Rotationally Restricted Mimics of Rigid Molecules: Nonspirocyclic Hydantoin Aldose Reductase Inhibitors

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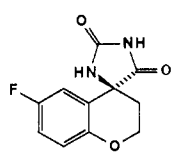
Sorbinil (1), a spirocyclic hydantoin, is a potent inhibitor of the enzyme aldose reductase. Simulation of the rigid spirocyclic ring orientation found in sorbinil was achieved with nonspirocyclic 5-[5′-chloro-2′-(alkylsulfonyl)-phenyl]hydantoins and 5-[5′-chloro-2′-[(*N*-alkylamino)sulfonyl]phenyl]hydantoins. The 2′-substituent (SO_2R) was sufficiently large to hinder rotation of the hydantoin ring, forcing an orientation similar to that of a spirocyclic hydantoin. Calculated conformational preference, X-ray data, and inhibitory IC_{50} values for these nonspirocyclic 2′-substituted (SO_2R) phenylhydantoins are in accord with what is expected for spirocyclic hydantoins and comparable to those of sorbinil.

Sorbinil (1) is a representative example of a class of hydantoin aldose reductase inhibitors[1] where the orientation of the hydantoin ring, relative to the aromatic ring, is fixed by a spiro-ring fusion. Of these spirocyclic hydantoins, sorbinil has proven to be one of the more potent compounds in laboratory models, and it is currently in clinical trials.[2] Structure–activity relationships within the arena of spirocyclic hydantoins have shown that opening of the ring bearing the hydantoin function results in a loss of activity.[1e] This suggests that the orientation of the hydantoin ring relative to the aromatic ring is critical for good activity. Thus, the nonspirocyclic hydantoins **2a** and **2b** are 30–60-fold less potent than 1 as inhibitors of human placental aldose reductase (HPAR). This observed decrease in activity may be attributed to the ability of the hydantoin ring to rotate about the σ bond that joins it to the aromatic ring. This hypothesis prompted us to explore the possibility of simulating the rigid nature of a spirocyclic hydantoin with a nonspirocyclic compound of general structure **3**. If "X" is sufficiently large, then rotation of the hydantoin ring would be hindered,[3] thus forcing it to maintain an alignment similar to that of the spirocyclic hydantoin sorbinil. Computer calculations, syntheses, and biological results for compounds of structure **3**, where "X" is either a sulfone ($X = SO_2R$) or a sulfonamide ($X = SO_2NRR'$), are described below.



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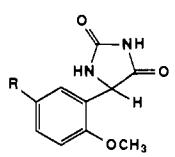
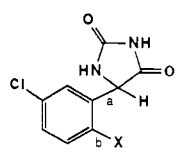


2a R = Cl
2b R = F



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Calculations

Energy calculations on a variety of compounds fitting general structure **3** were performed by using the CAMSEQ program.[4] Minimized structures, obtained from MMP2,[5] were submitted to CAMSEQ, and steric energy levels were determined for rotomers about bonds "a" and "b" in **3**. Thus, the CAMSEQ program yields steric energy values for rotations about two bonds that are depicted as isoenergy contour maps (CMAPS). On the basis of these calculations, sulfones ($X = SO_2R$) and sulfonamides ($X = SO_2NRR'$) were chosen as the substituents that would best hinder rotation of the hydantoin ring. Shown in Figure 1 is the CMAP for the methyl sulfone **4** with contour lines that identify rotational barriers of 1.0, 5.0, 10.0, and 50.0 kcal/mol. Rotation of the hydantoin ring about the C2–C3 bond is represented along the abcissa, while along the ordinate is rotation of the methyl sulfone about the C5–S6 bond. Rotating the hydantoin ring results in the major energy minima lining up when the dihedral angle for H1, C2, C3, and C4 is 180°. This alignment of the hydantoin ring, relative to the aromatic ring, is similar to that seen in spirocyclic hydantoins such as sorbinil. In addition, there is a fairly large energy barrier to overcome for the hydantoin ring to deviate from this alignment by more than ±60°. Rotation of the sulfone moiety gives the expected three minima 120° apart from one another. These minima occur when the hydantoin hydrogen (H1) is bifurcated by the two sulfone oxygens (180°) or by the methyl group along with one of the sulfone oxygens (60° and 300°). The ORTEP illustration of sulfone **4**, depicted in Figure 1, represents the energy minimum shown at the center of the CMAP (180° × 180°).

X-ray crystal structures were obtained on methyl sulfone **4** and the methoxy hydantoin **2b** and are shown in Figure 2. Interestingly, the X-ray structure for compound **2b** shows that the plane of the hydantoin is poised directly over the oxygen of the methoxy group. This represents almost a 180° rotation from that of a spirocyclic hydantoin. Although an X-ray structure is not always indicative of solution dynamics, it is clear that the hydantoin ring of **2b** is free to acquire an orientation that is expected to be suboptimal for binding to aldose reductase. In addition, CAMSEQ calculations predict a rather low rotational energy barrier for rotation of the hydantoin ring through 360° (5–10 kcal/mol; data not shown). We postulate that this rotational freedom may be responsible for the 60-fold decrease in potency relative to that of sorbinil. On the other hand, sulfone **4** crystallized with the hydantoin ring in an alignment similar to that seen with sorbinil and in agreement with what the computer calculations predict.

