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Oral Hypoglycemic Agents. Pyrimido[1,2-*a*]indoles and Related Compounds

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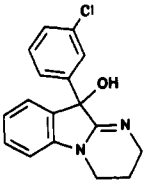
A series of pyrimido[1,2-*a*]indoles were synthesized and studied for their hypoglycemic activity following oral administration at a standard dose of 100 mg/kg to fed rats. The effect of 10-alkoxyalkyl, 10-alkyl, 10-aryl, and 3,3-dialkyl substitution on the activity of 10-hydroxypyrimido[1,2-*a*]indoles was investigated. Relative potencies of a number of the most active compounds were defined by three-point dose–response studies. The most potent compounds were those with either 3,3-dimethyl substituents, compounds **21**, **22**, and **38**, or 3,3-spirocyclohexane substituents, compounds **39** and **49**. 10-Aminopyrimido[1,2-*a*]indoles were in general less active than the 10-hydroxy analogues, and potency was further decreased by derivatizing the 10-amino group. The most potent 10-amino derivatives were **57** and **58**.

Introduction

Diabetes mellitus may be divided into two major subdivisions.[1] People with type I diabetes have little or no circulating insulin and require daily insulin injections to prevent ketoacidosis and death. In contrast, type II diabetics are often insulin resistant and, although having circulating insulin levels which are measurable, they have basal insulin levels and/or insulin secretory responses which are usually abnormal. The current therapy available for type II diabetes consists of diet, oral hypoglycemic agents, or insulin injections. Sulfonylureas are the only oral compounds currently approved by the FDA in the United States. These drugs exert their hypoglycemic actions by enhancing insulin release and possibly by improving intracellular metabolism of glucose.[2] Such treatments are not always effective, and the search for novel orally active non-insulin-releasing hypoglycemic agents continues.[3,4]

The present investigation was stimulated by the discovery that ciclazindol (1), a compound originally developed as an antidepressant agent,[5] had mild hypoglycemic properties following oral dosing in type II diabetic patients.[6]



(1)

Chemistry

The 10-hydroxypyrimido[1,2-*a*]indoles **1**, **13–39**, and **46–49** were prepared by one of two methods. In the first method, outlined in Scheme I, the compounds **1** and **13–39** were prepared from the precursor ketones **10–12** by Grignard reactions. The ketones **10–12** were obtained from the isatin **3** by alkylation to give **4** and **6** or cyanoethylation to give **5**, reductive cyclization to give **7–9**, and acetal hydrolysis. In the second method (Scheme II) the Grignard reactions[7] were carried out on isatin **2** prior to the

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(1) Halter, J. B.; Porte, D. Current Concepts of Insulin Secretion in Diabetes Mellitus. In *Diabetes Mellitus*; Rifkin, H., Raskin, P., Eds.; Brady Communications: Bowie, MD, 1981; Vol. 5, pp 33–42.
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(3) Steiner, K. E.; Lien, E. L. Hypoglycemic Agents which do not Release Insulin. *Prog. Med. Chem.* **1987**, *24*, pp 209–248.
(4) Mohrbacher, R. J.; Kiorpes, T. C.; Bowden, C. R. Pharmacologic Intervention in Diabetes Mellitus. In *Annu. Rep. Med. Chem.* **1987**, *22*, pp 213–222.
(5) Beckett, P. R.; Southgate, P. J.; Sugden, R. F. The Pharmacology of WY-23409, a New Antidepressant. *Naunyn-Schmiedeberg's Arch. Pharmacol. (Suppl.)* **1973**, Abstract no. 41, p R-27.
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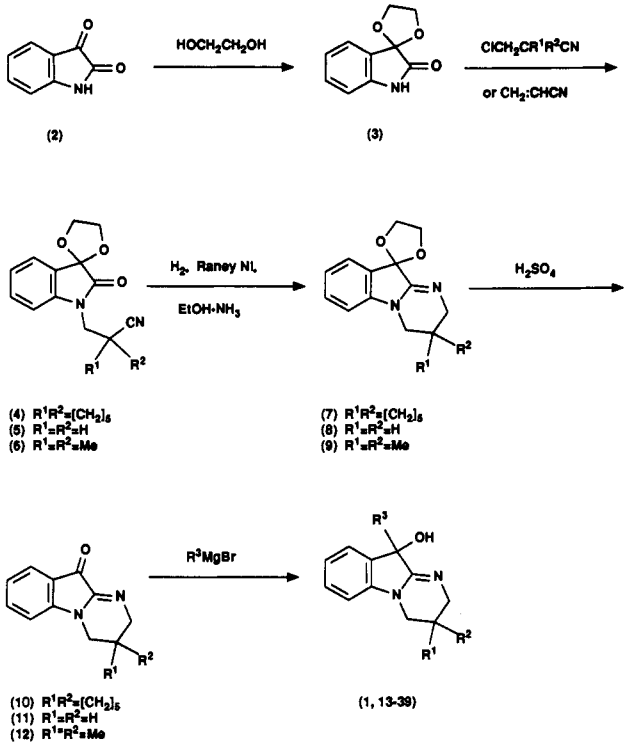
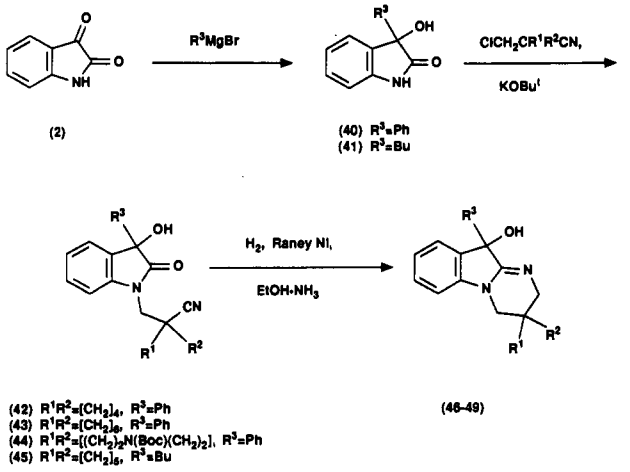
Scheme I



Scheme II



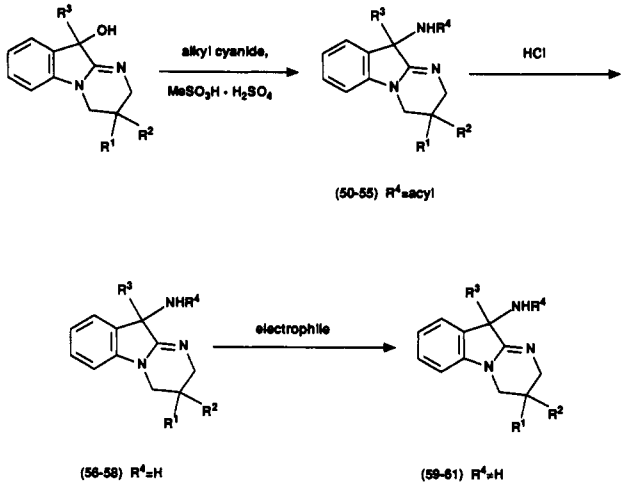
alkylation and reductive cyclization steps.

The 10-amidopyrimido[1,2-*a*]indoles **50–55** (Scheme III) were prepared by the Ritter reaction of the 10-hydroxypyrimido[1,2-*a*]indoles **1**, **37**, or **38** with an alkyl cyanide. Hydrolysis of the amides **50–52** gave the amines **56–58**; **58** was further elaborated to the derivatives **59–61**. The 11-acetamido[1,3]diazepino[1,2-*a*]indole **62** was made in similar fashion from the corresponding alcohol[8] by a Ritter reaction (Scheme IV).

