Antihyperglycemic *N*-Sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines: Synthesis, X-ray Structure Analysis, Conformational Behavior, Quantitative Structure–Property Relationships, and Quantitative Structure–Activity Relationships†,‡,§

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A series of 1-sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines, **4**, has been synthesized and evaluated for its effects on blood glucose-decreasing activity. These derivatives were prepared from 4,7-dihydro-1,3-dioxepins **1** via *vic*(acylamino)halogenodioxepanes **2** and dioxepinoazirines **3**. Quantitative structure–property relationship and quantitative structure–activity relationship models, based on X-ray and molecular mechanics analyses, to our knowledge the first in the field of antihyperglycemics, were developed. They allow the prediction of properties (RP-HPLC attention times) and activities (hypoglycemic activity ratio) by the Connolly's molecular surface areas. The lead compound in these models, sulfonyldioxepinoazirine **4i**, expressed superior antihyperglycemic activity in comparison to metformin in alloxanized mice, irrespective of route of application. It significantly reduced blood glucose levels in glucose-primed mice, but it did not cause a dose dependent decrease of blood glucose level in healthy (nondiabetic, control) animals.

Introduction

At the present time there are two clinically useful classes of oral antidiabetic compounds, *viz.* the sulfonylureas and biguanides. Although the sulfonylureas are therapeutically valuable, they do have disadvantages, *e.g.*, primary or secondary failure of efficacy and overt hypoglycemia.[2] The biguanides are the only other class of antihyperglycemic agents in current clinical practice, but they are limited to just a few non-U.S. markets, due to the fatal lactic acidosis effect.[2] Numerous other, structurally different hypoglycemic compounds have been under preclinical and clinical trials,[3] but only a few of these have reached preregistration or market status (Chart 1). However, extensive research efforts in that field have been committed in finding novel antihyperglycemic agents that would normalize elevated blood glucose levels without the potential of causing an overt hypoglycemic state.[4]

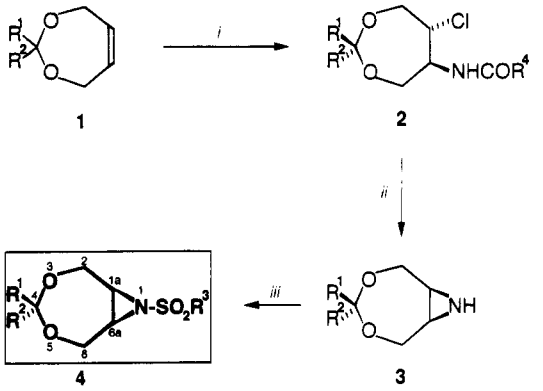
Recently, in the context of our investigation into hypoglycemics, we proposed that 1-sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines **4**, hitherto an unknown class of fused dioxepins, may represent a novel class of potent antihyperglycemic agents.[1,5,6] These discoveries prompted an analog program to maximize the activity of this new series and gain better understanding of the structure–activity relationships for this type of compounds.

Chemistry

The target 1-sulfonyldioxepinoazirines **4** were synthesized starting from easily available 4,7-dihydro-1,3-dioxepins **1**[7] as summarized in Scheme 1. The synthetic methods for the preparation of the key intermediates **2** and **3** were taken from our publications[6,8] and the patent application.[5] The compounds **4** (Table 1) were obtained by direct sulfonation of aziridines **3** in pyridine/methylene chloride in moderate to excellent yields. Their structures were assigned from their ^{1}H NMR (Table 2) and ^{13}C NMR (Table 3) spectral data (Figure 1), and most of them were confirmed by X-ray diffraction. Special attention was paid to the reaction of *exo*-4-isopropyl derivative **3b** (R^1 = H, R^2 = *i*-Pr) with 4-(acetylamino)benzenesulfonyl chloride which led to the formation of a 4.3:1 mixture of *exo*, **4k**, and *endo*, **4l**, isomers in a total yield of 73.8%.

We suggest that formation of both isomers **4k,l** is the consequence of isomerization during sulfonation of aziridine **3b** because the starting **3b** was a homogeneous crystalline substance (TLC, ^{1}H and ^{13}C NMR). On the other hand, **3b** furnished under the identical reaction conditions with 4-nitrobenzenesulfonyl chloride only the *exo* derivative **4j**. The structures of sulfonylazirines

Scheme 1[a]



[a] Reagents and conditions: (*i*) $NO_2Cl/CH_3CN/H_2O/^-OH$ (ref 8); (*ii*) KOH/H_2O, 25–90 °C, 15 min (refs 5 and 6); (*iii*) R^3SO_2Cl/pyridine/CH_2Cl_2, room temperature, 1 h.

† Chemistry of 1,3-Dioxepins. Part 9. For part 8, see ref 1.
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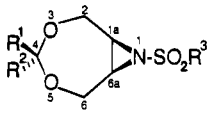
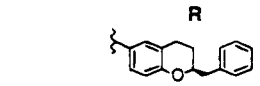
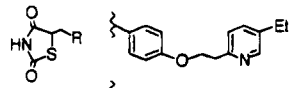
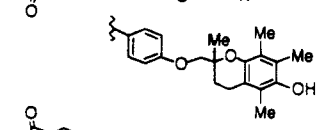
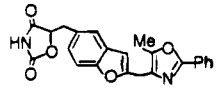
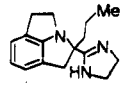
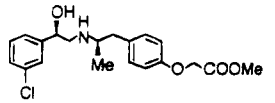
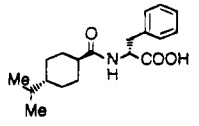
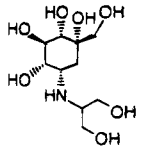
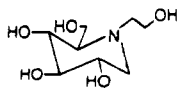
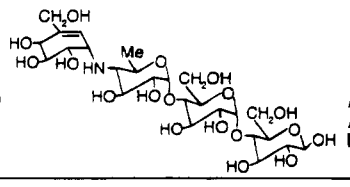
Table 1. Physical and Analytical Data of 1-Sulfonyldioxepino[5,6-*b*]azirines **4**



