δ 7.57 (s, C_6 H), 5.54 (m, CHO), 4.52 (m, NCH_2), 3.78 (d, CH_2O), 3.42 (s, CH_3); MS, *m/e* 199 (M^+), 183 (M - O), 125 [M - C(OH)CH_2OCH_3]. Anal. ($C_7H_9N_3O_4$) C, H, N.

The middle fraction was obtained as a crystalline product, which was characterized by IR and NMR as **3d**, and was recrystallized (absolute ethanol) to yield a total of 223 mg (35%): mp 159-160 °C; IR (KBr) 1500 and 1320 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 8.04 (s, C_5 H), 5.47 (m, CHO), 4.20 (m, NCH_2), 3.70 (d, CH_2O), 3.28 (s, CH_3); MS, *m/e* 199 (M^+), 183 (M - O), 125 [M - C(OH)CH_2OCH_3). Anal. ($C_7H_9N_3O_4$) C, H, N.

The lower fraction was obtained as an oil and assigned structure **2d**, which was crystallized (ethyl ether) to yield 106 mg (14%): mp 71-72 °C; IR (KBr) 3500 (OH), 1536 and 1326 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 8.08 (s, C_5 H), 4.63 (m, CHO), 4.00 (m, NCH_2), 3.48 (d, CH_2O), 3.33 (s, CH_3); MS, *m/e* 246 (M^+), 200 (M - NO_2), 183 [M - (NO_2 + OH)], 154 (M - $2NO_2$). Anal. ($C_7H_{10}N_4O_6$) C, H, N.

Reaction of 2,4(5)-Dinitroimidazole (1) with 1,2-Epoxy-3-hydroxypropane. A suspension of 1 (0.5 g, 3.2 mmol) in 5 mL of 1,2-epoxy-3-hydroxypropane was stirred at room temperature for 60 h (1 went into solution after 4 h); the reaction was followed by TLC (EtOAc); the excess oxirane appeared polymerized during the reaction. After the reaction was completed, the mixture was deposited on a silica gel column (60 g) and eluted first with chloroform (250 mL) and then followed by ethyl acetate (2.5 L); 25-mL fractions were collected. The fractions as monitored by TLC (EtOAc) were indicative of only a single component. The appropriate fractions were combined and concentrated to afford crystalline product **3e**, which was recrystallized (EtOAc) to yield 180 mg (31%): mp 167-168 °C dec; IR (KBr) 3336 (OH), 1516 and 1310 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 8.35 (s, C_5 H), 5.44 (m, CHO), 4.31 (m, NCH_2), 3.77 (dd, CH_2O); MS, *m/e* 185 (M^+), 169 (M - O). Anal. ($C_6H_7N_3O_4$) C, H, N.

General Procedure for Cyclization of 1-(2-Hydroxyalkyl)-2,4-dinitroimidazoles 2b-d into 6-Nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles 3b-d. In a typical experiment a solution of 100 mg of **2b** in 10 mL of absolute ethanol and 10 mL of propylene oxide was refluxed for 48 h at 40 °C. The solvent was evaporated under reduced pressure and the residue was characterized by NMR and MS as **3b**, which was recrystallized (absolute ethanol) to yield 47 mg (60%): mp 156-157 °C; IR (KBr) 1500 and 1315 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 8.39 (s, C_5 H), 5.64 (m, CHO), 4.27 (m, NCH_2), 1.41 (d, CH_3); MS, *m/e* 169 (M^+), 153 (M - O), 123 (M - NO_2). Anal. ($C_6H_7N_3O_3$) C, H, N. Compounds **3c** and **3d** were obtained similarly in 75 and 78% yield, respectively.

1-(2-Hydroxy3-methoxypropyl)-2,4-dinitroimidazole (2d). This compound was synthesized by the following modified procedure to obtain a higher yield than described above under the reaction of 1 with 1,2-epoxy-3-methoxypropane. To 1.2 g (7.6 mmol) of 1 was added 25 mL of 1,2-epoxy-3-methoxypropane, and the mixture was stirred at room temperature for 48 h. The excess of oxirane was removed under vacuum, and the residual oil was purified by column chromatography (silica gel), initially employing chloroform as eluant and then followed by chloroform-methanol (5:1). The UV-absorbing fractions were collected and crystallized (ethyl ether) to yield 0.56 g of **2d**. The filtrate consisted of a mixture of **2d**, **3d**, and **4d**, which were separated by preparative TLC (silica gel) using chloroform as eluant. The material corresponding to **2d** was collected and crystallized to yield an additional 0.32 g, mp 71-72 °C. The total yield by this procedure was 48%.

Radiosensitization Studies. The radiosensitization studies were carried out by employing asynchronous monolayer cultures of Chinese hamster cells (V-79). The techniques used for culturing and handling this cell line have been reported earlier.[15] The cells were grown as monolayers in 25-cm^2 plastic culture flasks (Falcon) in Eagles minimum essential medium (MEM) with 15% fetal calf serum.

