A Novel Series of N-(1-Aminoalkylidene)carboximidamides as Potential Hypoglycemic Agents

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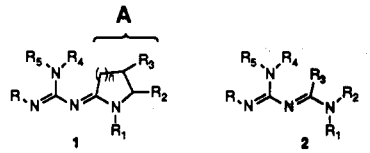
Received December 7, 1992

Nitrogen heterocyclic carboximidamides, such as linogliride, **1a**, have been shown to possess significant hypoglycemic activity and have shown clinical efficacy as potential antidiabetic agents. We evaluated the biological significance of the heterocyclic ring A of general structure **1**, which has always been maintained in this class of compounds, by preparing acyclic compounds of general structure **2**. Preliminary in vivo biological testing, i.e., the glucose tolerance test in rats, indicates that a number of the specific acyclic carboximidamides prepared, **6a–kk**, possessed significant hypoglycemic activity often comparable to, and in some cases better than, the activity noted for our model compound, **1a**. These results suggest that the heterocyclic ring A of **1** is not essential for hypoglycemic activity for this class of compounds.

Introduction

Diabetes mellitus is a chronic metabolic disorder which, when untreated or poorly controlled, can be debilitating to the point of causing blindness, heart disease, kidney disease, gangrene, and eventually death.[1] It has been estimated that about 5% of the population of the United States are diabetic to varying degrees.[2] Approximately 80–90% of known cases of diabetes mellitus are noninsulin dependent (NIDDM) diabetics.[2] For over 30 years the classical oral treatments for NIDDM have been the hypoglycemic sulfonylureas and biguanides.[3a] Over the past 10 years there have been reports that a novel series of heterocyclic imidamide compounds of general structure **1**,[4] which are unrelated structurally to the sulfonylureas or biguanides, have shown good clinical efficacy as oral, insulin secretagogue, hypoglycemic agents.[3b]

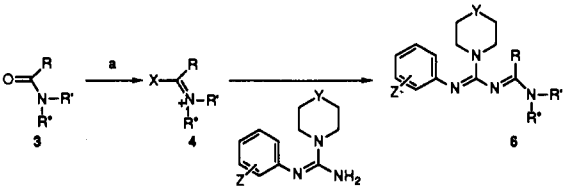


1a R=Ph; R_1=CH_3; R_2,R_3=H; n=1; R_4,R_5= $-CH_2CH_2OCH_2CH_2-$

In the broad series of the heterocyclic imidamides **1** reported, heterocyclic ring A in general structure **1** has always been conserved.[4] We chose to evaluate the biological significance of this ring by preparing acyclic compounds of general structure **2**.

Linogliride, **1a**, is a clinically efficacious hypoglycemic analog of the cyclic series **1** and has been extensively evaluated.[3b] Consequently, in planning the acyclic compounds to prepare, **1a** was chosen as the model compound. Besides opening ring A of **1a**, and varying the opened ring's acyclic moieties, no alteration of **1a** was made for the majority of the specific acyclic carboximidamides prepared, i.e., compounds **6a–kk**. By eliminating the variable of further changes to molecule **1a**, we felt the significance of ring A for **1**'s hypoglycemic activity could accurately be assessed.

Scheme I



Method	a	X for 4
A-1	Meerwein's Rgt	OEt
A-2	Phosgene	Cl
A-3	Dimethyl Sulfate	OMe

Chemistry

Initial plans were to synthesize compounds **6a–kk** using a classical method for the preparation of amidines (Scheme I). This route entails two steps including formation of an imidate or imidate salt type species, **4**, from an amide **3** followed by reaction of **4** with a nucleophilic guanidine **5** to give the desired product **6**. This route apparently has proven quite successful for the cyclic compounds **1** with their products being easily isolated.[4] However, for the synthesis of the acyclic compounds **6** this route was generally poor yielding and, more importantly, isolation of product **6** from starting material **5** often proved problematic. The problematic separation of **6** from unreacted **5** seemed most difficult when **6** was prepared from **3** with lower alkyl R group substituents. In those cases, a solubility difference for either crystallization or extraction of **6** from **5**, or a quickly operative, acceptable separation of **6** from **5** by column chromatography, were not easily found. We therefore opted to explore alternate syntheses (Schemes II–IV) in preparing our target compounds to determine if we could find cleaner, higher yielding pathways.

In Scheme II, guanidine **5** was reacted with a number of various acid anhydrides to cleanly give their amide products **7**. Treatment of the various amides **7** with Lawesson's reagent under mild conditions (0 °C to room temperature) led to the thioamides **8**. Generally, heating

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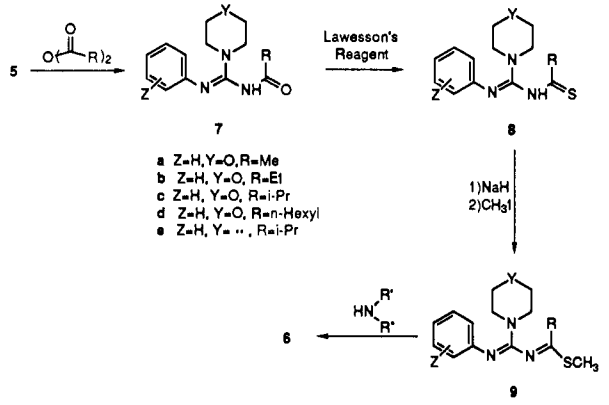
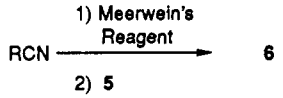
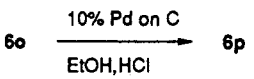
Scheme II. Method B



Scheme III. Method C



Scheme IV. Method D



of these thioamide reactions seemed to lead to appreciable decomposition of **8** based on TLC. Compounds **8** have been found, however, to be stable indefinitely as solid HCl salts following their workup. Reaction of compounds **8** with NaH to generate their respective anions followed by treatment with CH_3I led to compounds **9**. When isolated, compounds **9** also appeared quite stable and were sometimes held at room temperature for weeks prior to subsequent reactions without any decomposition. Reaction of **9** with a variety of amines led to a wide variety of N-substituted imidamides **6**. Although Scheme II proved longer than Scheme I and did not necessarily prove to be always higher yielding, it did offer, in some cases, distinct advantages. An obvious advantage to this scheme was the ability to quickly change R′ and R″ substituents on **6** with relative ease. Less obvious, but more importantly, was the advantage of being able to easily isolate certain final products **6**.

For Scheme III, nitrilium ions were formed by reacting their respective nitriles with either dimethyl sulfate (DMS) or Meerwein's reagent. The reactive nitrilium ions were then treated with a base guanidine **5** to generate desired products **6**. Again, although not a higher yielding reaction sequence than Scheme I, this route did prove useful for quickly preparing R′-monosubstituted nitrogen analogs of **6**.

