method A to yield **3d** (95.4 g, 81.9%): mp 105–108 °C; ^{1}H NMR ($CDCl_3$) δ 2.5 (s, 3 H), 2.65 (s, 6 H), 3.6 (s, 6 H), 7.35 (d, J = 3 Hz, 1 H), 8.0 (d, J = 3 Hz, 1 H), 8.2 (dd, J = 7 and 3 Hz, 1 H) ppm. Anal. ($C_{18}H_{18}N_2O_6S$) C, H, N.

(Q) Dimethyl 2,6-Dimethyl-4-[2-(methylsulfinyl)-5-nitrophenyl]pyridine-3,5-dicarboxylate (4d). **3d** (59 g, 0.15 mol) was dissolved in 500 mL of CH_2Cl_2, mixed portionwise with 3-chloroperbenzoic acid (26 g, 0.15 mmol) at room temperature, and stirred overnight. After workup (method A) **4d** was obtained (56 g, 91%): mp 120–121 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 2.7 (s, 6 H), 3.6 (s, 3 H), 3.7 (s, 3 H), 8.0–8.1 (m, 1 H), 8.3–8.5 (m, 2 H) ppm. Anal. ($C_{18}H_{18}N_2O_7S$) C, H, N, O.

(R) [2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine]-4-spiro-3′-(5′-nitro-2′,3′-dihydro-1′-benzothiophene 1′-oxide) (5d). **4d** (54.7 g, 0.135 mol) was reacted as per method C. Crystallization with ethyl acetate yielded **5d** (17.7 g, 32.3%): mp 257–259 °C; ^{1}H NMR ($CDCl_3$)/CD_3OD) δ 2.2 (s, 3 H), 2.3 (s, 3 H), 3.3 (s, 3 H), 3.4 (s, 3 H), 3.5 (d, J = 13 Hz, 1 H), 4.3 (d, J = 13 Hz, 1 H), 7.7–8.4 (m, 3 H) ppm; MS 406 (M^+, 15), 358 (15), 329 (100), 313 (40), 299 (95), 283 (25). Anal. ($C_{18}H_{18}N_2O_7S$) C, H, N.

(S) Dimethyl 4-(3-Nitrophenyl)-2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6d) and Dimethyl 4-(4-Nitrophenyl)-2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6e). **6a** (6.3 g, 20 mmol) was dissolved in 50 mL of concentrated sulfuric acid at room temperature and mixed portionwise with KNO_3 (2.4 g, 24 mmol) at 0 °C. After 15 min at room temperature, the solution was poured onto ice and filtered by suction and the mixture of **6d** and **6e** separated by Craig distribution (2300 stages, DMF/water). The yield was 0.4 g (5.6%) of **6d**, mp 135–137 °C, and 1.8 g (25%) of **6e**, mp 184–186 °C.

6d: ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 2.1 (s, 6 H), 3.3 (s, 6 H), 5.5 (s, NH), 7.1–8.4 (m, 4 H) ppm; ^{13}H NMR ($CDCl_3$) δ 19.9, 26.0, 43.9, 50.5, 109.2, 120.3, 122.8, 127.8, 134.1, 141.2, 167.9 ppm. Anal. ($C_{18}H_{20}N_2O_6$) C, H, N.

6e: ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 2.1 (s, 6 H), 3.2 (s, 6 H), 5.7 (s, NH), 7.6 (d, J = 9 Hz, 2 H), 8.1 (d, J = 9 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 19.7, 25.8, 44.2, 50.4, 108.9, 122.3, 128.8, 141.5, 145.4, 159.6, 168.0 ppm; MS 360 (M^+, 2), 345 (100), 299 (22), 238 (28). Anal. ($C_{18}H_{20}N_2O_6$) C, H, N.

Acknowledgment. The NMR spectroscopy was carried out by Dr. J. Kurz. The mass spectroscopy was performed by Dr. C. Wünsche.

Registry No. **2a**, 33404-18-1; **2b**, 125764-65-0; **2c**, 62658-88-2; **2d**, 125764-66-1; **3a**, 125764-67-2; **3b**, 125764-68-3; **3c**, 125764-69-4; **3d**, 125764-70-7; **4a**, 78672-50-1; **4b**, 81429-06-3; **4c**, 81429-05-2; **4d**, 125764-71-8; **5a**, 78685-46-8; **5b**, 81429-09-6; **5c**, 81429-08-5; **5d**, 125764-72-9; **6a**, 78672-51-2; **6b**, 81429-12-1; **6c**, 81429-10-9; **6d**, 125764-73-0; **6e**, 125764-74-1; **7a**, 81429-16-5; **7b**, 125764-75-2; **10**, 21881-77-6; Ca, 7440-70-2.

Supplementary Material Available: Table of bond distances, table of bond angles, table of torsional angles, table of positional parameters, and table of general displacement parameter expressions (4 pages). Ordering information is given on any current masthead page.

Synthesis and Antihyperglycemic Activity of Novel 5-(Naphthalenylsulfonyl)-2,4-thiazolidinediones

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A series of 5-(naphthalenylsulfonyl)-2,4-thiazolidinediones were synthesized and evaluated for antihyperglycemic activity in an insulin-resistant, genetically diabetic db/db mouse model of non-insulin-dependent diabetes mellitus (NIDDM). The sulfones could be synthesized by a novel, selective C-5 sulfonylation of dilithio-2,4-thiazolidinedione with appropriate sulfonyl chlorides. Within this series, naphthalene was found to be superior to other groups for eliciting antihyperglycemic activity, including the *p*-alkoxyphenyl group found in ciglitazone, a prototypical agent for this activity. Attachment of the 5-sulfonyl-2,4-thiazolidinedione moiety to the 2-naphthalene position led to optimum activity. Other linkers between the naphthalene and 2,4-thiazolidinedione rings, such as thio, methylene, oxy, and sulfinyl led to decreased antihyperglycemic activity. The best analogue, 5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31,637) was equipotent to ciglitazone in two animal models of NIDDM.