4	R^1	R^2	R^3	yield (%)	mp (°C)	recryst solvent[a]	formula[b]	X-ray
a	H	H	Me	46.3	98–100	EA/PE (5/2)	$C_6H_{11}NO_4S$	+[c]
b	H	H	Ph	78.9	125–127	EA/PE (3/2)	$C_{11}H_{13}NO_4S$	–
c	H	H	4-F-C_6H_4	78.7	146–147	EA	$C_{11}H_{12}FNO_4S$	+
d	H	H	4-Cl-C_6H_4	81.8	144–146	EA	$C_{11}H_{12}ClNO_4S$	+
e	H	H	4-Br-C_6H_4	71.0	142–145	EA/M (5/1)	$C_{11}H_{12}BrNO_4S$	–
f	H	H	4-Me-C_6H_4	54.8	160–161	EA	$C_{12}H_{15}NO_4S$	+
g	H	H	4-MeO-C_6H_4	80.7	145–147	EA	$C_{12}H_{15}NO_5S$	+
h	H	H	4-O_2N-C_6H_4	86.2	205–207	C	$C_{11}H_{12}N_2O_6S$	+
i	H	H	4-AcNH-C_6H_4	83.3	210–212	EA/M (1/1)	$C_{13}H_{16}N_2O_5S$	+[d]
j	H	*i*-Pr	4-O_2N-C_6H_4	90.4	143–145	PE/EA (5/4)	$C_{14}H_{18}N_2O_6S$	+
k	H	*i*-Pr	4-AcNH-C_6H_4	59.1	144–146	EA/M (1/1)	$C_{16}H_{22}N_2O_5S$	+
l	*i*-Pr	H	4-AcNH-C_6H_4	13.9	238–240	EA/M (3/1)	$C_{16}H_{22}N_2O_5S$	+
m	Me	Me	4-AcNH-C_6H_4	80.5	214–216	EA/M (1/1)	$C_{15}H_{20}N_2O_5S$	–

[a] EA = ethyl acetate, PE = petroleum ether, M = methanol, C = chloroform. [b] All compounds were analyzed for C, H, N, and S, and analytical results are within ±0.4% of the theoretical values. [c] See ref 1. [d] The asymmetric unit of **4i** contains two independent molecules, one of them having a dioxepinoazirine boat–chair pattern and the other one a twist–boat conformation (see ref 6).

Chart 1

	Structure	Name	Developer
1		Englitazone,[I] CP-68722, CP-72466	Pfizer
2		Pioglitazone,[II] AD-4833, U-72107A	Upjohn, Takeda, Abbott
3		Troglitazone,[III] CS-045, CI-991	Sankyo, Glaxo, Warner - Lambert
4		PC	Pfizer
5		Deriglidole,[II] SL-84.0418 SL-86.0715	Synthelabo
6		BRL-35135[II]	SmithKline Beecham, Mochida
7		A-4166,[II] AY-4166, YM-026	Ajinomoto, Yamanouchi, Sandoz, Roussel - Uclaf
8		Voglibose,[PR] AO-128,	Takeda,
9		Miglitol,[III] Bay-m-1099	Bayer
10		Acarbose,[L] AG-5421, Bay-g-5421,	Bayer

PC - Preclinical; I,II,III- Phases of Clinical Trial; PR - Preregistration, L - Launched

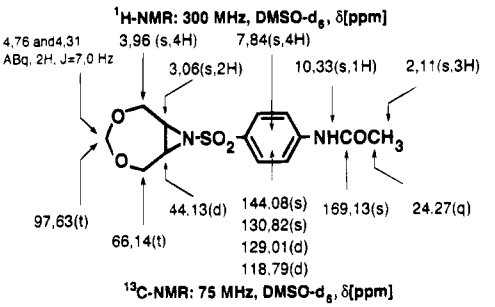


Figure 1. ^1H and ^{13}C NMR data for **4i**.

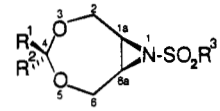
4j–l were also confirmed by X-ray diffraction.[9] The summary of some of their essential crystallographic data is given in Table 4, and structures of *exo* and *endo* isomers **4k,l** are shown in Figure 2.

Results and Discussion

Pharmacology. Table 5 exhibits the results of the hypoglycemic effects of **4** 1 h after subcutaneous administration of a 20 mg/kg dose in alloxanized mice. The data are given as percent of initial blood glucose level (%BGL) and as potency ratio to the effect of metformin as standard (HAR, hypoglycemic activity ratio; activity of metformin = 1). The HAR data were used in quantitative structure–activity relationships (QSAR). Additionally, the lead compound in the QSAR model was further examined in alloxanized mice, glucose-primed mice, and healthy (nondiabetic, control) mice and rats.

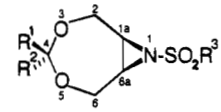
X-ray Diffraction Study. We have undertaken X-ray structure analysis of 10 sulfonyldioxepinoazirines **4** (signed with a plus in Table 1),[1,6,9] as the starting point for molecular modeling studies. Crystallographic evidence indicates that in 10 solved structures of **4**, 11 sulfonyldioxepinoazirine molecules exist, because the asymmetric unit of **4i** contains two crystallographically independent molecules, one of them having a dioxepinoazirine pattern of a boat–chair (**4i**-A) and the other one of a twist–boat conformation (**4i**-B)[6] (Figure 3). In eight of all studied structures, the dioxepinoazirine moiety existed in a boat–chair (BC), in two in a twist–boat (TB), and in only one in a chair–chair (CC) conformation (Figure 4). In addition, the sulfonyl group

Table 2. ^{1}H NMR Spectral Data of **4**



4	C4-H	C2,6-H	C1a,6a-H	R^3
a	4.93, 4.46 (ABq, 2H, 7.1)	4.25, 4.10 (2d, 4H, 13.7)	3.11 (s, 2H)	3.27 (s, 3H, Me)
b	4.89, 4.41 (ABq, 2H, 7.1)	4.08, 4.07 (2d, 4H, 14.6)	3.27 (s, 2H)	8.06–7.77 (m, 5H, Ph)
c	4.77, 4.30 (ABq, 2H, 7.2)	3.98, 3.95 (2d, 4H, 14.1)	3.17 (s, 2H0	8.01, 7.53 (2m, 4H, arom)
d	4.89, 4.41 (ABq, 2H, 7.1)	4.11, 4.06 (2d, 4H, 14.0)	3.30 (s, 2H)	8.03, 7.86 (2d, 4H, 8.7, arom)
e	4.85, 4.44 (ABq, 2H, 6.3)	4.07, 4.02 (2d, 4H, 13.5)	3.16 (s, 2H)	7.84, 7.70 (2d, 4H, 8.5, arom)
f	4.77, 4.30 (ABq, 2H, 7.1)	3.60 (s, 4H)	3.11 (s, 2H)	7.81, 7.48 (2d, 4H, 8.1, arom); 2.43 (s, 3H, Me)
g	4.88, 4.41 (ABq, 2H, 7.1)	4.06 (s, 4H)	3.18 (s, 2H)	7.96, 7.29 (2d, 4H, 8.5, arom); 3.99 (s, 3H, OMe)
h	4.79, 4.30 (ABq, 2H, 7.2)	4.03, 3.97 (2d, 4H, 14.1)	3.30 (s, 2H)	8.47, 8.22 (2d, 4H, 8.6, arom)
i	4.76, 4.31 (ABq, 2H, 7.0)	3.96 (s, 4H)	3.06 (s, 2H)	7.84 (s, 4H, arom); 2.11 (s, 3H, COMe); 10.33 (s, 1H, NH)
j	4.27 (d, 2H, 6.8)	4.41, 3.69 (2m, 4H)	3.46 (s, 2H)	0.91 (d, 6H, 6.6), 1.76 (m, 1H) (*i*-Pr); 8.57, 8.32 (2d, 4H, 8.7, arom)
k	4.15 (d, 2H, 6.6)	4.28, 3.53 (2m, 4H)	3.13 (s, 2H)	0.79 (d, 6H, 6.6), 1.89 (m, 1H) (*i*-Pr); 2.11 (s, 3H, COMe); 10.44 (s, 1H, NH); 7.84 (s, 4H, arom)
l	3.91 (d, 2H, 5.9)	4.06, 3.86 (2d, 4H, 14.0)	3.01 (s, 2H)	0.77 (d, 6H, 6.8), 1.63 (m, 1H) (*i*-Pr); 2.11 (s, 3H, COMe); 10.44 (s, 1H, NH); 7.84 (s, 4H, arom)
m		4.13, 3.78 (2d, 4H, 13.9)	3.14 (s, 2H)	1.37, 1.27 (2s, 6H, di-Me); 2.22 (s, 3H, COMe); 10.47 (s, 1H, NH); 7.94 (s, 4H, arom)