Scheme IV, which entailed hydrogenolysis of **6o** to **6p**, was used when it was found that aniline proved unreactive with **7** under the standard reaction conditions of Scheme II.

The chemistry explored to make the varied substitutions in our series show that overall the sequences employed were quite complementary.

Results and Discussion

As described in the Experimental Section, hypoglycemic activity of final compounds **6a–kk** (Table I) was measured using the rat oral glucose tolerance test. The mean maximum percent lowering values listed in Table I were determined at a single dose of 10 mg/kg, sc, and when deemed appropriate, an ED_{30} was calculated from dose–response studies.

Table I

no.	Y	Z	R	R′	R″	mean max. % low[a]	ED_{30} (95% CI)[b]
6a	O	H	H	CH_3	CH_3	22	ND
6b	O	H	Ph	CH_3	CH_3	25	ND
6c	O	H	CH_3	CH_3	CH_3	38	6.7 (5.2–10.1)
6d	O	H	Et	CH_3	CH_3	43	5.3 (3.3–9.1)
6e	O	H	CH_3	$-(CH_2)_5-$		46	5.3 (3.0–9.2)
6f	O	H	*i*-Pr	CH_3	CH_3	43	4.3 (3.0–5.6)
6g	O	H	CH_3	H	CH_3	45	2.6 (1.3–3.5)
6h	O	H	*n*-hexyl	CH_3	CH_3	31	ND
6i	O	H	CH_3	*n*-Bu	CH_3	33	7.6 (5.2–20.8)
6j	O	H	CH_3	H	*i*-Pr	42	3.9 (1.5–6.2)
6k	O	H	CH_3	Ph	CH_3	20	ND
6l	O	H	c-hexyl	CH_3	CH_3	27	ND
6m	O	H	*i*-Pr	H	CH_3	52	1.5 (1.1–1.9)
6n	O	H	CH_2Ph	CH_3	CH_3	27	ND
6o	O	H	CH_3	CH_2Ph	Ph	17	ND
6p	O	H	CH_3	H	Ph	26	ND
6q	O	H	*t*-Bu	CH_3	CH_3	40	9.6 (6.5–32)
6r	O	H	*i*-Pr	H	*i*-Pr	23	ND
6s	O	H	CH_3	$-(CH_2)_2O(CH_2)_2-$		24	ND
6t	O	H	CH_2-*t*-Bu	CH_3	CH_3	37	5.9 (3–36)
6u	O	H	CH_3	H	*t*-Bu	45	4.2 (1.9–6.6)
6v	O	H	CH_3	H	CH_2Ph	50	4.3 (2.3–6.4)
6w	O	H	CH_3	$-(CH_2)_2NMe(CH_2)_2-$		IA	
6x	O	H	CH_3	H	H	21	ND
6y	O	H	CH_3	H	*n*-Pr	56	0.97 (0.06–1.9)
6z		H	*i*-Pr	H	CH_3	43	ND
6aa	O	H	*i*-Pr	H	H	34	ND
6bb	O	H	*i*-Pr	H	Et	26	ND
6cc	O	H	*i*-Pr	H	*n*-Pr	31	ND
6dd	O	4-F	*i*-Pr	H	CH_3	42	ND
6ee	O	H	Et	H	CH_3	42	ND
6ff	O	H	CH_3	H	Et	48	4.6 (3.8–5.3)
6gg	O	H	CH_3	H	CH_2CO_2Et	IA	
6hh	O	H	CH_3	H	CH_2CH_2OH	15	ND
6ii	O	H	CH_3	H	$COCH_3$	22	ND
6jj	O	H	CH_3	H	SO_2CH_3	IA	
6kk	O	2-OMe	*i*-Pr	H	CH_3	21	ND
1a	O	H	$-(CH_2)_3-$		CH_3	34	6.1 (4.3–8.1)

[a] Mean maximum percent lowering were calculated as described in Experimental Section. The values were determined at a dose of 10 mg/kg, sc. [b] ED_{30} equals the dose (mg/kg) calculated from dose–response studies to produce a 30% maximum decrease of glucose from control. The 95% confidence interval (CI) is shown in parentheses. IA = inactive, ND = not determined.

As is clearly evident from Table I, the majority of acyclic compounds **6** prepared possessed significant hypoglycemic activity which was often comparable to, and in some cases better than, the activity for our model heterocycle, **1a**. Generally, minor molecular alterations of the acyclics **6** did not result in magnitudinal differences in activity. However, the differences were significant enough that, by breaking the series of **6** into subsets, some apparent trends can be observed in developing an SAR.

Examination of the R group of **6** indicates that an i-Pr or smaller alkyl substituent leads to a maximizing of activity. This is demonstrated by comparing a group of compounds where R is varied while maintaining Y, R′, and R″ as constants O, Me, and Me, respectively. From this series of compounds the following trends in activity are noted: **6a** (H) < **6c** (Me) ≤ **6d** (Et) ≤ **6f** (*i*-Pr) > **6q** (*t*-Bu) > **6h** (*n*-hexyl), **6l** (c-hexyl), **6b** (Ph), and **6n** (Bz). This trend seemed to vary slightly when groups bulkier than Me were attached at the R″ position. For example, when R was compared between Me and *i*-Pr, with R′ being held constant as H and R″ varied from Me to the bulkier Et, *n*-Pr, or *i*-Pr, the activity shifted toward the Me-substituted R proving more active in all cases (**6ff** > **6bb**; **6y** > **6cc**; **6j** > **6r**).

