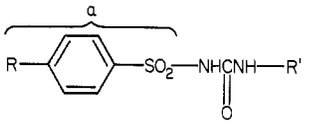
Sulfonyliminoimidazolidines. A New Class of Oral Hypoglycemic Agents. 1. 1-[[*p*-[2-(Acylamino)ethyl]phenyl]sulfonyl]-2-iminoimidazolidines[1]

Ernst H. Schweizer,* Fritz Märki, Claude Lehmann, and Henri Dietrich

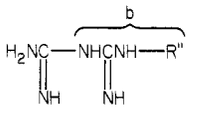
Research Department, Pharmaceuticals Division, Ciba-Geigy Limited, CH-4002 Basle, Switzerland. *Received May 14, 1982*

A series of 1-[[*p*-[2-(acylamino)ethyl]phenyl]sulfonyl]-2-iminoimidazolidines has been synthesized. Compounds from this new class of oral hypoglycemic agents lower blood glucose in normal and in streptozotocin-diabetic rats. Potent analogues were obtained by modification of the acyl residue. 1-[[*p*-[2-(Crotonylamino)ethyl]phenyl]-sulfonyl]-3-cyclohexyl-2-iminoimidazolidine (**44**) turned out to be the most potent compound in the normal rat (20 times tolbutamide), and 1-[[*p*-[2-(5-methylisoxazole-3-carboxamido)ethyl]phenyl]sulfonyl]-3-cyclohexyl-2-imino-imidazolidine (**30**) displayed the highest potency in the diabetic rat (similar to phenformin).

Oral therapy of non-insulin-dependent diabetes mellitus presently relies on compounds from two chemical classes, viz., sulfonylureas (e.g., **1** and **2**) and biguanides (e.g., **3**).



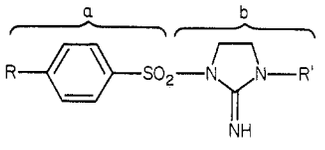
1, R = CH_3; R′ = *n*-C_4H_9 (tolbutamide)
2, R = 5-Cl-2-CH_3O-C_6H_3-$CONHCH_2CH_2$; R′ = cyclohexyl (glibenclamide)



3, R″ = $C_6H_5CH_2CH_2$ (phenformin)

While sulfonylureas lower blood sugar essentially by releasing insulin from the pancreas, biguanides act presumably by extrapancreatic mechanism(s).[2]

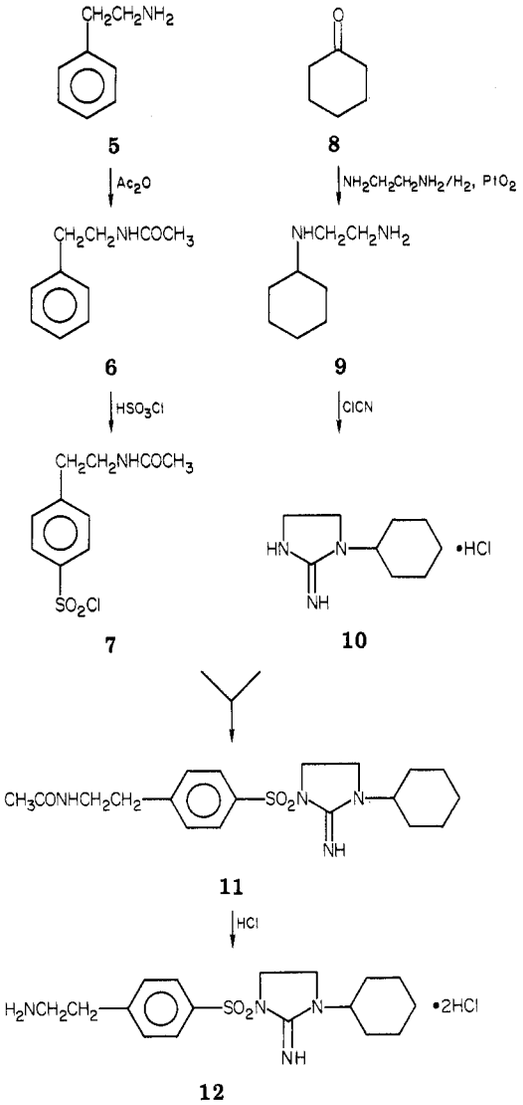
Combining structural parts of these two chemical classes (a and b) led to a new class of compounds, sulfonyliminoimidazolidines **4**. First we found a fairly good hypoglycemic effect with sulfanilyl-3-alkyl-2-iminoimidazolidines (**4a**). The most potent analogue, **4b**, was later subjected to clinical trials. It was active in man but did not reach the potency of tolbutamide[3] (**1**).



4a, R = NH_2; R′ = alkyl
b, R = NH_2; R′ = *n*-Bu
c, R = R″$CONHCH_2CH_2$; R′ = cyclohexyl

Further investigations showed, by analogy to sulfonylureas of the "second generation" [e.g., glibenclamide[4] (**2**)], that introducing an (acylamino)ethyl group for R in (phenylsulfonyl)iminoimidazolidine (**4**) markedly improved potency. Variation of the substituent R′ at the heterocycle resulted in an activity optimum with R′ = cyclohexyl, cyclopentyl, or *n*-, iso-, and *tert*-butyl. In this report we present syntheses and results of hypoglycemic evaluation of selected 1-[[*p*-[2-(acylamino)ethyl]phenyl]sulfonyl]-2-iminoimidazolidines of the general type **4c**.

Scheme I



Chemistry. 1-[[*p*-[2-(Acylamino)ethyl]phenyl]-sulfonyl]-2-iminoimidazolidines (**4c**) were prepared by the sequence outlined in Schemes I and II. [*p*-(2-Acetamidoethyl)phenyl]sulfonyl chloride[5] (**7**) was obtained by

(1) The majority of the compounds of type **4c** are described in one of the following British Patents: 1 269 000 [*Chem. Abstr.*, **73**, 77078 (1970)], 1 269 081 [*Chem. Abstr.*, **72**, 12725 (1970)], 1 305 836 [*Chem. Abstr.*, **74**, 141796 (1971)], 1 306 560 [*Chem. Abstr.*, **74**, 141797 (1971)], 1 306 602 [*Chem. Abstr.*, **74**, 125691 (1971)], and 1 313 578 [*Chem. Abstr.*, **74**, 100045 (1971)]. They are also described in corresponding patents of other countries, which include further compounds and other synthetic routes.
(2) W. G. Oakly, D. A. Pyke, and K. W. Taylor, in "Diabetes and Its Management", 3rd ed., Blackwell Scientific Publications, Oxford, 1978, p 76.
(3) H. Hobitz, L. Kerp, H. Otto, B. Sachsse, H. Mehnert, P. Göbel, and G. Keiser, unpublished results.
(4) H. Weber, W. Aumüller, K. Muth, R. Weyer, R. Heerdt, E. Fauland, A. Bänder, W. Pfaff, F. H. Schmidt, and H. Stork, *Arzneim.-Forsch.*, **19**, 1326 (1969).