Table 3. ^{13}C NMR Spectral Data of **4**



4	C4	C2,6	C1a,6a	C-arom	R^3
a	99.73	66.28	43.34		39.05 (Me)
b	97.58	66.08	44.30	137.72; 134.08; 129.70; 127.53	
c	79.55	66.03	44.43	(165.12; 134.06; 130.80; 116.95)[a]	
d	97.57	66.01	44.54	139.08; 136.55; 129.86; 129.52	
e	97.99	66.01	44.50	137.11; 132.53; 129.32; 128.94	
f	97.56	66.09	44.12	144.61; 134.74; 130.08; 127.59	21.21 (Me)
g	97.58	66.14	44.03	163.37; 129.94; 128.93; 114.80	55.91 (OMe)
h	97.53	65.70	45.02	150.57; 143.16; 129.16; 124.94	
i	97.63	66.14	44.13	144.08; 130.82; 129.01; 118.79	169.31, 24.27 (Ac)
j	110.52	64.39	43.93	150.62; 142.83; 129.76; 124.94	30.66, 17.71 (*i*-Pr)
k	110.95	65.14	42.99	144.26; 130.35; 129.04; 118.77	169.42, 24.29 (Ac); 30.95, 17.67 (*i*-Pr)
l	110.46	65.21	44.39	144.14; 130.65; 128.98; 118.76	129.27, 24.28 (Ac); 32.43, 17.48 (*i*-Pr)
m	102.15	58.58	43.57	143.91; 130.76; 128.56; 118.74	169.02, 24.61 (Ac); 23.98, 23.08 (di-Me)

[a] Doublets, J_{FC} = 253.0, 3.1, 9.9, and 22.8 Hz, respectively.

Table 4. Summary of Some Essential Crystallographic Data for Compounds **4j–l**[a]

	4j	**4k**	**4l**
crystal system	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	7.057(3)	6.086(2)	8.169(2)
b (Å)	9.615(6)	9.582(4)	10.215(2)
c (Å)	12.022(8)	16.399(6)	11.595(3)
α (deg)	89.98(4)	103.83(2)	85.19(2)
β (deg)	76.97(5)	98.68(3)	87.92(2)
γ (deg)	78.52(3)	101.39(2)	67.54(2)

[a] X-ray diffractions were performed on a Phillips PW 1100 diffractometer with Mo Kα radiation and a graphite monochromator. For further details of crystal structure determinations, see ref 9.

occupies two positions in relation to the aziridine ring with torsion angles O1–S–N–LP (LP = lone pair) of 180°, labeled with an asterisk (in nine structures), and −63°, labeled with a plus (in two structures). Finally, the substituent on the aziridine nitrogen is always in the *trans* and never in the *cis* position in relation to the dioxepine ring (Figure 4). The most frequent conformation is BC* (six molecules).[9] Superposition of some observed crystal state conformations of **4** clearly shows differences in the conformations of the dioxepinoazirine and sulfonylaziridine moieties of the sulfonyldioxepinoazirine molecules (Figure 3).

Molecular Mechanics Study. Computational investigations of geometry and relative stabilities were performed for all possible conformations of sulfonyldioxepinoazirines **4**. Experimental details of computational analysis, and a detailed comparison of the results obtained in such a manner together with the results of X-ray analysis, will be published separately.[9] Therefore, here are described only the results which were the basis for the computation of descriptors applied in quantitative structure–property relationship (QSPR) and QSAR studies.

Among all tested methods (semiempirical—AM1,[10] PM3;[10] empirical—Chem-X,[11] Alchemy III,[12] MMX[13]), the best reproduction of X-ray geometry and the most reasonable results of relative conformational stabilities[14] were achieved by the molecular mechanics MMX force field.[13] The most stable conformation of the studied sulfonyldioxepinoazirines **4** was found to be the boat–chair with torsion angle O1–S–N–LP = 180° (BC*), and this was the most frequent in the crystalline state

Table 5. Lipophilicity, Convex Connolly's Surface Area Ratios, and Hypoglycemic Activity of **4**

4	t_R (rel)[a]	ln t_R (rel)	log P[b]	S_{NS}/S_T[c]	%BGL ± SEM[e,f] (n = 6)	HAR[j]
b	1.7736	0.5730	−0.0550	0.6098	53.0 ± 6.0	3.36
c	2.3082	0.8365	0.1158	0.6309	76.0 ± 1.6[g]	1.71
d	5.0818	1.6257	0.5401	0.6751	77.0 ± 5.0[h]	1.64
e	6.2075	1.8258	0.8347	0.6979	107.0 ± 2.0[i]	−0.50
f	3.3711	1.2152	0.6215	0.6536	94.0 ± 3.1[i]	0.42
g	2.5157	0.9226	−0.1762	0.6393	78.0 ± 2.8	1.57
i	1.0000	0.0000	−0.9662	0.5849	37.0 ± 4.2	4.50
j	37.0570	3.6125		*d*	78.0 ± 2.0	1.57
k	16.4843	2.8024	0.9918	*d*	85.0 ± 3.1[h]	1.07
l	6.4654	1.8665	0.9918	0.6798	84.8 ± 3.0[h]	1.08
m	3.9245	1.3672	2.3442	0.6545	*k*	*k*
metformin					86.0 ± 4.0[h]	1.00

[a] HPLC relative retention time (**4i** = 1); separated on a Supelcosil LC-18 DB (25 cm × 4.6 mm I.D.) column using a methanol/acetate buffer in the gradient mode. [b] Calculated according to ref 17. [c] Convex Connolly's molecular surface area ratio of **4** BC* conformers, calculated by an in-house program based on ref 22. [d] Compounds **4j**,**k** adopt in solution several different conformations other than the BC* one. Therefore S_{NS}/S_T was not calculated. [e] Blood glucose level (percent of initial) 1 h following a 20 mg/kg sc dose of **4**. [f] $p < 0.001$ by two-tailed student's test. [g] $p < 0.005$. [h] $p < 0.01$. [i] $p > 0.05$. [j] Hypoglycemic activity ratio, calculated by eq 8; a minus sign indicates that **4e** increases blood glucose level. [k] Not tested in this series.