The limitations of oral agents currently employed for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) has led to an ongoing need for new therapies for this disease.[1] The sulfonylureas, which are in current use, suffer from potentially fatal hypoglycemic episodes and from primary or secondary treatment failures.[2] The other major class of oral agents, the biguanides, were banned by the Food and Drug Administration in 1977 due to toxicity problems associated with lactic acidosis.[3]

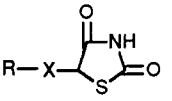
Advances in the understanding of glucose metabolism and insulin action have led to recent efforts to develop new oral agents for the treatment of NIDDM. Therapeutic agents currently in development act via a variety of different mechanisms to lower glucose levels including inhibition of fatty acid oxidation, α-glycosidase inhibition, antagonism of α_2-adrenoceptors, and inhibition of gluconeogenesis.[4]

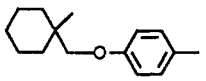
One of the most promising approaches for control of NIDDM is through potentiation of peripheral insulin action.[5,6] Ciglitazone (1), a *p*-alkoxybenzyl-substituted thiazolidinedione, represents a prototypical agent for this type of activity.[5] It has antihyperglycemic activity in insulin-resistant animal models without incidence of hypo-

(1) Lebovitz, H. E. *The Diabetes Annual/1*; Albert, K. G. M. M.; Krall, L. P., Ed.; Elsevier: New York, 1985; pp 93–110.
(2) Ferner, R. E. *Med. Clin. North Am.* **1988**, *72*, 1323–1335.
(3) *FDA Drug Bull.* **1977**, *7*, 13–16.
(4) Mohrbacher, R. J.; Kiorpes, T. C.; Bowden, C. R. *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: New York, 1987; Vol. 22, pp 213–222 and references therein.
(5) (a) Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T.; Kawmatsu, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3580. (b) Fujita, T.; Sugiyama, Y.; Taketomi, S.; Sohda, T.; Kawamatsu, Y.; Iwatsuka, H.; Suzuoki, Z. *Diabetes* **1983**, *32*, 804. (c) Chang, A. Y.; Wyse, B. M.; Gilchrist, B. J.; Peterson, T.; Diani, A. R. *Diabetes* **1983**, *32*, 830.
(6) (a) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. *J. Med. Chem.* **1989**, *32*, 421. (b) Kanji, M.; Fujita, T. U.S. Patent 4,687,777, 1987. (c) Eggler, J. F.; Holland, G. F.; Johnson, M. R.; Volkmann, R. A. U.S. Patent 4,738,972, 1988. (d) Kees, K. L.; Cheeseman, R. S.; Prozialeck, D. H.; Steiner, K. E. *J. Med. Chem.* **1989**, *32*, 11.

0022-2623/90/1833-1418$02.50/0

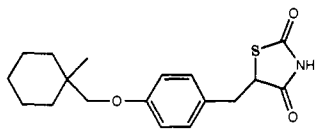
Table I. Various 2,4-Thiazolidinedione Analogues



compd	R	X	synthesis method[a]	mp, °C	recrystn solvent[b]	yield, %	% decrease in blood glucose[c,d]	pK_a
7	2-naphthyl	O	Ex	221–222 dec	W/E	31[g]	i	
8	2-naphthyl	CH_2	A[f]	144–145	T/U/V/Y	26[g]	−38 ± 13[i]	6.83
9	2-naphthyl	CH_2S	B	173–174	U/X	56	i	
10	2-naphthyl	CH_2SO_2	C	224–225	V/X	29	i	
11[e]	2-naphthyl	SO	Ex	157–158	T/Z	24	i	4.58
12	4-Br-phenyl	SO_2	A	164–165	T/U/V	12	i	
13	4-F-phenyl	SO_2	C	207–208	V/X	33		
14	*n*-octyl	S	B	91–92	V/X	29	i	
15	*n*-octyl	SO_2	C	113–114	Z	41	i	
16		SO_2	Ex	174–175	V/X/Y	38	i	
1	ciglitazone						−35 ± 10[h]	6.82

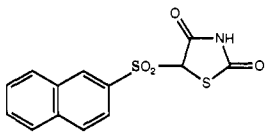
[a] A, B, C = general method, Ex = experimental procedure described. [b] T = acetonitrile, U = chloroform, V = hexane, W = acetone, X = ethyl acetate, Y = ether, Z = carbon tetrachloride. [c] Values (mean ± SE) are percent change relative to vehicle-treated group with use of four to six mice/group. [d] i = inactive, generally less than −15% change. [e] Percent C was 0.46 below theory. [f] 2-(Bromomethyl)naphthalene was used as the electrophile. [g] Yield after chromatography. [h] Mean ± SD value of 24 experiments. [i] $p < 0.05$.

glycemic episodes but has no effect on insulin-dependent or nondiabetic animals. Recently, other structurally analogous thiazolidinediones have been disclosed.[6a-c]



1

Described in this paper is a systematic variation of the lipophilic appendage on the thiazolidinedione ring, leading to the finding that naphthalene may replace the *p*-alkoxyphenyl group previously considered necessary for substantial activity.[5a] In addition, a sulfonyl linker between the naphthalene and the thiazolidinedione rings is found to lead to improved antihyperglycemic activity over a methylene group. These discoveries resulted in the identification of a novel naphthalenesulfonyl-substituted thiazolidinedione **2** (AY-31,637) with a pharmacological profile similar to that of ciglitazone in two genetic models of NIDDM.