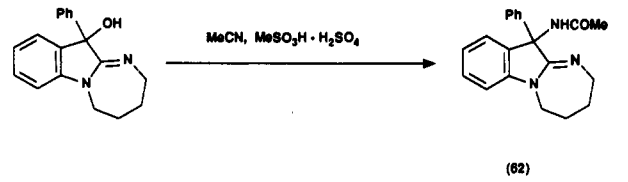
Results

The initial lead (**1**) in this active hypoglycemic series was also an effective antidepressant, and so the synthetic efforts were focused on the enhancement of hypoglycemic activity and the minimization of central nervous system (CNS) side effects. The structures of the compounds made

Scheme III



Scheme IV



and the results of initial hypoglycemic screening are presented in Table I.

The conclusions drawn from Table I are as follows:

10-Alkoxyalkyl Derivatives 13–22. The effect of replacing the 10-(3-chlorophenyl) substituent of ciclazindol (**1**) with 10-alkoxyalkyl groups was examined in compounds **13–22**. The 10-(4-methoxybutyl) compound **13** was more potent than either the 10-(4-ethoxybutyl) derivative **14** or the branched chain isomers **15** and **16**. The effect of placing methyl groups at the 3-positions of the pyrimido[1,2-*a*]indole was to increase activity; thus the 3,3-dimethyl compounds **18** and **19** were more potent than the 3,3-dihydro analogues **13** and **14**. In contrast with the poor activity displayed by the 3,3-dihydro compounds **15** and **16**, the branched chain compounds **21** and **22** in the 3,3-dimethyl series were very potent compounds.

10-Alkyl and 10-Aryl Derivatives 23–38. Compound **24** was the most potent hypoglycemic agent among the three straight-chain 10-alkyl substituted compounds **23–25**. All the branched-chain derivatives **26–33**, the 10-allyl compound **34**, and the three 10-aryl compounds **36–38** produced hypoglycemia.

Spiro Derivatives 39 and 46–49. The observation that the 3,3-dimethyl-substituted compounds were more potent than the corresponding 3,3-unsubstituted analogues was studied further by the synthesis of five spiro[cycloalkane-1,3′-pyrimido[1,2-*a*]indoles]. The three 10-phenyl derivatives **39**, **46**, and **47** were active. The most potent compound **39** was resolved but there was no difference in the activity of the enantiomers. Replacement of the 10-phenyl group of **39** by a butyl substituent produced **49**, the most potent spiro compound of the series.

10-Amino Derivatives 50–62. The replacement of the 10-hydroxy group by a 10-amino substituent led in general to a decrease in activity. The potency of the compounds correlated to some extent with the size of the 10-substituent, an effect best delineated in the 3,3-dimethyl series where the compounds substituted with 10-NH_2 (**58**), 10-NHCOMe (**52**), and 10-$NHSO_2Me$ (**59**) were more potent than the compounds substituted with 10-NHCOPr (**53**), 10-NHCOPh (**61**), and 10-NHCONHTs (**60**). The 3,3-

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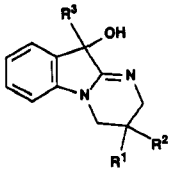
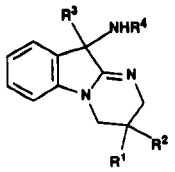
Table I. Physical and Pharmacological Data



1, 13–39, 46–49



50–61

62

compd	mp (°C)	cryst solvent[a]	formula[b]	yield[c] (%)	structure R[1]	R[2]	R[3]	R[4]	blood glucose[d] 2 h	4 h
1	275–280	A-B	$C_{17}H_{15}ClN_2O\cdot HCl$	71	H	H	3-Cl-C_6H_4		99	84
13	178–179	A-B	$C_{16}H_{22}N_2O_2\cdot HCl$	65	H	H	$(CH_2)_4OMe$		86[f]	87[f]
14	189–190	A-B	$C_{17}H_{24}N_2O_2\cdot HCl$	52	H	H	$(CH_2)_4OEt$		100	96
15	243–244	A-B	$C_{16}H_{22}N_2O_2\cdot HCl$	52	H	H	$CH_2CHMeCH_2OMe$		94	98
16	200–204	A-B	$C_{16}H_{22}N_2O_2\cdot HCl$	68	H	H	$(CH_2)_2CHMeOMe$		88[f]	95
17	192–194	C	$C_{14}H_{14}N_2O_2\cdot HCl$	38	H	H	$C{\equiv}CCH_2OH$		94	94
18	188–190	D	$C_{18}H_{26}N_2O_2\cdot HCl$	53	Me	Me	$(CH_2)_4OMe$		79[f]	87[f]
19	155–156	A-B	$C_{19}H_{28}N_2O_2\cdot HCl$	77	Me	Me	$(CH_2)_4OEt$		88	86
20	147–150	A-B	$C_{24}H_{20}N_2O_2\cdot HCl$	72	Me	Me	$(CH_2)_4OCH_2Ph$		76[f]	91
21	154–155	A	$C_{18}H_{26}N_2O_2\cdot HCl\cdot 0.25H_2O$	38	Me	Me	$CH_2CHMeCH_2OMe$		73[f]	72[f]
22	179–186	A-B	$C_{18}H_{26}N_2O_2\cdot HCl\cdot 0.25H_2O$	53	Me	Me	$(CH_2)_2CHMeOMe$		69[f]	73[f]
23	228–231	A-B	$C_{15}H_{20}N_2O\cdot HCl\cdot 0.5H_2O$	65	Me	Me	Et		89	93
24	213–215	A-B	$C_{17}H_{24}N_2O\cdot HCl\cdot 0.25H_2O$	54	Me	Me	Bu		58[f]	67[f]
25	178–180	A-B	$C_{19}H_{29}N_2O\cdot HCl\cdot 0.75H_2O$	64	Me	Me	hexyl		103	107
26	248–250	A-B	$C_{19}H_{20}N_2O\cdot HCl$	70	Me	Me	c-Pr		83[f]	81
27	220–222	A-B	$C_{17}H_{24}N_2O\cdot HCl$	67	Me	Me	CH_2CHMe_2		88[f]	77[f]
28	237–239	A-E	$C_{15}H_{20}N_2O\cdot HCl$	51	H	H	CH_2CHMe_2		79[f]	86[f]
29	203–205	A-B	$C_{18}H_{26}N_2O\cdot HCl$	60	Me	Me	$(CH_2)_2CHMe_2$		65[f]	78[f]
30	236–238	A-B	$C_{18}H_{26}N_2O\cdot HCl$	62	Me	Me	CH_2CMe_2		68[f]	81[f]
31	196–197	A-B	$C_{18}H_{26}N_2O\cdot HCl$	57	H	H	CH_2CHEt_2		82[f]	68[f]
32	227–229	A-B	$C_{20}H_{28}N_2O\cdot HCl$	63	Me	Me	CH_2-cyclohexyl		79[f]	84[f]
33	228–230	A-B	$C_{18}H_{24}N_2O\cdot HCl$	48	H	H	CH_2-cyclohexyl		77[f]	81[f]
34	188–196	D-E	$C_{16}H_{20}N_2O\cdot HCl\cdot 0.25H_2O$	59	Me	Me	$CH_2CH{=}CH_2$		86[f]	74
35	190–195	A-B	$C_{21}H_{24}N_2O\cdot HCl$	24	H	H	$(CH_2)_2CHMePh$		99	88[f]
36	266–268	A-B	$C_{21}H_{18}N_2O\cdot HCl$	82	H	H	2-naphthyl		88[f]	64[f]
37	264–270	C	$C_{17}H_{16}N_2O\cdot HCl$	81	H	H	Ph		86[f]	82[f]
38	260–261	C	$C_{19}H_{20}N_2O\cdot HCl$	52[e]	Me	Me	Ph		90	75[f]
39	273–274	B-D	$C_{22}H_{24}N_2O\cdot HCl$	46	$-(CH_2)_5-$		Ph		78[f]	60[f]
(−)-39	271–273	C	$C_{22}H_{24}N_2O\cdot HCl$	63	$-(CH_2)_5-$		Ph		81[f]	71[f]
(+)-39	269–271	C	$C_{22}H_{24}N_2O\cdot HCl$	73	$-(CH_2)_5-$		Ph		82[f]	69[f]
46	263–264	A-B	$C_{21}H_{22}N_2O\cdot HCl$	74	$-(CH_2)_4-$		Ph		75[f]	71[f]
47	265–267	A-B	$C_{23}H_{26}N_2O\cdot HCl$	49	$-(CH_2)_6-$		Ph		87[f]	76[f]
48	>300	C	$C_{21}H_{23}N_3O\cdot 2HCl\cdot 1.25H_2O$	60	$-(CH_2)_2NH(CH_2)_2-$		Ph		102	92
49	219–220	C-E	$C_{20}H_{28}N_2O\cdot HCl$	39	$-(CH_2)_5-$		Bu		60[f]	68[f]
50	275–285	A-B	$C_{19}H_{18}ClN_3O\cdot HCl\cdot 0.25H_2O$	5[e]	H	H	3-Cl-C_6H_4	COMe	89	85[f]
51	315–325	A-E	$C_{19}H_{19}N_3O\cdot HCl$	87	H	H	Ph	COMe	76[f]	75[f]
52	>300	A-E	$C_{21}H_{23}N_3O\cdot HCl\cdot 0.5H_2O$	85	Me	Me	Ph	COMe	85[f]	77[f]
53	275–280	A-B	$C_{23}H_{27}N_3O\cdot HCl\cdot 0.25H_2O$	25	Me	Me	Ph	COPr	101	77[f]
54	265–268	A-E	$C_{23}H_{21}N_3O\cdot HCl\cdot 0.25H_2O$	53	H	H	2-naphthyl	COMe	104	100
55	>300	A-E	$C_{23}H_{25}N_3O\cdot HCl\cdot 0.25H_2O$	21[e]	$-(CH_2)_4-$		Ph	COMe	99	90
56	274–276	A-B	$C_{17}H_{16}ClN_3\cdot HCl$	68[e]	H	H	3-Cl-C_6H_4	H	95	84[f]
57	260–265	A-E	$C_{17}H_{17}N_3\cdot 2HCl$	64[e]	H	H	Ph	H	84[f]	93
58	260–265	A-B	$C_{19}H_{21}N_3\cdot 2HCl\cdot 0.25H_2O$	61	Me	Me	Ph	H	78[f]	68[f]
59	160–165	A-B	$C_{20}H_{23}N_3O_2S\cdot HCl\cdot 0.75H_2O$	26	Me	Me	Ph	SO_2Me	76[f]	67[f]
60	253–255	A-B	$C_{27}H_{28}N_4O_3S\cdot HCl$	80	Me	Me	Ph	CONHTs	101	90
61	295–298	A-E	$C_{26}H_{25}N_3O\cdot HCl$	60	Me	Me	Ph	COPh	104	116
62	285–290	A-B	$C_{20}H_{21}N_3O\cdot HCl\cdot H_2O$	32					86	73[f]

