Substituted Tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-ones and Tetrahydropyrrolo[2,1-*b*]thiazol-5(6*H*)-ones as Hypoglycemic Agents[1]

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A series of substituted tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-ones and tetrahydropyrrolo[2,1-*b*]thiazol-5(6*H*)-ones was synthesized from amino alcohols or amino thiols and keto acids. A pharmacological model based on the results obtained with these compounds led to the synthesis and evaluation of a series of isoxazoles and other monocyclic compounds. These were evaluated for their ability to enhance glucose utilization in cultured L6 myocytes. The in vivo hypoglycemic efficacy and potency of these compounds were evaluated in a model of type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus), the *ob/ob* mouse. **25a(2*S*)** (SDZ PGU 693) was selected for further pharmacological studies.

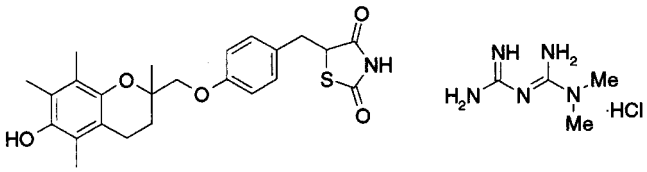
Introduction

Type 2 diabetes is a chronic, progressive metabolic disease, typically characterized by hyperglycemia, hyperlipidemia, and insulin resistance. Diabetes is most frequently diagnosed by the presentation of fasting hyperglycemia, severely impaired oral glucose tolerance, or the classical symptoms (polydipsia, polyphagia and polyuria).[2] Type 2 diabetes, diagnosed and undiagnosed, occurs in >5% of the U.S. population (affecting 16 million people in 1996).[3] In addition, the prediabetic state of impaired glucose tolerance (IGT, normal basal glycemia with impaired glucose tolerance) is even more prevalent affecting approximately 35−40 million adults in the United States, and many of these subjects will progress into overt type 2 diabetes.

As type 2 diabetic patients are frequently overweight, and since weight loss and exercise lessen insulin resistance, diet and exercise are usually the first prescribed treatments for most type 2 diabetic patients.[4,5] The rapid reversal of the positive effects of exercise and weight loss after noncompliance leaves a large number of patients in need of medication to help restore euglycemia. The importance of such treatments was recently emphasized when the Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that tight control of blood glucose reduced the development of retinopathy, nephropathy, and neuropathy each by >50% in insulin-dependent diabetes (IDDM).[6] Evidence is emerging that similar control of blood glucose levels is also effective in type 2 diabetic patients in preventing disease complications.[7,8]

While hyperglycemia has long been recognized as a risk factor for microvascular disease (i.e., retinopathy, nephropathy, neuropathy), a significant correlation between hyperinsulinemia and coronary artery disease (i.e., macrovascular complications) is now also generally recognized.[9,10] Furthermore, the Whitehall study of middle-aged men demonstrated that coronary heart disease mortality was approximately doubled for subjects with IGT.[11] Since the major mortality, morbidity, and cost associated with type 2 diabetes result from these complications, reducing hyperglycemia and hyperinsulinemia concurrently should have a beneficial effect in the treatment of this syndrome.[12] The goal of the studies reported here is the discovery of a novel compound to enhance peripheral insulin sensitivity.

Chart 1. Marketed Hypoglycemic Agents That Enhance Glucose Utilization



Metformin and troglitazone (Chart 1) are drugs available in the clinic which enhance insulin sensitivity. Metformin has been associated with serious lactic acidosis; however patients at risk can be identified and excluded from treatment with this drug.[13] Gastrointestinal side effects are common with metformin treatment (~one-quarter of patients drop from treatment protocols), but most patients can tolerate 2−3 g daily (5% have severe symptoms).[14] The low efficacy and the side-effect profile render metformin treatment suboptimal in the majority of asymptomatic diabetic patients. While metformin has been shown to decrease hepatic glucose production and increase glucose utilization, its biochemical mechanism of action is uncertain.[15]

Troglitazone is the first member of a novel class of compounds, the thiazolidinediones, to reach clinical practice. Troglitazone induces preadipocyte differentiation, probably via peroxisome−proliferator-activated receptor-γ (PPARγ) receptors.[16] While it is not clear whether the hypoglycemic mechanism requires preadi-