For toxicity tests, approximately 200 cells were placed in permanox petri dishes (60 × 15 mm, Lux Scientific Corp.) containing 3 mL of media and were allowed to attach for 2 h. The medium was then removed by aspiration and replaced by the medium containing the nitro compound under study. The cells were exposed to a range of concentrations of each drug for 2 h at 37 °C in air or in hypoxia. The plated cultures were rendered hypoxic in sealed containers capable of holding seven petri dishes, by purging with 95% nitrogen/5% CO_2 for 90 min. At the end of a 2-h period, the medium containing the drug was removed and replaced with 3 mL of fresh medium. Cultures were incubated for 6 days at 37 °C in an atmosphere of 95% air/5% CO_2; the resulting colonies were fixed in absolute ethanol, stained with Methylene blue, and counted.

Irradiation was carried out at room temperature by using a cobalt-60 source at a dose rate of approximately 280 rad/min. The petri dishes in the sealed containers were directly irradiated under aerobic and hypoxic conditions. Complete survival curves were obtained for each compound at the radiation doses of 400 to 3000 rad. The D_0 value was calculated for each compound and the ratio of the D_0 value for the hypoxic control cells to the D_0 value of hypoxic drug-treated cells provided the sensitizer enhancement ratio of the corresponding agent.

Effect of Structural Change on Acute Toxicity and Antiinflammatory Activity in a Series of Imidazothiazoles and Thiazolobenzimidazoles[1]

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The effect of structural change on the biological activity of a series of imidazothiazoles and thiazolobenzimidazoles is described. It was found that compounds with polar substituents at the 2 or 3 position of the ring system are less acutely toxic while maintaining antiinflammatory activity. Other structural changes, such as the incorporation of a *gem*-dimethyl substituent in the 6 position, increase acute toxicity and eliminate antiinflammatory activity. The compound with the best activity/toxicity ratio contains an alkyl sulfonyl substituent on the thiazole ring. The thiazolobenzimidazole analogues are more potent than the imidazole analogues.

In the course of compound screening as part of a search for novel antiinflammatory compounds, it was observed that a series of dihydroimidazothiazoles caused a reduction in carrageenin-induced edema.[2] Evaluation of the antiinflammatory activity of this initial series of compounds indicated that edema reduction in the carrageenin assay was observed for most of the analogues. Unfortunately,

(1) A portion of this work was presented at the 16th National Medicinal Chemistry Symposium, Kalamazoo, MI, June 1978.

(2) R. E. Moser, L. J. Powers, and Z. S. Ariyan, US Patent 4 041 167 (1977).

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Table I. Acylacetanilides

		$RCOCH_2CONHR'$					
no.	R	R'	mp, °C	yield, %	solvent	formula	method
1	CH_3	3'-CF_3	107–110	65	EtOH	$C_{11}H_{10}F_3NO_2$	A
3	C_6H_5	2',4',6'-$(CH_3)_3$	176–177	88	EtOH/H_2O	$C_{18}H_{19}NO_2$	B
4	CH_3	2'-F	75–78	32	EtOH	$C_{10}H_{10}FNO_2$	A

Table II. β-Keto Sulfones

			$RCOCHXSO_2R'$					
no.	R	X	R'	mp, °C	yield, %	solvent	formula	method
5	C_6H_5	Br	CH_3	89–90	74	EtOH	$C_9H_9BrO_3S$	D
6	C_6H_5	Cl	CH_3	104–106	82	EtOH	$C_9H_9ClO_3S$	E
7	CH_2Br	H	C_6H_5	93–95		EtOH	$C_9H_9BrO_3S$	D
8	CH_2Br	H	CH_3	105–107		$CHCl_3$	$C_4H_7BrO_3S$	E
9	C_6H_5	Cl	$C(CH_3)_3$	97–98	52	MeOH	$C_{12}H_{15}ClO_3S$	E
10	C_6H_5	Cl	C_6H_5	125–126	72	MeOH	$C_{14}H_{11}ClO_3S$	E
11	$(CH_3)_3C$	Br	CH_3	99–101	79	MeOH	$C_7H_{13}BrO_3S$	D
12	$(CH_3)_3C$	Cl	CH_3	77–78	85	MeOH/H_2O	$C_7H_{13}ClO_3S$	E
13	$(CH_3)_3C$	H	CH_3	62–63	57	MeOH	$C_7H_{14}O_3S$	E
14	C_6H_5	Br	C_6H_5	138–140	60	$CHCl_3$/EtOAc	$C_{14}H_{11}BrO_3S$	D

acute toxicity manifested by convulsant activity was also observed.

If the limiting toxicity is not an extension of the desired pharmacological effect, molecular modification of the lead compounds(s) can many times result in analogues of improved therapeutic properties. This separation of toxicity from desired activity can be achieved if the receptor surface involved in the toxic reaction differs significantly from the receptor surface involved in the desired effect. These differences can be either the distribution of electron density on the surface or the topography of the surface. The molecular modifications necessary to exploit these differences involve variations of the polarity of steric bulk of substituents.