[a] Recrystallization solvents: A, methanol; B, ether; C, ethanol; D, propan-2-ol; E, ethyl acetate. [b] Elemental analyses were within 0.4% of the calculated values. [c] Yield of free base. [d] Values as percent of vehicle control; six rats per group; dose 100 mg/kg po. [e] Yield of salt. [f] $p < 0.05$ vs vehicle control.

dihydro-10-phenyl-substituted compound **51** was more potent than the 3,3-dihydro-10-(2-naphthyl)-substituted compound **54** or the spirocyclopentane **55**. The single example of a [1,3]diazepino[1,2-*a*]indole **62** was found to be less potent than the pyrimido[1,2-*a*]indole analogue **51**.

The first compound selected for further development was **38**, an orally active and potent hypoglycemic agent. This compound caused a dose-dependent lowering of plasma glucose levels in normal fed rats and had a substantially better hypoglycemic efficacy and potency than ciclazindol (Figure 1). The maximal glucose lowering in fed rats occurred somewhere between 4 and 6 h (Figure 2), and the compound had a similar efficacy and potency in fasted animals (Figure 3). The hypoglycemic profile as illustrated in Figures 2 and 3 was qualitatively the same for all the pyrimido[1,2-*a*]indoles we examined. Unlike the sulfonylureas where hypoglycemic effects were accompanied by a rapid increase in circulating plasma insulin, administration of the pyrimido[1,2-*a*]indoles caused a decline in plasma glucose but no change in plasma insulin.

The process of compiling a more complete pharmacological profile of **38** indicated that this compound had some side effects arising from abnormal CNS activity. The extensive synthetic effort which was undertaken in order

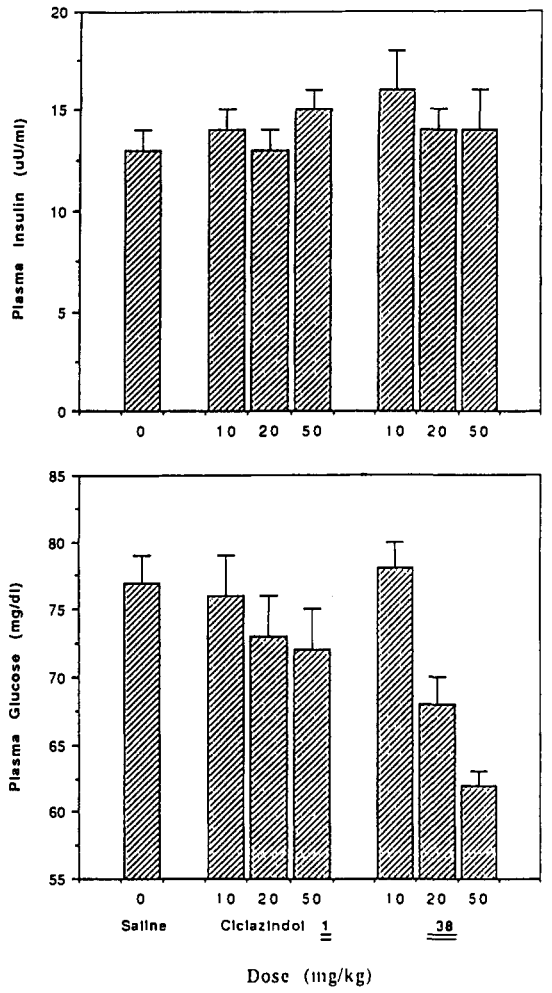


Figure 1. Ciclazindol (1) or compound **38** were administered subcutaneously 4 h prior to blood sampling in fed rats (280–430 g). Blood was obtained after decapitation and treated as described in Pharmacological Methods. Data are reported as the mean ± SEM of each group of eight animals.