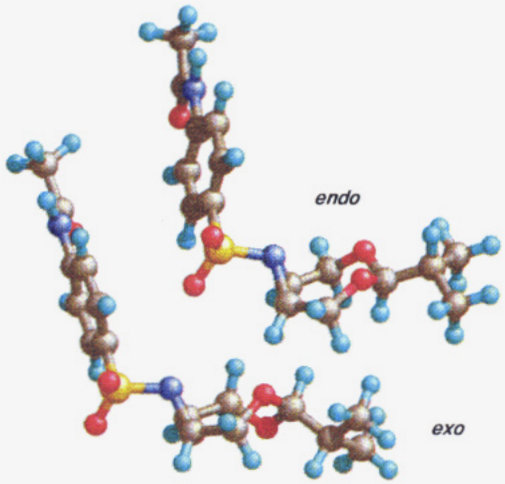


Figure 2. Ball and stick representation of 4-isopropyl isomers: *exo* (**4k**) and *endo* (**4l**).

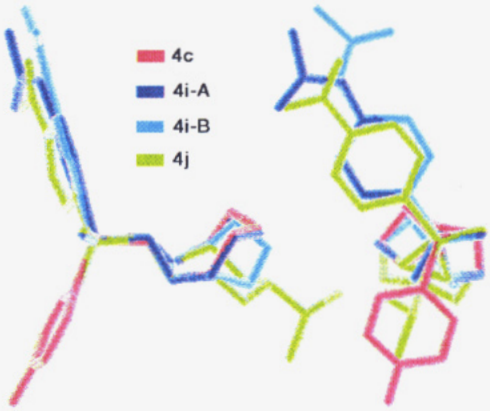


Figure 3. Superposition of crystal state conformations of sulfonyldioxepinoazirines **4c**, **4i**-A (crystallographically independent molecule A), **4i**-B (crystallographically independent molecule B), and **4j**. Hydrogen atoms are omitted for clarity.

as established by X-ray studies. This conformation is the most stable *in vacuo* and in media with dielectricity $\epsilon = 81$ (water, physiological media). Conformational space of *N*-arylsulfonyl derivatives **4** was also explored by dihedral driver routine for rotations of C−S (15° step, 0−180° range) and S−N (15° step, 0−360° range) single bonds. The relative strain energy contour plot (Figure 5) of a boat−chair class of conformations obtained for the model compound **4b** shows three minimums. Two of them, with dihedral angles (C−C−S−N, C−S−N−C) of 100° and 270° as well as 80° and 160°, respectively, correspond to the mirror symmetrical BC* global minimum conformations. These conformations are characterized by a low energy barrier for rotation around the C−S bond. A third local minimum with dihedral angles of 90° and 35° is 1.6 kcal/mol higher and corresponds to the BC^+ conformation. Fortunately, the general appearance of the contour plot does not depend upon the conformation of the dioxepinoazirine moiety (boat−chair, twist−boat, chair−chair).

These results are in good agreement with those obtained by X-ray diffraction for all studied sulfonyldioxepinoazirines **4**[9] (dots, Figure 5), as well as with those of other sulfonylaziridines filed in the Cambridge Structural Data Base[15] (pluses, Figure 5). Consequently, only the BC* conformation of **4** was chosen and used in QSPR and QSAR studies.

QSPR and QSAR Studies. The relative hypoglycemic activity of structurally very close sulfonyldioxepinoazirines **4** is expected to depend mostly upon their hydrophobicity. Therefore, it was reasonable to study the relationship between the hypoglycemic activity of **4** expressed as HAR and the hydrophobicity factor log P,[16] calculated from the atomic contribution constants[17] (Table 5). Usability of such log P values was tested by their correlation with the reverse phase HPLC retention times (RP-HPLC t_R)[18] of **4** as the experimental descriptor of hydrophobicity. The RP-HPLC t_R values were measured and expressed as a logarithm of relative retention times, ln t_R(rel) (t_R of **4i** = 1) (Table 5).

Unfortunately, such regression analysis performed on nine sulfonyldioxepinoazirines, **4b**−**g**,**i**,**l**,**m**, listed in Table 5 failed to show a significant correlation of their calculated log P(calc) with the experimental RP-HPLC relative retention times ln t_R(rel) (eq 1).

$$\ln t_R(\text{rel}) = 0.48(\pm 0.18) \times \log P(\text{calc}) + 0.91(\pm 0.17) \quad (1)$$

$$N = 9;\ r = 0.719;\ \text{EV} = 51.8\%;\ s = 0.459;\ F = 7.5;\ Q^2 = -0.593$$

Although the removal of the dimethyl derivative **4m**

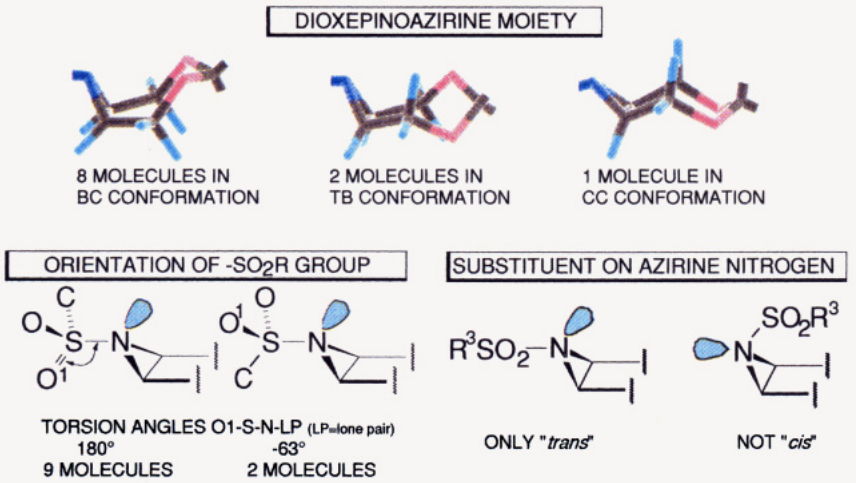


Figure 4. Conformational behavior of **4** in solid state according to ref 9.