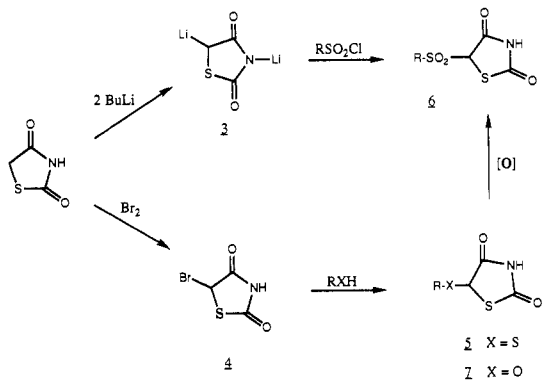


2

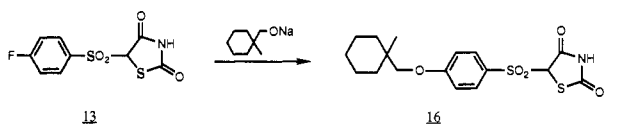
Synthesis

An efficient one-step route to the sulfonyl-2,4-thiazolidinediones employed a selective C-5 sulfonylation of dilithio-2,4-thiazolidinedione (**3**) upon treatment with a sulfonyl chloride (Scheme I). The dianion was readily prepared by the treatment of 2,4-thiazolidinedione with 2 equiv of *n*-butyllithium.[7] An alternative two-step sequence utilized a base-mediated coupling of a thiol with 5-bromo-2,4-thiazolidinedione (**4**) to provide the 5-thio intermediate **5**, which was oxidized to the sulfone **6** with an excess of hydrogen peroxide in acetic acid (Scheme I).[8]

Scheme I



Scheme II



The requisite 5-bromo-2,4-thiazolidinedione (**4**) was obtained by bromination of 2,4-thiazolidinedione with bromine in acetic acid. In an analogous reaction, coupling of 2-naphthol with **4** in the presence of base gave the corresponding ether **7** (Table I). Selective oxidation of the sulfide **5** to the corresponding sulfoxide **11** was effected by treatment with 1 molar equiv of *m*-chloroperbenzoic acid.

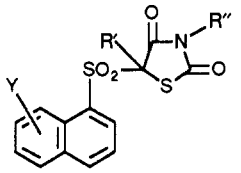
Selective N-methylation of the 2,4-thiazolidinedione ring was accomplished by treatment of naphthalene sulfone analogue **17** with equimolar amounts of sodium hydride and iodomethane to give **18** (Table II). Dimethylation of **17** took place upon treatment with excess potassium carbonate and iodomethane to give **22**. The C-5 methyl analogue **23** was synthesized by preparation of the dianion of 5-methyl-2,4-thiazolidinedione followed by treatment with 1-naphthalenesulfonyl chloride.

A route to the 4-alkoxyphenyl sulfone analogue bearing the lipophilic alkoxy group found in ciglitazone utilized a nucleophilic displacement of fluoride from 5-[(4-fluorophenyl)sulfonyl]-2,4-thiazolidinedione (**13**) by the alkoxide of (1-methylcyclohexyl)methanol (Scheme II). Treatment of **13** with (1-methylcyclohexyl)methanol in dimethyl-

(7) Alkali amides in liquid ammonia have been used to generate this dianion: Taylor, J. D.; Wolfe, J. F. *Synthesis* **1971**, 310.

(8) 5-(2-Naphthalenylsulfonyl)-2,4-thiazolidinedione (**2**) was synthesized by both routes. The products obtained were identical in every respect.

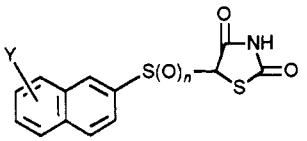
Table II. 1-Naphthalenyl Analogues



compd	R′	R″	Y	synthesis method[a]	mp, °C	recrystn solvent[b]	yield, %	% decrease in blood glucose[c,d]
17	H	H	5-Br	A	189–190	T/U	32	−29 ± 6[g]
18	H	Me	5-Br	Ex	150–151	U/Y	25	i
19	H	H	H	A	187–188	T/U/V	24[f]	−34 ± 9[g]
20	H	H	5-CF_3, 6-OMe	A	211–212	U/V/W	57[f]	−40 ± 8[g]
21	H	H	8-OMe	A	272–273	X/Z	28[f]	i
22	Me	Me	5-Br	Ex	160–161	U/V/Y	59	i
23	Me	H	H	A[e]	193–194	U	63	i

[a] A = general method, Ex = experimental procedure described. [b] T = acetonitrile, U = chloroform, V = hexane, W = methanol, X = tetrahydrofuran, Y = ether, Z = ethanol. [c] Values (mean ± SE) are percent change relative to vehicle-treated group with use of four to six mice/group. [d] i = inactive, generally less than −15% change. [e] The dianion of 5-methyl-2,4-thiazolidinedione was used. [f] Yield after chromatography. [g] $p < 0.05$.