Table II

compd	a	formula[b]	purification[c]	% yield	mp, °C
6a	A-1	$C_{14}H_{20}N_4O$	Et_2O	48	109–112
6b	A-2	$C_{20}H_{24}N_4O{\cdot}HCl$	Et_2O	24	215–218
6c	B	$C_{15}H_{22}N_4O{\cdot}{}^3/_2C_4H_4O_4$	EtOH	34	150–151
6d	B	$C_{16}H_{24}N_4O{\cdot}C_4H_4O_4$	CH_3CN	36	141–144
6e	B	$C_{18}H_{26}N_4O{\cdot}C_4H_4O_4$	*i*-PrOH/CH_3CN/Et_2O	30	154–157
6f	B	$C_{17}H_{26}N_4O$	hexane	33	88–90
6g	B	$C_{14}H_{20}N_4O{\cdot}{}^3/_2C_4H_4O_4$	*i*-PrOH/Et_2O	48	145–147
6h	B	$C_{20}H_{32}N_4O{\cdot}{}^3/_2C_4H_4O_4$	EtOH/Et_2O	*d*	140–143.5
6i	B	$C_{18}H_{28}N_4O{\cdot}C_4H_4O_4{\cdot}EtOH$	EtOH/Et_2O	41	94–99
6j	B	$C_{16}H_{24}N_4O$	Et_2O/hexane	46	142–145
6k	A-3	$C_{20}H_{24}N_4O{\cdot}C_4H_4O_4{\cdot}0.5H_2O$	EtOH/Et_2O	18	160–161.5
6l	A-1	$C_{20}H_{30}N_4O{\cdot}{}^3/_2C_4H_4O_4$	EtOH	13	169–170.5
6m	B	$C_{16}H_{24}N_4O$	Et_2O	27	155–158
6n	A-1	$C_{21}H_{26}N_4O{\cdot}C_4H_4O_4$	EtOH	51	169.5–171
6o	A-1	$C_{26}H_{28}N_4O{\cdot}C_7H_5NO_3S$	EtOH	24	170–173
6p	D	$C_{19}H_{22}N_4O{\cdot}C_7H_5NO_3S$	EtOH	25	180–181.5
6q	A-1	$C_{18}H_{28}N_4O{\cdot}C_7H_5NO_3S$	EtOH/Et_2O	7	131.5–133.5
6r	B	$C_{18}H_{28}N_4O$	cyclohexane	27	132–135
6s	B	$C_{17}H_{24}N_4O{\cdot}C_4H_4O_4{\cdot}0.33EtOH$	EtOH	65	185–187
6t	A-1	$C_{19}H_{30}N_4O{\cdot}{}^3/_2C_4H_4O_4$	EtOH	12	150–152
6u	B	$C_{17}H_{26}N_4O$	Et_2O	23	164–166.5
6v	B	$C_{20}H_{24}N_4O$	hexane	18	126.5–129
6w	B	$C_{18}H_{27}N_5O{\cdot}C_7H_5NO_3S$	*i*-PrOH	62	147–149
6x	A-1	$C_{13}H_{18}N_4O$	[e]15:1 MeOH–NH_4OH; cyclohexane	26	146–148
6y	B	$C_{16}H_{24}N_4O$	cyclohexane	66	100–103.5
6z	B	$C_{16}H_{24}N_4$	CH_2Cl_2/hexane	13	181.5–183.5
6aa	A-1	$C_{15}H_{22}N_4O$	[e]200:1 MeOH–NH_4OH; cyclohexane	47	123–126
6bb	C	$C_{17}H_{26}N_4O$[f]	*i*-PrOH; toluene	30	155–158
6cc	A-1	$C_{18}H_{28}N_4O$	[e]150:1 MeOH–NH_4OH; hexane	12	122.5–123.5
6dd	C	$C_{16}H_{23}FN_4O$	CH_2Cl_2/hexane	11	150–152
6ee	B	$C_{15}H_{22}N_4O$	cyclohexane	50	117–120
6ff	B	$C_{15}H_{22}N_4O{\cdot}C_4H_4O_4$	*i*-PrOH	71	155.5–158.5
6gg	B	$C_{17}H_{24}N_4O_3{\cdot}C_4H_4O_4$	*i*-PrOH	45	167.5–170
6hh	A-1	$C_{15}H_{22}N_4O_2$	[e]200:1 MeOH–NH_4OH; Et_2O	9	132–134
6ii	A-1	$C_{15}H_{20}N_4O_2$	Et_2O	54	146–149
6jj	B	$C_{14}H_{20}N_4O_3S$	[e]20:1 $CHCl_3$–MeOH; MeOH	6	173–174
6kk	C	$C_{17}H_{26}N_4O_2$	[e]9:1 MeOH–NH_4OH; CH_2Cl_2/hexane	12	149–151

[a] Method/reagent used to synthesize the product. [b] $C_4H_4O_4$ represents fumaric acid and $C_7H_5NO_3S$ represents saccharin; all products were analyzed for C, H, N; where specified H_2O analysis also performed. [c] Products were crystallized and/or recrystallized from listed solvents. [d] Not reported. [e] Crude material flash chromatographed on silica gel eluting with identified solvent system prior to crystallization with listed solvent. [f] C: calcd, 67.52. Found, 66.32.

It also appeared that the R′- and R″-substituted nitrogen proved most active with monoalkyl substitution when compared to unsubstituted or disubstituted molecules of similar structures. In the sets of structures where R was Me or *i*-Pr and R′ and R″ were sequentially varied from Me to H substitutions, the activity trend was consistently monoalkylated > dialkylated > unalkylated substitution (**6g** > **6c** > **6x**; **6m** > **6f** > **6aa**).

In the few cases where functionality was added to the R′ and R″ positions of **6** the activity was either significantly reduced if not lost entirely. This conclusion is illustrated with the following comparisons: **6e** > **6s** > **6w**; **6y** > **6hh**; **6j** > **6ii**; and **6u** > **6jj**.

In summary, this work demonstrates that the heterocyclic ring A of **1** is not essential for the imidamide class of compounds to maintain significant hypoglycemic activity. In fact, it appears that based on our preliminary biological data that the opened ring series **6** may possess more significant hypoglycemic activity than series **1**. This is demonstrated by the activities of **6g**, **6m**, and **6y**, which all proved more potent than **1a**. Further biological evaluation of the series of **6** will help determine if their overall pharmacological profile is as favorable as, and hopefully better than, that for **1a**.

Experimental Section

All final products included in Table II were characterized by 90-MHz ^1H NMR (Varian EM 390), IR (Nicolet 60SX), and elemental analyses. When NMR's are reported they are from primary spectra. The elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA, and water analysis, when necessary, was performed by Scandinavian Labs, Herlev, Denmark. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. All reagents were commercially available unless specified. Table II also identifies the typical procedure followed to prepare each respective final product. Variance from these typical procedures is outlined below for all compounds where modifications were required.

Typical Procedure for Method A-1. *N*-[(Dimethylamino)-methylene]-*N*′-phenyl-4-morpholinecarboximidamide (6a). A solution of DMF, **3a** (9 mL, 112.5 mmol), in CH_2Cl_2 (75 mL) was added to freshly prepared[5] $Et_3O^+BF_4^-$ (112.5 mmol) in CH_2Cl_2 (400 mL) at room temperature under Ar over 10 min. After 6 h **5a**[4] (23.25 g, 112.5 mmol) in CH_2Cl_2 (100 mL) was added to the reaction mixture at room temperature over 5 min. After 16 h the mixture was extracted with water and then 15% NaOH. The organic phase was separated, dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 29.24 g of crude product. This material was triturated in Et_2O to yield 14.10 g (48%) of **6a**. ^1H NMR ($CDCl_3$): δ 2.7–3.0 (overlapping singlets,

6H, CH_3), 3.5–3.7 (d, 4H, NCH_2CH_2O), 3.7–3.9 (d, 4H, NCH_2CH_2O), 6.7–7.3 (m, 5H, Ar), 7.3–7.4 (s, 1H, CH).