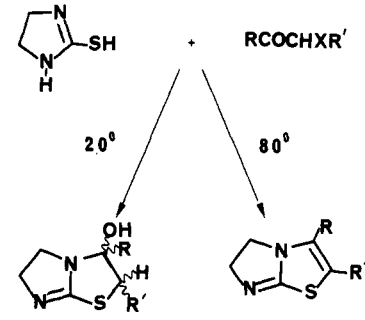
We wish to report the results of three types of structural modification on the separation of antiinflammatory and convulsant activity. One structural variation involves the incorporation of polar substituents, amides and sulfones, at the 2 position of the imidazothiazole ring. This type of structural modification was suggested following qualitative evaluation of our previously reported data.[2]

In order to explore differences in the steric requirements of the receptors, 6,6-dimethylimidazothiazoles were synthesized. These analogues significantly decrease the possibility for the 7-nitrogen to interact with the receptor surface. Cis and trans analogues of a thiazolobenzimidazole ring system were also synthesized (Tables IV and V). These analogues, like the 6,6-dimethylimidazothiazoles, should have significantly increased steric requirements at the receptor site relative to the simple imidazothiazole ring system.

3-Hydroxytetrahydroimidazothiazoles have biological activity similar to the corresponding dihydroimidazothiazoles that result from the dehydration of these 3-hydroxy compounds. Since all the previously described[2] 3-hydroxy compounds are rapidly dehydrated, the role of the hydroxyl group in antiinflammatory activity and toxicity could not be defined. In order to address this question, a series of 3-hydroxy compounds was designed in which dehydration is not favored. This design involved either incorporating *gem*-dialkyl groups at the 2 position of the ring system or the incorporation of an electron-withdrawing substituent at the 3 position of the ring system.

Chemistry. The general route to the dihydroimidazolthiazole ring system is shown in Scheme I.[3-5] The

Scheme I



1-haloketones can be formed in situ from the corresponding ketone.[6] As indicated in Scheme I, the 3-hydroxyimidazothiazoles can be prepared by allowing the reaction to take place at room temperature. If the reactants, or the 3-hydroxy compound, are heated in refluxing ethanol, the dihydroimidazothiazole is formed when a hydrogen is present at the 2 position and an alkyl or aromatic substituent is at the 3 position. To form 6,6-dimethylimidazothiazoles, 4,4-dimethyl-2-mercaptoimidazoline[7] was used rather than 2-mercaptoimidazoline.

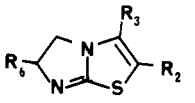
The acetoacetanilides (Table I) were synthesized by reaction of diketene with a substituted aniline or amine in benzene. The benzoylacetanilide 1 was formed by heating trimethylaniline in refluxing ethyl benzoylacetate. The acylacetanilides were chlorinated with sulfuryl chloride, and the resulting 2-chloro compounds were used without further purification.

A methylsulfonyl group was incorporated into the 2 position of the dihydroimidazothiazole ring by halogenation of sulfonylacetophenone derivatives and condensation of the halogenated product with 2-mercaptoimidazoline Scheme II.

As illustrated in Scheme II, the desired 2-(methylsulfonyl)imidazothiazole (27% yield) is not the major product of the reaction. Reduction of the 1-bromo com-

(3) W. Wilson and R. Woodger, *J. Chem. Soc.*, 2943 (1955).
(4) M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).
(5) V. K. Chadha and H. K. Pujari, *Can. J. Chem.*, **47**, 2843 (1969)
(6) V. K. Chadha, H. S. Chaudhary, and H. K. Pujari, *Indian J Chem.*, **8**, 885 (1970).
(7) R. Granger, H. Orzalesi, and Y. Robbe, *Trav. Soc. Pharm Montpellier*, **25**, 305 (1965).