Table III. 2-Naphthalenyl Analogues



compd	n	Y	synthesis method[a]	mp, °C	recrystn solvent[b]	yield, %	% decrease in blood glucose[c,d]	pK_a
2	2	H	C	196–197	U/V/W	47	−63 ± 9[h]	3.95
24	2	6-OCO_2Et	C	167–168	V/X	55	i	
25	2	5-Br, 6-OMe	C	231–232	X	29	i	
26	2	6-OCH_2Ph	C	195–196	V/X	31	i	
27[e]	2	6,7-$(OCO_2Et)_2$	C	185–186	T/U/V/Y	65	i	
28	2	5-CF_3, 6-OMe	C	203–205	V/X	56	i	
29	2	1-Br	C	221	Z	26	i	
30[f]	0	H	B	137–138	U	46	−29 ± 7[h]	5.58
31	0	6-OCO_2Et	B	127–128	U/V/X	37[g]	i	
32	0	6-OH	Ex	182–183	S/W	99[g]	−19 ± 11	
33	0	6,7-$(OCO_2Et)_2$	B	138–139	T/U/V/Y	42	−22 ± 16	
34	0	5-CF_3, 6-OMe	B	153–154	V/X	34[g]	−32 ± 3[h]	
35	0	6,7-$(OH)_2$	Ex	256–257	X	40	i	
36	0	1-Br	B	128–129	V/X	84[g]	i	

[a] B, C = general method, Ex = experimental procedure described. [b] S = water, T = acetonitrile, U = chloroform, V = hexane, W = methanol, X = ethyl acetate, Y = ether, Z = acetic acid. [c] Values (mean ± SE) are percent change relative to vehicle-treated group with use of four to six mice/group. [d] i = inactive, generally less than −15% change. [e] Isolated as a hemihydrate. [f] Percent C was 0.53 below theory. [g] Yield after chromatography. [h] $p < 0.05$.

formamide in the presence of sodium hydride gave the desired analogue **16**.

Results and Discussion

Variation of the substituents on the thiazolidinedione heterocycle led to the identification of the naphthalene ring as the optimal group for eliciting antihyperglycemic activity within the series of 5-sulfonyl-2,4-thiazolidinediones (Tables I–III). The use of other lipophilic attachments, such as a long-chain aliphatic group (**15**), a *p*-alkoxyphenyl group (**16**) (as in ciglitazone), or a *p*-bromophenyl group (**12**), led to a loss of activity. Replacement of the sulfonyl group with other linkers between the naphthalene and thiazolidinedione rings similarly led to a diminishment or a loss of activity. For example, connecting groups such as thio (**30–36**), sulfinyl (**11**), oxy (**7**), and methylene (**8**) all led to less potent or inactive compounds. Isolation of the naphthalene ring from the sulfonyl group by insertion of a methylene spacer gave an inactive analogue **10**.

Attachment of the 5-sulfonyl-2,4-thiazolidinedione moiety to the 2-naphthalene position was superior to the 1-position and resulted in the most potent analogue 5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (**2**). Attempts were made to further improve activity by substitution of the naphthalene ring. In the series of 1-naphthalene sulfones (Table II) antihyperglycemic activity could be maintained but not dramatically improved by naphthalene substitution. The most potent analogue **20** contained the 6-methoxy-5-(trifluoromethyl)-1-naphthalenyl group. In contrast, in the series of 2-naphthalene sulfones (Table III) all naphthalene substitution led to a loss of activity. In the series of 2-naphthalene sulfides, however, antihyperglycemic activity could be maintained by certain naphthalene substitution (Table III).

An acidic function is a requisite for antihyperglycemic activity as suggested by the loss of potency upon N-methylation of the thiazolidinedione ring (**18** and **22**). However, antihyperglycemic activity was found to vary independently of acid strength as shown by measurements of the effect of different linkers on the pK_a of the thiazolidinedione ring (Tables I and III). While the most potent analogue **2** was the most acidic (due to the electron-withdrawing sulfonyl group), the less active methylene analogue **8** and ciglitazone (**1**) were the least acidic. The

Table IV. Effect of **2** on the Plasma Glucose Level of Diabetic db/db Mice

treatment[a]	plasma glucose, mg/dL	
	18-h fasted	fed
vehicle	310 ± 27	450 ± 30
1	285 ± 28	313 ± 26[b]
2	243 ± 27[b]	352 ± 40[b]

[a] Drugs were administered to db/db mice at 100 mg/kg per day for 4 days; N = 4–6 mice per group. [b] $p < 0.05$ versus vehicle group.

Table V. Effect of **2** on Blood Lactate and Glucose Levels in Fasted Rats

treatment[a]	blood lactate, mg/dL	plasma glucose, mg/dL
vehicle	7.8 ± 0.6	82 ± 3
phenformin	12.2 ± 1.1[b]	85 ± 2
1	8.0 ± 0.5	83 ± 2
2	7.2 ± 0.3	77 ± 2

[a] Drugs administered to 24 h fasted Sprague–Dawley rats at 200 mg/kg per day in four divided doses, ip. Rats were anesthetized with halothane, and blood was collected from the iliac artery. N = 8 rats per group. [b] $p < 0.05$ versus vehicle group.

active thio compound **30** and the inactive sulfinyl analogue **11** had intermediate pK_a's. These compounds would all be largely ionized at physiological pH, and as long as this condition is met, it appears that structural features override acid strength in determining potency.