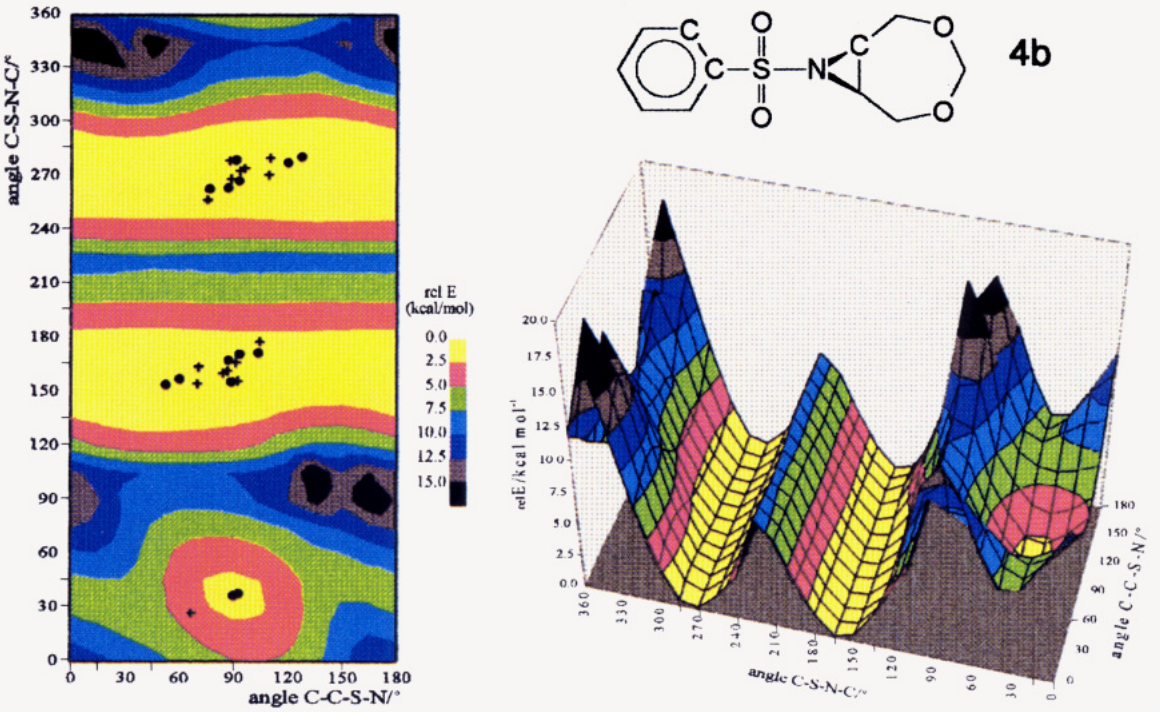


Figure 5. Relative strain energy ($E_{rel} = E - E_{min}$) contour plot of the model compound **4b** obtained by varying together torsional angles C–C–S–N and C–S–N–C by 15° steps and the corresponding 3D representation. Dots: the studied **4** from X-ray. Pluses: other sulfonylaziridines filed in ref 15.

from the regression (eq 2) increased the correlation coefficient:

$$\ln t_R(\text{rel}) = 0.97(\pm 0.13) \times \log P(\text{calc}) + 0.88(\pm 0.08) \quad (2)$$

$$N = 8;\ r = 0.953;\ \text{EV} = 90.7\%;\ s = 0.215;\ F = 58.7;\ Q^2 = 0.097$$

it was obvious that, on the basis of atomic contributions, log P(calc) is not sensitive to conformational changes and isomerization, and therefore, eqs 1 and 2 are not satisfactory models for the hydrophobicity of **4**.

However, since the polarity of molecular surfaces is a conformationally dependent descriptor of hydrophobicity,[19] we turned our attention to the analytically calculated Connolly's surface as the most reliable and mathematically unambiguous model of molecular surface (if the atoms are approximated as hard spheres).[20]

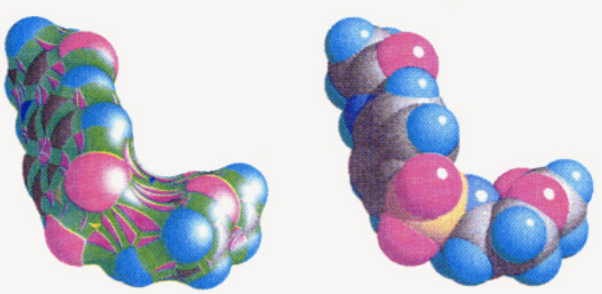


Figure 6. Connolly's molecular surface (left) and space-filling (right) models of **4i**. Convex surface: red—oxygen, yellow—sulfur, blue—nitrogen, gray—carbon, and cyan—hydrogen. Saddle-shaped surface: green. Concave surface: violet.

Therefore the Connolly's surfaces (Figure 6) were calculated for BC* conformations of **4** (probe radii 1.4 Å) and sorted into three classes: convex, concave, and saddle-shaped surfaces. The convex surfaces, representing actually the atoms' surfaces (*i.e*, spheres) in the

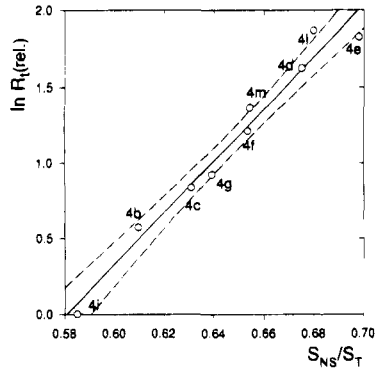


Figure 7. Graphic representation of relation in t_R(rel) vs $S_{NS/ST}$ (eq 4). Confidence interval (95%) is in dashed line.