Table II. Relative Potencies of the Most Active Compounds

compd	relative potency	compd	relative potency
18	0.05 (0.001–0.17)[a,b]	**39**	1.33 (0.67–3.27)
21	0.47 (0.12–1.32)	**46**	0.10 (0.11–3.12)
22	1.10 (no error limits)	**47**	0.30 (0.06–0.83)[b]
26	0.11 (no error limits)[b]	**49**	3.69 (1.40–23.64)[b]
27	0.69 (10^{-7}–6.89)	**50**	0.50 (no error limits)[b]
30	0.65 (0.35–1.06)	**51**	0.03 (no error limits)[b]
31	0.86 (0.16–8.63)	**52**	0.03 (no error limits)[b]
33	0.12 (0.01–0.41)[b]	**57**	0.47 (0.04–1.20)[a]
36	0.01 (0.002–0.41)[b]	**58**	0.90 (0.13–5.30)
37	0.52 (0.16–1.03)	**59**	0.04 (no error limits)[b]
38	1	**62**	0.13 (0.0004–0.65)[b]

[a] Blood collected 2 h following dosing. [b] $p < 0.05$ vs standard compound **38**.

to dissociate hypoglycemic activity from unwanted side effects resulted in the identification of compounds **22**, **39**, and **49** which had potencies equivalent to or greater than that of **38** (Table II). On the basis of the overall pharmacological and toxicological profile of **39**, this compound was selected for further development and will be the subject of a more detailed report characterizing its hypoglycemic activity.

Discussion

The synthetic effort summarized in this paper was prompted by the observation that the antidepressant ciclazindol caused a decline in plasma glucose levels in

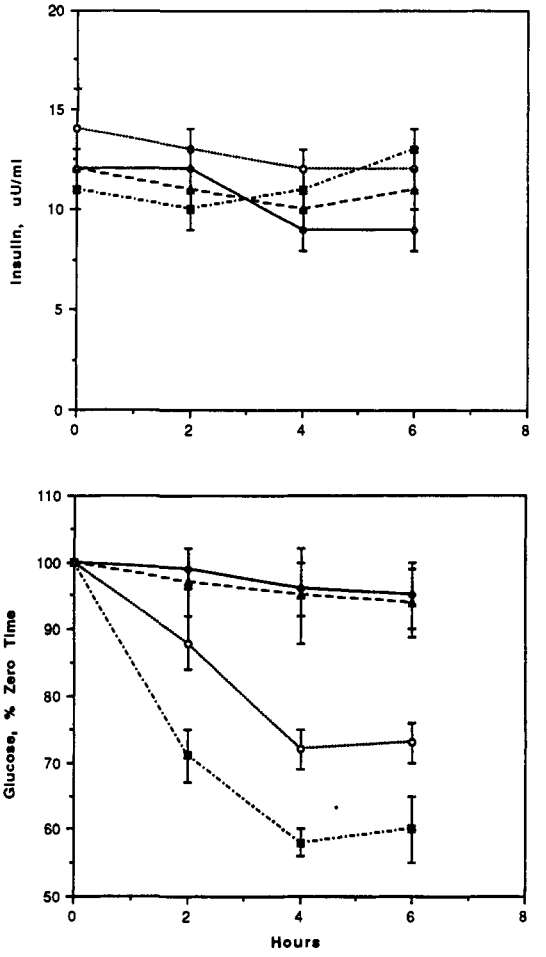


Figure 2. Compound **38** was administered orally at zero time to fed rats (280–320 g). Tail-tip blood samples were obtained just prior to drug administration and at the times indicated. Blood samples were processed as described in Pharmacological Methods. Data are reported as the mean ± SEM of six animals except for the vehicle-treated group which is the mean of 12 animals: (◇) vehicle, (▲) 10 mg/kg, (○) 20 mg/kg, (■) 50 mg/kg.

non-insulin-dependent diabetic individuals (NIDDMs). It has been suggested that the hypoglycemic activity of ciclazindol might be the result of a stimulation of muscle glucose uptake.[6,9] Since hypoglycemic agents with exclusively extrapancreatic actions are not widely available, it was deemed of interest to maximize the hypoglycemic potential of ciclazindol. A number of compounds were synthesized with improved hypoglycemic potency and efficacy of which **22**, **38**, **39**, and **49** were the best.

Compound **39** was resolved but the enantiomers were equipotent as hypoglycemic agents following oral administration. An experiment in which the enantiomers were dissolved in aqueous acid at pH 2 for 1 week revealed that neither racemization (as judged by analytical chiral HPLC) nor decomposition[10] (as judged by NMR spectrometry) was

(9) Kirby, M. J.; Turner, P. Ciclazindol and Mazindol on Glucose Uptake into Human Isolated Skeletal Muscle: No Interaction of Mazindol with Methysergide. *Br. J. Clin. Pharmacol.* **1977**, *4*, pp 459–461.

(10) Pyrimido[1,2-*a*]indoles undergo acid-catalyzed rearrangement reactions. For instance, compound 1 gives 6-(3-chlorophenyl)-1,2,3,4,5,6-hexahydro-1,6-methano-1,5-benzodiazocin-11-one in 14% yield after heating under reflux in xylene for 7 days in the presence of a catalytic quantity of toluene *p*-sulfonic acid. See: Cliffe, I. A.; Heatherington, K.; White, A. C. Rearrangements of Pyrimido- and Diazepino-[1,2-a]indoles: Syntheses of 1,5-Benzodiazocines and 1,6-Benzodiazonines. *J. Chem. Soc., Perkin Trans. 1* **1991**, pp 1975–1979.

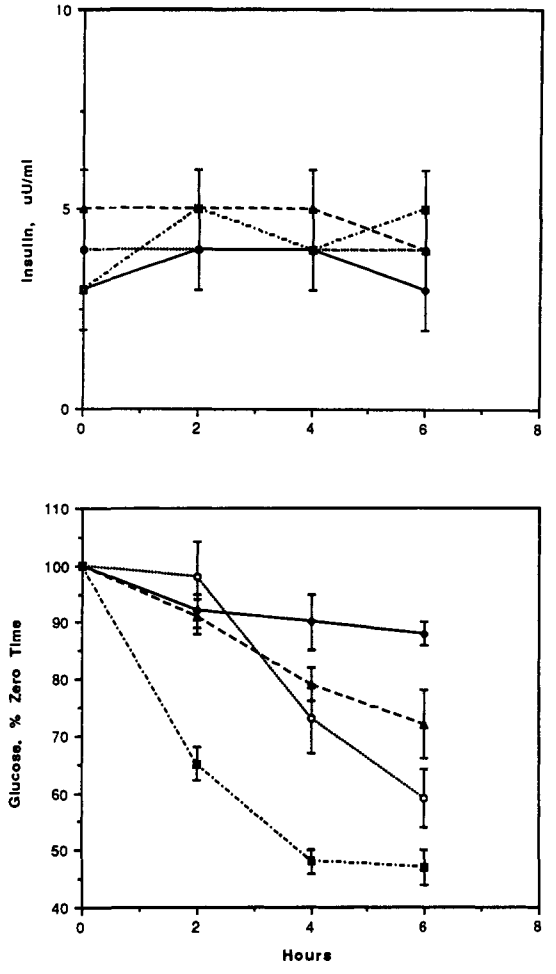


Figure 3. Compound **38** was administered orally at zero time to 18-h fasted rats (280–320 g). Tail-tip blood samples were obtained just prior to drug administration and at the times indicated. Blood samples were processed as indicated in the Pharmacological Methods. Data are expressed as the mean ± SEM of each group of six animals except for the vehicle-treated group which contained 12 animals: (◇) vehicle, (▲) 10 mg/kg, (○) 20 mg/kg, (■) 50 mg/kg.

occurring. It appears therefore that the enantiomers are chemically stable at low pH, and that chemical racemization is unlikely to occur following oral dosing. The possibility of enzymatic racemization cannot of course be excluded.