0022-2623/83/1826-0964$01.50/0

Scheme II

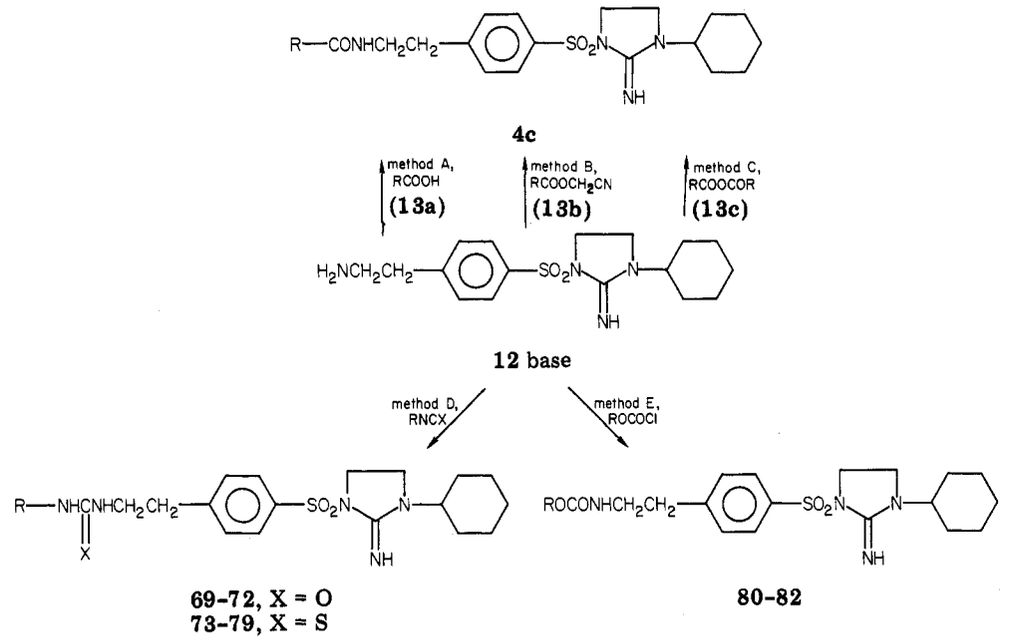
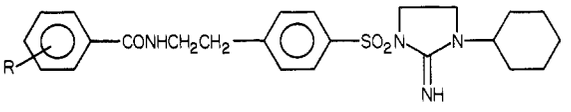


Table I. Aromatic Substituents



compd	R	mp, °C	yield,[a] %	formula[b]	method	hypoglycemic activity[c] ED_{20}^{N}	ED_{50}^{N}	ED_{20}^{D}
14	H	170-173	63	$C_{24}H_{30}N_4O_3S$	A	0.021	0.20	
15	2-Cl	191-192	56	$C_{24}H_{29}ClN_4O_3S$	A	0.023	0.23	
16	2-CH_3	198-199	81	$C_{25}H_{32}N_4O_3S$	A	0.022	>0.85[d]	
17	2-OCH_3	178-179	42	$C_{25}H_{32}N_4O_4S$	A	0.093	>0.83[d]	
18	3-OCH_3	166-167	58	$C_{25}H_{32}N_4O_4S$	A	0.062	0.38	0.31
19	2-SCH_3	184-186	38	$C_{25}H_{32}N_4O_3S_2$	A	0.064	0.62	
20	4-OCH_3	153-154	83	$C_{25}H_{32}N_4O_4S$	A	0.064	0.83	
21	3,4-Cl_2	227-228	76	$C_{24}H_{28}Cl_2N_4O_3S$	A	0.37	>0.76[d]	
22	3,4-$(OCH_3)_2$	203-205	79	$C_{26}H_{34}N_4O_5S$	A	0.066	0.78	
23	2-OCH_3-5-Cl	167-170	73	$C_{25}H_{31}ClN_4O_4S$	A	0.12	>0.77[d]	
tolbutamide						0.056	0.30	>1[d,e]
glibenclamide						0.0040	0.020	>0.5[d,e]
phenformin						>1[d,e]	>1[d,e]	0.16

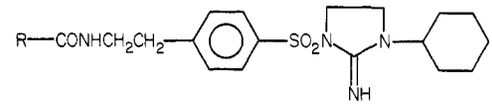
[a] No attempt was made to maximize yield. [b] Analyzed for C, H, and N; analytical results were within ±0.4% of theoretical values. [c] Oral dose (millimoles per kilogram) lowering blood glucose by a mean ($N \geq 5$) of 20 and 50%, respectively, in normal rats (ED_{20}^{N}, ED_{50}^{N}) and of 20% in diabetic rats (ED_{20}^{D}). [d] Highest dose tested. [e] Inactive (less than 10% blood sugar decrease).