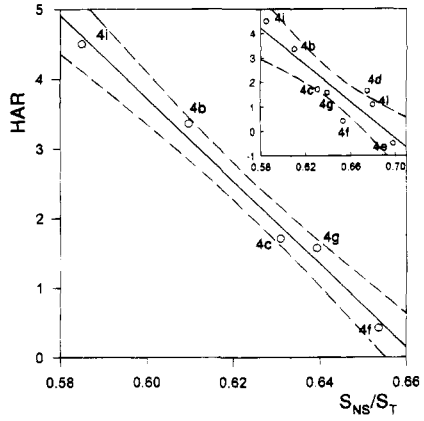


Figure 8. Graphic representation of relation HAR vs $S_{NS/ST}$ (eq 6). Confidence interval (95%) is in dashed line. Inset: HAR vs $S_{NS/ST}$ (eq 7).

molecule, were then sorted into additional subclasses: polar, nonpolar unsaturated, and nonpolar saturated surfaces. However, since both polar and nonpolar unsaturated surfaces of the molecule contribute to the hydrophilicity of the molecule,[21] we calculated the convex polar surface area (S_P), convex nonpolar unsaturated area (S_{NU}), convex nonpolar saturated area (S_{NS}), and total convex surface area of the molecule (S_T) (eq 3) for each molecule using an in-house program based on ref 22.

$$S_T = S_P + S_{NU} + S_{NS} \quad (3)$$

A hydrophobicity descriptor, which we further used in our calculations, was the S_{NS}/S_T ratio (Table 5) which represents the contribution of the hydrophobic surface to the total molecular surface. It is in a very good correlation with ln t_R(rel) for all nine compounds **4** (eq 4) (Figure 7). In the correlation were not included *exo*-

$$\ln t_R(\text{rel}) = 17.0(\pm 1.2) \times (S_{NS}/S_T) + 9.4(\pm 0.7) \quad (4)$$

$$N = 9;\ r = 0.985;\ \text{EV} = 97.0\%;\ s = 0.114;\ F = 226.2;\ Q^2 = 0.941$$

isopropyl derivatives **4j,k** due to the prediction that they in solution adopt several different conformations other than the BC* one (see Molecular Mechanics Study). It is also possible that such *exo* derivatives might be involved in some specific interactions with the stationary phase of the RP-HPLC column, and therefore their t_R values would not be the only measure of hydrophobicity. However, eq 4 is an almost generally valid (eight different chemical elements in nine compounds), single variant, highly predictive ($Q^2 = 0.941$), and physically unambiguous model of hydrophobicity of sulfonyldioxepinoazirines **4**.

Since the goal of this study was to find a model for prediction of sulfonyldioxepinoazirine hypoglycemic activity, we correlated HAR with ln t_R(rel) as the experimental descriptor of hydrophobicity (eq 5)

$$\text{HAR} = -3.4(\pm 0.4) \times \ln t_R(\text{rel}) + 4.8(\pm 0.3) \quad (5)$$

$$N = 5;\ r = 0.978;\ \text{EV} = 95.7\%;\ s = 0.378;\ F = 66.3;\ Q^2 = 0.781$$

and on the other hand HAR vs S_{NS}/S_T as the theoretical (calculated) descriptor of hydrophobicity (eq 6, Figure 8).

$$\text{HAR} = -60(\pm 4) \times (S_{NS}/S_T) + 39(\pm 3) \quad (6)$$

$$N = 5;\ r = 0.993;\ \text{EV} = 98.7\%;\ s = 0.215;\ F = 221.0;\ Q^2 = 0.957$$

Both equations have high correlation coefficients for five sulfonyldioxepinoazirines, **4b,c,f,g,i**. However, HAR, ln t_R(rel), and S_{NS}/S_T available values of the other three, **4d,e,l** did not correlate as well (eq 7, Figure 8, inset).

$$\text{HAR} = -38(\pm 7) \times (S_{NS}/S_T) + 26(\pm 5) \quad (7)$$

$$N = 8;\ r = 0.900;\ \text{EV} = 80.9\%;\ s = 0.745;\ F = 25.5;\ Q^2 = 0.681$$

A serious limitation for such a QSAR study using *in vivo* data is an assumption that all studied compounds have the same or similar pharmacokinetics, distribution, drug metabolism, and total clearance.[23] Some of this limitation may be also one of the reasons for the rather poor fit of **4d,e,l** derivatives in the above-mentioned correlation.

In any case, the obtained QSAR model is based upon the theoretical data (calculated S_{NS}/S_T) and characterized by good correlation and the small deviation coefficients, as well as the high predictability ($Q^2 = 0.957$) (eq 6) (Figure 8). Therefore, it seemed to be a good model for predicting the HAR of **4** based on the solvent accessible, convex Connolly's molecular surface area of the most stable conformers. Indeed, eq 6 even for such a reduced set of **4** clearly showed a relationship between the polarity of **4** and the hypoglycemic activity expressed as HAR. It is reasonable to propose that the hypothetically more hydrophilic derivatives of **4** could be more active in this hyperglycemic model. The most potent compound in this series, the 1-[4-(acetylamino)phenylsulfonyl] derivative **4i**, was further examined.

Evaluation of Compound 4i. As shown in Figure 9, compound **4i** is superior to metformin in a subcutaneous 20 mg/kg dose in alloxanized mice. The decrease of blood glucose level (in percent) reached a minimum after 1 h (~60%) but after 6 h still retained about 30% of glucose-lowering activity. At the same time, metformin reduced the blood glucose level by only 15% and 20%, respectively. Also, as shown in Figure 10, the intravenous administration of the same dose of **4i** in the same model showed practically the same effect as in the sc route of application but reached it in a significantly shorter period (after 40 min). In the case of per os application of **4i**, as expected, the decrease of

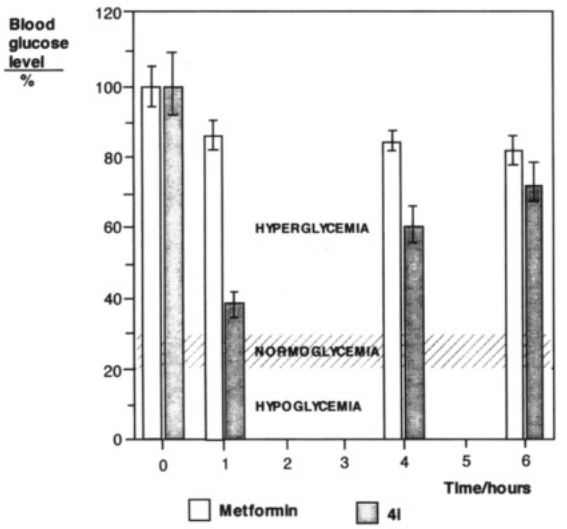


Figure 9. Antihyperglycemic activity of sulfonyldioxepinoazirine **4i** and metformin in alloxanized mice at sc 20 mg/kg dose. Each value presents the mean with the SE ($n = 6$).