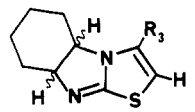
Table III. Dihydroimidazothiazoles



no.	R_2	R_3	R_6	mp, °C	yield, %	solvent[a]	formula	method
15	2',4',6'-$(CH_3)_3$ [b]	CH_3	H	>280	36	1	$C_{16}H_{19}N_3OS\cdot HCl$	I
16	2'-F [b]	CH_3	H	>270	59	2	$C_{13}H_{12}N_2OS\cdot HCl$	I
17	H	c	H	192-195	46	1	$C_{15}H_{16}N_2O_2S\cdot HBr$	I
18	3'-CF_3 [b]	CH_3	H	271-275	86	3	$C_{14}H_{12}F_3N_3OS\cdot HCl$	I
19	2',4',6'-$(CH_3)_3$ [b]	CH_3	CH_3	215-217		5	$C_{17}H_{21}N_3OS$	I
20	2',6'-Cl_2 [b]	CH_3	H	296-298	23	1	$C_{13}H_{11}Cl_2N_3OS\cdot HCl$	I
21	2',4',6'-$(CH_3)_3$ [b]	C_6H_5	H	270-271	40	1	$C_{21}H_{21}N_3OS\cdot HCl$	I
22	d	CH_3	H	253-254	7	1	$C_{13}H_{19}N_3OS\cdot HCl$	I
23	$COOC_2H_5$	CH_3	H	187-188	50	6	$C_9H_{12}N_2O_2S\cdot HCl$	I
24	2',6'-Br_2 [b]	CH_3	H	>280	11	3	$C_{13}H_{11}Br_2N_3OS\cdot HCl$	I
25	H	CH_3	$(CH_3)_2$	220-225	50	1	$C_8H_{12}N_2S\cdot HCl$	G, I
26	H	C_6H_5	$(CH_3)_2$	260-261	64	3	$C_{13}H_{14}N_2S\cdot HBr$	G, I
27	2',4',6'-$(CH_3)_3$ [b]	CH_3	$(CH_3)_2$	242-245	24	1	$C_{18}H_{23}N_3OS\cdot HCl$	G, I
28	CH_3SO_2	C_6H_5	H	183-185	36	5	$C_{12}H_{12}N_2O_2S_2$	J
29	C_6H_5	C_6H_5	H	267-268	50	4	$C_{17}H_{14}N_2S\cdot HBr$	J
30	H	$CH_2SO_2\cdot C_6H_5$	$(CH_3)_2$	>285 dec	80	4	$C_{12}H_{12}N_2O_2S_2\cdot HBr$	G, I
31	H	e	$(CH_3)_2$	>280 dec	70	3	$C_{15}H_{12}N_2O_2S_2\cdot HCl$	G, I
32	H	$CH_2SO_2CH_3$	H	245-250 dec	50	4	$C_7H_{10}N_2O_2S_2\cdot HBr$	I
33	$C_6H_5SO_2$	C_6H_5	H	168-170	47	2	$C_{17}H_{14}N_2O_2S_2$	J

[a] Recrystallization solvents: 1, EtOAc/MeOH; 2, MeOH; 3, EtOH; 4, H_2O; 5, MeOH/H_2O; 6, EtOAc, EtOH. [b] Substituents on $CONHC_6H_5$. [c] R_3 = 4'-$(CH_2COOC_2H_5)C_6H_4$. [d] R_2 = CO-*N*-*cis*-2,5-dimethylpyrrolidine. [e] R_3 = 4'-$CH_3C_6H_4$-SO_2CH_2.

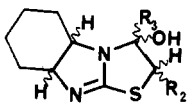
Table IV. Hexahydrothiazolobenzimidazoles



no.	R_3	isomer	mp, °C	yield, %	solvent[a]	formula	method
34	CH_3	trans	216-217	89	1	$C_{10}H_{14}N_2S\cdot HCl$	I
35	CH_3	cis	166-167		1	$C_{10}H_{14}N_2S\cdot HCl$	I
36	$C(CH_3)_3$	trans	247-248		1	$C_{13}H_{21}N_2S\cdot HCl$	I

[a] See Table III, footnote *a*.

Table V. 3-Hydroxyoctahydrothiazolobenzimidazole



no.	R_2	R_3	isomer	mp, °C	yield, %	solvent[a]	formula	method
37	H	CH_3	trans	184-185	80	1	$C_{10}H_{16}N_2OS\cdot HCl$	H-1
38	$(CH_3)_2$	C_6H_5	trans	273-275	30	1	$C_{17}H_{22}N_2OS\cdot HCl$	H-1
39	H	$CO_2C_2H_5$	trans	83-87	94	b	$C_{12}H_{18}N_2O_2S\cdot HBr$	H-3
40	H	CF_3	trans	215-218 dec	65	b	$C_{10}H_{13}F_3N_2OS\cdot HBr$	H-2

[a] See Table III, footnote *a*. [b] Lypholized.

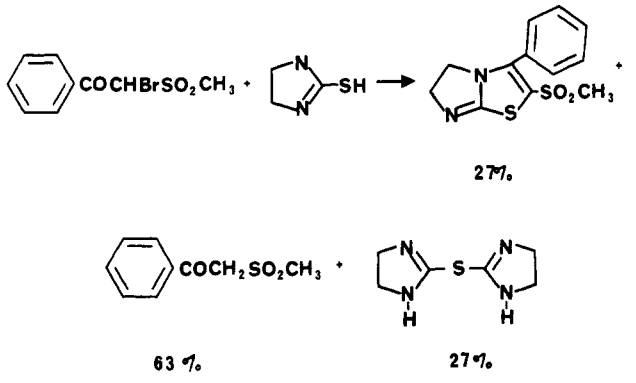
pound to 1-(methylsulfonyl)acetophenone is the predominant reaction. The other reaction product, **2**, has been reported as a decomposition product of 2-mercaptoimidazoline in the environment.[8] It has also been reported to be a product of the reaction of 2-mercaptoimidazoline and 5,5-dibromohydrouracil.[9] The structure of **2** was assigned on the basis of spectral data, primarily the mass spectrum, as well as the elemental analyses of both the base and the monohydrobromide salt. The structure of the 2-(methylsulfonyl)acetophenone was confirmed by X-ray structure analyses (Figure 1).