The data reported herein on **38** are not incompatible with a mechanism of action related to glucose uptake, but specific studies designed to assess the effects of **38** or other members of the pyrimido[1,2-*a*]indoles on activity and/or recruitment of glucose transporters in muscle have not been completed. Definition of the cellular mechanism(s) of action, the quantitative contribution of different mechanisms to overall glucose-lowering, and whether these actions are tissue specific will only be clarified by future studies.

Experimental Section

Melting points were determined on a Gallenkamp MF B-595-010M apparatus and are uncorrected. ^{1}H NMR (200 MHz) spectra were recorded using a Bruker WP-200SY spectrometer, and chemical shifts (δ) are reported in ppm downfield of Me_4Si as internal standard. IR spectra were recorded using a Varian EM360 spectrometer, and IR band positions are reported in wavenumbers. The spectra of all compounds were consistent with the assigned structures. TLC analyses were performed with silica gel 60 F_{254} plates (E. Merck), and chromatographic separations were carried out on silica gel 60 (70–230 mesh), Merck (230–400 mesh) Kieselgel (medium pressure), or aluminum oxide, activity II–III according to Brockmann. Elemental analyses for C, H, and N were determined by our own analytical group under the supervision of Dr. K. Heatherington and were within ±0.4% of the theoretical values.

Spiro[1,3-dioxolane-2,3′-indol]-2′(1′*H*)-one (3). Isatin **2** (7.35 g, 50 mmol), ethylene glycol (11.2 mL, 200 mmol), and *p*-toluenesulfonic acid monohydrate (2 g, 10 mmol) in benzene (300 mL) were heated under reflux in an apparatus fitted with a water separator for 5 h. The reaction mixture was cooled to room temperature, washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and water (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was crystallized from MeOH to give **3** (9.5 g, 99%), mp 131–132 °C. Anal. ($C_{10}H_9NO_3$) C, H, N.

1-[[1′-[2′(1′*H*)-Oxospiro[1,3-dioxolane-2,3′-indol]yl]]-methyl]cyclohexanecarbonitrile (4). The ketal **3** (1.91 g, 10 mmol) was added in one portion to a stirred solution of $KOBu^t$ (1.34 g, 11.9 mmol) in dry DMSO (20 mL) under N_2. After 10 min, 1-(chloromethyl)cyclohexanecarbonitrile[11] (1.96 g, 12.4 mmol) was added dropwise, and the solution was heated at 130 °C for 24 h. The solution was cooled to room temperature, poured into iced water (100 mL), and stirred vigorously for 18 h. The solid was separated, dried, and recrystallized from 2-propanol (IPA) to give **4** (1.41 g, 46%): mp 130–130.5 °C; IR ν_{max} (Nujol)/cm^{-1} 2980–2850, 2230 (C≡N), 1750 (C=O), 1364, 1128, and 755; ^{1}H NMR δ_H ($CDCl_3$) 1.10–2.30 [10 H, complex, $(CH_2)_5$], 3.79 (2 H, s, NCH_2), 4.30–4.65 (4 H, complex, OCH_2CH_2O), and 7.10–7.45 (4 H, complex, aromatic protons). Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

3-[1′-[2′(1′*H*)-Oxospiro[1,3-dioxolane-2,3′-indol]yl]]-propanenitrile (5). The reaction of **3** with acrylonitrile in boiling EtOH in the presence of 40% aqueous benzyltrimethylammonium hydroxide as catalyst[12] gave **5** which was used unpurified in the preparation of **8**.

2,2-Dimethyl-3-[1′-[2′(1′*H*)-oxospiro[1,3-dioxolane-2,3′-indol]yl]]propanenitrile (6). This compound was prepared following the method used for **4**, mp 112–113 °C. Anal. ($C_{15}H_{16}N_2O_3$) C, H, N.

2′,3′,4′,10′-Tetrahydro-1,3-dioxolane-2-spiro-10′-pyrimido[1,2-*a*]indole-3′-spirocyclohexane (7). Ethanolic NH_3 (100 mL) and one spatula of Raney nickel were added to a solution of **4** (1.25 g, 4.0 mmol) in EtOH (100 mL). The mixture was hydrogenated at 50 °C and at 4–5 atm for 2 h, cooled to room temperature, filtered through kieselguhr, and concentrated in vacuo. The residue was recrystallized from hexane to give **7** (0.36 g, 30%): mp 71–107 °C; IR ν_{max} (Nujol)/cm^{-1} 2980–2850, 1680, 1615, 1464, 1204, and 748; ^{1}H NMR δ_H ($CDCl_3$) 1.35–1.75 [10 H, complex, $(CH_2)_5$], 3.30 (2 H, s, NCH_2), 3.40 (2 H, s, NCH_2), 4.30 (2 H, m) and 4.57 (2 H, m) (OCH_2CH_2O), 6.63 (1 H, 2), 6.93 (1 H, 3), and 7.40 (2 H, 3) (aromatic protons). Anal. ($C_{18}H_{22}N_2O_2$) C, H, N.

Compounds **8**, mp 114–115 °C. Anal. ($C_{13}H_{14}N_2O_2$) C, H, N, and **9**: mp 109–110 °C. Anal. ($C_{15}H_{18}N_2O$) C, H, N, were prepared by related reactions.

3′,4′-Dihydrospiro[cyclohexane-1,3′-pyrimido[1,2-*a*]indol]-10′(2′*H*)-one (10). Powdered **7** (53.7 g, 180 mmol) was added portionwise with stirring to concentrated H_2SO_4 (195 mL) at 0–8 °C. The solution was maintained at room temperature for 1 h, poured onto iced water, basified with concentrated aqueous NH_3, and the mixture was extracted with $CHCl_3$ (3 × 1000 mL). The extracts were dried (Na_2SO_4), concentrated in vacuo, and purified by chromatography to give **10** (42.5 g, 93%): mp 143–144 °C; IR ν_{max} (Nujol)/cm^{-1} 2920, 1714, 1608, 1468, 1378, and 759; ^{1}H NMR δ_H ($CDCl_3$) 1.30–1.60 [10 H, complex $(CH_2)_5$], 3.33 (2 H, s, NCH_2), 3.63 (2 H, s, NCH_2), 6.78 (1 H, 2), 6.98 (1 H, 2), and 7.45–7.65 (2 H, complex) (aromatic protons). Anal. ($C_{16}H_{18}N_2O$) C, H, N.

Compounds **11**, mp 121–122 °C. Anal. ($C_{11}H_{10}N_2O$) C, H, N, and **12**, mp 125–126 °C. Anal. ($C_{13}H_{14}N_2O$) C, H, N, were prepared in an analogous fashion.

Compounds 13–39. Representative Examples. 10-Hydroxy-10-(4-methoxybutyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indole (13). The Grignard reagent prepared from 4-

(11) Cliffe, I. A.; Todd, R. S.; White, A. C. Synthesis of 2,2-Dialkyl-3-halopropanenitriles from 2,2-Dialkylethanenitriles and Dihalomethanes. *Synth. Commun.* **1990**, *20*, pp 1757–1767.
(12) White, A. C.; Black, R. M. GB 1,366,133, September 11, 1974.

bromo-1-methoxybutane (10.2 g, 61 mmol) and Mg turnings (1.46 g, 61 mmol) in Et_2O (60 mL) was treated dropwise with 11 (3.72 g, 20 mmol) in 1,2-dichloroethane (20 mL) under Ar at 0 °C. After 1 h, the solution was poured onto iced water (100 mL) and saturated aqueous NH_4Cl (60 mL), stirred for 20 min, and concentrated in vacuo, and the aqueous residue was extracted with $CHCl_3$ (3 × 100 mL). The extracts were dried (Na_2SO_4) and concentrated in vacuo. Et_2O (20 mL) was added, and the product was filtered and recrystallized from EtOAc to give **13** (3.55 g, 65%).