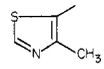
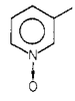
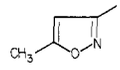
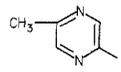
sulfochlorination of *N*-phenethylacetamide[6] (**6**). 1-Cyclohexyl-2-iminoimidazolidine hydrochloride (**10**) resulted from the reaction of cyanogen chloride with *N*-cyclohexylethylenediamine (**9**). The latter was prepared from cyclohexanone (**8**) according to A. J. Bruno et al.[7] By condensation of **7** and **10**, 1-[[*p*-(2-acetamidoethyl)-phenyl]sulfonyl]-3-cyclohexyl-2-iminoimidazolidine (**11**) was obtained, from which 1-[[*p*-(2-aminoethyl)phenyl]-sulfonyl]-3-cyclohexyl-2-iminoimidazolidine dihydrochloride (**12**) resulted by hydrolysis with HCl. Acylation of **12** was performed by one of the following procedures, the proper choice depending on the residue R: condensation of **12** and acids **13a** by means of dehydrating agents, e.g., dicyclohexylcarbodiimide (method A); reaction of **12** with activated esters **13b** (method B); or reaction of **12** with anhydrides **13c** (method C). Reaction of **12** with acid chlorides of **13a** yielded a mixture of products—including acylation at the imino nitrogen—and was, therefore, not found satisfactory. Ureido and thioureido derivates (Table VI) were obtained by addition of **12** to isocyanates and isothiocyanates (method D), whereas the urethanes were synthesized by reaction of **12** with alkyl or aryl chloroformates (method E). The amino acid derivatives in Table VII were prepared according to method A or B, in general, with N-protected amino acids **13a** or the corresponding activated esters **13b**. In this case, an additional step (removal of the protecting group) is necessary. For details of the preparative work and additional synthetic routes, refer to the Experimental Section and ref 1.

Hypoglycemic Activity. Hypoglycemic activity was evaluated in two animal models, the normal and the streptozotocin-diabetic rat. While sulfonylureas lower blood sugar in normal rats, they are completely inactive in the diabetic rat model as used in this study, i.e., when

(5) E. Miller, J. M. Sprague, L. W. Kissinger, and L. F. McBurney, *J. Am. Chem. Soc.*, **62**, 2099 (1940).
(6) J. L. E. Erickson, *Chem. Ber.*, **59B**, 2665 (1926).
(7) A. J. Bruno, S. Chaberek, and A. E. Martell, *J. Am. Chem. Soc.*, **78**, 2726 (1956).

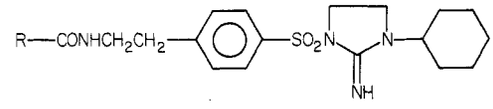
Table II. Heterocyclic Substituents



compd	R	mp, °C	yield,[a] %	formula[b]	method	hypoglycemic activity[c] ED_{20}^N	ED_{50}^N	ED_{20}^D
24		170-171	83	$C_{23}H_{29}N_5O_3S$	A	0.034	0.16	>0.22[d]
25		167-168	86	$C_{23}H_{29}N_5O_3S$	A	>0.83[d]		
26		143-144	72	$C_{22}H_{28}N_4O_4S$	A	0.013	0.16	0.22
27		170-172	53	$C_{22}H_{28}N_4O_3S_2$	A	0.022	0.17	
28		164-165[f]	64	$C_{22}H_{31}N_5O_4S_2$	A	>0.22[d,e]		
29		135-136	74	$C_{23}H_{29}N_5O_4S$	A	0.042		>0.64[d,e]
30		150-152	57	$C_{22}H_{29}N_5O_4S$	A	0.022	0.13	0.14
31		160-161	63	$C_{22}H_{28}N_6O_3S$	A	0.12	0.48	>0.22[d]
32		72-75[g]	26	$C_{22}H_{31}ClN_6O_4S$	B	0.20	>0.59[d]	>0.59[d]
33		100-103[f]	97	$C_{23}H_{32}N_6O_4S$	A	0.010	0.10	>0.61[d]

[a] No attempt was made to maximize yield. [b] Analyzed for C, H, and N; analytical results were within ±0.4% of theoretical values. [c] Oral dose (millimoles per kilogram) lowering blood glucose by a mean ($N \geq 5$) of 20 and 50%, respectively, in normal rats (ED_{20}^N, ED_{50}^N) and of 20% in diabetic rats (ED_{20}^D). For potency of reference compounds refer to Table I. [d] Highest dose tested. [e] Inactive (less than 10% blood sugar decrease). [f] Monohydrate. [g] Monohydrate hydrochloride.

Table III. Alkyl and Cycloalkyl Substituents



compd	R	mp, °C	yield,[a] %	formula[b]	method	hypoglycemic activity[c] ED_{20}^N	ED_{50}^N	ED_{20}^D
34	H	135-136	69	$C_{18}H_{26}N_4O_3S$	A	0.053	0.26	
35	CH_3	181-183	84	$C_{19}H_{28}N_4O_3S$	A	0.038	0.24	
36	$CH_3(CH_2)_2$	144	69	$C_{21}H_{32}N_4O_3S$	A	0.024	0.083	0.52
37	$CH_3(CH_2)_3$	154-155	72	$C_{22}H_{34}N_4O_3S$	B	0.035	0.12	
38	$(CH_3)_2CHCH_2$	180-181	53	$C_{22}H_{34}N_4O_3S$	A	0.046	0.15	
39	$(CH_3CH_2)_2CH$	169-170	77	$C_{23}H_{36}N_4O_3S$	A	0.098	>0.89[d]	
40	c-C_3H_5	172-173	62	$C_{21}H_{30}N_4O_3S$	A	0.034	0.15	
41	c-C_4H_7-$(CH_2)_2$	208-209	74	$C_{24}H_{36}N_4O_3S$	A	0.052	0.20	

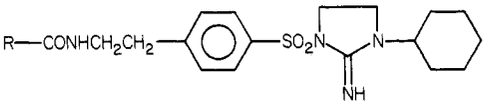
[a] No attempt was made to maximize yield. [b] Analyzed for C, H, and N; analytical results were within ±0.4% of theoretical values. [c] Oral dose (millimoles per kilogram) lowering blood glucose by a mean ($N \geq 5$) of 20 and 50%, respectively, in normal rats (ED_{20}^N, ED_{50}^N) and of 20% in diabetic rats (ED_{20}^D). For potency of reference compounds, refer to Table I. [d] Highest dose tested.

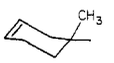
diabetes was induced by a single intravenous dose of 55 mg/kg of streptozotocin at least 1 month before the experiment. Biguanides are practically inactive in the normal rat but lower blood glucose in the diabetic rat (data of reference compounds are given in Table I). Sulfonyliminoimidazolidines, on the other hand, display hypoglycemic activity in normal and in diabetic rats, although the potency of the compounds described in this report was more prominent in normal rats.

Out of several hundred analogues synthesized,[1] **44** (Table IV) turned out to be the most potent compound in the normal rat (ED_{20}^N = 0.0028 mmol/kg, 20 times tolbutamide), whereas **30** (Table II) displayed the highest potency in the diabetic rat (ED_{20}^D = 0.14 mmol/kg, similar to phenformin).