(1) For recent reviews of aldose reductase inhibitors and the polyol pathway hypothesis, see: (a) Lipinski, C. A.; Hutson, N. J. *Annu. Rep. Med. Chem.* **1984**, *19*, 169. (b) Kador, P. F.; Robison, W. G.; Kinoshita, J. H. *Annu. Rev. Pharmacol. Toxicol.* **1985**, *25*, 691. (c) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. *J. Med. Chem.* **1985**, *28*, 841. (d) Sarges, R. *Trends in Medicinal Chemistry, Proceedings of the 9th International Symposium on Medicinal Chemistry, Berlin, 1986*; Mutschler, E.; Winterfeldt, E., Eds.; VCH: Weinheimn, 1987; pp 551–564. (e) See: Sarges, R.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. *J. Med. Chem.* **1988**, *31*, 230 and references therein.

(2) Sarges, R.; Peterson, M. J. *Metabolism* **1986**, *35* (4 Suppl. 1), 101.

(3) (a) Pettersson, I.; Sandstroem, J. *Acta Chem. Scand., Ser B.* **1984**, *38*, 397. (b) Voegtle, F.; Gruetze, J.; Naetscher, R.; Wieder, W.; Weber, E.; Gruen, R. *Chem. Ber.* **1975**, *108*, 1694.

(4) Weintraub, H. J. R. CAMSEQ/M: A Microprocessor-Based Conformational Analysis System. In *Computer Assisted Drug Design*; Olson, E. C., Christopherson, Eds.; ACS Symposium Series 112, American Chemical Society: Washington, DC, 1979; pp 353–370.

(5) Allinger, N. L.; Yuh, Y. H. QCPE-Program No. 395, 400, MMP2.

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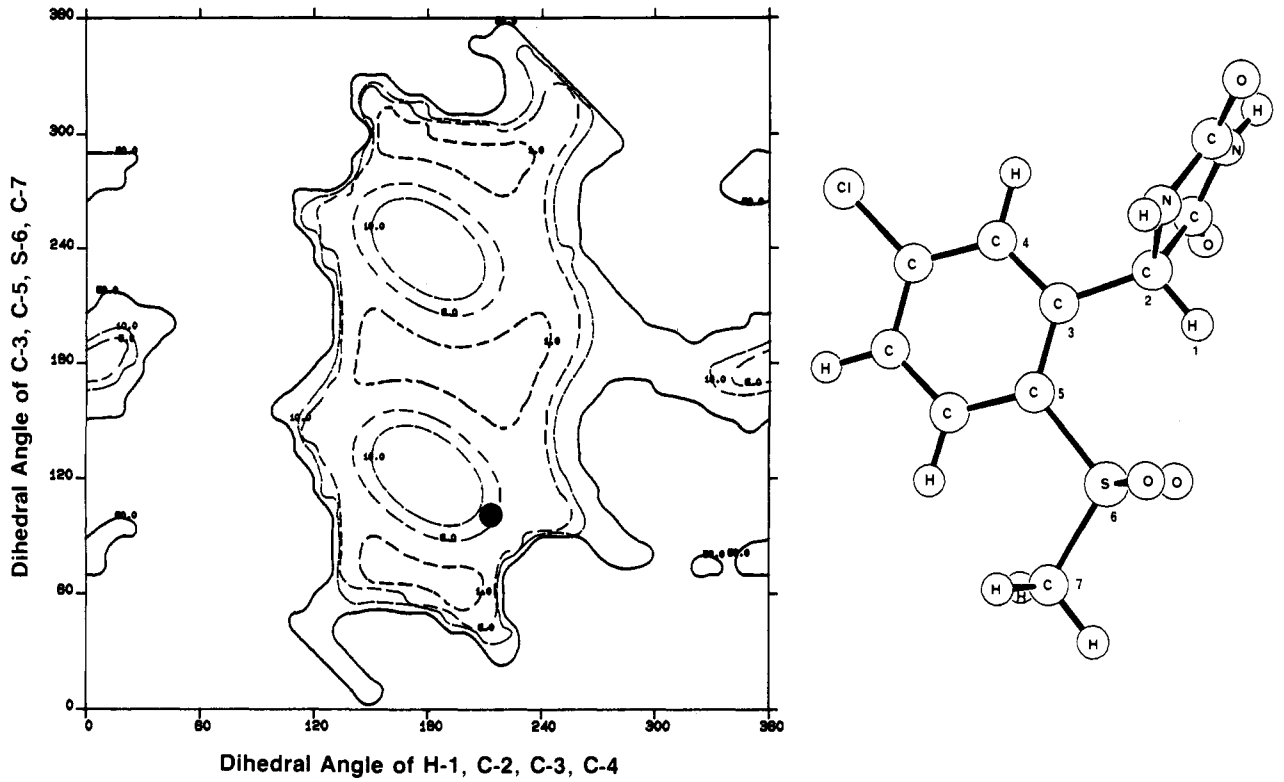
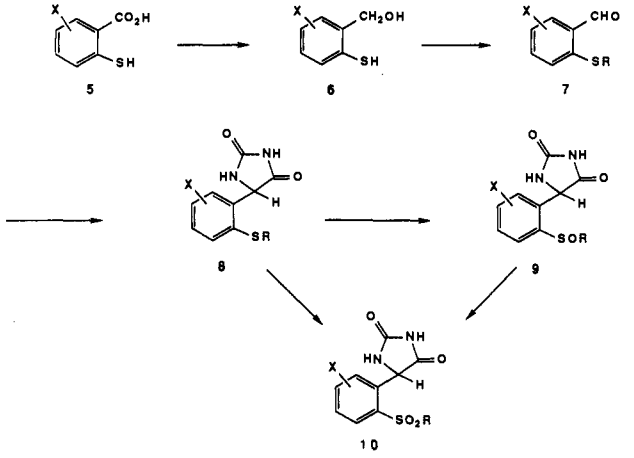


Figure 1. CAMSEQ contour map for compound **4**. The contour lines represent barriers to rotation in kilocalories/mole. The abscissa indicates rotation of the hydantoin ring relative to the phenyl ring. The ordinate indicates rotation of the sulfone moiety relative to the phenyl ring. The dot on the contour locates the conformer found in the X-ray structure of **4**.