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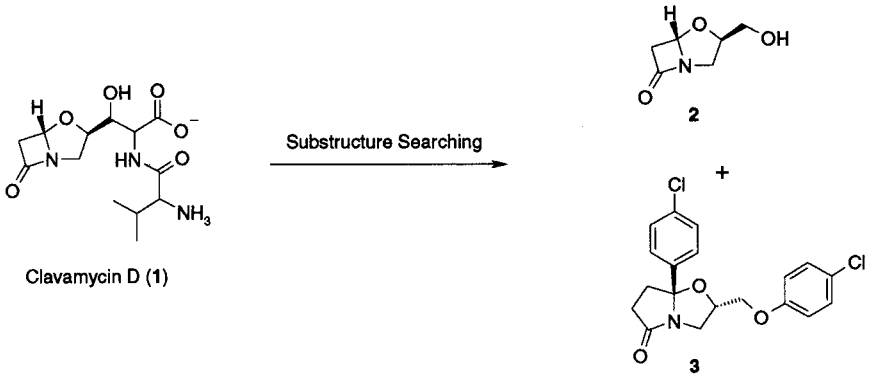
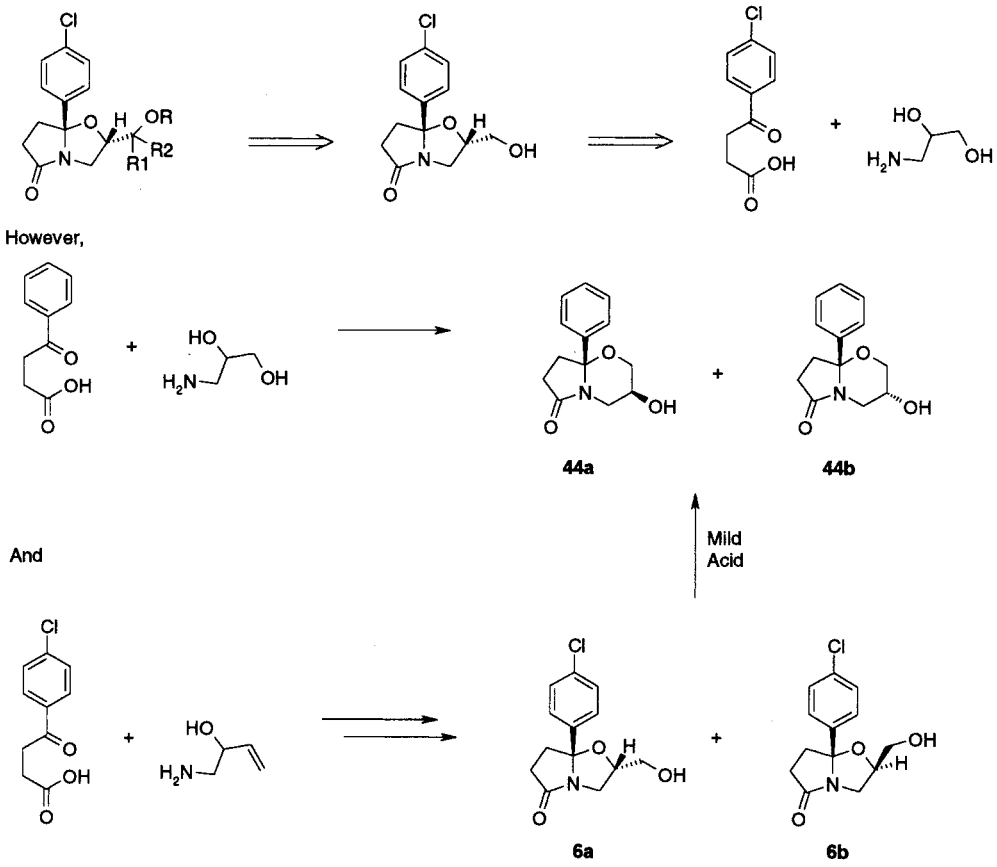
Scheme 1. Lead Structures



Scheme 2. Initial Strategy



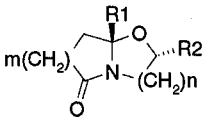
pocyte differentiation, the maximum glucose-lowering effect of troglitazone is similar to that seen with metformin (about 40 mg/dL). Thiazolidinediones have been shown to improve insulin sensitivity/glucose utilization in rodents and to enhance insulin sensitivity in humans.[17] For these reasons, the title compounds' efficacy was compared to that of metformin and/or troglitazone as standards.