Dose–response relationships in the normal rat can be judged from the ED_{20}^N and ED_{50}^N values given in the tables. While the ratio ED_{50}^N/ED_{20}^N was around 10 for

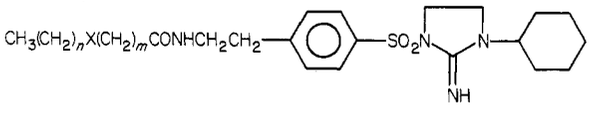
Table IV. Alkenyl and Cycloalkenyl Substituents



compd	R	mp, °C	yield,[a] %	formula[b]	method	hypoglycemic activity[c] ED_{20}^N	ED_{50}^N	ED_{20}^D
42	CH_2=CH	145-146	43	$C_{20}H_{28}N_4O_3S$	A	0.042	0.21	
43	CH_2=C(CH_3)	155-156	52	$C_{21}H_{30}N_4O_3S$	A	0.024	0.22	
44	*trans*-CH_3CH=CH	159-160	60, 80	$C_{21}H_{30}N_4O_3S$	A, C	0.0028	0.0096	0.18
45	*cis*-CH_3CH=CH	92-94	85	$C_{21}H_{30}N_4O_3S$	A	0.0038	0.038	
46	*trans*-CH_3CH=C(CH_3)	140-142	43	$C_{22}H_{32}N_4O_3S$	A	0.0035	0.017	
47	CH_2=$CHCH_2CH_2$	110-112	28	$C_{22}H_{32}N_4O_3S$	B	0.0069	0.015	0.36
48	*trans*-$(CH_3)_2CHCH$=CH	160-162	52	$C_{23}H_{34}N_4O_3S$	A	0.0096	0.034	
49	*trans*-$CH_3(CH_2)_2CH$=CH	153-156	67	$C_{23}H_{34}N_4O_3S$	A	0.0090	0.022	0.81
50	*trans*-C_6H_5CH=CH	165-168	56	$C_{26}H_{32}N_4O_3S$	A	0.11	>0.63[d]	
51	CH_2=C(C_6H_5)	140-142[e]	33	$C_{26}H_{34}N_4O_4S$	A	0.014	0.048	0.96
52		190-192	45	$C_{24}H_{34}N_4O_3S$	A	0.0044	0.015	0.39
53		158-160	23	$C_{25}H_{36}N_4O_3S$	A	0.053	0.17	
54		200-201	52	$C_{25}H_{36}N_4O_3S$	A	0.11	0.91	

[a] No attempt was made to maximize yield. [b] Analyzed for C, H, and N; analytical results were with ±0.4% of theoretical values. [c] Oral dose (millimoles per kilogram) lowering blood glucose by a mean ($N \geq 5$) of 20 and 50%, respectively, in normal rats (ED_{20}^N, ED_{50}^N) and of 20% in diabetic rats (ED_{20}^D). For potency of reference compounds refer to Table I. [d] Highest dose tested. [e] Monohydrate.

Table V. Alkyl Substituents with Interrupted Carbon Chains



compd	n	X	m	mp, °C	yield,[a] %	formula[b]	method	hypoglycemic activity[c] ED_{20}^N	ED_{50}^N	ED_{20}^D
55	0	O	1	150-151[f]	47	$C_{20}H_{32}N_5O_5S$	A	>0.92[d,e]		
56	1	O	1	111-113	52	$C_{21}H_{32}N_4O_4S$	A	0.044	0.15	
57	2	O	1	100-102	43	$C_{22}H_{34}N_4O_4S$	A	0.10	0.35	
58	0	O	2	130-132	39	$C_{21}H_{32}N_4O_4S$	A	0.033	0.22	
59	0	S	1	120-121	55	$C_{20}H_{30}N_4O_3S_2$	B	0.081	0.19	
60	1	S	1	128-130	62	$C_{21}H_{32}N_4O_3S_2$	B	0.055	0.20	0.57
61	2	S	1	110-111	67	$C_{22}H_{34}N_4O_3S_2$	B	0.10	0.55	
62	0	S	2	160-162	71	$C_{21}H_{32}N_4O_3S_2$	B	0.053	0.20	
63	0	SO	1	120-122	73	$C_{20}H_{30}N_4O_4S_2$	A	0.12		>0.66[d,e]
64	1	SO	1	137	65	$C_{21}H_{32}N_4O_4S_2$	B	0.074	0.24	0.85
65	2	SO	1	85-87	17	$C_{22}H_{34}N_4O_4S_2$	A	0.071		>0.62[d,e]
66	0	SO	2	149-150	53	$C_{21}H_{32}N_4O_4S_2$	A	0.056	0.20	0.86
67	1	SO	2	130-131	39	$C_{22}H_{34}N_4O_4S_2$	A	0.031	0.20	>0.62[d]
68	1	SO_2	1	144-146	64	$C_{21}H_{32}N_4O_5S_2$	B	0.11	0.53	0.83

[a] No attempt was made to maximize yield. [b] Analyzed for C, H, and N; analytical results were with ±0.4% of theoretical values. [c] Oral dose (millimoles per kilogram) lowering blood glucose by a mean ($N \geq 5$) of 20 and 50%, respectively, in normal rats (ED_{20}^N, ED_{50}^N) and of 20% in diabetic rats (ED_{20}^D). For potency of reference compounds refer to Table I. [d] Highest dose tested. [e] Inactive (less than 10% blood sugar decrease). [f] Monohydrate.

the majority of compounds, some, e.g., **36** (Table III) or **91** (Table VII), had a much steeper dose–response curve with a ratio of about 3.

Sulfonyliminoimidazolidines were found to have a relatively short duration of action in the rat; maximal hypoglycemic effects generally occurred 1 to 2 h after administration. A few analogues, e.g., **64** (Table V), had a longer duration (4–8 h).

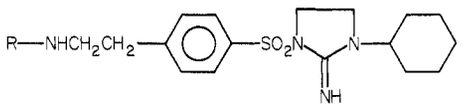
Not all compounds have been tested in diabetic rats; keeping large numbers of diabetic rats for many weeks makes this animal model not practical for large-scale testing. Five out of 31 compounds studied had no or negligible activity (<10% blood sugar decrease); the remaining 26, however, were definitely active with ED_{20}^D values between 0.14 and approximately 1 mmol/kg. Neither tolbutamide nor glibenclamide showed any activity in this model.