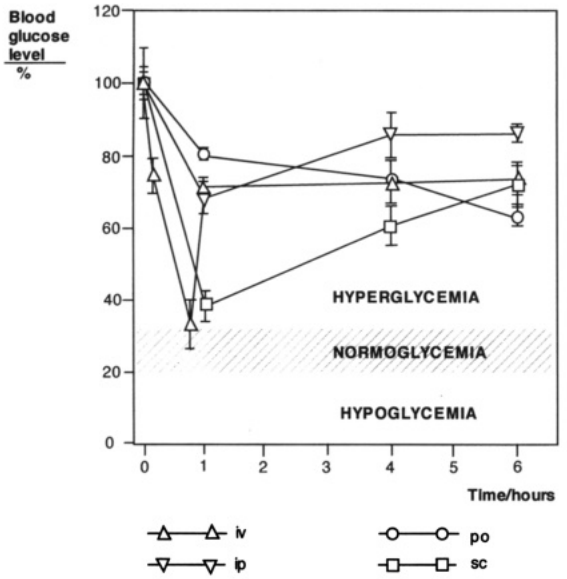


Figure 10. Antihyperglycemic activity of sulfonyldioxepinoazirine **4i** in alloxanized mice at 20 mg/kg iv, ip, po, and sc doses. Each value represents the mean with the SE ($n = 6$).

the blood glucose level was considerably slower. Six hours after **4i** administration, it attained about 60% of the initial value. Intraperitoneal activity of **4i** had a similar time course profile as in the iv route of application. Unfortunately, the concentration of blood glucose was not measured within the first hour following the ip application of drug. Thus, the maximum of activity may not have been observed.

It should be noted that hypoglycemia was not observed in any case, even after the application of 5 time higher doses of drug. Sulfonyldioxepinoazirine **4i**, in a subcutaneous 20 mg/kg dose, 1 h after application, also showed good antihyperglycemic activity in glucose-primed fasted mice (Figure 11). Finally, as shown in Table 6, intravenously and subcutaneously administrated compound **4i** did not cause a dose dependent decrease of blood glucose level in healthy (nondiabetic, control) mice and rats. Therefore, it is plausible to conclude that 1-sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines **4** may represent a new class of potent antihyperglycemic agents.

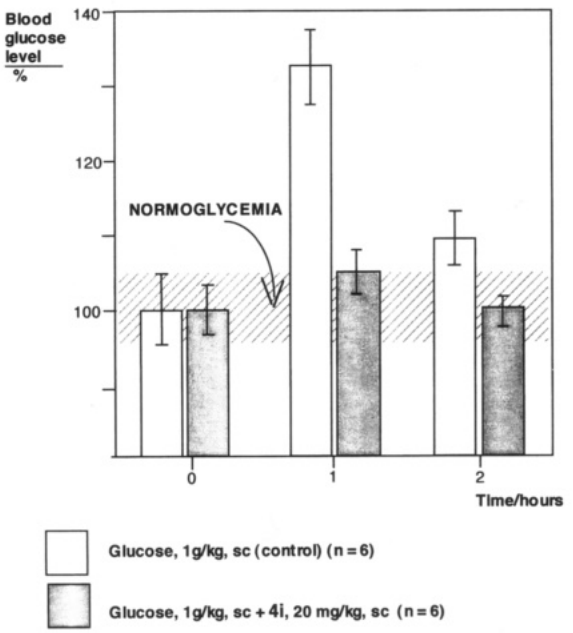


Figure 11. Antihyperglycemic activity of sulfonyldioxepinoazirine **4i** in glucose-primed mice. Each value represents the mean with the SE ($n = 6$).

Conclusions and Projections

A series of 1-sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirines **4**, hitherto an unknown class of fused dioxepins, was synthesized, and the antihyperglycemic activity, by several models and routes of administration, was established. Using a variety of experimental and computational techniques, we developed QSPR and QSAR models, to our knowledge the first in the field of antihyperglycemic agents. These models allow prediction of the observed physical properties (RP-HPLC t_R) and hypoglycemic activity (expressed as HAR) by, to solvent accessible, convex surface area of the most stable drug's conformer (convex Connolly's surface area). This study also suggested that hypothetically more hydrophilic derivatives of **4** could be more active in this hyperglycemic model.

Of course, these results have generated a new set of questions: On the basis of the presented biological profile, what is the mechanism of activity of these drugs? What is the pharmacophore? Is the activity observed due to the administered substance and/or its metabolite(s)? These questions identify the areas of additional investigations related to organic synthesis, pharmacology, and drug metabolism of this series of potent antihyperglycemic agents.

Experimental Section

Chemistry. General Information. Melting points were determined using a Fischer-Johns apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded by a Varian XL-GEM 300 spectrometer, with TMS as internal standard; the values of chemical shifts (δ) are given in ppm and coupling constants (J) in hertz; DMSO-d_6 was used as solvent. Mass spectra were scanned on a Shimadzu GCMS-QP 1000A instrument operating at 70 eV. TLC was performed using Merck Kieselgel 60 F_{254} silica plates, and components were visualized using UV light and iodine vapor. HPLC was performed using a Hewlett Packard 1090 system. The unit was operated in the gradient mode using a methanol/acetate buffer (column Supelcosil LC-18 DB, 25 cm × 4.6 mm i.d.). Compounds were purified by column chromatography using Merck Kieselgel 60 (70−230 mesh) and were homogeneous by

Table 6. Effect of **4i** on Blood Glucose Level in Healthy (Control, Nondiabetic) Mice and Rats at Different Doses and Routes of Application

animals	appl/dose (mg/kg)	N^a	blood glucose (mmol/L of whole blood) 0 min	40 min	60 min	120 min
mice	iv/5	10	8.35 ± 0.89	8.61 ± 1.60	8.72 ± 1.42	
	iv/20	12	8.83 ± 0.58	9.30 ± 0.59	8.82 ± 0.91	
	sc/20	6	12.43 ± 0.69		14.41 ± 0.75	13.15 ± 0.72
	sc/100	6	11.72 ± 2.45		12.09 ± 1.01	13.17 ± 0.70
rats	sc/20	7	5.52 ± 0.19		5.44 ± 0.18	

[a] Number of animals used.

TLC or/and HPLC, unless otherwise stated. Solvents were PA grade and used without further purification. Sulfonyl chlorides used were obtained from commercial sources, and *vic*-(acylamino)halogenodioxepanes **2**[8] and tetrahydrodioxepino-[5,6-*b*]azirines **3**[5,6] were prepared previously. Chemical yields were not optimized.

General Procedure for the Preparation of 1-Sulfonyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]-azirines 4a-j,m. This procedure is illustrated for the preparation of 1-(methylsulfonyl)-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]-dioxepino[5,6-*b*]azirine (**4a**). A mixture of **3a** (288 mg, 2.50 mmol), methansulfonyl chloride (0.25 mL), pyridine (0.35 mL), and methylene chloride (5.0 mL) was stirred at room temperature for 60 min. Upon addition of an additional 20 mL of methylene chloride, the mixture was worked up with 2 × 10 mL of aqueous sodium hydroxide solution (1:1); the organic layer was separated, washed with 10 mL of water, neutralized with diluted hydrochloric acid up to pH 6, washed once more with 10 mL of water, and dried over anhydrous sodium sulfate. The evaporation of methylene chloride yielded crude, TLC pure sulfonylazirine **4a**: 223 mg (46.3%); mp 96–98 °C. An analytical sample was obtained by recrystallization from an ethyl acetate–petroleum ether (5:2) mixture: mp 98–100 °C; MS (rel intensity) *m/e* 194 (2.2) $[M + 1]^+$, 114 (17.0), 79 (61.3).