To discover novel compounds which have the ability to increase cellular glucose uptake, an adipocyte glucose transport assay was established. In this assay, clavamycin D (**1**) was found to increase [^{3}H]glucose incorporation into lipids in adipocytes in the presence of submaximal concentrations of insulin and to enhance 2-deoxyglucose uptake into 3T3L1 adipocytes using a modification of the method described by Clancy and Czech.[18] This suggested that the compound increases the sensitivity of the adipocyte to insulin. Substructure and similarity searches of the compound collection of Sandoz[19] based on **1** led to the identification of (hydroxymethyl)clavam **(2)** and (+)-*trans*-2-[(4-chlorophenoxy)methyl]-7α-(4-chlorophenyl)tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one **(3)**, which increased glucose utilization by L6 myocytes (a muscle cell line) and lowered blood glucose levels in vivo in the diabetic obese *ob/ob* mouse (Scheme 1). As a result of these findings, a synthetic program was initiated based on these related structures.

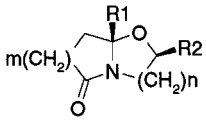
Chemistry

The alcohols **6a** and **6b** were targeted for synthesis as being ideal intermediates for this program (Scheme 2). However, attempts to prepare **6a** and **6b** directly from 3-amino-1,2-propanediol and 3-(4-chlorobenzoyl)-propionic acid led to the exclusive formation of **44a** and **44b**. The synthesis of **6a** and **6b** was accomplished from 1-amino-2-hydroxybut-3-ene. However, these com-

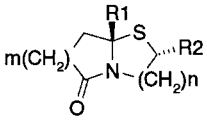
Table 1. Physical and in Vitro Properties of Tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one Analogues



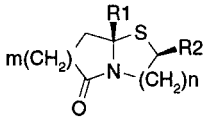
3-39a



3-37b



40-42



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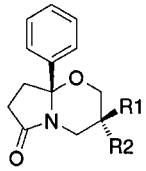
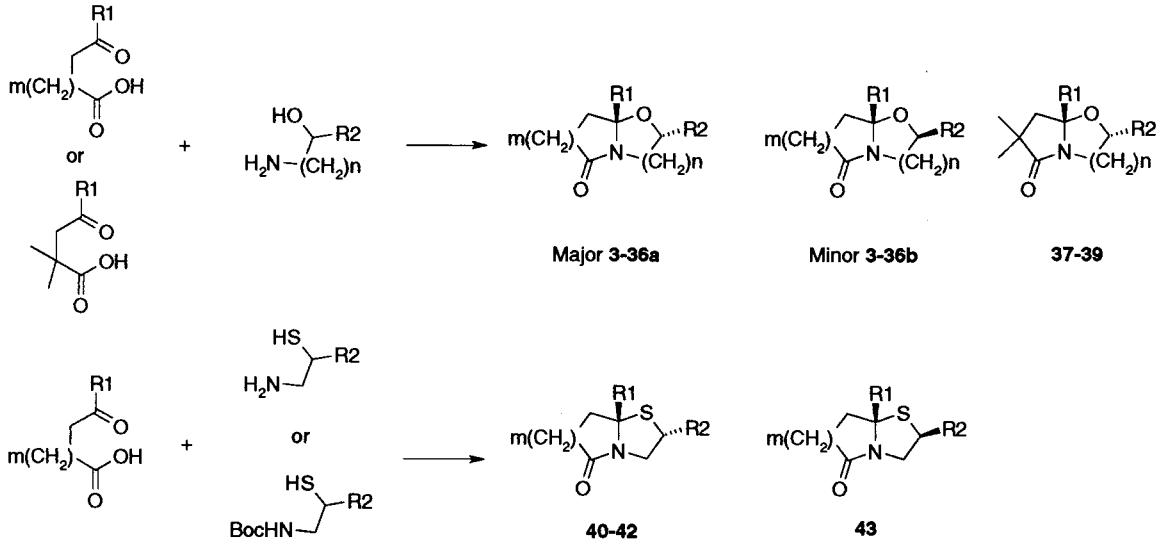