Results of further studies on hypoglycemic effect, X-ray structure, and mechanism of action of **44** (Table IV), the most potent sulfonyliminoimidazolidine of the present series, will appear elsewhere.[8,9]

Structure–Activity Relationships. The hypoglycemic activity of selected 1-[[*p*-[2-(acylamino)ethyl]-phenyl]sulfonyl]-2-iminoimidazolidines in normal and in streptozotocin-diabetic rats is shown in Tables I–VII.

(8) E. Schweizer, F. Märki, and G. Rihs, *J. Med. Chem.*, following paper in this issue.
(9) F. Märki, W. Albrecht, and M. de Gasparo, *Arzneim.-Forsch.*, in press.

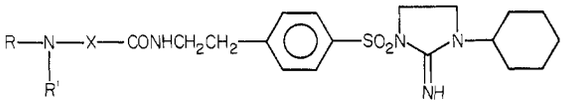
Table VI. Ureido, Thioureido, and Urethane Derivatives



compd	R	mp, °C	yield,[a] %	formula[b]	method	hypoglycemic activity[c] ED_{20}^N	ED_{50}^N	ED_{20}^D
69	H_2NCO	160-161	35	$C_{18}H_{27}N_5O_3S$	D	0.39		>0.76[d,e]
70	$CH_3(CH_2)_3NHCO$	161.5-162	57	$C_{22}H_{35}N_5O_3S$	D	0.067	0.33	
71	C_6H_5NHCO	210.5-212	64	$C_{24}H_{31}N_5O_3S$	D	0.85		
72	$CH_3(CH_2)_3N(CH_3)CO$	134-136	61	$C_{23}H_{37}N_5O_3S$	D	0.054	0.32	
73	CH_3NHCS	187-188	73	$C_{19}H_{29}N_5O_2S_2$	D	0.031	0.24	
74	CH_3CH_2NHCS	140	69	$C_{20}H_{31}N_5O_2S_2$	D	0.016	0.14	
75	$CH_3(CH_2)_3NHCS$	186-187	82	$C_{22}H_{35}N_5O_2S_2$	D	0.015	0.21	
76	$CH_3(CH_2)_5NHCS$	172.5-173	63	$C_{24}H_{39}N_5O_2S_2$	D	0.30	>0.61[d]	
77	c-C_5H_9-NHCS	206-207	87	$C_{23}H_{35}N_5O_2S_2$	D	0.050	0.21	
78	c-C_6H_{11}-NHCS	214-215	79	$C_{24}H_{37}N_5O_2S_2$	D	0.16	>0.82[d]	
79	C_6H_5-NHCS	188-189	91	$C_{24}H_{31}N_5O_2S_2$	D	0.063	0.63	
80	CH_3CH_2OCO	116-117	51	$C_{20}H_{30}N_4O_4S$	E	0.035	0.17	
81	$CH_3(CH_2)_3OCO$	123-124	63	$C_{22}H_{34}N_4O_4S$	E	0.079	0.89	0.89
82	C_6H_5OCO	151-152	77	$C_{24}H_{30}N_4O_4S$	E	0.042	>0.85[d]	

[a] No attempt was made to maximize yield. [b] Analyzed for C, H, and N; analytical results were with ±0.4% of theoretical values. [c] Oral dose (millimoles per kilogram) lowering blood glucose by a mean ($N \geq 5$) of 20 and 50%, respectively, in normal rats (ED_{20}^N, ED_{50}^N) and of 20% in diabetic rats (ED_{20}^D). For potency of reference compounds, refer to Table I. [d] Highest dose tested. [e] Inactive (less than 10% blood sugar decrease).

Table VII. Amino Acid Derivatives



compd	R	R'	X	mp, °C	yield,[a] %	formula[b]	method	hypoglycemic activity[c] ED_{20}^N	ED_{50}^N	ED_{20}^D
83	H	H	CH_2	97-100[d]	72	$C_{19}H_{31}Cl_2N_5O_3S$	A	0.39		0.62
84	C_6H_5	H	CH_2	156-159[e]	61	$C_{25}H_{37}Cl_2N_5O_4S$	A	0.064	0.32	0.40
85	CH_3	CH_3	CH_2	108-110	61	$C_{21}H_{33}N_5O_3S$	A	0.057	0.18	
86	H	H	$CH(CH_3)$	97-100[e]	55	$C_{20}H_{35}Cl_2N_5O_4S$	A	0.059	0.16	0.46
87	C_6H_5	H	$CH(CH_3)$	177-179	58	$C_{26}H_{35}N_5O_3S$	B	0.060	0.20	0.40
88	CH_3	CH_3	$CH(CH_3)$	119-121[f]	54	$C_{22}H_{37}N_5O_4S$	A	0.024	0.062	
89	H	H	$(CH_2)_2$	90-92[d]	67	$C_{20}H_{33}Cl_2N_5O_3S$	A	0.065	0.37	0.76
90	C_6H_5	H	$(CH_2)_2$	127-129	63	$C_{26}H_{35}N_5O_3S$	B	0.24		0.80
91	H	H	$CH(C_6H_5)$	65-68[d]	70	$C_{25}H_{35}Cl_2N_5O_3S$	A	0.029	0.076	>0.18[g,h]
92	CH_3	CH_3	$CH(C_6H_5)$	70-74[i]	55	$C_{27}H_{41}N_5O_5S$	A	0.037	0.17	>0.55[g]

[a] No attempt was made to maximize yield. [b] Analyzed for C, H, and N; analytical results were with ±0.4% of theoretical values. [c] Oral dose (millimoles per kilogram) lowering blood glucose by a mean ($N \geq 5$) of 20 and 50%, respectively, in normal rats (ED_{20}^N, ED_{50}^N) and of 20% in diabetic rats (ED_{20}^D). For potency of reference compounds, refer to Table I. [d] Dihydrochloride. [e] Monohydrate dihydrochloride. [f] Monohydrate. [g] Highest dose tested. [h] Inactive (less than 10% blood sugar decrease). [i] Dihydrate.

Some effects of structural variation of the acyl residue on biological activity, mainly in the normal rat, will be discussed.

Substitution of an aromatic acyl group (Table I) with Cl and/or OCH_3 in various positions of the benzene ring did not improve potency above that of the unsubstituted benzamido derivative **14**. In fact, compound **23** with the side chain identical with that of glibenclamide in the sulfonylurea series[4] was about six times less potent than **14**.