10-Hydroxy-10-(3-hydroxy-1-propynyl)-2,3,4,10-tetrahydropyrimido[1,2-*a*]indole (17). (a) The Grignard reagent prepared from 2-(2-propynyloxy)-3,4,5,6-tetrahydropyran (9.25 g, 64.2 mmol) and EtMgBr [from EtBr (5.99 g, 60 mmol) and Mg (1.6 g, 66.7 mmol)] was reacted with 11 using the procedure outlined for 14. The crude product was purified by chromatography to give **10-hydroxy-10-[3-[2-(3,4,5,6-tetrahydro-2*H*-pyranyl)oxy]prop-1-ynyl]-2,3,4,10-tetrahydropyrimido[1,2-*a*]indole** (6.16 g, 38%), mp 173–175 °C (from EtOAc). Anal. ($C_{18}H_{22}N_2O_3$) C, H, N. (b) Treatment of the above product with ethanolic HCl gave **17** as the hydrochloride salt: mp 192–194 °C (from ethanol); IR ν_{max} (Nujol)/cm^{-1} 3300–2800, 1688, 1465, 1155, 1029, and 760; ^{1}H NMR δ_H [$(CD_3)_2SO$] 1.15 (2 H, m, CCH_2C), 3.65 (2 H, m, NCH_2), 3.95 (2 H, m, NCH_2), 4.13 (2 H, d, CH_2O), 5.50 (1 H, t, CH_2OH), 7.31 (2 H, 3), 7.52 (1 H, 3), and 7.61 (1 H, 2) (aromatic protons), 7.92 (1 H, s, OH), and 11.75 (1 H, br, NH^+). Anal. ($C_{14}H_{14}N_2O_2$·HCl) C, H, N.

Resolution of 39. (−)-Di-*p*-toluoyl-L-tartaric acid (40.03 g, 0.1 mol) was added rapidly to a stirred suspension of **39** (33.25 g, 0.1 mol) in acetone (1 L). The solution was stirred at room temperature for 15 h, and the crystalline precipitate was filtered, washed with acetone (2 × 50 mL), and dried in vacuo to give **39** as the (−)-di-*p*-toluoyltartrate (31.64 g, 86%): mp 149 °C dec; $[\alpha]_D$ −93° (*c* 0.2% in EtOH). The combined filtrate and washings were converted to the free base, suspended in acetone (570 mL), and treated rapidly with (+)-di-*p*-toluoyl-D-tartaric acid (23.05 g, 0.57 mol). The solution was stirred at room temperature for 15 h, and the precipitate was filtered, washed with acetone (2 × 50 mL), and dried in vacuo to give **39** as the (+)-di-*p*-toluoyltartrate (33.60 g, 91%): mp 149 °C; $[\alpha]_D$ +95° (*c* 0.2% in EtOH). Each enantiomer was converted to a free base, suspended in EtOH (200 mL), acidified with ethereal HCl, and evaporated in vacuo, and the crystalline products were washed with EtOH (2 × 20 mL) and Et_2O (2 × 20 mL) to give (−)-**39** as the hydrochloride [(13.51 g, 73%), $[\alpha]_D$ +220° (*c* 0.2% in $CHCl_3$)].

Compounds 42–45. Representative Examples. 1-[[1-[3-Hydroxy-2(3*H*)-oxo-3-phenylindolyl]]methyl]cycloheptanecarbonitrile (43). Compound **40**[7] (9.0 g, 35.3 mmol) was added portionwise to a stirred solution of $KOBu^t$ (4.9 g, 43.8 mmol) in DMSO (100 mL) under N_2. After 10 min, 1-(chloromethyl)cycloheptanecarbonitrile[11] (6.9 g, 40.2 mmol) was added. The solution was heated at 130 °C for 18 h, cooled to room temperature, and poured into water (500 mL). The aqueous mixture was extracted with Et_2O (3 × 200 mL), and the extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized from IPA to give **43** (3.74 g, 27%): mp 202.5–203.5 °C; IR ν_{max} (Nujol)/cm^{-1} 3370, 2980–2850, 2250, 1720, 1415, and 755; ^{1}H NMR δ_H ($CDCl_3$) 1.05–2.11 [10 H, complex, $(CH_2)_5$], 3.33 (1 H, s, OH), 3.74 (1 H, d) and 4.03 (1 H, d) (NCH_2), 7.06–7.45 (9 H, complex, aromatic protons). Anal. ($C_{22}H_{22}N_2O_2$) C, H, N.

***tert*-Butyl 4-[[1-[3-Hydroxy-2(3*H*)-oxo-3-phenylindolyl]]methyl]-4-cyanopiperidine-1-carboxylate (44).** The reaction of **40** (5.05 g, 19.8 mmol) with $KOBu^t$ (2.77 g, 24.7 mmol) and *tert*-butyl 4-(chloromethyl)-4-cyanopiperidine-1-carboxylate[11] (5.7 g, 22.0 mmol) by the procedure used for **43** gave **44** (5.5 g, 62%): mp 197–198 °C (from EtOAc); IR ν_{max} (Nujol)/cm^{-1} 3390, 2970–2850, 1710, 1678, 1466, and 742; ^{1}H NMR δ_H ($CDCl_3$) 1.45 [9 H, s, $C(CH_3)_3$], 1.58–2.03 (4 H, complex, CH_2CCH_2), 3.0 (2 H, 4) and 4.15 (2 H, br) (CH_2NCH_2), 3.18 (1 H, s, OH), 3.81 (1 H, d, J = 15) and 4.07 (1 H, d, J = 15) (NCH_2CCN), and 7.10–7.45 (9 H, complex, aromatic protons). Anal. ($C_{26}H_{29}N_3O_4$) C, H, N.

Compounds **42** [mp 155–157 °C (from Et_2O). Anal. ($C_{21}H_{20}N_2O_2$) C, H, N] and **45** [mp 124–125 °C (from cyclohexane). Anal. ($C_{23}H_{24}N_2O_2$·0.25H_2O) C, H, N] were made by similar procedures.

Compounds 46–49. Representative Example. 2′,3′,4′,10′-Tetrahydro-10′-hydroxy-10′-phenylspiro[piperidine-4,3′-pyrimido[1,2-*a*]indole] (48). (a) Compound **44** was reduced by the method outlined for **7** to give **2′,3′,4′,10′-tetrahydro-10′-hydroxy-10′-phenyl-1-(*tert*-butoxycarbonyl)spiro[piperidine-4,3′-pyrimido[1,2-*a*]indole]**, mp 209–210 °C (from EtOAc). Anal. ($C_{26}H_{31}N_3O_3$) C, H, N. (b) A suspension of the above product in ethanolic HCl was warmed to effect solution. The solvent was evaporated in vacuo, and the residual gum was crystallized from MeOH to give **48** as the dihydrochloride salt: mp >300 °C (from ethanol); IR ν_{max} (Nujol)/cm^{-1} 1678, 1460, 1376, 1300, and 765; ^{1}H NMR δ_H [$(CD_3)_2SO$] 1.75 (4 H, br, $CH_2CH_2NCH_2CH_2$), 3.2–3.5 (6 H, complex) and 4.15 (2 H, 4) (4 × NCH_2), 7.37–7.63 (9 H, complex, aromatic protons), 7.77 (1 H, s, OH), 9.15 (1 H, s, NH^+), 9.40 (1 H, s, NH^+), and 11.35 (1 H, s, NH^+). Anal. ($C_{21}H_{23}N_3O$·2HCl·1.25H_2O) C, H, N.