***N*-[Cyclohexyl(dimethylamino)methylene]-*N'*-phenyl-4-morpholinecarboximidamide–(*E*)-2-Butenedioate (2:3) (6l).** The desired product was prepared via the procedure used for **6a** after substituting *N,N*-dimethylcyclohexanecarboxamide, **3b**, in place of **3a**. Compound **3b** was prepared simply by reacting cyclohexanecarbonyl chloride with dimethylamine. The workup of the reaction for **6l** also varied from the typical procedure. The reaction mixture (73-mmol scale) was concentrated under reduced pressure and H_2O (2 L) added to the residue. This mixture was extracted three times with Et_2O (300-mL portions). The aqueous phase was then extracted twice with CH_2Cl_2 (350-mL portions). The CH_2Cl_2 extracts were combined and washed with 15% NaOH (400 mL). The organic phase was dried over K_2CO_3, filtered, and concentrated under reduced pressure. The residue (13.13 g) was dissolved in EtOH (40 mL) and combined with fumaric acid (4.01 g, 34.6 mmol) which was dissolved in hot EtOH. The warm salt solution was filtered through Dicalite and cooled. The resulting solid which precipitated from the cooled filtrate was filtered and rinsed with a small amount of *i*-PrOH and Et_2O to yield 4.92 g (13%) of **6l** as a white solid.

***N*-[1-(Dimethylamino)-2-phenylethylidene]-*N'*-phenyl-4-morpholinecarboximidamide–(*E*)-2-Butenedioate (6n).** The desired product was prepared by following the procedure used for **6a** after substituting *N,N*-dimethylbenzeneacetamide, **3c**, in place of **3a**. Compound **3c** was prepared by reacting phenylacetyl chloride with dimethylamine. The workup of the reaction for **6n** also varied from the typical procedure. After the reaction was complete the reaction mixture (73-mmol scale) was extracted twice with 3 N HCl (150-mL portions). The organic phase was then extracted with 15% NaOH (200 mL), dried over K_2CO_3, filtered, and concentrated under reduced pressure to yield a brown oil (21.09 g). The fumarate salt **6n** was prepared in a similar manner as **6l**.

***N'*-Phenyl-*N*-[1-[phenyl(phenylmethyl)amino]ethylidene]-4-morpholinecarboximidamide Complex with 1,2-Benzisothiazol-3(2*H*)-one 1,1-Dioxide (6o).** The desired product was prepared via the procedure used for **6a** after substituting *N*-phenyl-*N*-benzylacetamide, **3d**, in place of **3a**. Compound **3d** was prepared simply by reacting acetyl chloride with *N*-phenyl-*N*-benzylamine.

***N*-[1-(Dimethylamino)-2,2-dimethylpropylidene]-*N'*-phenyl-4-morpholinecarboximidamide Complex with 1,2-Benzisothiazol-3(2*H*)-one 1,1-Dioxide (6q).** The desired product was prepared by following the procedure used for **6a** after substituting *N,N*-dimethyltrimethylacetamide, **3e**, in place of 3a. Compound **3e** was prepared by reacting trimethylacetyl chloride with dimethylamine. The workup of **6q** also varied from the typical procedure, following instead the workup for **6l**.

***N*-[1-(Dimethylamino)-3,3-dimethylbutylidene]-*N'*-phenyl-4-morpholinecarboximidamide–(*E*)-2-Butenedioate (2:3) (6t).** The desired product was prepared by following the procedure used for **6a** after substituting *N,N*-dimethyl-*tert*-butylacetamide, **3f**, in place of **3a**. Compound **3e** was prepared by reacting *tert*-butylacetyl chloride with dimethylamine. The workup of **6t** also varied from the typical procedure. After the initial reaction mixture was concentrated, it was attempted to partition the residue between Et_2O and H_2O, however a white solid precipitated between the biphasic solution. The solid was filtered and partitioned between 15% NaOH and CH_2Cl_2. The CH_2Cl_2 phase was dried over K_2CO_3, filtered, and concentrated under reduced pressure to yield a clear oil. The fumarate salt **6t** was then prepared from this oil in a similar manner as **6l**.

***N*-[1-Amino-2-methylpropylidene]-*N'*-phenyl-4-morpholinecarboximidamide (6aa).** The desired product was prepared by following procedure A-1 with a number of variations. Isobutyramide, **3g** (3.92 g, 45 mmol), was converted to its imidate salt following the general Meerwein conditions of A-1 and subsequently converted to its free base by treatment of the reaction mixture with 50% Na_2CO_3 (100 mL). The resulting mixture was filtered and the organic phase dried over K_2CO_3, filtered, and distilled under reduced pressure to yield 2.24 g of said free base imidate, **4g**, as a liquid. A sample of **4g** (2.24 g, 19.6 mmol) was combined with **5a** (2.00 g, 9.8 mmol) and THF (10 mL) and then warmed to reflux for 4 days. Then a second portion of **4g** (4.00 g, 35.1 mmol) was added to the reaction mixture, and heating was continued an additional 12 days. The reaction mixture was concentrated under reduced pressure and purified as described in Table II.

***N*-[2-Methyl-1-(propylamino)propylidene]-*N'*-phenyl-4-morpholinecarboximidamide (6cc).** The desired product was prepared via the procedure used for **6a** after substituting *N*-(*n*-propyl)isobutyramide, **3h**, in place of **3a**. Compound **3h** was prepared by reacting isobutyryl chloride with propylamine. Also the **6cc** reaction mixture was stirred for 12 days prior to the standard workup.

***N*-[1-[(2-Hydroxyethyl)amino]ethylidene]-*N'*-phenyl-4-morpholinecarboximidamide (6hh).** The desired product was prepared by following the procedure used for **6a** after substituting *N*-[2-(acetyloxy)ethyl]acetamide, **3i**, in place of **3a**. Compound **3i** was prepared by reacting acetic anhydride with *N*-acetylethanolamine. Also the **6hh** reaction mixture was stirred for 6 days at reflux prior to the standard workup and then purified as described in Table II.

***N*-[1-[[(4-Morpholinyl)(phenylimino)methyl]imino]ethyl]-acetamide (6ii).** The desired product was prepared via a variation of procedure A-1. Under N_2, **5a** (5.12 g, 25 mmol) was added to *N*-acetylacetimidic acid ethyl ester,[6] **4j** (12.9 g, 100 mmol), at room temperature. After the mixture was stirred for 4 days, the resulting solid was filtered and purified as described in Table II.