Several compounds with interesting activity were obtained in the series with heterocyclic acyl residues (Table II). Of all the analogues studied in the diabetic rat, compound **30** had the highest potency (similar to phenformin). By variation of the size of alkyl and cycloalkyl substituents (Table III), optimal activity was obtained with analogue **36**.

Several analogues with outstanding potency were obtained in the series with alkenyl substituents (Table IV). Compound **44** with a crotonyl residue was 20 times more potent than tolbutamide in the normal rat and only slightly less potent than phenformin in the diabetic rat. The stereochemistry of the alkenyl group had an effect on the potency; the trans isomer **44** was one-third more potent than the cis isomer **45**.

A clear structure–activity relationship was observed with some of the analogues shown in Table V. Interrupting the three-carbon chain of the alkyl substituent ($n, m = 1$) by heteroatoms led to a steady decrease of potency in the series O, S, SO, SO_2 (analogues **56**, **60**, **64**, and **68**). Likewise, potency decreased in three pairs of analogues with the heteroatoms O, S, and SO, when m was changed from 2 to 1 (analogue pairs **58**, **55**; **62**, **59**; **66**, **63**).

Compounds containing an ureido, thioureido, or an urethane group (Table VI) were also active. Thioureido derivatives were generally more potent than the corresponding ureido or amido analogues. The highest potency in this series was observed with an alkyl chain of two to four carbon atoms (**74** and **75**).

Hypoglycemic activities of various amino acid derivatives are shown in Table VII. Exchanging a hydrogen of the α-amino group by phenyl increased potency in the glycine

derivative **83**, had no effect in the alanine derivative **86**, and decreased potency in the β-alanine derivative **89** (compounds **84**, **87**, and **90**). Dimethylation of the α-amino group of the glycine derivative **83** and the alanine derivative **86** increased potency (compounds **85** and **88**) and slightly decreased potency in the phenylglycine derivative **91** (compound **92**).

These structure-activity relationships of the sulfonyliminoimidazolidines studied indicate that hypoglycemic activity is observed over a wide range of structural modifications of acyl substituents. We conclude that sulfonyliminoimidazolidines represent a new class of oral hypoglycemic agents. Apart from potent hypoglycemic activity in normal rats (up to 20 times tolbutamide), they also lower blood sugar in streptozotocin-diabetic rats. This additional effect clearly distinguishes sulfonyliminoimidazolidines from sulfonylureas.

Experimental Section

Chemistry. The compounds were prepared by methods A–E (see above and Schemes I and II).[1] These methods are illustrated by the preparation of specific compounds. Melting points were obtained on a Büchi apparatus and are uncorrected. Microanalysis was within ±0.4% of the theoretical values. No attempt was made to maximize yield. The starting materials **5** and **8** (Scheme I) are commerically available.

1-Cyclohexyl-2-iminoimidazolidine Hydrochloride (10). *N*-Cyclohexylethylenediamine (**9**) was prepared from cyclohexanone (**8**) according to A. J. Bruno et al.[7] Cyanogen chloride (64.5 g, 1.05 mol) was added to a solution of 142.2 g (1 mol) **9** in 500 mL of benzene over a period of 3 h. The crystallized product was filtered and washed twice with 100 mL of petroleum ether: yield 231 g (100%); mp 166–170 °C.

1-[[*p*-(2-Acetamidoethyl)phenyl]sulfonyl]-3-cyclohexyl-2-iminoimidazolidine (11). [*p*-(2-Acetamidoethyl)phenyl]-sulfonyl chloride (**7**) was prepared from *N*-phenethylacetamide[6] (**6**) according to Miller et al.[5] A suspension of 261 g (1 mol) of **7** in 1500 mL of acetone was added to a solution of 231 g (1 mol) of **10** in 800 mL of H_2O. In a period of 1 h, a solution of 80 g of NaOH in 250 mL of H_2O was dropped in. After the addition was completed, the reaction mixture was heated to reflux for a period of 1 h. The acetone was distilled off, whereafter the product crystallized. After cooling, the product (**11**) was collected by filtration: yield 215 g (55%); mp 181–182 °C.

1-[[*p*-(2-Aminoethyl)phenyl]sulfonyl]-3-cyclohexyl-2-iminoimidazolidine Dihydrochloride (12). A mixture of 187 g (0.488 mol) of **11** and 1500 mL of 2 N HCl was heated to reflux for a period of 6 h. After filtration, the solvent was evaporated in vacuo, and the residue was heated with 300 mL of EtOH. The crystals were filtered to afford **12**: yield 171.5 g (82.8%); mp 247–250 °C.

1-[[*p*-[2-(Butyrylamino)ethyl]phenyl]sulfonyl]-3-cyclohexyl-2-iminoimidazolidine (36). Method A. To a mixture of 35 g (0.1 mol) of **12** base (prepared by adding the dihydrochloride of **12** to 7.5 N NaOH, extracting with CH_2Cl_2, evaporating, and crystallizing the resulting oil, mp 107–109 °C) and 8.8 g (0.1 mol) *n*-butyric acid in 250 mL acetonitrile and 150 mL of tetrahydrofuran was added 20.6 g (0.1 mol) of *N,N'*-dicyclohexylcarbodiimide at 0 °C over a period of 1 h. After stirring for 12 h at room temperature, the reaction mixture was filtered, the solvent was evaporated in vacuo, and the residue was crystallized from 1,1,1-trichloroethane to afford **36**: yield 31 g (73.8%); mp 144 °C.

Cyanomethyl Ethylsulfinylacetate (13b). To a solution of 254 g (2.51 mol) of triethylamine and 253 g (3.34 mol) of chloroacetonitrile in 1000 mL of ethyl acetate was added dropwise at 0 °C 201 g (1.67 mol) of ethylthioacetic acid, prepared according to Ramberg.[10] After the solution was stirred over a period of 12 h, the $(C_2H_5)_3N$·HCl was removed by filtration, the ethyl acetate solution was washed with H_2O, dried, and filtered, and the solvent was evaporated. Distillation of the residue afforded cyanomethyl ethylmercaptoacetate: yield 238 g (90%); bp 77–81 °C (0.04 mm).

