CH ₃	3-Cl	2	F	F	220–220.5	T	C, H, N ^o	36% at 1 ⁱ	49 (25.5–94.1)
8z	H	3-F	2	F	F	217–218	T	C, H, N ^p	0.06	2 (0.9–4.5)
8aa	3-CH ₃ O	3-CH ₃ O	2	F	F	155.5–156.5	T	C, H, N	4	67 (38.0–118.0)
8bb	2-Cl	4-CH ₃ O	2	F	F	176–177	T	C, H, N	6	0.56 (0.29–1.09)
8cc	H	H	2	F	Br	217–218	T	C, H, N	0.85	6.6 (3.1–14.0)
8dd	4-CH ₃ O	4-CH ₃ O	2	F	Br	187–188	T	C, H, N	2.4	0.3 (0.16–0.57)
8ee	4-CH ₃ O	4-CH ₃ O	2	F	I	190–192	T	C, H, N	5	16.7 (6.5–42.8)
8ff	H	H	2	Cl	Cl	223–223.5	T	C, H, N	1.7	34.2 (27.2–42.9)
8gg	4-CH ₃ O	4-CH ₃ O	2	Br	Br	222–223	T	C, H, N ^q	>9	10.8 (4.5–25.9)

^a–^j See corresponding footnotes in Table I. ^kC: calcd, 56.54; found, 56.95. ^lC: calcd, 51.92; found, 52.4. ^mC: calcd, 55.13; found, 55.66. ⁿC: calcd, 55.33; found, 55.75. ^oC: calcd, 49.95; found, 50.37. ^pN: calcd, 6.96; found, 7.38. ^qC: calcd, 40.30; found, 40.71.

measured and the adjuvant-injected rats were culled and distributed to treatment groups of 10 of equal disease severity. Nonarthritic controls were distributed to two groups of 10. The

rats were given oral doses of compound or PVA-Acacia (polyvinyl alcohol 1%, Gum acacia, USP 5%, methylparaben 0.5%) (10 mL/kg) by gavage on that day and on the six following days. One

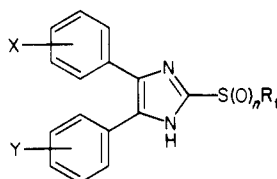
Table III. Difluoromethyl Derivatives



no.	X	Y	n	mp, °C	recryst solvent ^a	anal. ^b	rat adjuvant arthritis: ED ₅₀ (po), mg/kg	mouse PQW: ED ₅₀ (po), mg/kg
9a	H	H	0	227-228	T	C, H, N	27	>130
9b	4-F	4-F	0	192.5-194	T/MCH	C, H, N ^k	0.42	>130
9c	4-Cl	4-Cl	0	222-223	T	C, H, N	0.35	78 (20.6-296.0)
9d	4-CH ₃ O	4-CH ₃ O	0	170.5-172	T	C, H, N	1.8	112 (51.5-243)
10	4-Cl	4-Cl	1	203-206	DE ^f	C, H, N	0.19	1.3 (0.66-2.55)
11a	H	H	2	265	T	C, H, N	0.35	6 (2.3-15.7)
11b	4-F	4-F	2	246.5-247	T	C, H, N	0.1	1.4 (0.68-2.89)
11c	4-Cl	4-Cl	2	244-245	T	C, H, N	0.35	2.3 (1.2-4.5)
11d	4-CH ₃ O	4-CH ₃ O	2	186-187	T	C, H, N	0.5	1.5 (0.8-2.7)

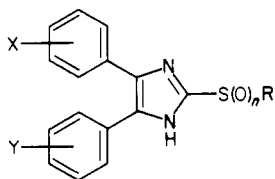
^{a-f}See corresponding footnotes in Table I. ^kC: calcd, 56.80; found, 57.72.