In the same manner were prepared 1-(phenylsulfonyl)-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**4b**), 1-[(4-fluorophenyl)sulfonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]-dioxepino[5,6-*b*]azirine (**4c**), 1-[(4-chlorophenyl)sulfonyl]-1a,2,6,-6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**4d**), 1-[(4-bromophenyl)sulfonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]-dioxepino[5,6-*b*]azirine (**4e**), 1-[(4-methylphenyl)sulfonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**4f**), 1-[(4-methoxyphenyl)sulfonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**4g**), 1-[(4-nitrophenyl)sulfonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**4h**), 1-[[4-(acetylamino)phenyl]sulfonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (**4i**), *exo*-4-isopropyl-1-[(4-nitrophenyl)sulfonyl]-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino-[5,6-*b*]azirine (**4j**), and 1-[[4-(acetylamino)phenyl]sulfonyl]-4,4-dimethyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]-azirine (**4m**). Data are listed in Tables 1–3 and Figure 1.

***exo*- and *endo*-1-[[4-(Acetylamino)phenyl]sulfonyl]-4-isopropyl-1a,2,6,6a-tetrahydro-1*H*,4*H*-[1,3]dioxepino[5,6-*b*]azirine (4k,l).** Starting from *exo*-**3b** (R^1 = H, R^2 = *i*-Pr) (190 mg, 1.21 mmol), 4-(acetylamino)benzenesulfonyl chloride (367.0 mg, 1.5712 mmol), pyridine (0.164 mL), and methylene chloride (5.0 mL) according to the general procedure, the crude product (316 mg, 73.8%), by TLC and HPLC only as the mixture of *exo* (**4k**) and *endo* (**4l**) isomers, was obtained. The isomers were separated by column chromatography using Merck Kiessel gel 60 (70–230 mesh) and toluene–ethyl acetate (1:1) as eluent. The first eluted was the *exo* isomer **4k** (253 mg, 59.1%; mp 140–142 °C), which was recrystallized from an ethyl acetate–methanol (1:1) mixture: mp 144–146 °C; MS (rel intensity) *m/e* 354 (1.1) $[M]^+$, 198 (100), 156 (14.7). The *endo* isomer **4l** was the second (59.5 mg, 13.8%; mp 236–240 °C), which was recrystallized from an ethyl acetate-methanol (3:1) mixture: mp 238–240 °C; MS (rel intensity) *m/e* 354 (2.3) $[M]^+$, 198 (100), 156 (25.2). Their structures were consistent with analytical and spectral data (Tables 1–3) and confirmed by X-ray analysis (Figure 2, Table 4).

Molecular Modeling. Statistical calculations were performed by the SAS package[24] ported on an IBM PC platform. log *P* values were calculated on the basis of atomic addition constants:

$$\log P(\text{calc}) = \sum n_i a_i$$

tabulated in ref 17. Connolly's molecular surfaces were calculated and plotted by an in-house program developed on the basis of Connolly's primal algorithm[22] with minor improvements.

Convex surfaces were sorted in subgroups in the following manner. N, O, and amide H atoms contribute to S_P surface because they could contribute to the formation of strong H-bonds. sp^2-hybridized C atoms contribute to S_{NU} surface, and S_{NS} surface is contributed by the atom types: C_{sp^3}, H (except amide type), S (sulfonamide type), F (C–F type), Cl (C–Cl type), and Br (C–Br type).

Molecular coordinates of **4** needed in Connolly's molecular surface calculations were obtained by geometry optimization of the BC* conformation with the MMX force field[13] on an IBM PC 486/DOS platform. Chem-X[11] (ported on DEC Alpha 400/OSF and IBM PC 486/Windows) and Alchemy III[12] (ported on IBM PC 486/Windows) were used for editing and visualization of molecules. van der Waals radii of atoms were taken from ref 25, and the probe (H_2O) molecule was assumed to be a sphere with radius 1.4 Å.

Pharmacological Methods. Alloxanized, Diabetic Mice. The experiments of the evaluation of hypoglycemic activity were performed on CBA strain mice of either sex weighing 20–25 g. They were caged with food and water *ad libitum* on a lighting schedule of 12 h of light–12 h of darkness. Hyperglycemia was induced by a single injection of 65 mg/kg alloxan monohydrate (Sigma) into the tail vein. The animals were used for testing 48 h after alloxan injection. The initial sample of blood (0.025 mL) was taken from the tail vein, and the 20 mg/kg test material (new compound of the formula **4** or metformin, 1,1-dimethylbiguanide hydrochloride; Sigma), dissolved in a minimum volume of DMSO and diluted by saline–0.9% NaCl, was given by single subcutaneous, intravenous, or intraperitoneal injection or by stomach tube (per os). Additional blood samples were taken at different intervals (40–360 min) depending on the way of application. Blood glucose was assayed by an enzymatic–colorimetric method[26] (Glukoza *plus* kit; PLIVA d.d., Zagreb, Croatia). The results are expressed as mmol/L of whole blood. The initial blood sample was the control value, and it is taken as 100%. Antihyperglycemic effects of a 20 mg/kg dose of **4**, 1 h following the subcutaneous administration of drug, are given as percent of initial blood glucose level (%BGL, Table 5). Hypoglycemic activity ratios (HAR values, Table 5) used for QSAR are expressed as potency ratio to the effect of metformin and were calculated by eq 8.

$$\text{HAR} = (100 - \%\text{BGL of } \mathbf{4})/(100 - \%\text{BGL of metformin}) \quad (8)$$

For other results, see Figures 8–10.

Glucose-Primed Mice. Two groups of six CBA strain mice weighing 20–25 g were fasted for 16 h. Then in one group each animal received 1000 mg/kg glucose subcutaneously in a volume of 10 mL of water/kg of body weight. In the other group each animal received simultaneously 1000 mg/kg glucose and 20 mg/kg **4i**, subcutaneously. Blood was sampled and the glucose level analyzed and expressed as above (see Figure 11).

Healthy (Nondiabetic, Control) Mice and Rats. Groups of CBA strain mice weighing 20–25 g and Fischer strain rats weighing 160–200 g were fasted for a period of 16 h prior to treatment. The drug was administered at zero time, the blood samples were drawn from the tail vein, and the glucose level was analyzed and expressed as above (see Table 6).

Acknowledgment. Financial support by the Ministry of Science and Technology of the Republic of Croatia is gratefully acknowledged.

Supporting Information Available: One table containing C,H,N,S analyses of sulfonyldioxepinoazirines **4** (1 page). Ordering information is given on any current masthead page.

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