A solution of 226 g (1.42 mol) of this product in 500 mL of CH_3OH was added dropwise to a solution of 334 g (1.54 mol) of sodium periodate in 3000 mL of H_2O at 0–5 °C. After stirring for a period of 12 h, the reaction mixture was filtered, and the filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 layer was evaporated in vacuo to afford raw **13b** [yield 163 g (65%)], which was used (due to instability) without further purification.

1-[[*p*-[2-[α-(Ethylsulfinyl)acetamido]ethyl]phenyl]-sulfonyl]-3-cyclohexyl-2-iminoimidazolidine (64). Method B. A solution of 85 g (0.486 mol) **13b** in 200 mL of ethyl acetate was added dropwise to a solution of 153 g (0.44 mol) of **12** base in 800 mL of ethyl acetate over a period of 4 h. After the solution was stirred for 12 h, **64** was isolated by filtration: yield 172 g (85%); mp 137 °C after recrystallization from ethyl acetate.

1-[[*p*-[2-(Crotonylamino)ethyl]phenyl]sulfonyl]-3-cyclohexyl-2-iminoimidazolidine (44). Method C. To a solution of 3.5 g (0.01 mol) of **12** base in 100 mL of absolute dioxane was added at 0 °C a solution of 1.5 g (0.01 mol) of crotonic acid anhydride (**13c**) in 5 mL of absolute dioxane. After the solution was stirred at room temperature for a period of 12 h, the solvent was distilled off, and the residue was dissolved in 300 mL of CH_2Cl_2. This solution was washed with 50 mL of H_2O, 50 mL of 0.5 N NaOH, and again with 50 mL of H_2O. After the solution was dried and filtered, the solvent was distilled off, and the residue was crystallized from ethyl acetate to afford **44**: yield 3.3 g (79%); mp 159–160 °C.

Hypoglycemic Activity. Compounds were administered at several dose levels (up to 400 mg/kg) by gavage as suspensions in 0.5% methylcellulose in 0.9% saline (5 mL/kg) to groups of five Tif:RAIf strain rats (170–250 g). Controls received vehicle only. Normal rats were allowed food ad libitum up to 6.5 h before dosing, and streptozotocin-diabetic rats were fed up to dosing, after which food was removed. Diabetes was induced by a single intravenous injection of 55 mg/kg of streptozotocin[11] at least 1 month before the experiment; the blood glucose range was 15–25 mmol/L. Blood glucose concentrations were determined before and 2, 4.5, and 7.5 h after dosing in normal rats, and before and 3 and 6 h after dosing in diabetic rats. Blood (0.1 mL) was collected from the retro-orbital venous plexus under short anesthesia (inhalation of oxygen/carbon dioxide, 1:1, for 45 s[12]). Glucose was assayed enzymatically by the glucose oxidase/peroxidase method[13] adapted to the Technicon Auto-Analyzer. The maximal mean decrease of blood glucose at different dose levels was plotted, and the doses lowering blood glucose by 20 and 50% of the predose value were determined graphically (ED_{20}^N, ED_{50}^N in normal rats; ED_{20}^D in diabetic rats). ED values (millimoles per kilogram) of reference compounds are listed in Table I.

Acknowledgment. The authors thank W. Albrecht, J. Motz, P. Häner, and P. Zbinden for valuable contributions at different stages of this work and E. Koncz, J. Schaffner, and E. Scholer for expert secretarial help.

Registry No. **5**, 64-04-0; **6**, 877-95-2; **7**, 35450-53-4; **8**, 108-94-1; **9**, 5700-53-8; **10**, 51099-11-7; **11**, 26075-79-6; **12**, 25862-65-1; **12** base, 31858-85-2; **13a**, 107-92-6; **13b**, 85389-96-4; **13c**, 623-68-7; **14**, 85389-97-5; **15**, 26034-63-9; **16**, 25864-89-5; **17**, 25862-30-0; **18**, 25919-85-1; **19**, 25865-15-0; **20**, 25865-14-9; **21**, 34958-25-3; **22**, 25862-64-0; **23**, 25921-68-0; **24**, 31858-84-1; **25**, 31815-65-3; **26**, 31815-20-0; **27**, 31815-22-2; **28**, 31815-35-7; **29**, 85389-98-6; **30**, 85389-99-7; **31**, 85390-00-7; **32**·HCl, 85390-01-8; **33**, 85390-02-9; **34**, 25919-82-8; **35**, 26075-79-6; **36**, 25864-94-2; **37**, 26075-82-1; **38**, 25919-83-9; **39**, 25865-13-8; **40**, 25864-93-1; **41**, 85390-03-0; **42**, 85390-04-1; **43**, 85390-05-2; **44**, 85390-06-3; **45**, 85390-07-4; **46**, 85390-08-5; **47**, 85390-09-6; **48**, 85390-10-9; **49**, 85390-11-0; **50**, 85390-12-1; **51**, 85390-13-2; **52**, 85390-14-3; **53**, 25865-17-2; **54**, 26034-64-0; **55**, 32048-50-3; **56**, 32152-61-7; **57**, 32048-66-1; **58**, 85390-15-4; **59**, 32048-28-5; **60**, 32048-30-9; **61**, 32048-34-3; **62**, 32152-62-8; **63**, 85390-16-5; **64**, 32160-73-9; **65**, 85390-17-6; **66**,

(10) L. Ramberg, *Chem. Ber.*, **40**, 2588 (1907).

(11) A. Junod, A. E. Lambert, L. Orci, R. Pictet, A. E. Gonet, and A. E. Renold, *Proc. Soc. Exp. Biol. Med.*, **126**, 201 (1967).

(12) C. J. Green, "Animal Handbooks 8", London Laboratory Animals Ltd., London, 1979, p 154.

(13) W. Werner, H.-G. Rey, and H. Wielinger, *Z. Anal. Chem.*, **252**, 224 (1970).

85390-18-7; **67**, 85390-19-8; **68**, 32160-68-2; **69**, 85390-20-1; **70**, 31478-68-9; **71**, 31478-71-4; **72**, 31431-44-4; **73**, 31545-14-9; **74**, 31431-53-5; **75**, 31478-70-3; **76**, 31431-66-0; **77**, 31545-21-8; **78**, 31545-23-0; **79**, 31478-72-5; **80**, 31850-03-0; **81**, 31850-04-1; **82**, 31850-05-2; **83**·2HCl, 85390-21-2; **84**·2HCl, 85390-22-3; **85**, 85390-23-4; **86**·2HCl, 85390-24-5; **87**, 85390-25-6; **88**, 85390-26-7; **89**·2HCl, 85390-27-8; **90**, 85390-28-9; **91**·2HCl, 85390-29-0; **92**, 85390-30-3; $NH_2CH_2CH_2NH_2$, 107-15-3; ClCN, 506-77-4; chloroacetonitrile, 107-14-2; ethylthioacetic acid, 627-04-3; cyanomethyl ethylmercaptoacetate, 85390-31-4.