Table IV. Perfluoroalkyl Derivatives



no.	X	Y	n	R _f	mp, °C	recryst solvent ^a	anal. ^b	rat adjuvant arthritis: ED ₅₀ (po), mg/kg	mouse PQW: ED ₅₀ (po), mg/kg
12a	H	H	0	CF ₃	254-256	T	C, H, N	27% at 1 ^g	>130
12b	4-F	4-F	0	CF ₃	227-229	T	C, H, N	0.035	15.6 (5.3-45.9)
12c	H	3,4-Cl ₂	0	CF ₃	241-242	T/EA	C, H, N ^k	7	>130
12d	4-CH ₃ O	4-CH ₃ O	0	CF ₃	181-182	T/MCH	C, H, N	1.5	
12e	4-F	4-CH ₃ O	0	CF ₃	156-157.5	MCH/T	C, H, N	2.7	78 (30.9-197.0)
12f	4-F	4-F	0	CF ₂ CF ₃	235-237	MCH/T	C, H, N	0.2	
13a	4-F	4-F	1	CF ₃	205.5-206	E/W	C, H, N	0.06	40 (20.0-81.0)
13b	4-CH ₃ O	4-CH ₃ O	1	CF ₃	166-167	E/W	C, H, N	3	37 (10.9-125.8)
14a	H	H	2	CF ₃	292-293.5	T	C, H, N	0.03	0.75 (0.37-1.52)
14b	4-F	4-F	2	CF ₃	264-265	T	C, H, N	0.016	0.19 (0.07-0.50)
14c	H	3,4-Cl ₂	2	CF ₃	195.5-197	T	C, H, N ^l	0.35	16 (7.7-33.2)
14d	4-CH ₃ O	4-CH ₃ O	2	CF ₃	201-202.5	H ^d	C, H, N	0.33	0.043 (0.028-0.065)
14e	4-F	4-CH ₃ O	2	CF ₃	187-188	T/MCH	C, H, N	1.4	0.12 (0.05-0.27)

^{a-f}See corresponding footnotes in Table I. ^kC: calcd, 49.37; found, 50.36. H: calcd, 2.33; found, 2.74. ^lC: calcd, 45.62; found, 46.15.

Table V. Most Potent Analgesics (ED₅₀ < 1 mg/kg)

no.	X	Y	n	R	mouse PQW: ED ₅₀ (po), mg/kg
8n	H	4-C ₂ H ₅ O	2	CF ₂ CHF ₂	0.95 (0.49-1.84)
8f	H	4-F	2	CF ₂ CHF ₂	0.86 (0.48-1.53)
4o	4-CH ₃ O	4-CH ₃ O	1	CH ₂ CF ₃	0.86 (0.33-2.23)
7e	4-CH ₃ O	4-CH ₃ O	1	CF ₂ CHF ₂	0.8 (0.23-2.73)
14a	H	H	2	CF ₃	0.75 (0.37-1.52)
8d	4-F	4-F	2	CF ₂ CHF ₂	0.67 (0.37-1.22)
5aa	4-CH ₃ O	4-CH ₃ O	2	CH ₂ CF ₃	0.58 (0.31-1.10)
8bb	2-Cl	4-CH ₃ O	2	CF ₂ CHF ₂	0.56 (0.29-1.09)
8b	4-CH ₃ O	4-CH ₃ O	2	CF ₂ CHF ₂	0.53 (0.23-1.22)
8c	H	H	2	CF ₂ CHF ₂	0.48 (0.28-0.81)
8m	H	4-CH ₃ O	2	CF ₂ CHF ₂	0.33 (0.20-0.53)
8dd	4-CH ₃ O	4-CH ₃ O	2	CF ₂ CHBrF	0.3 (0.16-0.57)
8o	4-F	4-CH ₃ O	2	CF ₂ CHF ₂	0.28 (0.09-0.86)
14b	4-F	4-F	2	CF ₃	0.19 (0.07-0.50)
14e	4-F	4-CH ₃ O	2	CF ₃	0.12 (0.05-0.27)
8l	4-CH ₃ O	4-CH ₃ O	2	CF ₂ CHF ₂	0.11 (0.05-0.23)
14d	4-CH ₃ O	4-CH ₃ O	2	CF ₃	0.043 (0.028-0.065)

day after the last dose, the paw volumes (uninjected, left hind paw) were measured with a Ugo basile volume differential meter, Model 7101. Percent decrease from control paw volume was calculated according to the following (where mean paw volume is in mL):

$$\frac{(\text{arthritic control} - \text{treatment gp})}{(\text{arthritic control} - \text{nonarthritic control})} \times 100$$

Dose-response regression lines of the percent decrease were plotted on semilog paper by visual fit, and the ED_{50%} decrease from control paw volume was determined by inspection.