The reaction of 1-chloro-1-(methylsulfonyl)acetophenone (**6**) with 2-mercaptoimidazothiazole proceeds very slowly. After the mixture is heated at reflux in ethanol for 3 days, the formation of some 1-(methylsulfonyl)acetophenone is indicated by TLC. Likewise, the reaction of 1-bromo-1-(methylsulfonyl)pinacolone (**11**) with 2-mercaptoimidazoline results in reduction to 1-(methylsulfonyl)pinacolone (**13**).

Biological Activity. The antiinflammatory activity and acute toxicity of the compounds is summarized in Table VI. The 2-carboxamide derivatives retain antiinflammatory activity and have lower acute toxicity. The

(8) P. A. Cruickshank and H. C. Jarrow, *J. Agr. Food Chem.*, **21**, 333 (1973).
(9) T. B. Johnson and C. O. Edens, *J. Am. Chem. Soc.*, **63**, 1058 (1941).

Scheme II. Products of the Reaction of 1-(Methylsulfonyl)-1-bromoacetophenone with 2-Mercaptoimidazoline



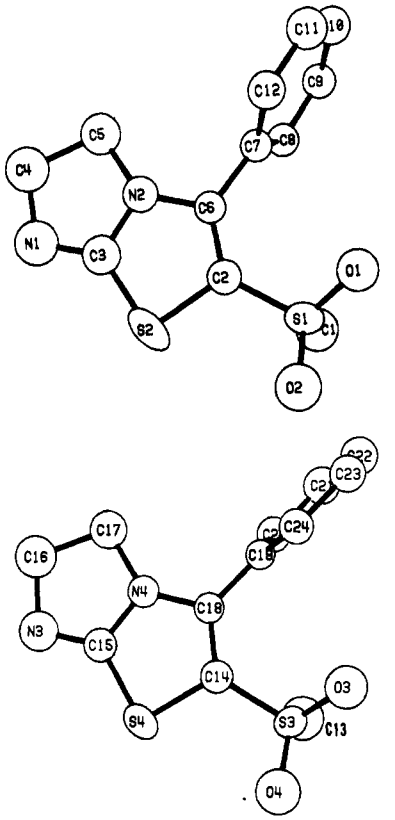


Figure 1. X-ray structure of **28**. The two drawings represent the two conformers present in the crystalline state.

analogues which have the best activity/toxicity ratios, **18** and **19**, still have some acute toxicity at a dose of 300 mg/kg (ip) in mice. Increasing steric bulk at the 6 position of the imidazothiazole ring by incorporation of *gem*-dimethyl substituents (**15**, **26**, and **27**) eliminates antiinflammatory activity. These derivatives do retain the convulsant activity observed in the original imidazothiazoles. The cis and trans isomers of 3-methyltetrahydrothiazolobenzimidazole do not differ significantly in activity/toxicity ratios. It appears that the cis isomer is somewhat less toxic and has less antiinflammatory activity than the trans isomer; however, these differences are not significant.

Three stable 3-hydroxyimidazothiazoles were prepared. One analogue, **38**, is stable due to the presence of a *gem*-dimethyl substituent which prevents dehydration. This compound has a slight antiinflammatory activity and is nontoxic, having a NTD_{50} of greater than 1000 mg/kg. Two 3-hydroxy compounds, **39** and **40**, are stable due to the presence of an electron-withdrawing substituent at the 3 position. These compounds retain some antiinflammatory activity and are relatively nontoxic.

The most favorable separation of toxicity and activity resulted from the incorporation of a methylsulfonyl substitutent at the 2 position of the imdazothiazole ring, **28**. A 2-(phenylsulfonyl) analogue, **33**, is less potent as an antiinflammatory agent.

Three of the compounds were evaluated in the developed adjuvant arthritis assay (Table VII). Compound **28**

Table VI. Antiinflammatory Activity. Carrageenin Model

compd	dose, mg/kg	% reduction	LD_{50}, mg/kg
15	40	11	60
16	75	15	100
17	150	0	180
18	200	36	240
19	200	24	400
20			60
21	50	23	80
22	200	20	240
23	50	2	180
24	30	0	40
25	40	0	60
26	40	0	60
27	40	3	60
28	200	43	>300
	100	30	
	30	26	
	10	33	
	3	15	
29	25	14	40
30	200	5	ND[a]
31	200	6	ND
32	200	11	ND
33	100	15	ND
	30	6	
	10	10	
34	50	100	20
	25	76	
35	50	80	20
	25	57	
	1	15	
36	ND[a]		20
37	50	45	ND
	30	7	
	25	7	
	10	15	
	3	10	
38	200	15	ND
	200	30	
39	200	3	ND
40	200	18	ND
indomethacin	3.0	39	160
	1.0	22	
	0.3	11	

[a] Not determined.