Scheme I

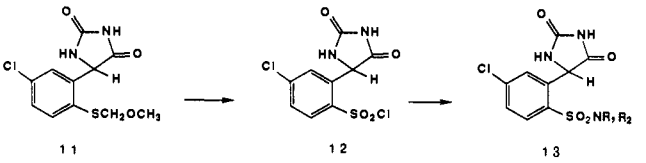


On the basis of the CAMSEQ calculations and the X-ray structure of sulfone **4**, we predicted that phenylhydantoins, with either a sulfone or aminosulfonyl at the ortho position of the aromatic ring, would be inhibitors of the enzyme aldose reductase with potency in vitro similar to that of spirocyclic hydantoins.

Chemistry

The synthetic route used for the preparation of 5-(2′-sulfonylphenyl)hydantoins is outlined in Scheme I. Thiosalicylic acid derivatives **5** were reduced with $LiAlH_4$ to the 2-mercaptobenzyl alcohols **6**. These compounds were alkylated with the desired electrophile (e.g. alkyl halides) and then oxidized by MnO_2 to aldehydes **7**. Hydantoin formation was accomplished by using the standard Bucherer–Bergs reaction.[6] Oxidation of **8** with $KMnO_4$ gave the desired sulfones **10**. Alternatively, **8** could be oxidized with $NaIO_4$ to give the corresponding sulfoxides, which then could be oxidized to the desired sulfones with $KMnO_4$.

Scheme II



The preparation of 5-[2′-(aminosulfonyl)-5′-chlorophenyl]hydantoins is shown in Scheme II. 5-[5′-Chloro-2′-[(methoxymethyl)thio]phenyl]hydantoin (**11**) was prepared by the method described in Scheme I with bromomethyl methyl ether as the electrophile. Treatment of **11** with chlorine gas[7] in aqueous dioxane gave 5-[5′-chloro-2′-(chlorosulfonyl)phenyl]hydantoin (**12**). Reaction of **12** with amines gave the desired aminosulfonyl derivatives **13**.

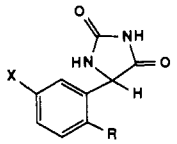
Pharmacology

On the basis of the calculations, nonspirocyclic hydantoins with sulfone moieties at the 2-position were predicted to be good inhibitors of aldose reductase (HPAR), due to hindered rotation of the hydantoin ring. The calculations also suggest that potency should decrease as one proceeds from sulfones to sulfoxides and sulfides because of the progressively lessened steric hindrance at the 2-position. Table I shows these comparisons for the methyl and *p*-chlorobenzyl series. The sulfones **4** and **16** had IC_{50} values of 0.05 and 0.27 μM, respectively. These values are comparable to that of sorbinil, a structurally ridged spirocyclic hydantoin with an IC_{50} of 0.12 μM. The sulfide derivatives **15** and **18** exhibited IC_{50} values 4–10 times greater than

(6) Bucherer, H. T.; Fischbeck, H. T. *J. Prakt. Chem.* **1934**, *140*, 69. Bergs, H. Ger. Pat. 566,094, 1929.

(7) Langler, R. F.; Marini, Z. A.; Spalding, E. S. *Can. J. Chem.* **1979**, *57*, 3193.

Table I



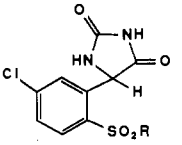
no.	X	R	IC_{50},[a] μM
4	Cl	SO_2CH_3	0.05 ± 0.002
14	Cl	$SOCH_3$	0.25 ± 0.01
15	Cl	SCH_3	0.62 ± 0.01
16	Cl	$SO_2CH_2(4\text{-}ClC_6H_4)$	0.27 ± 0.01
17	Cl	$SOCH_2(4\text{-}ClC_6H_4)$	0.47 ± 0.01
18	Cl	$SCH_2(4\text{-}ClC_6H_4)$	1.20 ± 0.10
2a	Cl	OCH_3	3.87 ± 0.06
2b	F	OCH_3	7.47 ± 0.15
1 (sorbinil)			0.12 ± 0.01

[a] Concentration that causes a 50% inhibition of human placental aldose reductase with glyceraldehyde as substrate. IC_{50} was determined by a least square fit of the linear portion of the dose response curve (n = 3).

that of their corresponding sulfones. The sulfoxides **14** and **17** were intermediate in potency. Thus a relationship exists between inhibitory potency and the bulk of the substituent at the 2-position, implying that the sulfone moiety at the 2-position is sufficiently large to hinder rotation of the hydantoin ring and fix it in an orientation similar to that of a spirocyclic hydantoin.