Typical Procedure for Method A-2. *N*-[(Dimethylamino)-phenylmethylene]-*N'*-phenyl-4-morpholinecarboximidamide Hydrochloride (6b). A freshly prepared phosgene solution (30 mL of 2 M in toluene; 60 mmol) was added at room temperature to a solution of *N,N*-dimethylbenzamide (3.4 g, 22.5 mmol) in CH_2Cl_2 (40 mL) at room temperature and immediately warmed to reflux under N_2. After 15 min the reaction mixture was cooled to room temperature and an additional portion of phosgene solution was added (20 mL, 40 mmol). The reaction mixture was then rewarmed to reflux for an additional hour, at which point gas evolution ceased. The reaction mixture was then concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (30 mL) and combined with **5a** (4.65 g, 22.5 mmol) in CH_2Cl_2 (40 mL). After 21 h the reaction mixture was extracted with water. The aqueous phase was then extracted three times with $CHCl_3$. The $CHCl_3$ extracts were combined and concentrated under reduced pressure to give 4.35 g of crude product as a yellow oil. This material was triturated in Et_2O to yield 2.00 g (24%) of **6b**. ^1H NMR ($CDCl_3$): δ 2.9 (s, 3H, CH_3), 3.3 (s, 3H, CH_3), 3.7–3.85 (s, 8H, morpholinyl), 6.7–7.3 (m, 10H, Ar), 11.1–11.2 (bs, 1H, HCl).

Typical Procedure for Method A-3. *N*-[1-(Methylphenylamino)ethylidene]-*N'*-phenyl-4-morpholinecarboximidamide–(*E*)-2-Butenedioate–Hydrate (2:2:1) (6k). Under N_2, *N*-methyl-*N*-phenylacetamide (13.6 g, 90 mmol) and dimethyl sulfate (8.4 mL, 90 mmol) were combined at room temperature and then immediately warmed on a steam bath for 30 min. The reaction was recooled to room temperature, and then **5a** (18.45 g, 90 mmol) in CH_2Cl_2 (140 mL) was added over 1 min which caused the reaction to warm to a gentle reflux. After 1 h, the resulting solid was filtered off and the filtrate was concentrated under reduced pressure. The concentrated residue was combined with 3 N HCl (150 mL) and extracted four times with Et_2O (100-mL portions). The aqueous phase was then extracted three times with $CHCl_3$ (100-mL portions). The $CHCl_3$ extracts were combined, extracted with 15% NaOH, dried over K_2CO_3, filtered, and concentrated under reduced pressure to yield 14.20 g of clear oil. This oil was dissolved in Et_2O, filtered through Dicalite, and combined with fumaric acid (3.58 g, 30.9 mmol) which had been dissolved in EtOH (100 mL). The resulting white solid was filtered and rinsed with EtOH and then Et_2O to yield 7.42 g (18%) of **6k**. ^1H NMR (DMSO-d_6): δ 1.5 (s, 3H, CCH_3), 3.2 (s, 3H, NCH_3), 3.4–3.7 (bd, 8H, morpholinyl), 6.5 (s, 2H, $CHCO_2H$), 6.7–7.3 (m, 13H, Ar, CO_2H, and 0.5 H_2O).

Typical Procedure Sequence for Method B. *N*-[(4-Morpholinyl)(phenylimino)methyl]acetamide (7a). Under N_2 over 30 min acetic anhydride (4.4 mL, 45 mmol) in CH_2Cl_2 (60 mL) was added to a room temperature mixture of **5a** (9.2 g, 45 mmol) and K_2CO_3 (6.4 g, 45 mmol) in CH_2Cl_2 (80 mL). After 2.5 h the mixture was extracted with 15% NaOH. The aqueous

phase was then saturated with NaCl and extracted several times with $CHCl_3$. The combined $CHCl_3$ extracts were dried over K_2CO_3, filtered, and concentrated under reduced pressure to yield 10.04 g (90%) of **7a** as a clear oil which crystallized to a white solid upon standing, mp 92–95 °C. ^1H NMR ($CDCl_3$): δ 2.1 (s, 3H, $COCH_3$), 3.3–3.5 (m, 4H, NCH_2CH_2O), 3.5–3.7 (bd, 4H, NCH_2CH_2O), 6.8–7.2 (m, 5H, Ar). Anal. ($C_{13}H_{17}N_3O_2$) C, H, N.

***N*-[(4-Morpholinyl)(phenylimino)methyl]propanamide (7b).** The desired product was prepared via the procedure used for **7a** after substituting propionic anhydride in place of acetic anhydride to yield **7b** as a white solid in 79% yield, mp 105–108 °C.

2-Methyl-*N*-[(4-morpholinyl)(phenylimino)methyl]-propanamide (7c). The desired product was prepared via the procedure used for **7a** after substituting isobutyric anhydride in place of acetic anhydride to yield **7c** as a white solid in 82% yield.

***N*-[(4-Morpholinyl)(phenylimino)methyl]heptanamide (7d).** The desired product was prepared via the procedure used for **7a** after substituting heptanoic anhydride in place of acetic anhydride to yield **7d** as a white solid in 71% yield, mp 69–76 °C.

2-Methyl-*N*-[(4-pyrrolidinyl)(phenylimino)methyl]-propanamide (7e). The desired product was prepared via the procedure used for **7a** after substituting isobutyric anhydride in place of acetic anhydride and **5c**[4] in place of **5a**. The workup also varied in that the reaction mixture was filtered after 16 h and extracted with a NaCl saturated 15% NaOH solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a yellow oil. This oil was crystallized from EtOAc to yield **7e** as a white solid in 49% yield, mp 82–85 °C.

***N*-[(4-Morpholinyl)(phenylimino)methyl]ethanethioamide Hydrochloride (8a).** Under N_2, Lawesson's reagent (16.48 g, 41.2 mmol) was added to a 0–5 °C solution of **7a** (18.57 g, 74.9 mmol) in THF (400 mL). After 3.5 h the reaction was warmed to room temperature and stirred an additional 16 h. The mixture was then concentrated under reduced pressure. The residue was dissolved in acetone (150 mL) and treated with ethereal HCl (75 mL). The resulting solid was filtered and rinsed with acetone and then Et_2O to yield 12.48 g (56%) of **8a** as a yellow solid, mp 181–184 °C. ^1H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 3.8 (s, 8H, morpholinyl), 7.2–7.4 (bd, 6H, Ar and *H*Cl). Anal. ($C_{13}H_{17}N_3OS$·HCl) C, H, N.