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Registry No. 2 (Ar = Ar' = 4-FC₆H₄), 73181-88-1; 2 (Ar = Ar' = Ph), 2349-58-8; 2 (Ar = Ar' = 4-ClC₆H₄), 23187-08-8; 2 (Ar = 4-FC₆H₄, Ar' = 4-ClC₆H₄), 97059-85-3; 2 (Ar = Ar' = 4-CH₃OC₆H₄), 39908-69-5; 2 (Ar = Ph, Ar' = 4-CH₃OC₆H₄), 97059-86-4; 2 (Ar = Ar' = 4-CH₃C₆H₄), 73181-95-0; 2 (Ar = Ar' = 4-CF₃C₆H₄), 73627-37-9; 2 (Ar = Ph, Ar' = 4-CF₃C₆H₄), 97059-87-5; 2 (Ar = 4-FC₆H₄, Ar' = 4-CF₃C₆H₄), 97059-88-6; 2 (Ar = 4-ClC₆H₄, Ar' = 4-CF₃C₆H₄), 97059-89-7; 2 (Ar = Ph, Ar' = 3-FC₆H₄), 97059-90-0; 2 (Ar = Ph, Ar' = 3-ClC₆H₄), 97059-91-1; 2 (Ar = Ph, Ar' = 3,4-Cl₂C₆H₃), 85284-07-7; 2 (Ar = Ph, Ar' = 4-FC₆H₄), 97060-25-8;

2 (Ar = Ph, Ar' = 4-ClC₆H₄), 23187-09-9; 2 (Ar = Ph, Ar' = 4-(CH₃)₂NC₆H₄), 73181-80-3; 2 (Ar = Ph, Ar' = 4-EtOC₆H₄), 97060-26-9; 2 (Ar = 4-FC₆H₄, Ar' = 4-CH₃OC₆H₄), 97071-44-8; 2 (Ar = 4-FC₆H₄, Ar' = 4-CH₃SC₆H₄), 97060-27-0; 3a, 3653-22-3; 3b, 62894-49-9; 3c, 34926-08-4; 3d, 62894-54-6; 3e, 49855-26-7; 3f, 97059-92-2; 3g, 97059-93-3; 3h, 97059-94-4; 3i, 62894-55-7; 3j, 62939-41-7; 3k, 62894-56-8; 3l, 73918-90-8; 3m, 73918-91-9; 3n, 73918-89-5; 3o, 60220-29-3; 3p, 62894-32-0; 3q, 62894-41-1; 3r, 62894-48-8; 3s, 62894-33-1; 3t, 97059-95-5; 3u, 94286-02-9; 3v, 62894-25-1; 3w, 62894-31-9; 3x, 62894-28-4; 3y, 97059-96-6; 3z, 62894-37-5; 3aa, 97059-97-7; 3bb, 62894-34-2; 3cc, 62894-39-7; 4a, 97059-98-8; 4b, 73919-13-8; 4c, 62894-77-3; 4d, 62894-74-0; 4e, 73919-23-0; 4f, 73919-16-1; 4g, 73919-21-8; 4h, 97059-99-9; 4i, 62894-35-3; 4j, 62894-79-5; 4k, 97060-00-9; 4l, 97060-01-0; 4m, 62894-26-2; 4n, 62894-76-2; 4o, 62894-29-5; 4p, 97060-02-1; 4q, 97060-03-2; 4r, 97060-04-3; 4s, 62895-14-1; 4t, 62894-38-6; 5a, 62894-90-0; 5b, 62894-85-3; 5c, 73919-17-2; 5d, 62895-01-6; 5e, 62894-96-6; 5f, 62894-75-1; 5g, 97060-05-4; 5h, 73919-15-0; 5i, 97060-06-5; 5j, 97060-07-6; 5k, 62895-03-8; 5l, 62895-04-9; 5m, 97060-08-7; 5n, 73919-22-9; 5o, 73919-24-1; 5p, 73919-20-7; 5q, 97060-09-8; 5r, 62894-36-4; 5s, 97060-10-1; 5t, 62894-80-8; 5u, 62894-73-9; 5v, 62894-81-9; 5w, 97060-11-2; 5x, 62894-27-3; 5y, 62894-88-6; 5z, 62939-40-6; 5aa, 62894-30-8; 5bb, 97060-12-3; 5cc, 97060-13-4; 5dd, 97060-14-5; 5ee, 62895-16-3; 5ff, 62895-15-2; 6a, 62894-43-3; 6b, 62894-40-0; 6c, 62894-59-1; 6d, 62894-58-0; 6e, 62894-67-1; 6f, 62894-63-7; 6g, 73918-97-5; 6h, 62894-60-4; 6i,