Table II summarizes the biological results for a series of sulfones and sulfonamides. Optimal inhibition of HPAR within the sulfone series was obtained with methyl derivative **4** and pentyl derivative **21**. Benzyl derivative **32** was the best of the sulfonamides at inhibiting aldose reductase. Although having an aromatic ring in the side chain results in the most active analogue, the exact placement of the aromatic ring on the side chain appears to be critical. Comparing compounds **31** to **35** demonstrates the importance of where the aromatic ring is positioned. In the sulfone series, branching at the position α to the sulfur atom, as with isopropyl derivative **23**, results in a modest 2-fold increase in the IC_{50} value as compared to its corresponding unsubstituted analogue **19**. However, the sulfonamide series is much more sensitive to substitution α to sulfur, resulting in greater than a 30-fold increase in IC_{50} values as one goes from N-methyl sulfonamide **26** to N,N-dimethyl sulfonamide **27**. Substitution on the aromatic ring and its effect on activity is shown in Table III for a series of methyl sulfones. The 5-fluoro derivative **36** is 10 times less effective at inhibiting aldose reductase than the corresponding chloro derivative **4**. This is in contrast to that of the methoxy series, where the 5-fluoro derivative **2a** is actually more potent than the

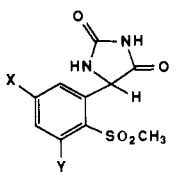
Table II



no.	R	mp, °C	isolation[a]	yield,[b] %	formula[c]	IC_{50},[e] μM
19	CH_2CH_3	218–219	iP	44 (10)	$C_{11}H_{11}N_2O_4SCl$	0.18 ± 0.02
20	$CH_2CH_2CH_3$	188–189	iP	23 (10)	$C_{12}H_{13}N_2O_4SCl$	0.25 ± 0.02
21	$(CH_2)_4CH_3$	160–161	*	15 (29)	$C_{14}H_{17}N_2O_4SCl$	0.05 ± 0.002
22	$(CH_2)_5CH_3$	188–189	*	25 (88)	$C_{15}H_{19}N_2O_4SCl$	0.23 ± 0.01
23	$CH(CH_3)_2$	221–222	iP	55 (6)	$C_{12}H_{13}N_2O_4SCl$	0.38 ± 0.04
24	$CH_2CH_2(4\text{-}ClC_6H_4)$	229–231	H_2O	78 (52)	$C_{17}H_{14}N_2O_4SCl\cdot{}^1/_4H_2O$	0.22[e]
25	NH_2	227–228	*	54	$C_9H_8N_3O_4SCl$	0.15 ± 0.006
26	$NHCH_3$	205–207	E-H	72	$C_{10}H_{10}N_3O_4SCl$	0.13 ± 0.01
27	$N(CH_3)_2$	239–241	E-H	80	$C_{11}H_{12}N_3O_4SCl$	4.47 ± 0.21
28	$NH(CH_2)_2CH_3$	162–163	E	65	$C_{12}H_{14}N_3O_4SCl$	0.58 ± 0.06
29	$NH(CH_2)_3CH_3$	169–171	E	65	$C_{13}H_{16}N_3O_4SCl$	0.70 ± 0.04
30	$NH(CH_2)_4CH_3$	146–148	E	48	$C_{14}H_{18}N_3O_4SCl$	0.19 ± 0.02
31	$NHpC_6H_4F$	244–245	C	57	$C_{15}H_{11}N_3O_4SClF$	0.23 ± 0.01
32	$NHCH_2C_6H_5$	122–124	*	19	$C_{16}H_{14}N_3O_4SCl$	0.03 ± 0.004
33	$NH(CH_2)_2C_6H_5$	177–178	*	27	$C_{17}H_{16}N_3O_4SCl$	1.26 ± 0.43
34	$NH(CH_2)_3C_6H_5$	145–147	*	64	$C_{18}H_{18}N_3O_4SCl$	0.10 ± 0.08
35	$NH(CH_2)_4C_6H_5$	151–153	E	40	$C_{19}H_{20}N_3O_4SCl$	5.63 ± 0.91

[a] iP = isopropyl ether; E = ether; H = hexane; C = chloroform; * = chromatograph on silica gel with 1:1 ether/hexane. [b] For **19–24** the yield is for oxidation of sulfide to sulfone and (yield) is for the preparation of the corresponding 2-(alkylthio)hydantoin. [c] All new compounds were analyzed for C, H, N. [d] See footnote *a* in Table I. [e] Single point determination (IC_{50} for sorbinil was 0.50 μM).

Table III



no.	X	Y	mp, °C	isolation[a]	yield,[b] %	formula[c]	IC_{50},[d] μM
36	F	H	222–224	iP	61 (19)	$C_{10}H_9N_2O_4SF$	0.61 ± 0.10
37	Cl	CH_3	258–259	E	70 (20)	$C_{11}H_{11}N_2O_4SCl$	0.27 ± 0.03
38	Cl	CF_3	231–233	iP	50 (14)	$C_{11}H_8N_2O_4SClF_3$	0.58 ± 0.02
39	Cl	Cl	225–227	E	90 (10)	$C_{10}H_8N_2O_4SCl_2$	0.61 ± 0.04

[a] iP = isopropyl ether; E = ether; H = hexane. [b] For **36–39** the yield is for oxidation of sulfide to sulfone and (yield) is for the preparation of the corresponding 2-(alkylthio)hydantoin. [c] All new compounds were analyzed for C, H, N. [d] See footnote *a* in Table I.

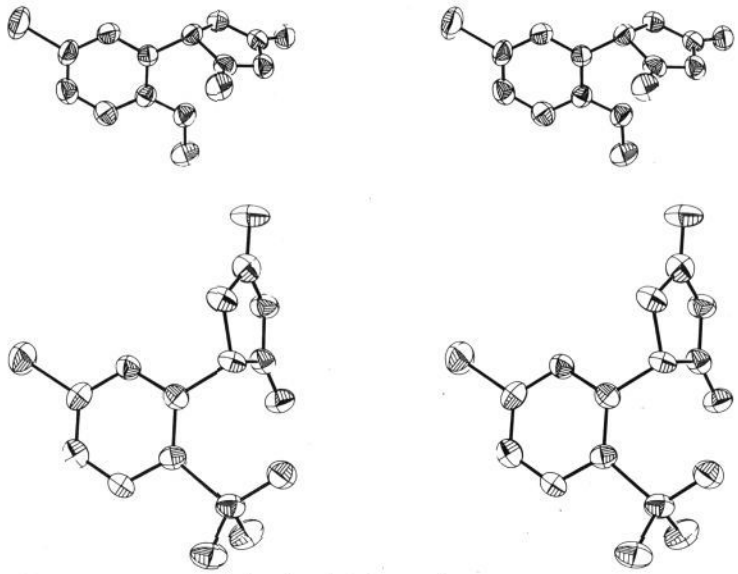


Figure 2. Stereoview of the X-ray structure for **2b** (top) and **4** (bottom).