Compounds 50–55. Representative Examples. 10-Acetamido-2,3,4,10-tetrahydro-3,3-dimethyl-10-phenylpyrimido-[1,2-*a*]indole (52). A solution of **38** (10.38 g, 35.5 mmol) in MeCN (75 mL) and methanesulfonic acid (4.2 mL, 64.7 mmol) was added dropwise with judicious cooling over 40 min to a preheated flask containing concentrated H_2SO_4 (38 mL, 0.7 mmol) at such a rate that the temperature remained steady at 50–55 °C. The solution was cooled to room temperature, poured into water (600 mL), and basified with NaOH (50 g, 1.25 mol) and Na_2CO_3. The mixture was extracted with $CHCl_3$ (3 × 350 mL), and the combined extracts were washed with water (350 mL), dried ($MgSO_4$), and concentrated in vacuo to give **52** (10.3 g, 87%). The hydrochloride salt was prepared in standard fashion: mp >300 °C (from methanol–ethyl acetate); IR ν_{max} (Nujol)/cm^{-1} 1675, 1610, 1465, 1295, 1255, and 778; ^{1}H NMR δ_H [$(CD_3)_2SO$] 0.89 (3 H, s) and 1.11 (3 H, s) (CH_3CCH_3), 1.99 (3 H, s, $NCCH_3$), 3.23 (2 H, br) and 3.72 (2 H, br) (CH_2CCH_2), 7.35–7.56 (9 H, complex, aromatic protons), 9.70 (1 H, s, NHCO), and 11.75 (1 H, s, NH^+). Anal. ($C_{21}H_{23}N_3O$·HCl·0.5H_2O) C, H, N.

10-Butanamido-2,3,4,10-tetrahydro-3,3-dimethyl-10-phenylpyrimido[1,2-*a*]indole (53). Compound **38** (2.19 g, 7.5 mmol) in butyronitrile (16 mL, 0.18 mol) and methanesulfonic acid (100 drops) was added dropwise over 10 min to concentrated H_2SO_4 (8 mL, 0.15 mol) at 50–55 °C with stirring. Workup as for **52** gave **53** (0.67 g, 25%). The hydrochloride salt had the following: mp 275–280 °C (from methanol–ether); IR ν_{max} (Nujol)/cm^{-1} 1685, 1658, 1612, 1462, 1297, and 755; ^{1}H NMR δ_H [$(CD_3)_2SO$] 0.80 (3 H, t, J = 7, CH_3CH_2), 0.90 (3 H, s) and 1.12 (3 H, s) (CH_3CCH_3), 1.47 (2 H, 4, CH_3CH_2), 2.27 (2 H, t, J = 7, $CH_3CH_2CH_2$), 3.24 (2 H, br) and 3.73 (2 H, br) (CH_2CCH_2), 7.25–7.60 (9 H, complex, aromatic protons), 9.63 (1 H, s, NHCO), and 11.33 (1 H, s, NH^+). Anal. ($C_{23}H_{27}N_3O$·HCl·0.25H_2O) C, H, N.

Compounds 56–58. Representative Example. 10-Amino-2,3,4,10-tetrahydro-3,3-dimethyl-10-phenylpyrimido[1,2-*a*]-indole (58). A solution of the free base of **52** (7.76 g, 23.3 mmol) in concentrated HCl (35 mL) was heated with stirring at 110 °C for 3.5 h, cooled to room temperature, diluted with water (350 mL), basified with concentrated aqueous NH_3, and extracted with $CHCl_3$ (2 × 200 mL), and the combined extracts were washed with water (350 mL), dried ($MgSO_4$), and concentrated in vacuo to give **58** (4.13 g, 61%). The dihydrochloride salt had the following: mp 260–265 °C (from methanol–ether); IR ν_{max} (Nujol)/cm^{-1} 1685, 1465, 1378, 1308, 1022, and 758; ^{1}H NMR δ_H [$(CD_3)_2SO$] 1.12 (3 H, s) and 1.18 (3 H, s) (CH_3CCH_3), 3.45 (2 H, 4) and 3.90 (2 H, 4) (CH_2CCH_2), 7.25–7.75 (9 H, complex, aromatic protons), 10.0 (3 H, br, NH_3^+), and 11.75 (1 H, br, NH^+). Anal. ($C_{19}H_{21}N_3$·2HCl·0.25H_2O) C, H, N.

2,3,4,10-Tetrahydro-3,3-dimethyl-10-[(methylsulfonyl)-amino]-10-phenylpyrimido[1,2-*a*]indole (59). Methanesulfonyl chloride (1 mL, 12.9 mmol) was added to **58** (1.2 g, 4.1 mmol) in dry pyridine (50 mL). After 1 h, the solution was concentrated in vacuo, and the residual oil was dissolved in CH_2Cl_2 (50 mL), washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and water (50 mL), dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography to give **59** (0.39 g, 26%). The hydrochloride salt had the following: mp 160–165 °C (from methanol–ether); IR ν_{max} (Nujol)/cm^{-1} 1678, 1460, 1375, 1300, 1150, and 760; ^{1}H NMR δ_H [$(CD_3)_2SO$] 0.87 (3 H, s) and 1.13 (3 H, s) (CH_3CCH_3), 2.83 (3 H, s, SCH_3), 3.30 (2 H, br) and 3.75 (2 H, 4)

(CH_2CCH_2), 7.30–7.67 (9 H, complex, aromatic protons), 9.15 (1 H, s, NHS), and 11.35 (1 H, s, NH^+). Anal. ($C_{20}H_{23}N_3O_2S$·HCl·0.75H_2O) C, H, N.

2,3,4,10-Tetrahydro-3,3-dimethyl-10-[3-[(4-methylphenyl)sulfonyl]ureido]-10-phenylpyrimido[1,2-*a*]indole (60). *p*-Toluenesulfonyl isocyanate (1.0 g, 5.1 mmol) in MeCN (5 mL) was added dropwise to a stirred solution of **58** (1.17 g, 4.0 mmol) in MeCN (50 mL). After 1 h, the solution was concentrated in vacuo to give a glass which was induced to crystallize by trituration with EtOAc–MeOH (5:1; 6 mL). The solid was suspended in MeOH (30 mL), and the mixture was acidified with ethereal HCl. A solution was formed from which a solid precipitated after a few minutes. The solid was filtered, washed with Et_2O, and dried in vacuo to give **60** as the hydrochloride salt (1.69 g, 80%): mp 253–255 °C (from methanol–ether); IR ν_{max} (Nujol)/cm^{-1} 1702, 1678, 1460, 1332, 1296, 1155, and 1090; ^1H NMR δ_H [$(CD_3)_2SO$] 0.86 (3 H, s) and 0.98 (3 H, s) (CH_3CCH_3), 2.39 (3 H, s, CH_3), 3.15 (2 H, 4) and 3.73 (2 H, br) (CH_2CCH_2), 7.20–7.75 (13 H, complex, aromatic protons), 8.82 (1 H, s), 11.33 (1 H, s) and 11.65 (1 H, s) (NHCONH and NH^+). Anal. ($C_{27}H_{28}N_4O_3S$·HCl) C, H, N.