Table VII. Developed Adjuvant Arthritis Assay

compd	dose, mg/kg po	% reduction in edema (LHF) day 21	day 22	day 23
34	30	10	19	18
	10	10	18	19
	3	0	2	2
37	10	3	2	11
28	300	10	19	17
	100	11	26	16
	30	10	15	7
indomethacin	3	17	25	35
	1	21	29	29
	0.3	13	21	19

Table VIII. Phenylquinone Writhing Assay

compd	dose, mg/kg	% analgesia
28	10	10
	30	60
	100	90
indomethacin	0.3	20
	1.0	60
	3.0	70
tolmetin	10	40
	30	60
	100	80
ibuprofen	3	30
	10	50
	30	90
aspirin	30	20
	100	60
	300	90

Table IX. Comparison of Approximate Activity and Safety[a]

	PQW ED_{50}	Carr ED_{50}	UD_{50}	NTD_{50}	LD_{50}
28	~30	~30	>100	690	>1000
indomethacin	1	1	2-6[b]	110	160
tolmetin	22	20	63[b]	>1000	
phenylbutazone	64	50	40-75[b]	690	>300
naproxen	12	3	10[b]	370	>1000
ibuprofen	8	15	60[b]	470	>1000
aspirin	85	70	3-27[b]	200	

[a] PQW, phenylquinone writhing; Carr, carrageenin assay (ED_{50} = dose which gives one-half of average maximal [40%] response); UD, ulcerogenic dose; NTD, neurotoxicity dose; LD, lethal dose (NPP assay). All doses are in milligrams per killograms. [b] Data from A. P. Roszkowski, W. H. Rocks II, A. J. Tomolonis, and L. M. Miller, *J. Pharmacol. Exp. Ther.*, **179**, 114-123 (1971), and G. D. Pasquale and D. Mellace, *Agents Actions*, **7**, 481-485 (1977).

is active in this assay and as an analgetic agent in the phenylquinone writhing assay (Table VIII). As summarized in Table IX, the antiinflammatory/analgetic properties of **28** relative to toxicity compares favorably with the present commercial standards.

Experimental Section

Elemental analyses were performed by the Central Analytical Department of Diamond Shamrock or by Galbraith Laboratories of Knoxville, TN. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Structural assignments are supported where necessary by IR, NMR, and mass spectra. For each synthetic step, the technique involved is illustrated for one specific compound. In the case of unique syntheses, complete experimental details are presented. The sulfonyl ketones used in this project were purchased from Parrish Chemical Co., Provo, UT. 1,2-Diaminocyclohexane was purchased from Pfaltz and Bauer, Inc., Stamford, CT, as a mixture of cis and trans isomers (3:7), which were separated into the pure stereoisomers using the methods of Saito and Kidani.[10]

^1H NMR spectra were obtained with a Brucker WH90 spectrophotometer or a Perkin-Elmer R24B spectrophotometer in $CDCl_3$ using Me_4Si as an internal standard. IR spectra were determined as KBr disks on a Perkin-Elmer Model 297 spectrophotometer. Mass spectra were determined by direct inlet introduction on a Varian/Mat-Ch-7 mass spectrometer with a Varian Data System SS-166. The X-ray analyses of **28** were determined by Molecular Structure Corp., College Station, TX.

The experimental procedures for the neuropharmacological profile–LD_{50} determination[11] and carrageenin-induced edema assay[12] have been described previously.

Method A. Carboxanilides. Diketene Method. 2-Fluoroaniline (22 g, 0.2 mol) was dissolved in C_6H_6. Diketene (17 g, 0.2 mol) was added slowly to the solution. The reaction mixture was allowed to stir at 23 °C for 18 h and then concentrated. The resulting white solid was recrystallized from EtOH to give 12.5 g of **4**.

Method B. Carboxanilides–Acylacetate Method. 2,4,6-Trimethylaniline (13.52 g, 0.1 mol) was heated to boiling and added to a boiling solution of ethyl benzoylacetate (0.1 mol, 19.22 g) after both liquids had been removed from the hot plate. A vigorous reaction took place. The reaction mixture was then returned to the hot plate and boiled for an additional 5 min. The reaction mixture, which solidified on cooling, was recrystallized from EtOH/*i*-PrOH to give **3**: yield 24.8 g; mp 176–177 °C.

Method C. Chlorination of Carboxanilides. Compound **2** (17.5 g, 0.062 mol) was slurried in 250 mL of hot C_6H_6. SO_2Cl_2 (8.4 g, 0.062 mol) was added slowly to the solution. The solution was allowed to cool to 25 °C and stand for 2 h. The resulting precipitate was harvested by filtration and air-dried to give 17 g of 2-chloro-2′,4′,6′-trimethylbenzoylacetanilide, which was used without further purification.