5-chloro derivative **2b** (Table I). Addition of a methyl group at the 3-position (**37**) caused a 5-fold increase in the IC_{50} value, whereas addition of a strong electron withdrawing group as in **38** and **39** results in a 10-fold increase in the IC_{50} value relative to that for **4**.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by the Pfizer Central Research Microanalysis laboratory, and results obtained for specified elements are within ±0.4% of the theoretical values unless otherwise denoted. IR spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer using the stipulated solvents and are reported in reciprocal centimeters. ^1H NMR spectra of $CDCl_3$ or $(CD_3)_2SO$ solutions [$(CH_3)_4Si$, δ 0] were recorded on a Brucker 250-MHz instrument. Low-resolution mass spectral data were recorded on an Hitachi RMU6-E spectrometer. Inhibitory IC_{50} values were determined from concentrations of 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} by using the method of Sarges and Peterson with human placental aldose reductase.[2]

5-[5′-Chloro-2′-(methylthio)phenyl]imidazolidine-2,4-dione (15). A solution of 5-chloro-2-mercaptobenzoic acid[9] (40.0 g, 0.21 mol) in dry tetrahydrofuran (250 mL) was added dropwise to a slurry of lithium aluminum hydride (10.0 g, 0.26 mol) in dry tetrahydrofuran (50 mL) at 0 °C. Following completion of addition, the reaction mixture was warmed and held at room temperature for 3 h. It was cooled to 0 °C and ethyl acetate (40 mL) was added to quench excess lithium aluminum hydride. The quenched reaction was stirred for 30 min and then cautiously treated with water (10 mL), followed by 1 N sodium hydroxide (40 mL). The aluminum salts that precipitated were removed by filtration and dissolved in 10% hydrochloric acid, and the solution was extracted with ethyl acetate. The extract was combined with the filtrate (from the aluminum filtration) and washed successively with 10% hydrogen chloride, water, and brine. It was dried ($MgSO_4$) and evaporated under reduced pressure to give 35.0 g of 4-chloro-2-[(hydroxymethyl)thio]phenol as an oily solid.

Sodium methoxide (11.5 g, 0.21 mol) was added to a solution of 4-chloro-2-[(hydroxymethyl)thio]phenol (35.0 g, 0.20 mol) in *N,N*-dimethylformamide (300 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and then iodomethane (15 mL, 0.24 mol) was added. The mixture was stirred an additional 30 min and then poured into water (500 mL). The product was extracted into ether and washed successively with water and brine and then dried ($MgSO_4$) and evaporated under reduced pressure to give 5-chloro-2-(methylthio)benzyl alcohol.

The latter compound was dissolved in methylene chloride (600 mL) and was treated with manganese dioxide (250 g) at room temperature for 6 h. The reaction mixture was filtered and evaporated under reduced pressure to give 33.0 g of 5-chloro-2-(methylthio)benzaldehyde as an oily solid.

The oily solid (33.0 g, 0.18 mol), potassium cyanide (23.0 g, 0.36 mol), ammonium carbonate (68.0 g, 0.71 mol), and 20% aqueous ethanol (1200 mL) was heated at 60 °C for 24 h. It was then cooled and carefully poured into 10% hydrogen chloride (1000 mL) (**Caution**: **HCN**) and the product was extracted into ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a partially solidified oil. Trituration of this residue with ether afforded 27.5 g (50% overall yield) of the title compound as an off-white solid: mp 183–185 °C; MS *m/e* 256 (M^+), 209 (100). Anal. ($C_{10}H_9N_2O_2SCl$) C, H, N.

5-[5′-Chloro-2′-[(methoxymethyl)thio]phenyl]imidazolidine-2,4-dione (11): prepared as described for **15**; 25% overall yield from 5-chloro-2-mercaptobenzoic acid: mp 159–161 °C. Anal. ($C_{11}H_{11}N_2O_3SCl$) C, H, N.

5-[5′-Chloro-2′-[(*p*-chlorobenzyl)thio]phenyl]imidazolidine-2,4-dione (18): prepared as described for **15**; 37% overall yield from 5-chloro-2-mercaptobenzoic acid: mp 139–140 °C. Anal. ($C_{16}H_{12}N_2O_2SCl_2$) C, H, N.

5-[5′-Chloro-2′-(methylsulfinyl)phenyl]imidazolidine-2,4-dione (14). 15 (1.0 g, 3.9 mmol) in ethanol (50 mL) and water (8 mL) was treated with sodium periodate (1.7 g, 7.8 mmol) at room temperature for 16 h. The mixture was poured into water (50 mL) and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated at reduced pressure to give 0.4 g (37% yield) of a white solid comprising a mixture of diastereomeric sulfoxides: mp 165–170 °C; IR (KBr) 1012 cm^{-1} (S=O); high-resolution MS calculated for $C_{10}H_9N_2SO_3{}^{35}Cl$ 272.0022, found 272.0006.

5-[5′-Chloro-2′-[(*p*-chlorobenzyl)sulfinyl]phenyl]imidazolidine-2,4-dione (17): prepared as described for **14**; 91% yield: mp 165–170 °C.