10-Benzamido-2,3,4,10-tetrahydro-3,3-dimethyl-10-phenylpyrimido[1,2-*a*]indole (61). Benzoyl chloride (0.9 mL, 7.7 mmol) was added dropwise to **58** (1.12 g, 3.8 mmol) in NEt_3 (1 mL) and pyridine (40 mL). After 1 h, the solution was concentrated in vacuo. The residue was azeotroped in vacuo with toluene (50 mL) and dissolved in CH_2Cl_2 (50 mL). The solution was washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow foam which crystallized from Et_2O–CH_2Cl_2 (1:1). The solid was recrystallized from EtOAc–cyclohexane and converted in the usual manner into the hydrochloride salt of **61** (0.99 g, 60%): mp 295–298 °C (from methanol–ethyl acetate); IR ν_{max} (Nujol)/cm^{-1} 1678, 1642, 1611, 1465, 1296, and 694; ^1H NMR δ_H [$(CD_3)_2SO$] 0.85 (3 H, s) and 1.16 (3 H, s) (CH_3CCH_3), 3.24 (2 H, 4) and 3.77 (2 H, br) (CH_2CCH_2), 7.27–7.65 (12 H, complex) and 7.96 (2 H, br d) (aromatic protons), 10.15 (1 H, s, NH) and 10.40 (1 H, s, NH^+). Anal. ($C_{26}H_{25}N_3O$·HCl) C, H, N.

11-Acetamido-2,3,4,5-tetrahydro-11-phenyl-11*H*-[1,3]diazepino[1,2-*a*]indole (62). This compound was prepared from 2,4,5,11-tetrahydro-11-phenyl-3*H*-[1,3]diazepino[1,2-*a*]indol-11-ol[8] using the procedure outlined for **52**. The hydrochloride salt had the following: mp 285–290 °C (from methanol–ether); IR ν_{max} (Nujol)/cm^{-1} 1665, 1608, 1465, 1374, 1326, and 786; ^1H NMR δ_H [$(CD_3)_2SO$] 1.99 (3 H, s, CH_3), 1.85–2.20 (4 H, complex, CCH_2CH_2C), 3.50–3.85 (2 H, complex) and 3.95–4.40 (2 H, complex) (CH_2CCCH_2), 7.27 (2 H, m) and 7.40–7.50 (7 H, complex) (aromatic protons), 9.66 (1 H, s, NH), and 10.85 (1 H, t, NH^+). Anal. ($C_{20}H_{21}N_3O$·HCl·H_2O) C, H, N.

Pharmacological Methods. The pharmacological tests were carried out on fed male Charles River Sprague–Dawley CD rats weighing 280–320 g. All drugs were administered as indicated, either orally (po) or by subcutaneous injection (sc), as solutions in water or as suspensions in 0.5% carboxymethylcellulose to groups of six rats. The total volumes were 1 mL/kg. A control group was treated in parallel with an equal volume of the appropriate vehicle (either water or 0.5% carboxymethylcellulose). For the dose–response study at a single time point (4 h) reported in Figure 1, blood was obtained following decapitation and treated as indicated below for the three-point dose–response studies. For the dose–response/time-course studies, blood samples (0.3 mL) were obtained from the tail vein 2 and 4 h after dosing. All blood samples were placed in 1.2 mg of EDTA and 600 units of Trasylol. Plasma levels of glucose were determined by the glucose oxidase–peroxidase method.[13] Statistical significance was determined by the Student–Newman–Keuls test.

The potencies of a number of active compounds were further defined by three-point dose–response studies employing **38** as a standard. Test compounds or **38** were administered in doses of 10, 30, and 100 mg/kg po to groups of eight rats (a few studies employed doses of 10, 20, and 50 mg/kg po). After 4 h the rats were exsanguinated following decapitation. Blood was collected in Trasylol–EDTA (12 mg of EDTA and 6000 units of Trasylol per 5 mL of blood). Relative potencies were determined using a linear regression and multiple parallel line analysis.

Registry No. **1**, 139163-47-6; **1**·free base, 139068-73-8; **2**, 91-56-5; **3**, 6714-68-7; **4**, 139017-66-6; **5**, 10349-82-3; **6**, 37647-56-6; **7**, 112905-96-1; **8**, 37603-46-6; **9**, 37647-57-7; **10**, 112905-97-2; **11**, 37603-48-8; **12**, 37647-71-5; **13**, 139017-67-7; **13**·free base, 139017-68-8; **14**, 139017-69-9; **14**·free base, 139017-70-2; **15**, 112889-93-7; **15**·free base, 112889-73-3; **16**, 112889-92-6; **16**·free base, 112889-72-2; **17**, 139017-71-3; **17**·free base, 139017-72-4; **18**, 139017-73-5; **18**·free base, 139017-74-6; **19**, 139017-75-7; **19**·free base, 139017-76-8; **20**, 139017-77-9; **20**·free base, 139017-78-0; **21**, 112889-87-9; **21**·free base, 112889-69-7; **22**, 112889-88-0; **22**·free base, 112889-70-0; **23**, 139017-79-1; **23**·free base, 139017-80-4; **24**, 139017-81-5; **24**·free base, 139017-82-6; **25**, 139017-83-7; **25**·free base, 139017-84-8; **26**, 139017-85-9; **26**·free base, 139017-86-0; **27**, 139017-87-1; **27**·free base, 139017-88-2; **28**, 139017-89-3; **28**·free base, 139017-90-6; **29**, 139017-91-7; **29**·free base, 139017-92-8; **30**, 139017-93-9; **30**·free base, 139017-94-0; **31**, 139017-95-1; **31**·free base, 139017-96-2; **32**, 139017-97-3; **32**·free base, 139017-98-4; **33**, 139017-99-5; **33**·free base, 139018-00-1; **34**, 139018-01-2; **34**·free base, 139018-02-3; **35**, 139018-03-4; **35**·free base, 139018-04-5; **36**, 139018-05-6; **36**·free base, 139018-06-7; **37**, 139018-07-8; **37**·free base, 139018-08-9; **38**, 139018-09-0; **38**·free base, 139018-10-3; **39**, 139018-11-4; **39**·free base, 139018-11-4; (−)-**39**, 139018-12-5; (−)-**39**·free base, 112905-93-8; (+)-**39**, 139018-13-6; (+)-**39**·free base, 112905-94-9; **40**, 139018-14-7; **41**, 139018-15-8; **42**, 139018-16-9; **43**, 139018-17-0; **44**, 139018-18-1; **45**, 139018-19-2; **46**, 139018-20-5; **46**·free base, 139018-21-6; **47**, 139018-22-7; **47**·free base, 139018-23-8; **48**, 139018-24-9; **48**·free base, 139018-25-0; **49**, 139018-26-1; **49**·free base, 139018-27-2; **50**, 139018-28-3; **50**·free base, 139018-29-4; **51**, 139018-30-7; **51**·free base, 139018-31-8; **52**, 139018-32-9; **52**·free base, 139018-33-0; **53**, 139018-34-1; **53**·free base, 139018-35-2; **54**, 139018-36-3; **54**·free base, 139018-37-4; **55**, 139018-38-5; **55**·free base, 139018-39-6; **56**, 139018-40-9; **56**·free base, 139018-41-0; **57**, 139018-42-1; **57**·free base, 139018-43-2; **58**, 139018-44-3; **58**·free base, 139018-45-4; **59**, 139018-46-5; **59**·free base, 139018-47-6; **60**, 139018-48-7; **60**·free base, 139018-49-8; **61**, 139018-50-1; **61**·free base, 139018-51-2; **62**, 139018-52-3; **62**·free base, 139018-53-4.

(13) Huggett, A. St. G.; Nixon, D. A. Use of Glucose Oxidase, Peroxidase, and O-Dianisidine in Determination of Blood and Urinary Glucose. *Lancet* **1957**, pp 368–370.