44a,b

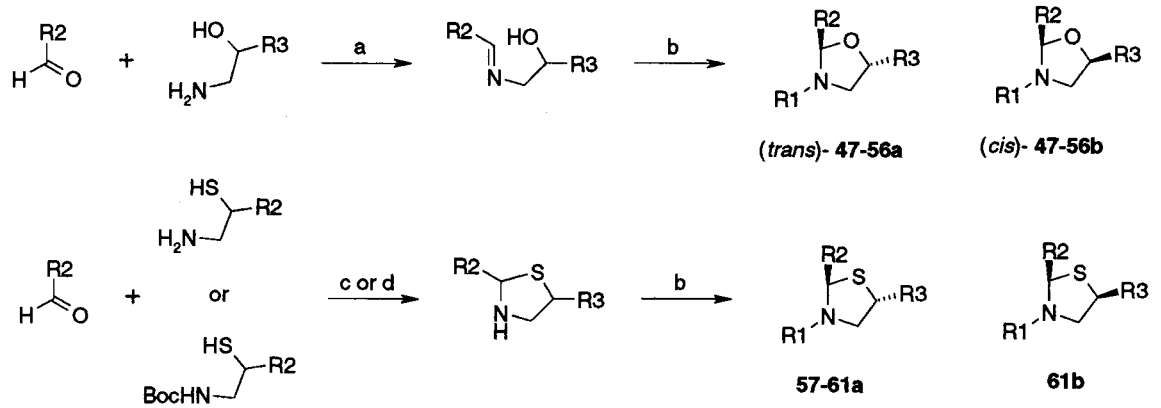
entry	*m*, *n*	R1	R2	% yield (method)	mp (°C)	formula	anal.[a]	140% at (μM)[b]
metformin								1000
troglitazone								30
1								10
2								30
3a	1, 1	4-ClPh	CH_2O(4-ClPh)	51 (A)	99−100	$C_{19}H_{17}NO_3Cl_2$	C, H, N, Cl	30
4	1, 1	4-ClPh	H	45 (A)	83−84	$C_{24}H_{19}NO_3Cl_2$	C, H, N, Cl	>1000
5a	1, 1	4-ClPh	CH_2CH_2Ph	34 (A)	oil	$C_{20}H_{20}NO_2Cl$	C, H, N, Cl	>300
6a	1, 1	4-ClPh	CH_2OH	11 (B)	115−117	$C_{13}H_{14}NO_3Cl$	C, H, N	>300
7a	1, 1	4-ClPh	CH_2O*t*-Bu	39 (A)	92−94	$C_{17}H_{22}NO_3Cl$	C, H, N, Cl	300
8a	1, 1	4-ClPh	CH_2Oallyl	47 (A)	oil	$C_{16}H_{18}NO_3Cl$	C, H, N, Cl	>300
9a	1, 1	4-ClPh	CH_2OCH_2COOMe	68 (C)	oil	$C_{16}H_{18}NO_5Cl$	C, H, N, Cl	>300
10a	1, 1	4-ClPh	$CH_2OCH_2CH_2OH$	45 (C)	91−93	$C_{15}H_{18}NO_4Cl$	C, H, N, Cl	>300
11a	1, 1	4-ClPh	CH_2O(4-MeOPh)	31 (A)	104−106	$C_{20}H_{20}NO_4Cl$	C, H, N, Cl	100
12a	1, 1	3,4-diClPh	CH_2S(4-ClPh)	42 (A)	80−83	$C_{19}H_{16}NO_2SCl_3$	C, H, N, Cl, S	100
13a	1, 1	4-ClPh	CH_2NH(4-ClPh)	31 (A)	133−139	$C_{19}H_{18}N_2O_2Cl_2$	C, H, N, Cl	>300
14a	1, 1	4-ClPh	CH_2NAc(4-ClPh)	37 (D)	65−67	$C_{22}H_{20}N_2O_3Cl_2$	C, H, N	>300
15	1, 1	4-(PhO)Ph	H	80 (A)	68	$C_{18}H_{17}NO_3$	C, H, N	300
16a	1, 1	4-(PhO)Ph	CH_2O(4-ClPh)	32 (A)	81−82	$C_{25}H_{22}NO_4Cl$	C, H, N, Cl	10
17a	2, 1	Ph	CH_2O(4-ClPh)	32 (A)	124−126	$C_{20}H_{20}NO_3Cl$	C, H, N	30
18a	2, 1	4-(PhO)Ph	CH_2O(4-ClPh)	38 (A)	127	$C_{26}H_{24}NO_4Cl$	C, H, N, Cl	100
19	2, 1	4-(PhO)Ph	H	76 (A)	115−116	$C_{19}H_{19}NO_3$	C, H, N	30
20a	1, 2	4-ClPh	CH_2O(4-ClPh)	35 (A)	128−129	$C_{20}H_{19}NO_3Cl_2$	C, H, N	>300
21a	1, 1	Me	CH_2O(4-ClPh)	25 (A)	118−120	$C_{14}H_{16}NO_3Cl$	C, H, N	>300
22a	1, 1	*t*-Bu	CH_2O(4-ClPh)	26 (A)	119−121	$C_{17}H_{22}NO_3Cl$	C, H, N, Cl	>300
23a	1, 1	*c*-hexyl	CH_2O(4-ClPh)	47 (A)	94−96	$C_{19}H_{24}NO_3Cl$	C, H, N, Cl	100