5-[5′-Chloro-2′-(methylsulfonyl)phenyl]imidazolidine-2,4-dione (4). Potassium permanganate (11.0 g, 0.07 mol) in water (10 mL) was added to a slurry of **15** (9.0 g, 0.035 mol) in glacial acetic acid (100 mL) at 0 °C. The reaction mixture was stired at 0 °C for 30 min and then poured into 500 mL of a 10% solution of sodium bisulfite in water. The product was extracted into ethyl acetate. The organic extract was washed with water and brine, then dried ($MgSO_4$), and evaporated under reduced pressure. The white solid residue was triturated with ether, filtered, and air-dried to give 8.5 g (84%) of the title compound: mp 238–240 °C; MS

(8) Kador, P. F.; Goosey, J. D.; Sharpless, N. E. *Eur. J. Med. Chem.* **1981**, *16*, 293.
(9) Katz, L.; Karger, L. S.; Schroeder, W.; Cohen, M. S. *J. Org. Chem.* **1953**, *18*, 1380.

Table IV. Crystal Data for **2b** and **4**

	2b	4
	A. Crystal Parameters	
formula	$C_{10}H_9N_2O_3Cl$ (240.6)	$C_{10}H_9N_2O_4SCl$ (288.7)
crystallization medium	95% ethanol	methanol
crystal size, mm	0.12 × 0.15 × 0.19	0.11 × 0.13 × 0.14
cell dimensions	a = 7.792 (2) Å	a = 13.08 (1) Å
	b = 12.122 (4) Å	b = 5.045 (5) Å
	c = 12.003 (4) Å	c = 18.04 (1) Å
	α = 90.0°	α = 90.0°
	β = 103.56 (2)°	β = 98.88 (5)°
	γ = 90.0°	γ = 90.0°
	V = 1102.1 (6) Å^3	V = 1176.16 (1) Å^3
space group	$P2_1/c$	$P2_1/c$
molecules/unit cell	4	4
density obsd, g/cm^3	1.44	1.59
density calcd, g/cm^3	1.45	1.63
linear absorption coeff, cm^{-1}	30.80	46.62
	B. Refinement Parameters	
no. of reflections	1131	1190
nonzero reflections ($I > 3.0\sigma$)	935	953
R index = $\sum\|\|F_o\| - \|F_c\|\|/\sum\|F_o\|$	0.052	0.52
GOF = $[\sum w(F_o^2 - F_c^2)^2/(m-s)]^{1/2}$	1.77	1.42
scale factor	1.602 (6)	1.511 (4)
secondary extinction coeff	4 (1) × 10^{-3}	39 (8) × 10^{-4}

m/e 288 (M^+), 209 (100); 250-MHz NMR (DMSO-d_6) δ 11.10 (br s, 1 H), 8.30 (s, 1 H), 8.04 (d, J = 9, 1 H), 7.75 (d, J = 9, 1 H), 7.56 (s, 1 H), 6.28 (s, 1 H), 3.42 (s, 3 H). Anal. ($C_{10}H_9N_2O_4SCl$) C, H, N.

5-[5′-Chloro-2′-[(*p*-chlorobenzyl)sulfonyl]phenyl]-imidazolidine-2,4-dione (16): prepared as described for **4**; 15% yield: mp 165–167 °C. Anal. ($C_{16}H_{12}N_2O_4SCl_2 \cdot {}^1/_2$ether) C, H, N.

Compounds 19–24 in Table II. 5-[5′-Chloro-2′-(alkylthio)-phenyl]imidazolidine-2,4-diones were prepared as in **15** with substitution of iodomethane with the appropriate alkyl halide. The corresponding sulfones were prepared as in **4**. Yields are reported in Table II.

Compounds 36–39 in Table III. Substituted [2′-(methylthio)phenyl]imidazolidine-2,4-diones were prepared as in **15** with the appropriate mercaptobenzoic acid as the starting material. The corresponding sulfones were prepared as in **4**. Yields are reported in Table III.

5-[5′-Chloro-2′-(chlorosulfonyl)phenyl]imidazolidine-2,4-dione (12). A solution of **11** (3.5 g, 0.012 mol) in dioxane (175 mL) and water (50 mL) was cooled to 0 °C and perfused with chlorine gas until a yellow color persisted. After 15 min the mixture was poured into 200 mL of ice-cold 10% aqueous sodium bisulfite solution and the product was extracted into ethyl acetate. The organic extract was washed with water and brine, then dried ($MgSO_4$), and evaporated under reduced pressure to give a white solid. Trituration of the solid in ether/hexane (1:1) followed by filtration gave 2.8 g (74% yield) of the title compound, which was used without purification: mp 211–212 °C; 250-MHz NMR (DMSO-d_6) δ 10.92 (br s), 8.00 (br s, 1 H), 7.80 (d, 1 H, J = 8 Hz), 7.43 (d, 1 H, J = 8 Hz), 7.12 (s, 1 H), 6.20 (s, 1 H).

5-[5′-Chloro-2′-(aminosulfonyl)phenyl]imidazolidine-2,4-dione (25). Ammonia gas was passed into a slurry of **12** (5.0 g, 0.016 mol) in methylene chloride (100 mL) at 0 °C until the mixture became homogeneous and yellow in color. Stirring at 0 °C was continued for 1 h after which the reaction mixture was poured into 10% hydrogen chloride (200 mL) and the product was extracted into ethyl acetate. The organic extract was washed successively with water, 10% hydrogen chloride, water, and brine, then dried ($MgSO_4$), and evaporated under reduced pressure. Trituration of the residue with ethyl acetate gave 2.7 g (59%) of a white solid: mp 239–240 °C; 250-MHz NMR (DMSO-d_6) δ 11.08 (br s, 1 H), 8.44 (s, 1 H), 7.97 (d, 1 H, J = 8 Hz), 7.69 (d, 1 H, J = 8 Hz), 7.63 (br s, 2 H), 7.46 (s, 1 H), 6.13 (s, 1 H). Anal. ($C_9H_8N_3O_4SCl$) C, H, N.