The strong activity of naphthalene sulfone **2** during the insulin-tolerance test (Table III) led to its selection for further pharmacologic evaluation. As shown in Table IV, **2** lowered the plasma glucose of the diabetic db/db mice in the fasted as well as fed states without the administration of exogenous insulin. In another animal model of insulin resistance, the obese Zucker rat, **2** and ciglitazone significantly improved the glucose intolerance of these animals (Figure 1, top). In contrast to the activity of **2** in the insulin-resistant animals, **2** did not alter the plasma glucose level of the normal lean rat either before or during a subcutaneous glucose tolerance test (SCGTT) (Figure 1, bottom). As expected, the sulfonylurea tolbutamide caused a significant lowering of plasma glucose levels in the normal rat.

An initial evaluation of the safety of **2** demonstrated that the compound did not induce elevations of blood lactate which were observed with the biguanide phenformin (Table V). In confirmation of the above studies, **2** did not induce hypoglycemia. Furthermore, a single dose of **2** (1 g/kg, po) did not induce any lethalities or observable side effects in male Swiss CD-1 mice.

In conclusion, we have found that the 2-naphthalenesulfonyl moiety in combination with the 2,4-thiazolidinedione ring gives rise to a novel antihyperglycemic agent **2** (AY-31,637). Further work on naphthalene-based antihyperglycemic agents is in progress in these laboratories.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz on a Varian XL-200 spectrometer or at 400 MHz on a Brucker AM-400 spectrometer. Infrared spectra were recorded as KBr pellets on a Perkin-Elmer Model 781 spectrophotometer. Mass spectra were recorded on either a Finnigan Model 8230, a Hewlett-Packard Model 5995A, or a Kratos MS50 mass spectrometer. Analyses were carried out on a Perkin-Elmer Model 240 or a Controll Equipment Model 240XA CHN analyzer. All compounds exhibited ^{1}H NMR, IR, analytical, and mass spectral data consistent with the proposed structures.

Sulfonyl chlorides and mercaptans were commercially available or were prepared by standard literature methods.[9] Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen immediately before use. Column chromatography was done with E. Merck silica gel 60 (0.040–0.063 mm). Acid-washed silica gel refers to E. Merck silica gel which was stirred with 2% phosphoric acid in methanol, filtered, and then dried at 120 °C for 12 h.

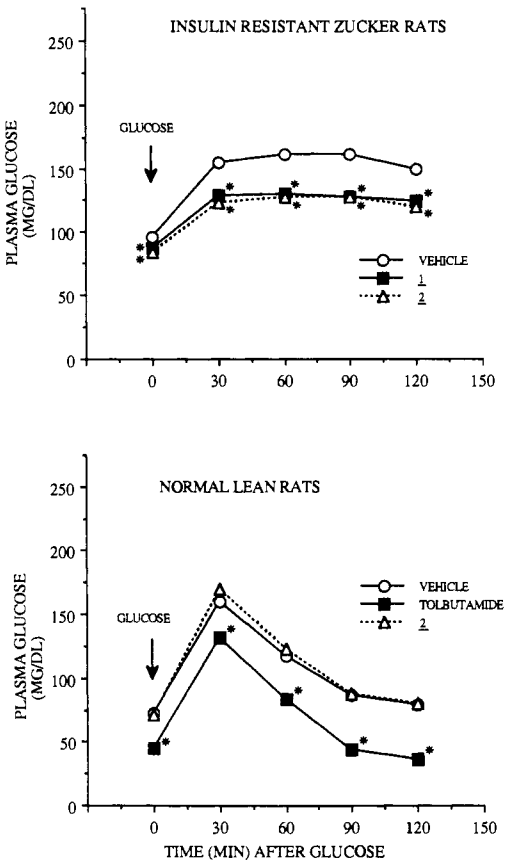


Figure 1. Compounds (100 mg/kg per day, po, 1 day for lean rats and 4 days for Zucker rats) or vehicle were administered 1 h prior to the glucose tolerance test (1 g/kg, sc). Blood samples were collected from the tail-tip of unanesthetized rats. N = 3–4 rats per group, (*) $p < 0.05$ versus vehicle group using Dunnett's multiple comparison test.

Method A. 5-[(5-Bromo-1-naphthalenyl)sulfonyl]-2,4-thiazolidinedione (17). To a stirred solution of 2,4-thiazolidinedione (5.5 g, 47 mmol) in THF (275 mL) at −78 °C under nitrogen was added *n*-butyllithium (62 mL, 99 mmol) portionwise over 15 min. The mixture was maintained at −78 °C for 15 min and then warmed to 0 °C for 30 min to complete the dianion formation. Upon recooling to −78 °C, 5-bromo-1-naphthalenesulfonyl chloride (16 g, 52 mmol) was added as a solid, all at once. After 30 min the orange solution was allowed to warm to 25 °C. After 1.5 h the reaction mixture was treated with 5% aqueous sulfuric acid. The aqueous phase was washed with chloroform (3×), and the combined organic extracts were concentrated to an oil which was taken up in 5% aqueous sodium bicarbonate and extracted with chloroform (3×). The aqueous phase was acidified to pH <1 with concentrated hydrochloric acid and extracted with chloroform (3×). The combined organic extracts of the acidified aqueous phase were dried (magnesium sulfate) and then concentrated to give an oil, which was purified by chromatography (acid-washed silica gel, 10:1 chloroform/acetonitrile) to give 17 (7.6 g, 42% yield): mp 189–190 °C (acetonitrile/chloroform): ^{1}H

(9) For representative examples, see: Zinke, T.; Dereser, R. *Chem. Ber.* **1917**, *51*, 352. Sutter, C. M.; Weston, A. W. *Org. React.* **1946**, *3*, 141–197. Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1979**, *44*, 2642. Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* **1980**, *21*, 3099. Urquhart, G. G.; Gates, J. W.; Conner, R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 363. Bonfiglio, J. N. *J. Org. Chem.* **1986**, *51*, 2833.