Method D. Bromination of Sulfonyl Ketones. 1-(Methylsulfonyl)acetophenone (60 g, 0.26 mol) was slurried in $CHCl_3$ (500 mL) with $AlCl_3$ (1 g), and Br_2 (15 mL, 0.3 mol) was added dropwise to the stirred reaction mixture. After 3 h at 25 °C, the reaction mixture was purged with argon to remove most of the HBr (NaOH trap). The reaction mixture was washed with H_2O containing $Na_2S_2O_5$ (1 g) and with a saturated solution of NaCl. The organic layer was dried (Na_2SO_4) and the solvent removed. The residue was recrystallized from EtOH/MeCN (800 mL, 7:1) to give 67.9 g (84%) of **15**.

Method E. Chlorination of Sulfonyl Ketones. 1-(Methylsulfonyl)acetophenone (10 g, 0.054 mol), SO_2Cl_2 (5.8 mL), and $AlCl_3$ (0.3 g) were stirred in $CHCl_3$ (125 mL) for 18 h at 25 °C. The solvent was removed and the residue recrystallized from EtOH to give 9.7 g (82%) of **6**.

Method F. Oxidation of Methyl Sulfides. Methylthiopinacolone (Eagle River, 156 g, 1.07 mol) in CH_2Cl_2 was added slowly (12 h) to a slurry of *m*-chloroperbenzoic acid (450 g) in CH_2Cl_2. The reaction mixture was filtered after 27 h and the solvent removed from the filtrate. The residue was dissolved in hexane/CH_2Cl_2 and washed with 5% $NaHCO_3$. The organic layer was dried and the solvent removed to give a residue which recrystallized from MeOH to give **13**.

Method G. 2-Thioimidazolines. *trans*-1,2-Cyclohexanediamine[10] (20 g, 0.18 mol) was stirred in EtOH/H_2O (50 mL, 1:1) at 60 °C and CS_2 (16 mL) was added over a period of 1 h. A solid separated, which dissolved on continued heating. After 1 h, concentrated HCl (1.5 mL) was added and heating continued for 18 h (N_2 atmosphere). The reaction mixture was filtered and the filtrate cooled to 5 °C. The resulting crystalline solid was harvested by filtration, washed with 50% EtOH, and dried to give 19 g (69%) of *trans*-2-thiohexahydrobenzimidazole (**41**), mp 196–197 °C. Anal. ($C_7H_{12}N_2S$) C, H, N, S.

The cis stereoisomer, **42**, was prepared from *cis*-1,2-diaminocyclohexane,[10] mp 165–166 °C. Anal. ($C_7H_{12}N_2S$) C, H, N, S.

Method H. 3-Hydroxyimidazothiazoles. H-1. Compound **41** (2.0 g, 12.8 mmol) and chloroacetone (1.05 mL, 14 mmol) were dissolved in EtOH (40 mL) at 25 °C. After stirring for 18 h the reaction mixture contained a white precipitate. Et_2O (60 mL) was added and the suspension cooled to 5 °C. The solid was separated, dried, and washed with Et_2O to give 2.54 g (80%) of **37**.

H-2. In a 250-mL flask was placed **41** (4.0 g, 0.0256 mol), THF (100 mL), and then 3-bromo-1,1,1-trifluoromethylpropanone (5.5 g, 0.0288 mol) in THF (75 mL) was added dropwise. After 4.5 h at reflux, the reaction mixture was filtered and the precipitate washed with Et_2O. TLC (Quantum Industries silica gel; $CHCl_3$/EtOAc/MeOH, 49:49:2) indicated no starting thiol remained in the reaction product. The precipitate was dried in the drying pistol for 12 h at 80 °C to give **40**.

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H-3. To a 250-mL flask was added **41** (15.63 g, 0.1 mol), ethyl 2-bromopyruvate (19.5 g, 0.1 mol), and EtOH (150 mL). After the mixture was stirred for 3 days, an additional 3.0 g of ethyl 2-bromopyruvate was added. After an additional 18 h, a precipitate had formed. The reaction mixture was concentrated and Et_2O was added. The precipitate was harvested and washed with Et_2O. A subsample of the product was dissolved in water and lypholized to give **39**.

Method I. Dihydroimidazothiazoles. Compound **41** (2.0 g, 12.8 mmol) and chloroacetone (1.05 mL, 14 mmol) were dissolved in EtOH, and the solution was heated to reflux. After 18 h, the reaction mixture was cooled and concentrated to 20 mL. Et_2O (60 mL) was added to give a white precipitate, which was harvested to give 2.3 g of **34**.