Compounds 26–35 in Table II: prepared as described for **25** with substitution for ammonia by the appropriate amine. Yields are reported in Table II.

5-(5′-Chloro-2′-methoxyphenyl)imidazolidine-2,4-dione (2a): 5-Chloro-2-methoxybenzaldehyde (2.30 g, 0.014 mol), potassium cyanide (1.76 g, 0.027 mol), and ammonium carbonate (5.18 g, 0.054 mol) were dissolved in 110 mL of ethanol and heated at 60 °C for 18 h. The reaction mixture was concentrated to 30 mL, acidified with 1 N HCl, and filtered. The pale yellow crystals thus obtained were recrystallized from 95% aqueous ethanol: 2.03 g (63%), mp 207–209 °C; IR (KBr) 1770 (ms), 1721 (s), 1699 (s) cm^{-1}. Anal. ($C_{10}H_9ClN_2O_3$) C, H, N.

5-(5′-Fluoro-2′-methoxyphenyl)imidazolidine-2,4-dione (2b): prepared as described for **2a** from 5-fluoro-2-methoxybenzaldehyde in 65% yield: mp 216–218 °C. Anal. ($C_{10}H_9FN_2O_3$), C, H, N.

Single-Crystal X-ray Analysis. A representative crystal was surveyed and a 1-Å data set was collected on a Nicolet R3m/μ diffractometer. The diffractometer was equipped with a graphite monochromator and copper radiation (λ = 1.541 78 Å). Atomic scattering factors were taken from the *International Tables for X-ray Crystallography*.[10] All crystallographic calculations were facilitated by the SHELXTL (G. M. Sheldrick, 1981) system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table IV.

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl and amide hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least-squares refinement were all less than 0.1 of their corresponding standard deviations. The final R index was 0.052. A final difference Fourier revealed no missing or misplaced electron density. Heavy atoms for **2b** and **4** are depicted in Figure 2. Coordinates for hydrogen atoms are available as supplementary material.

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Registry No. **2a**, 120121-09-7; **2b**, 120121-08-6; **3** (X = SEt), 120121-39-3; **3** (X = $SCH_2CH_2CH_3$), 120121-40-6; **3** (X = $S(CH_2)_4CH_3$), 120121-41-7; **3** (X = $S(CH_2)_5CH_3$), 120121-42-8; **3** (X = $SCH(CH_3)_2$), 120121-43-9; **3** (X = $SCH_2CH_2(4\text{-}ClC_6H_4)$), 120121-44-0; **4**, 120121-10-0; **11**, 120121-11-1; **12**, 120121-12-2; **14**, 92539-55-4; **15**, 120121-13-3; **16**, 120121-14-4; **17**, 91827-59-7; **18**, 120121-15-5; **19**, 120121-16-6; **20**, 120121-17-7; **21**, 120121-18-8; **22**, 120121-19-9; **23**, 120121-20-2; **24**, 120121-21-3; **25**, 120121-22-4; **26**, 120121-23-5; **27**, 120121-24-6; **28**, 120121-25-7; **29**, 120121-26-8; **30**, 120121-27-9; **31**, 120121-28-0; **32**, 120121-29-1; **33**, 120121-30-4; **34**, 120121-31-5; **35**, 120121-32-6; **36**, 120121-33-7; **37**, 120121-34-8; **38**, 120121-35-9; **39**, 120121-36-0; NH_2CH_3, 74-89-5; $NH(CH_3)_2$, 124-40-3; $NH_2(CH_2)_2CH_3$, 107-10-8; $NH_2(CH_2)_3CH_3$, 109-73-9; $NH_2(CH_2)_4CH_3$, 110-58-7; *p*-$NH_2C_6H_4F$, 371-40-4; $NH_2CH_2C_6H_5$, 100-46-9; $NH_2(CH_2)_2C_6H_5$, 64-04-0; $NH_2(CH_2)_3C_6H_5$, 2038-57-5; $NH_2(CH_2)_4C_6H_5$, 13214-66-9; aldose reductase, 9028-31-3; 5-chloro-2-mercaptobenzoic acid, 20324-50-9; 4-chloro-2-[(hydroxymethyl)thio]phenol, 120121-37-1; 5-chloro-2-(methylthio)benzyl alcohol, 120121-38-2; 5-chloro-2-(methylthio)benzaldehyde, 91827-45-1; 5-chloro-2-methoxybenzaldehyde, 7035-09-8; 5-fluoro-2-methoxybenzaldehyde, 19415-51-1; 5-fluoro-2-mercaptobenzoic acid, 120121-07-5; 5-chloro-3-methyl-2-mercaptobenzoic acid, 120121-45-1; 5-chloro-3-(trifluoromethyl)-2-mercaptobenzoic acid, 120121-46-2; 3,5-dichloro-2-mercaptobenzoic acid, 57446-10-3; 5-[5-fluoro-2-(methylthio)-phenyl]imidazolidine-2,4-dione, 120144-45-8; 5-[5-chloro-3-

(10) *International Tables for X-Ray Crystallography*; Ibers, J. A., Hamilton, W. C., Eds.; Kynoch: Birmingham, England, 1974; Vol. IV.

methyl-2-(methylthio)phenyl]imidazolidine-2,4-dione, 120121-47-3; 5-[5-chloro-2-(methylthio)-3-(trifluoromethyl)phenyl]-imidazolidine-2,4-dione, 120121-48-4; 5-[3,5-dichloro-2-(methylthio)phenyl]imidazolidine-2,4-dione, 120121-49-5.