Sulfonyliminoimidazolidines. A New Class of Oral Hypoglycemic Agents. 2. Mode of Action and X-ray Structure of 1-[[*p*-[2-(Crotonylamino)ethyl]phenyl]sulfonyl]-3-cyclohexyl-2-iminoimidazolidine†

Ernst H. Schweizer,‡ Fritz Märki,*‡ and Grety Rihs§

Research Department, Pharmaceuticals Division, and Central Research Services, Ciba-Geigy Limited, Basle, Switzerland.
Received June 4, 1982

Hypoglycemic sulfonyliminoimidazolidines were shown to stimulate insulin release in vitro (rabbit pancreas) and in vivo (normal rats) comparable to tolbutamide and to inhibit glucose oxidation in isolated rat fat cells in vitro similar to phenformin. These results support the hypothesis that the hypoglycemic effect of the compounds in normal and in diabetic animals may be due to a combination of mechanisms operative in sulfonylureas and biguanides. Determination of the three-dimensional structure of the potent analogue 1 by X-ray crystallography enabled us to identify specific regions of the molecule presumed to be involved in the molecular mode of action of sulfonyliminoimidazolidines.

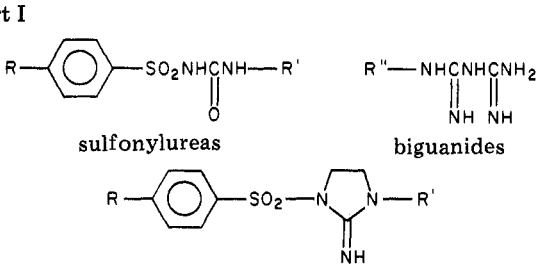
Sulfonyliminoimidazolidines have recently been presented as a new class of oral hypoglycemic agents.[1] By combining structural elements of sulfonylureas and biguanides within one molecule (Chart I), these compounds display hypoglycemic activity in normal and in streptozotocin diabetic rats.

Sulfonylureas are known to lower blood glucose in normal animals by releasing insulin from the pancreas and are, therefore, inactive in the streptozotocin-diabetic rat model. Biguanides, on the other hand, produce hypoglycemia in diabetic animals by extrapancreatic mechanisms and are devoid of significant activity in normal animals.[2] We now propose that sulfonyliminoimidazolidines owe their dual activity (i.e., hypoglycemic effect in normal and diabetic rats) to a combination of mechanisms operative in sulfonylureas and biguanides. To test this hypothesis, we studied the effects of selected sulfonyliminoimidazolidines on insulin release in vitro and in vivo (sulfonylurea-type activity) and on glucose oxidation by rat fat cells in vitro (biguanide-type activity). Elucidation of the three-dimensional structure of the highly potent sulfonyliminoimidazolidine analogue 1 by X-ray crystallography then enabled us to analyze the structure–activity relationship at the molecular level.

Biological Activity. Three models have been selected to test representative sulfonyliminoimidazolidine compounds for sulfonylurea-type and biguanide-type activities: stimulation of insulin release by pieces of rabbit pancreas in vitro, increase of plasma insulin in normal rats in vivo (sulfonylurea type), and inhibition of glucose oxidation by isolated rat fat cells in vitro (biguanide type). Sulfonylureas show no detectable activity in the latter model, while biguanides are inactive in the first two models. Effects of several sulfonyliminoimidazolidine compounds in these tests are shown in Tables I–III.

Insulin release in vitro was stimulated by the sulfonyliminoimidazolidines 1–4 and by the sulfonylurea tolbutamide (Table I). A two- to threefold increase above basal release was observed with 1–4 in the upper concentration range studied (0.1 mmol/L and above), whereas an approximately fourfold increase was obtained with tolbutamide. In the lower concentration range, 1 was clearly more potent than the other compounds; the minimal effective concentration was 3 times lower than that of **2**, **3**, and tolbutamide and 10 times lower than that of **4**, the analogue with the lowest potency.

Chart I



Sulfonyliminoimidazolidines also stimulated insulin release in vivo. As shown in Table II, compounds 1–4 increased plasma insulin in normal rats at hypoglycemic doses. A blood glucose decrease in the range of 30–50% correlated with a two- to fourfold increase of plasma insulin. Hypoglycemic and β-cytotropic potency increased in the order **4** < **3** < **2** < **1**. The sulfonylurea tolbutamide showed hypoglycemic and β-cytotropic activity, whereas the biguanide phenformin (1-phenethylbiguanide) was inactive, despite a very high dose.

Glucose oxidation in isolated fat cells was inhibited by the sulfonyliminoimidazolidines 1–4 and by the biguanide phenformin with IC_{50} values between 0.18 and 0.020 mmol/L, while tolbutamide was inactive (Table III). Several quaternary pyridinium salts,[3] shown to lower blood glucose in diabetic animals by a biguanide-type mecha-

† Ciba-Geigy number CGP 11112.
‡ Research Department, Pharmaceuticals Division.
§ Central Research Services.

(1) E. H. Schweizer, F. Märki, C. Lehmann, and H. Dietrich, *J. Med. Chem.*, preceding paper in this issue.
(2) (a) W. G. Oakley, D. A. Pyke, and K. W. Taylor, in "Diabetes and Its Management", 3rd ed., Blackwell Scientific Publications, Oxford, 1978, p 76. (b) I. Polacek and J. Ouart, *Diabetes*, **23**, 25 (1974). (c) G. Proske, G. Osterloh, R. Beckmann, F. Lagler, G. Michael, and H. Mückter, *Arzneim.-Forsch.*, **12**, 314 (1962).
(3) V. J. Bauer, H. P. Dalalian, W. J. Fanshawe, S. R. Safir, E. C. Tocus, and C. R. Boshart, *J. Med. Chem.*, 11, 981 (1968).

0022-2623/83/1826-0970$01.50/0