NMR (DMSO-d_6, 200 MHz) δ 6.60 (s, 1 H, C*H*, exchanges with D_2O), 7.7–8.7 (m, 6 H, Ar*H*).

Method B. 5-[(1-Bromo-2-naphthalenyl)thio]-2,4-thiazolidinedione (36). A solution of 4 (2.54 g, 13 mmol) and 1-bromo-2-mercaptonaphthalene (2.91 g, 13 mmol) in THF (100 mL) under nitrogen at −78 °C was treated with lithium diisopropylamide (14.7 mL, 28.6 mmol, 1.94 M in THF). After 30 min, the mixture was allowed to warm to 25 °C. After 1 h, 2 N aqueous hydrochloric acid was added. The aqueous phase was extracted with ethyl acetate (3×), and the combined organic extracts were dried (magnesium sulfate) and concentrated to give a yellow oil (5.27 g). Chromatography of this material (acid-washed silica gel, chloroform) gave **36** (3.68 g, 83% yield): mp 128–129 °C (hexane/ethyl acetate); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.42 (s, 1 H, C*H*), 7.6–8.2 (m, 6 H, Ar*H*).

Method C. 5-(2-Naphthalenylsulfonyl)-2,4-thiazolidinedione (2). To a solution of **30** (2.5 g, 9.1 mmol) in acetic acid (100 mL) at 60 °C was added 30% aqueous hydrogen peroxide (10 mL, 88 mmol). This was followed by two equivalent additions of hydrogen peroxide at reaction times of 30 and 90 min. At 3 h, the reaction mixture was poured into water (600 mL) and the aqueous phase extracted with ethyl acetate (3×). The combined organic extracts were dried (magnesium sulfate) and concentrated to give an oil which was purified by chromatography (C-18 silica gel, 70:30 methanol/water) to give **2** as a foam (1.7 g, 62% yield). Crystallization from hexane/chloroform/methanol gave white needles (1.31 g, 47% yield): mp 196–197 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.75 (s, 1 H, C*H*, exchanges with D_2O), 7.7–8.6 (m, 7 H, Ar*H*).

5-Bromo-2,4-thiazolidinedione (4). To a solution of 2,4-thiazolidinedione (100 g, 0.855 mol) in acetic acid (250 mL) at 85 °C was added bromine (42.7 mL, 0.855 mol) dropwise over 1 h. After an additional 1 h at 85 °C, the solution was allowed to cool to ambient temperature and then poured into water (1 L). The crude product was extracted into ether, dried (magnesium sulfate), and concentrated to give a yellow oil (127 g) which was filtered through a short column of silica gel (8:1 chloroform/acetonitrile). The resulting oil was triturated with hexane to give 4 as a white powder (95.0 g, 57% yield): mp 61–62 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 6.41 (s, 1 H, C*H*), 11.30 (s, 1 H, N*H*).

5-(2-Naphthalenyloxy)-2,4-thiazolidinedione (7). By a procedure similar to that of method B a solution of 2-naphthol (5.0 g, 35 mmol) and 5-bromo-2,4-thiazolidinedione (6.8 g, 35 mmol) in THF (200 mL) was treated with lithium bis(trimethylsilyl)amide (76 mL, 76 mmol, 1.0 M in THF) to give, after chromatography (acid-washed silica gel, chloroform/acetonitrile), **7** (2.8 g, 31% yield): mp 221–222 °C (acetone/ethyl acetate); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.52 (s, 1 H, OC*H*), 7.1–8.0 (m, 6 H, Ar*H*), 10.57 (s, 1 H, Ar*H*).

5-(2-Naphthalenylsulfinyl)-2,4-thiazolidinedione (11). To a solution of **30** (1.0 g, 3.6 mmol) in dichloromethane (100 mL) was added *m*-chloroperbenzoic acid (0.74 g, 85%, 3.6 mmol) portionwise over 30 min. After an additional 30 min, dimethyl sulfide (0.5 mL) was added and the solution concentrated. The resulting solid was washed repeatedly with hot carbon tetrachloride to remove *m*-chlorobenzoic acid. Recrystallization of the remaining solid (1.1 g) gave 11 as a 3:1 mixture of diastereomers (0.55 g, 52% yield): mp 157–158 °C (acetonitrile/carbon tetrachloride); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.31 (s, 0.75 H, C*H*), 6.49 (s, 0.25 H, C*H*), 7.61–8.19 (m, 6 H, Ar*H*), 8.25 (s, 0.25 H, Ar*H*), 8.31 (s, 0.75 H, Ar*H*). HPLC analysis (C_{18} silica gel, 30% acetonitrile/70% 0.01 M aqueous $NH_4H_2PO_4$, 1.5 mL/min) of the diastereomeric mixture gave two peaks which tailed into each other, indicating an on column interconversion (t_R = 5.71 min (major isomer); t_R = 3.86 min (minor isomer)). Reinjection of the material corresponding to each peak reproduced the original HPLC trace.