Supplementary Material Available: Coordinates, anistropic temperature factors, distances, and angles for compound **2b** and **4** (8 pages). Ordering information is given on any current masthead page.

Thienylpyrazoloquinolines with High Affinity to Benzodiazepine Receptors: Continuous Shift from Inverse Agonist to Agonist Properties Depending on the Size of the Alkyl Substituent

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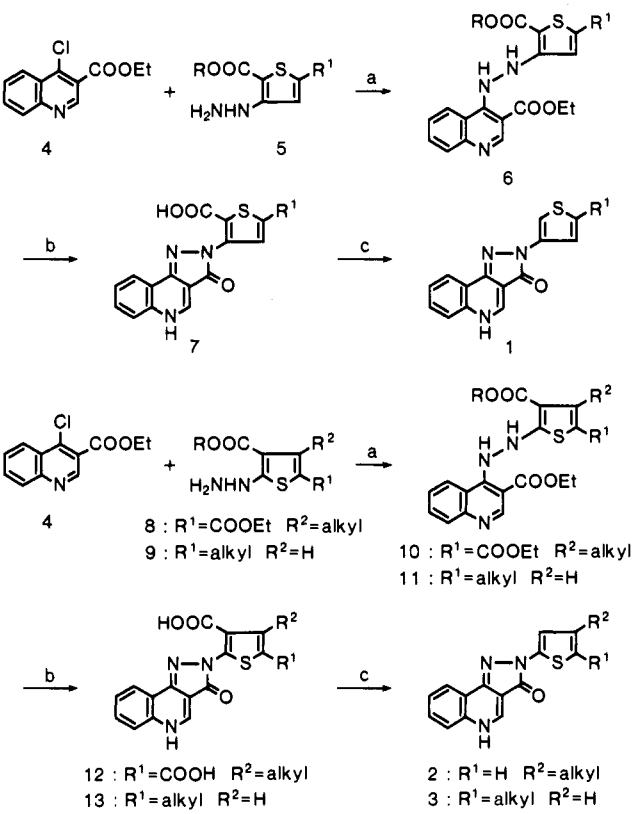
2-(5-Alkylthien-3-yl)- (**1**), 2-(4-alkylthien-2-yl)- (**2**), and 2-(5-alkylthien-2-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolines (**3**) were prepared in four steps starting from ethyl 4-chloroquinoline-3-carboxylate (**4**) and hydrazinothiophenecarboxylates **5**, **8**, and **9**. All the assayed compounds possessed high affinities for benzodiazepine receptors (K_i = 0.3–2.6 nM). The activities of agonists and inverse agonists were assessed on the basis of inhibition or facilitation of pentylenetetrazole-induced convulsions, respectively. Introduction of alkyl groups of different sizes into the unsubstituted inverse agonistic compounds results in a corresponding shift in the activity from an inverse agonist to an antagonist to an agonist. The susceptibility of such a shift increases in the order of **1** < **2** < **3**. This tendency may be explained by slight differences in the geometry of the alkyl substituents among the three series.

A recent study[1] using the gene-cloning technique has found that the GABA/benzodiazepine receptor[2] has a membrane-spanning ion channel similar to that of the nicotinic acetylcholine receptor, and the binding sites for GABA and benzodiazepines (BZ) have been proposed to be located in the N-terminal extracellular domains. Although the exact structural features of the binding sites remain obscure, it is more likely that the BZ receptor ligand allosterically influences the GABA binding site which is presumably located close to the BZ binding site.

The BZ receptor ligands are thought to comprise a continuous spectrum of agents with a graduated range of pharmacological efficacies at the receptor:[3] (1) full inverse agonists (negative efficacy; anxiogenic/convulsant), (2) partial inverse agonists (intermediate negative efficacy; proconvulsant), (3) pure antagonists (nil efficacy; antagonism toward the other classes), (4) partial agonists, and (5) full agonists (positive efficacy; anxiolytic/anticonvulsant). The inverse agonist β-CCM enhances the performance in several animal models of learning and memory,[4] whereas the agonist diazepam impairs such performance in humans,[5] suggesting that partial inverse agonists lacking anxiogenic or convulsant effects may provide a new type of nootropic drugs. Some series of the BZ receptor ligands have been described[3,6] in which slight structural modifications can produce a change in the activity from an inverse agonist to an antagonist or to an agonist. Also, several papers[7] have reported the structural requirements for the agonists, antagonists, and inverse agonists from comparisons of various ligands belonging to chemically different classes, but no definite conclusion has been reached.

We have previously described[8] the structure–activity relationships of thienylpyrazoloquinolines, in which **1b** (S-135[9]) with a 5-methylthien-3-yl group possessed potent inverse agonistic activity, while its isomer **3b** with a 5-methylthien-2-yl group had agonist activity. The 4-methylthien-2-yl isomer **2b** exhibited weak inverse agonist properties. Moreover, the coplanarity of the thiophene ring with the pyrazoloquinoline skeleton was found to be necessary for high-affinity binding to the BZ receptors. Assuming that the thiophene ring is a regular pentagon, the

Scheme I[a]



[a] (a) EtOH/room temperature. (b) 1 N aqueous NaOH/EtOH/room temperature, then reflux. (c) Cu/quinoline/190–200 °C.

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