***N*-[(4-Morpholinyl)(phenylimino)methyl]propanethioamide Hydrochloride (8b).** The desired product was prepared via the procedure used for **8a** after substituting **7b** in place of **7a** to yield **8b** as a yellow solid in 69% yield, mp 176–179 °C. Anal. ($C_{14}H_{19}N_3OS$·HCl) C, H, N.

2-Methyl-*N*-[(4-morpholinyl)(phenylimino)methyl]-propanethioamide Hydrochloride (8c). The desired product was prepared by following the procedure used for **8a** after substituting **7c** in place of **7a**. The reaction mixture also had to be warmed for 2 h prior to workup to complete the reaction. The workup varied slightly in that for a 75-mmol scale of **7a** the reaction mixture was concentrated down to a final volume of 125 mL of THF, and this solution was treated directly with ethereal HCl (50 mL). The resulting yellow solid was filtered to yield 5.63 g (25%) of **8c**.

***N*-[(4-Morpholinyl)(phenylimino)methyl]heptanethioamide (8d).** The desired product was prepared via the procedure used for **8a** after substituting **7d** in place of **7a**. The workup varied in that the desired product was purified by silica gel flash chromatographing the reaction mixture residue, eluting with 1:2 acetone–hexane, to yield **8d** as a yellow oil in 17% yield which was used directly as the free base for conversion to **9d**. TLC 1:1 EtOAc–hexane R_f = 0.7.

2-Methyl-*N*-[(4-pyrrolidinyl)(phenylimino)methyl]-propanethioamide Hydrochloride (8e). The desired product was prepared by following the procedure used for **8a** after substituting **7e** in place of **7a**. The workup varied in that the desired product was isolated by treating the reaction mixture (83-mmol scale of **7e** in 120 mL THF) with ethereal HCl (20 mL), then CH_3CN (30 mL), and then an additional portion of Et_2O (225 mL) to yield 14.77 g (57%) of **8e** as a yellow solid. TLC of salt **8e** 1:1 EtOAc–hexane R_f = 0.7.

***N*-[1-(methylthio)ethylidene]-*N'*-phenyl-4-morpholinecarboximidamide (9a).** Under Ar over 1 min **8a** (17.94 g, 60 mmol) was added neat to a 0 °C mixture of hexane-washed NaH (5.76 g of 50% oil dispersion, 120 mmol) in THF (140 mL). After 25 min the reaction mixture was warmed to room temperature and stirred an additional 2 h. Methyl iodide (3.72 mL, 60 mmol) was then added neat to the reaction mixture. After being stirred for 2 h the mixture was concentrated under reduced pressure and partitioned between 15% NaOH and CH_2Cl_2. The organic phase was rewashed with 15% NaOH and then brine, dried over K_2CO_3, filtered, and concentrated under reduced pressure to yield 14.26 g (86%) of **9a** as a yellow oil which crystallized upon standing. This material was used without further purification. ^1H NMR ($CDCl_3$): δ 1.8 (s, 3H, CCH_3), 2.2 (s, 3H, SCH_3), 3.3–3.5 (m, 4H, NCH_2CH_2O), 3.6–3.8 (m, 4H, NCH_2CH_2O), 6.6–7.2 (m, 5H, Ar).

***N*-[1-(Methylthio)propylidene]-*N'*-phenyl-4-morpholinecarboximidamide (9b).** The desired product was prepared via the procedure for **9a** after substituting **8b** in place of **8a** with the exception that the product was not isolated but rather was prepared in situ and used directly.

***N*-[2-Methyl-1-(methylthio)propylidene]-*N'*-phenyl-4-morpholinecarboximidamide (9c).** The desired product was prepared via the procedure for **9a** after substituting **8c** in place of **8a** with the exception that the product was not isolated but rather was prepared in situ and used directly.

***N*-[1-(Methylthio)heptylidene]-*N'*-phenyl-4-morpholinecarboximidamide (9d).** The desired product was prepared via the procedure for **9a** after substituting **8d** in place of **8a** with the following exceptions. Only 1 equiv of NaH was used in the reaction since **8d** was a free base and the final product was not isolated, but rather was prepared in situ and used directly.

***N*-[2-Methyl-1-(methylthio)propylidene]-*N'*-phenyl-4-pyrrolidinecarboximidamide (9e).** The desired product was prepared by following the procedure for **9a** after substituting **8e** in place of **8a** with the exception that the product was not isolated but rather was prepared in situ and used directly.

***N*-[1-(Dimethylamino)ethylidene]-*N'*-phenyl-4-morpholinecarboximidamide–(*E*)-2-Butenedioate (2:3) (6c).** Under Ar at room temperature dimethylamine was bubbled into a solution of **9a** (2.77 g, 10 mmol) in THF (200 mL) for 15 min. After 16 h the mixture was concentrated under reduced pressure and then partitioned between $CHCl_3$ and 15% NaOH. The organic phase was dried over K_2CO_3, filtered, and concentrated under reduced pressure to yield 3.0 g of yellowish oil. This oil was triturated in Et_2O (10 mL) to give 1.8 g of white solid. This white solid was dissolved in EtOH (10 mL) and combined with fumaric acid (0.76 g, 6.6 mmol) which was dissolved in hot EtOH (10 mL). The resulting solution was filtered through Dicalite and cooled. The resulting solid was filtered and rinsed with a small amount of EtOH and then Et_2O. Upon addition of the Et_2O to the filtrate, more solid precipitated from the solution. This material was also filtered and rinsed with EtOH and Et_2O. The solid fractions were combined to yield 1.53 g (34%) of **6c** as a white solid. ^1H NMR (DMSO-d_6): δ 1.8 (s, 3H, CCH_3), 2.8 (s, 6H, $N(CH_3)_2$), 3.4–3.7 (bs, 8H, morpholinyl), 6.4 (s, 3H, $CHCO_2H$), 6.8–7.3 (m, 5H, Ar), 10.8–11.2 (bs, 3H, $CHCO_2H$).

***N*-(1-Piperidinylethylidene)-*N'*-phenyl-4-morpholinecarboximidamide–(*E*)-2-Butenedioate (6e).** The desired product was prepared by following the procedure for **6c** after substituting piperidine (1 molar equiv to **9a**) in place of dimethylamine. Also, after the reaction mixture was stirred for 48 h at room temperature, it was refluxed an additional 48 h prior to the standard workup.

***N*-[1-(Dimethylamino)-2-methylpropylidene]-*N'*-phenyl-4-morpholinecarboximidamide (6f).** The desired product was prepared by following the procedure for **6c**, after substituting **9c** in place of **9a** with the exception that the reaction mixture was warmed to 68 °C for 5 days in a pressure bottle prior to the standard workup.