5-[[4-[(1-Methylcyclohexyl)methoxy]phenyl]sulfonyl]-2,4-thiazolidinedione (16). Sodium hydride (3.17 g, 66.1 mmol, 50% in oil) was added to a solution of (1-methylcyclohexyl)-methanol (8.47 g, 66.1 mmol) in dimethylformamide (30 mL). The mixture was heated to 55 °C for 30 min. A solution of **13** (1.82 g, 6.61 mmol) in dimethylformamide (20 mL) was then added. After 3 h at 55 °C, the reaction mixture was poured into 2 N aqueous hydrochloric acid. The aqueous phase was extracted with ethyl acetate (3×). The organic extracts were dried (magnesium sulfate) and then concentrated to an oil which was purified by chromatography (C-18 silica gel, 70:30 methanol/water). The resulting white foam (1.31 g) was rechromatographed (acid-washed silica gel, chloroform) and then recrystallized from hexane/ethyl acetate/ether to give **16** as a white powder (0.97 g, 38% yield): mp 174–175 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.00 (s, 3 H, CH_3), 1.20–1.60 (m, 10 H, cyclohexyl CH_2's), 3.82 (s, 2 H, OCH_2), 6.56 (s, 1 H, C*H*), 7.22 (d, J = 9 Hz, 2 H, Ar*H*), 7.80 (d, J = 9 Hz, 2 H, Ar*H*).

5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3-methyl-2,4-thiazolidinedione (18). To a solution of **17** (2.0 g, 5.2 mmol) in THF/dimethylformamide (1:1, 40 mL) at 25 °C under nitrogen was added sodium hydride (0.25 g, 5.2 mmol, 50% in oil). After 30 min, iodomethane (0.32 mL, 5.2 mmol) was added. The reaction was stirred for 1 h and then partitioned between 5% aqueous sulfuric acid and chloroform. The organic phase was dried (magnesium sulfate) and concentrated to give crude product. Chromatography (silica gel, chloroform) and recrystallization (2×, chloroform/ether) gave **18** (520 mg, 25% yield): mp 150–151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.03 (s, 3 H, CH_3), 5.59 (s, 1 H, C*H*), 7.6–8.8 (m, 6 H, Ar*H*).

5-[(5-Bromo-1-naphthalenyl)sulfonyl]-3,5-dimethyl-2,4-thiazolidinedione (22). To a solution of **17** (1.1 g, 2.9 mmol) in acetone (50 mL) at 25 °C was added anhydrous potassium carbonate (3.9 g, 29 mmol) and iodomethane (1.8 mL, 29 mmol). After 1 h, the mixture was filtered and the filtrate concentrated. Purification by chromatography (acid-washed silica gel, carbon tetrachloride/chloroform) followed by recrystallization (chloroform/hexane/ether) gave **22** (0.69 g, 59% yield): mp 160–161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3 H, CH_3), 2.69 (s, 3 H, NCH_3), 7.5–8.9 (m, 6 H, Ar*H*).

5-[(6-Hydroxy-2-naphthalenyl)thio]-2,4-thiazolidinedione (32). Potassium hydroxide (2.47 g, 44.0 mmol) was added to a suspension of **31** (8.0 g, 22 mmol) in methanol (50 mL) at 25 °C. After 30 min, the resulting solution was acidified to pH = 1 with 2.0 N hydrochloric acid, concentrated to remove the methanol, and then extracted with ethyl acetate (3×). The combined extracts were dried (magnesium sulfate) and concentrated to give **32** as a powder (6.4 g, 99% yield): mp 182–183 °C (chloroform/ethyl acetate); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.07 (s, 1 H, C*H*), 7.1–8.0 (m, 6 H, Ar*H*). Analogue **35** was prepared similarly, with the use of 3 molar equiv of potassium hydroxide.

Pharmacological Procedures. The series of analogues were evaluated for their ability to lower the plasma glucose levels of diabetic db/db mice during an insulin tolerance test (ITT). The genetically diabetic db/db mice (C57BL/KsJ; Jackson Laboratories, male, 3–7 months of age) were dosed by oral gavage with compound (100 mg/kg) once daily for 4 days. The animals were fasted 18 h before the final dose. Insulin (0.5 unit/kg, sc) was administered 2 h after the drug and the unanesthetized mice were bled from the tail-tip 2 h later. Plasma glucose levels were determined by an Abbott VP Analyzer. The evaluation of antidiabetic activity, as shown in Tables I–III, was based on the percent decrease in plasma glucose levels relative to a vehicle-treated control group (2% Tween 80/saline).

As shown in Table IV, the activity of the naphthalene sulfone **2** was assessed also in db/db mice that did not receive a supplemental dose of insulin. The mice received **2** once daily for 4 days. The fourth drug dosage was administered to either fed or fasted (18 h) mice and a blood sample was obtained from the tail-tip 2 h later.

A possible effect of **2** on blood lactate levels was determined by previously published methods (Table V).[10]

Acknowledgment. We gratefully acknowledge the excellent assistance of B. Mihan, L. Carl, and M. Houlihan. We also thank Dr. T. Chau for performing the acute toxicity test.