62894-71-7; 6j, 62894-57-9; 6k, 62894-62-6; 6l, 73918-96-4; 6m, 73918-95-3; 6n, 97060-15-6; 6o, 62894-61-5; 6p, 62894-65-9; 6q, 62894-66-0; 6r, 97060-16-7; 6s, 62894-68-2; 6t, 73918-99-7; 6u, 73918-98-6; 6v, 62894-70-6; 6w, 62894-69-3; 6x, 73918-83-9; 7a, 62894-84-2; 7b, 73919-11-6; 7c, 62894-86-4; 7d, 87483-32-7; 7e, 62894-83-1; 7f, 73919-03-6; 8b, 71078-11-0; 8c, 62894-78-4; 8d, 62894-89-7; 8e, 62894-87-5; 8f, 62895-08-3; 8g, 73919-14-9; 8h, 73919-00-3; 8i, 73919-12-7; 8j, 97060-17-8; 8k, 97060-18-9; 8l, 62894-82-0; 8m, 62894-98-8; 8n, 71078-12-1; 8o, 73919-10-5; 8p, 62894-97-7; 8q, 62895-12-9; 8r, 62895-05-0; 8s, 97060-19-0; 8t, 62895-06-1; 8u, 62895-07-2; 8v, 97060-20-3; 8w, 62895-09-4; 8x, 73919-19-4; 8y, 97060-21-4; 8z, 73919-18-3; 8aa, 62895-00-5; 8bb, 62894-99-9; 8cc, 73919-04-7; 8dd, 62895-11-8; 8ee, 73919-05-8; 8ff, 62894-93-3; 8gg, 97060-22-5; 9a, 62894-51-3; 9b, 62894-53-5; 9c, 62894-52-4; 9d, 62894-50-2; 10, 62895-10-7; 11a, 62894-92-2; 11b, 62894-95-5; 11c, 62894-94-4; 11d, 62894-91-1; 12a, 62894-46-6; 12b, 73918-81-7; 12c, 73918-88-4; 12d, 73918-84-0; 12e, 73918-86-2; 12f, 73918-87-3; 13a, 97060-23-6; 13b, 85284-10-2; 14a, 62894-47-7; 14b, 73919-02-5; 14c, 73919-09-2; 14d, 71078-10-9; 14e, 73919-07-0; 2-mercapto-4,5-bis[3,4-(methylenedioxy)phenyl]imidazole, 66660-00-2; 4,5-bis[3,4-(methylenedioxy)phenyl]imidazole, 5549-84-8; 4,4'-difluorobenzoin, 53458-16-5; thiourea, 62-56-6; 4,5-bis(4-fluorophenyl)imidazole, 68163-71-3; formamide, 75-12-7; 1-(tetrahydropyran-2-yl)-4,5-bis(4-fluorophenyl)imidazole, 74767-58-1.

8-Substituted Guanosine and 2'-Deoxyguanosine Derivatives as Potential Inducers of the Differentiation of Friend Erythroleukemia Cells¹

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A variety of 8-substituted guanosine and 2'-deoxyguanosine derivatives were synthesized and tested as inducers of the differentiation of Friend murine erythroleukemia cells in culture. The most active agents in the guanosine series were 8-substituted -N(CH₃)₂, -NHCH₃, -NH₂, -OH, and -SO₂CH₃, which caused 68, 42, 34, 33, and 30% of erythroleukemia cells to attain benzidine positivity, a functional measure of maturation, at concentrations of 5, 1, 0.4, 5, and 5 mM, respectively. The 8-OH derivative of the 2'-deoxyguanosine series produced comparable activity, causing 62% benzidine-positive cells at a level of 0.2 mM. These findings indicate that 8-substituted analogues of guanosine and 2'-deoxyguanosine have the potential to terminate leukemia cell proliferation through conversion to end-stage differentiated cells.

Most of the chemotherapeutic agents employed for the treatment of the leukemias act by cytodestructive mechanisms. An alternative to this approach, which is based upon the concept that leukemia is a disease of blocked maturation, envisions the use of agents to convert neoplastic cells to end-stage cells with no proliferative capability through induction of differentiation. The Friend murine erythroleukemia has been shown to have the capacity to undergo both morphological and functional maturation after exposure to a large number of different chemicals including polar solvents,³ hormones,⁴ vitamins,^{5,6}

tumor promoters⁷ and cancer chemotherapeutic agents.^{8,9}

Among the antineoplastic agents that are capable of initiating maturation are the 6-thiopurines, 6-thioguanine, and 6-mercaptopurine. These antileukemic drugs are at best weak inducers of the differentiation of Friend erythroleukemia and HL-60 human promyelocytic leukemia cells¹⁰⁻¹² but are potent initiators of maturation in variants

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