***N*-[1-(Methylamino)ethylidene]-*N'*-phenyl-4-morpholinecarboximidamide–(*E*)-2-Butenedioate (2:3) (6g).** The desired product was prepared via the procedure for **6c** after substituting monomethylamine in place of dimethylamine. Also, after the reaction mixture was stirred for 24 h a second portion of monomethylamine was added to the reaction mixture, and the

reaction mixture was stirred an additional 24 h prior to the standard workup.

N-[1-(Butylmethylamino)ethylidene]-N'-phenyl-4-morpholinecarboximidamide–(E)-2-Butenedioate–Ethanol (1:1:1) (6i). The desired product was prepared by following the procedure for **6c** after substituting *N*-methyl-*N*-butylamine (10 molar equiv to **9a**) in place of dimethylamine.

N-[1-[(1-Methylethyl)amino]ethylidene]-N'-phenyl-4-morpholinecarboximidamide (6j). Under Ar, **9a** (4.71 g, 17.4 mmol) was combined with *i*-$PrNH_2$ (30 mL, 353 mmol), and this neat reaction mixture was stirred at room temperature for 16 h and then at 45 °C in a pressure bottle for 3 days prior to the standard workup.

N-[2-Methyl-1-(methylamino)propylidene]-N'-phenyl-4-morpholinecarboximidamide (6m). The desired product was prepared by following the procedure for **6c** after substituting **9c** in place of **9a** and monomethylamine in place of dimethylamine. Also, the reaction mixture was stirred for 5 days in a pressure bottle prior to the standard workup.

N-[2-Methyl-1-[(1-methylethyl)amino]propylidene]-N'-phenyl-4-morpholinecarboximidamide (6r). Under Ar, **9c** (1.20 g, 3.93 mmol) was combined with *i*-$PrNH_2$ (100 mL, 1.17 mol), and this neat reaction was stirred at 62 °C in a pressure bottle for 5 days prior to the standard workup. One slight variation in the workup was that Et_2O was used for extractions in place of CH_2Cl_2.

N-(1-Morpholinylethylidene)-N'-phenyl-4-morpholinecarboximidamide–(E)-2-Butenedioate–Ethanol (3:3:1) (6s). Under N_2, **9a** (1.40 g, 5 mmol) was combined with morpholine (10 mL, 115 mmol) and THF (40 mL) at room temperature and immediately warmed to 60 °C. After 5 days the reaction mixture was treated by the standard workup.

N-[1-[(1,1-Dimethylethyl)amino]ethylidene]-N'-phenyl-4-morpholinecarboximidamide (6u). Under Ar, **9a** (1.94 g, 7.0 mmol) was combined with *t*-$BuNH_2$ (100 mL, 0.95 mol), and this neat reaction was stirred at 75 °C in a pressure bottle for 26 days prior to the standard workup.

N'-Phenyl-N-[1-(phenylmethylamino)ethylidene]-4-morpholinecarboximidamide (6v). Under Ar, **9a** (1.51 g, 5.49 mmol) was combined with benzylamine (6 mL, 54.9 mmol), and this neat reaction mixture was stirred at room temperature for 6 days. The reaction mixture was then dissolved in $CHCl_3$, washed twice with 3 N HCl and once with 15% NaOH, dried over K_2CO_3, filtered, and concentrated under reduced pressure. After preparing a fumarate salt in a similar manner as **6l**, the sample was free based and crystallized from hexane to give 0.33 g (18%) of **6v** as a white solid.

N-[1-(4-Methyl-1-piperazinyl)ethylidene]-N'-phenyl-4-morpholinecarboximidamide Complex with 1,2-Benzisothiazol-3(2H)-one 1,1-Dioxide (6w). Under Ar, **9a** (2.08 g, 7.5 mmol) was combined with *N*-methylpiperazine (16 mL, 150 mmol), and this neat reaction mixture was stirred at room temperature for 5 days. The reaction mixture was then concentrated under reduced pressure, and salt formation pursued directly.

N'-Phenyl-N-[1-(n-propylamino)ethylidene]-4-morpholinecarboximidamide (6y). Under Ar, **9a** (2.00 g, 7.22 mmol) was combined with *N*-propylamine (20 mL, 243 mmol), and this neat reaction mixture was stirred at room temperature for 3 days. The reaction mixture was then concentrated under reduced pressure and crystallized directly.

N-[2-Methyl-1-(methylamino)propylidene]-N'-phenyl-4-pyrrolidinecarboximidamide (6z). The desired product was prepared by following the procedure for **6c** after substituting **9e** in place of **9a** and monomethylamine in place of dimethylamine. Also, the reaction mixture was stirred for 4 days prior to the standard workup.

N-[1-(Ethylamino)ethylidene]-N'-phenyl-4-morpholinecarboximidamide–(E)-2-Butenedioate (6ff). The desired product was prepared via the procedure for **6c** after substituting ethylamine in place of dimethylamine. Also, the reaction mixture was stirred for 12 days prior to the standard workup.

N-[1-[(2-Ethoxy-2-oxoethyl)amino]ethylidene]-N'-phenyl-4-morpholinecarboximidamide–(E)-2-Butenedioate (1:1) (6gg). The desired product was prepared via the procedure for **6c** after substituting glycine ethyl ester hydrochloride (1 molar equiv to **9a**) in place of dimethylamine and stirring the reaction mixture at reflux for 3 days prior to the standard workup.

N-[1-[(Methylsulfonyl)amino]ethylidene]-N'-phenyl-4-morpholinecarboximidamide (6jj). Under Ar, **9a** (12.59 g, 45.45 mmol) was combined with methanesulfonamide (4.32 g, 45.45 mmol), and this neat reaction was warmed to 90 °C for 18 h. The reaction mixture was then cooled, dissolved in $CHCl_3$, and chromatographed directly.