Method J. 2-(Methylsulfonyl)dihydroimidazothiazoles. 2-Mercaptoimidazoline (3.5 g, 35 mmol) and **5** (20 g, 72 mmol) were heated in EtOH at reflux for 24 h. The hot reaction mixture was filtered, and the residue (4.7 g) was washed with EtOH and Et_2O. The residue was dissolved in hot H_2O (50 mL), and $NaHCO_3$ was added until the solution was basic. The slurry was cooled in ice, and CH_2Cl_2 was added. After 30 min, the slurry was filtered and the residue was washed with CH_2Cl_2. This residue was recrystallized from H_2O and dried under vacuum at 145 °C to give **2**: mp 220 °C dec (lit.[9] 218–220 °C); mass spectrum, M^+ 170.0 (33%). Anal. ($C_6H_7N_2O_2S$) C, H, N, S. An aliquot (325 mg) of **2** was dissolved in hot water, and the solution was acidified with 50% HBr/H_2O. When the solution cooled, crystals of **2**·HBr separated, which were dried at 145 °C, mp 305 °C. Anal. ($C_6H_7N_2O_2S$·HBr) C, H, N, S, Br.

The CH_2Cl_2 layer from the filtrate was evaporated to give 3.2 g of **28**, which was recrystallized from MeOH.

The EtOH was removed from the reaction mixture filtrate to give a residue (16.2 g). ^1H NMR of this residue indicated it was a mixture of **5** and 1-(methylsulfonyl)acetophenone in a ratio of 1:2.

Developed Adjuvant Arthritis Assay.[13,14] Five male Wistar–Lewis rats weighing about 100 g were used in each group. On day 1, 0.1 mL of a suspension of heat-killed *Mycobacterium tuberculosis* (3.5 mg/mL) was injected into the left hind foot pad of each rat. The rats were then kept in cages, two to three rats per cage, for 20 days; food and water were available ad libitum. On day 20, all animals with "developed" arthritis (swelling of all four paws and secondary involvement of the tail and ears) were used in the study. The test compounds and the standard control were given orally as a solution or suspension in 0.25% methylcellulose (0.005 mL/g of body weight). The animals were administered compounds by gavage on days 20 and 22. The left and right hind paw volumes, body weight, and degree of secondary involvement were recorded daily on days 20 through 23. The decrease or increase in mean volume per group per day was calculated as a percent change from day 20.

Phenylquinone Writhing Assay.[15] A control group of ten male mice was administered 0.25 mL of a fresh solution of 0.02% phenylquinone in aqueous ethanol (95:5) by interperitoneal injection. Writhing occurred in the control group within 3 min and all the mice were writhing within 10 min. The test compound, dissolved or suspended in 0.25% methylcellulose (0.25 mL per mouse), was administered orally to a group of 10 mice. After the designated time interval of a dose group had elapsed, the mice were challenged with 0.25 mL of phenylquinone solution, ip. The percentage of mice protected from writhing was recorded.

Acute Ulcerogenicity.[15] Ten male Sprague–Dawley rats (ca. 160 g each) were fasted for 24 h (water ad libitum) and then given a po dose of the test compound or the vehicle alone. Four hours postdose, the animals were sacrificed (CO_2) and the stomach was removed and cut open along the greater curvature. The stomachs were visually examined by a nonbiased investigator for ulcers, pitting, and/or hemorrhagic spots in the gastric wall. The UD_{50}, the dose producing gastric lesions, ulcers and/or hemorrhage in 50% of the animals tested, was determined by the method of Litchfield and Wilcoxon.[16]

Neurotoxicity. NTD_{50}.[17] The mean neurotoxic dose is the dose of drug administered orally or intraperitoneally to mice that causes minimal recognizable neurotoxocity in 50% of the animals tested as determined by the following five end points.

(1) Positional Sense Test. If the hind leg of a normal mouse is gently lowered over the end of a table, it will quickly be lifted back to a normal position. Neurological deficit is indicated by the inability to rapidly correct the abnormal position of the limb.

(2) Righting Test. If a mouse is placed on its back, it will quickly right itself and assume a normal posture. Neurological deficit is indicated by the inability to rapidly correct for the abnormal body posture.

(3) Gait and Stance Test. Neurological deficit is indicated by a circular or zigzag gait, ataxia, abnormal spread of the legs, abnormal body posture, tremor, hyperactivity, lack of exploratory behavior, somnolence, stupor, catalepsy, etc.

(4) Muscle Tone Test. Normal animals have a certain amount of skeletal muscle tone which is apparent to the observer on handling. Neurological deficit is indicated by a loss of skeletal muscle tone characterized by hypotonia or flaccidity.

(5) Equilibrium Test. If a normal mouse is placed on a narrow edge, such as the rim of a cage, it can maintain its equilibrium and walk along the rim; neurological deficit is indicated by the inability to do so.

Abnormal neurological status disclosed by any one of these five tests was taken as the end point for the NTD_{50} determination. However, if other side effects (hematuria, hyperpnea, etc.) consistently appear at doses lower than those causing neurological deficit, they were taken as the end point.

Supplementary Material Available: Atomic coordinates and thermal parameters (Table X), bond distances (Table XI), and bond angles (Table XII) pertaining to the X-ray structure determination of compound **28** (6 pages). Ordering information is given in any current masthead page.

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