Registry No. 2, 125518-46-9; **3**, 125518-47-0; **4**, 125518-48-1; **7**, 125518-49-2; **8**, 125518-50-5; **9**, 125518-51-6; **10**, 125518-52-7; **11** (isomer 1), 125518-53-8; **11** (isomer 2), 125518-54-9; **12**, 125518-55-0; **13**, 125518-56-1; **14**, 125518-57-2; **15**, 125518-58-3; **16**, 125518-59-4; **17**, 125518-60-7; **18**, 125518-61-8; **19**, 125540-45-6;

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20, 125518-62-9; 21, 125518-63-0; 22, 125518-64-1; 23, 125518-65-2; 24, 125518-66-3; 25, 125518-67-4; 26, 125518-68-5; 27, 125518-69-6; 28, 125518-70-9; 29, 125518-71-0; 30, 125518-72-1; 31, 125518-73-2; 32, 125518-74-3; 33, 125518-75-4; 34, 125518-76-5; 35, 125518-77-6; 36, 125518-78-7; p-$BrC_6H_4SO_2Cl$, 98-58-8; $H_3C(CH_2)_7SH$, 111-88-6; 2,4-thiazolidinedione, 2295-31-0; 5-bromo-1-naphthalenesulfonyl chloride, 50638-04-5; 1-bromo-2-mercaptonaphthalene, 90767-26-3; 2-naphthol, 135-19-3; (1-methylcyclohexyl)methanol, 14064-13-2; 5-[(4-fluorophenyl)thio]-2,4-thiazolidinedione, 125518-79-8; 2-(bromomethyl)naphthalene, 939-26-4; 2-(methylthio)naphthalene, 1076-67-1; 1-naphthalenesulfonyl chloride, 85-46-1; 5-(trifluoromethyl)-6-methoxy-1-naphthalenesulfonyl chloride, 113699-68-6; 8-methoxy-1-naphthalenesulfonyl chloride, 56875-58-2; 5-methyl-2,4-thiazolidinedione, 3805-23-0; 5-[(5-bromo-6-methoxy-2-naphthalenyl)thio]-2,4-thiazolidinedione, 125518-80-1; 5-[(6-(benzyloxy)-2-naphthalenyl)thio]-2,4-thiazolidinedione, 125518-81-2; 2-naphthalenethiol, 91-60-1; 6-[(ethoxycarbonyl)oxy]-2-mercaptonaphthalene, 125518-82-3; 6,7-bis[(ethoxycarbonyl)oxy]-2-mercaptonaphthalene, 125518-83-4; 6-methoxy-2-mercapto-5-(trifluoromethyl)naphthalene, 125518-84-5.

Molecular Design, Synthesis, and Antiinflammatory Activity of a Series of β-Aminoxypropionic Acids[1]

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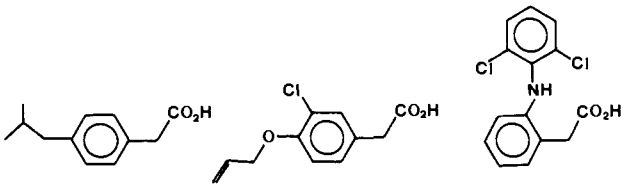
Previous experimental and theoretical studies carried out on the mechanism of action of adrenergic drugs have shown that the (methyleneaminoxy)methyl moiety (C=$NOCH_2$, MAOMM) can be considered as a "bioisostere" of an aryl group (Ar). On this basis, a series of substituted β-aminoxypropionic acids (AOPAs) were synthesized as analogues of antiinflammatory arylacetic acids (ArAAs), in which the Ar portion is substituted by the MAOMM, with the aim of evaluating whether any antiinflammatory activity could be obtained from this class of drugs after the substitution of the Ar with the MAOMM. The antiinflammatory activity of the AOPAs synthesized was determined by carrageenan-induced rat paw edema, using diclofenac as the reference drug. The pharmacological data showed that most of the AOPAs examined exhibit a significant antiinflammatory activity, which in the case of the (*E*)-3-(benzylideneaminoxy)propionic acid (**7q**) is very close to that of the reference drug. Structural and theoretical studies were carried out in order to compare the conformation and the molecular reactivity of the AOPAs with those of the ArAAs. Pharmacological results showed that the ArAAs also generally exhibit an antiinflammatory activity after the substitution of the Ar with the MAOMM, thus supporting the hypothesis of a bioisosterelike relationship between these two moieties in this class of NSAIDs.

Nonsteroidal antiinflammatory drugs (NSAIDs) are a family of compounds which are chemically not very homogeneous. A large number of chemical structures have been found to exhibit antiinflammatory activity. Even if a general correlation between chemical features and biological activity is not found, drugs of this type can be subdivided into large classes of compounds with some general features in common.[2]

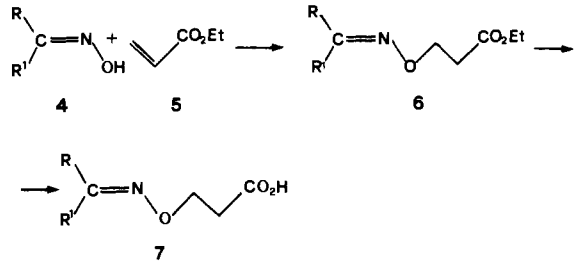
The arylacetic acid (ArAA) class has become one of the most widely developed and investigated over the past 2 decades. Many agents of this class, e.g. ibufenac (**1**), aclofenac (**2**), and diclofenac (**3**), are at present widely used in therapeutic practice.[2]



1 ibufenac **2** aclofenac **3** diclofenac

Previous experimental and theoretical studies[3] in the field of adrenergic drugs have indicated that, at least in the case of these type of drugs, the (methyleneaminoxy)-methyl moiety (C=$NOCH_2$, MAOMM) can be considered as a "bioisostere"[4] of either aryls (Ar) or other aromatic groups (see Figure 1).[3] These results suggested that it might be possible to effect the substitution of an Ar with

Scheme I



4 **5** **6** **7**

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