Typical Procedure for Method C. N'-(4-Fluorophenyl)-N-[2-methyl-1-(methylamino)propylidene]-4-morpholinecarboximidamide (6dd). Under N_2 at room temperature, $Me_3O^+BF_4^-$ (10.42 g, 70.4 mmol) and *i*-BuCN (7.3 mL, 80.6 mmol) were combined in CH_2Cl_2 (55 mL) and immediately warmed to reflux. After 36 h the mixture was cooled to room temperature and added over 15 min to a 0 °C solution of **5b**[4] (14.28 g, 64 mmol) in CH_2Cl_2 (60 mL). The resulting mixture was stirred at 0 °C an additional 5 min and then at room temperature for 5 h. The resulting precipitate was then filtered and rinsed several times with CH_2Cl_2. The combined filtrates were then cooled to 0 °C, basified (pH > 9) with 3 N NaOH, dried over K_2CO_3, filtered, and concentrated under reduced pressure to give 18.09 g of a pale yellow oil. This oil was treated with Et_2O and the resulting solid filtered. The Et_2O filtrate was concentrated under reduced pressure to yield 6.15 g of a yellow oil. This oil was converted to a crystalline solid by treating with a CH_2Cl_2/hexane solution. The resulting solid was recrystallized from CH_2Cl_2/hexane to yield 2.13 g (11%) of **6dd** as a white solid. ^1H NMR ($CDCl_3$): δ 0.5–1.0 (bs, 6H, $HC(CH_3)_2$), 2.3–2.6 (m, 1H, $HC(CH_3)_2$), 2.65–2.8 (d, 3H, $NHCH_3$), 3.3–3.6 (m, 4H, NCH_2CH_2O), 3.6–3.8 (bd, 4H, NCH_2CH_2O), 4.2–4.6 (bs, 1H, $HNCH_3$), 6.6–6.9 (m, 5H, Ar).

N-[1-(Ethylamino)-2-methylpropylidene]-N'-phenyl-4-morpholinecarboximidamide (6bb). The desired product was prepared via the procedure for **6dd** after substituting Meerwein's reagent in place of $Me_3O^+BF_4^-$ and *i*-PrCN in place of *i*-BuCN with the imidate formation being run at room temperature rather than at reflux. Also, the addition of reagents was reversed from the standard conditions with solid **5a** being added to the preformed imidate solution to form the desired **6bb** prior to the standard workup.

Method D. N'-Phenyl-N-[1-(phenylamino)ethylidene]-4-morpholinecarboximidamide Complex with 1,2-Benzisothiazol-3(2H)-one 1,1-Dioxide (6p). Under Ar, free base **6o** (9.75 g, 23.56 mmol), 10% Pd on C (1.95 g), concentrated HCl (3 mL), and EtOH (150 mL) were combined in a Parr bottle which was subsequently pressurized with H_2 (46 psi) for 48 h. The reaction mixture was then filtered through Dicalite and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O. The organic phase was separated, rewashed with 15% NaOH, dried over K_2CO_3, filtered, and concentrated under reduced pressure. The residue was dissolved in EtOH (10 mL) and combined with a solution of saccharin (1.83 g, 10 mmol) in EtOH (15 mL). The resulting solid was filtered and rinsed with a small amount of EtOH and Et_2O to yield 2.97 g (26%) of **6p** as a white solid. ^1H NMR (DMSO-d_6): δ 1.95 (s, 3H, CH_3), 3.6–3.9 (bs, 8H, morpholinyl), 6.9–7.7 (m, 14H, Ar), 10.0–10.2 (bs, 1H, $CONHSO_2$).

Biological Testing: Rat Oral Glucose Tolerance Test. The rat oral glucose tolerance test was used as the primary test for hypoglycemic activity as described previously.[7,8] Vehicle (distilled H_2O or 0.5% hydroxypropyl methyl cellulose) and test compounds in vehicle were administered subcutaneously (0.5 mL) at 30 min prior to a standard oral glucose load (1.0 g/kg body weight). Compounds were routinely tested at a dose of 10 mg/kg body weight calculated as the free base. The most active compounds were then tested at 10, 5, and 2.5 mg/kg, sc for dose–response evaluation and calculation of ED_{30}. The mean glucose values of the controls are compared statistically to the mean values of the experimental groups at each corresponding time point by the unpaired student's *t*-test. If the compound lowered blood glucose significantly at any time point at a 95% confidence limit, the compound was considered to have hypoglycemic activity. The maximum percent lowering of blood glucose from the corresponding mean values of the control group was determined for each rat in the experimental groups and used to calculate the mean maximum percent lowering of glucose from control. The ED_{30} (dose producing a 30% decrease from control)

and the 95% confidence interval (CI) were determined from regression analysis of the mean maximum percent decrease from control versus log dose (mg/kg).

Acknowledgment. We thank Susan Campbell, David Herr, Gary Caldwell, and John Masucci for obtaining much of the spectral data for this paper. We are also grateful to Carol Marchione, Nate H. Wallace, David M. Morris, Debra J. Bryan, and Thomas W. Corcoran who carried out the biological experiments, to James Fortunato for nomenclature assistance for all compounds, and to Royce Rasmussen for advice and discussion.

References

(1) McMillan, D. E. Pathophysiology of Diabetic Macro- and Micro Vascular Disease. In *Diabetes Mellitus, Theorey and Practice*, 3rd ed.; Ellenberg, M., Rifkin, H., Eds; Medical Examination Publishing Co., Inc.: New York, 1983; pp 343–359.

(2) *The Physican's Guide to Type II Diabetes (NIDDM)-Diagnosis and Treatment*; Rifkin, H., Ed. in Chief; American Diabetes Association, Inc.: New York, 1984: pp 1–20.

(3) (a) Campbell, I. W. Sulfonylureas and metformin: efficacy and inadequacy. In *New Antidiabetic Drugs*; Bailey, C. J., Flatt, P. R., Eds.; Smith-Gordon and Company Limited: London, 1990; pp 33–53. (b) Tuman, R. W.; Tutwiler, G. F.; Bowden, C. R. Linogliride: a guanidine insulin secretagogue. In *New Antidiabetic Drugs*; Bailey, C. J., Flatt, P. R., Eds.; Smith-Gordon and Company Limited: London, 1990; pp 163–171.

(4) Rasmussen, C. R Nitrogen Heterocyclic Carboximidamide Compounds. U.S. Patent 4,211,867, July 8, 1980.

(5) Meerwein, H. Triethyloxonium Fluoroborate. In *Organic Syntheses*; Baumgarten, H. E., Ed.; John Wiley and Sons: New York, 1973; Collect. Vol. V, pp 1080–82.

(6) Kupfer, R.; Nagel, M.; Wurthwein, E.-U.; Allmann, R. Synthesis and structure of alkyl *N*-acylimidates. *Chem. Ber.* **1985**, *118*, 3089–3104.

(7) Tutwiler, G. F.; Tuman, R. W.; Joseph, J. M.; Mihan, B. B.; Fawthrop, H.; Brentzel, H. J. Pharmacologic Profile and Insulin Secretagogue Effect of Linogliride (McN-3935), a New, Orally Effective Hypoglycemic Agent. *Drug Dev. Res.* **1986**, *9*, 273–292.

(8) Marchione, C. S.; Tuman, R. W. Linogliride Fumarate, an Oral Hypoglycemic Agent, Improves Oral Glucose Tolerance in a Rat Model of Non-Insulin-Dependent Diabetes Mellitus (NIDDM). *Drug Dev. Res.* **1989**, *17*, 161–168.