24a	1, 1	Ph	CH_2O(4-ClPh)	35 (A)	95−97	$C_{19}H_{18}NO_3Cl$	C, H, N, Cl	100
25a	1, 1	3,4-diClPh	CH_2O(4-ClPh)	44 (A)	126−127.5	$C_{19}H_{16}NO_3Cl_3$	C, H, N, Cl	10
25a(2*R*)	1, 1	3,4-diClPh	CH_2O(4-ClPh)	19 (A)	102−104	$C_{13}H_{14}NO_3Cl$	C, H, N, Cl	30
25a(2*S*)	1, 1	3,4-diClPh	CH_2O(4-ClPh)	24 (A)	102−104	$C_{19}H_{16}NO_3Cl_3$	C, H, N, Cl	10
26a	1, 1	4-(MeO)Ph	CH_2O(4-ClPh)	52 (A)	128	$C_{20}H_{20}NO_4Cl$	C, H, N, Cl	30
27a	1, 1	4-Cl-3-CF_3Ph	CH_2O(4-ClPh)	34 (A)	101.5−103.5	$C_{20}H_{16}NO_3Cl_2F_3$	C, H, N, Cl	10
28a	1, 1	4-FPh	CH_2O(4-ClPh)	55 (A)	99−100	$C_{19}H_{17}NO_3ClF$	C, H, N, Cl	30
29a	1, 1	2-naphthyl	CH_2O(4-ClPh)	36 (A)	137	$C_{23}H_{20}NO_3Cl$	C, H, N, Cl	30
30a	1, 1	1-naphthyl	CH_2O(4-ClPh)	52 (A)	166−167	$C_{23}H_{20}NO_3Cl$	C, H, N, Cl	>300
31a	1, 1	4-biphenyl	CH_2O(4-ClPh)	49 (A)	141−142	$C_{25}H_{22}NO_3Cl$	C, H, N, Cl	10
32a	1, 1	*c*	CH_2O(4-ClPh)	54 (A)	142−144	$C_{27}H_{24}NO_3Cl$	C, H, N, Cl	30
33a	1, 1	*d*	CH_2O(4-ClPh)	38 (A)	145−147	$C_{25}H_{20}NO_3Cl$	C, H, N, Cl	30
34a	1, 1	4-pyridyl	CH_2O(4-ClPh)	32 (A)	131−133	$C_{18}H_{17}N_2O_3Cl$	C, H, N, Cl	30
35a	1, 1	3-pyridyl	CH_2O(4-ClPh)	28 (A)	83−85	$C_{18}H_{17}N_2O_3Cl$	C, H, N, Cl	300
36a	1, 1	3-indolyl	CH_2O(4-ClPh)	26 (A)	168−170	$C_{21}H_{19}N_2O_3Cl$	C, H, N, Cl	>300
37a	1, 1 (diMe)	4-ClPh	CH_2O(4-ClPh)	50 (A)	124−126	$C_{21}H_{21}NO_3Cl_2$	C, H, N, Cl	30
38a	1, 1 (diMe)	4-(PhO)Ph	H	78 (A)	oil	$C_{20}H_{21}NO_3$	C, H, N	10
39a	1, 1 (diMe)	4-(PhO)Ph	CH_2O(4-ClPh)	73 (A)	120−121	$C_{27}H_{26}NO_4Cl$	C, H, N, Cl	30
5b	1, 1	4-ClPh	CH_2CH_2Ph	13 (A)	oil	$C_{20}H_{20}NO_2Cl$	C, H, N, Cl	>300
6b	1, 1	4-ClPh	CH_2OH	23 (B)	144−146	$C_{13}H_{14}NO_3Cl$	C, H, N	>300
12b	1, 1	3,4-diClPh	CH_2S(4-ClPh)	20 (A)	76−79	$C_{19}H_{16}NO_2SCl_3$	C, H, N, Cl, S	100
13b	1, 1	4-ClPh	CH_2NH(4-ClPh)	5 (A)	96−98	$C_{19}H_{18}N_2O_2Cl_2$	C, H, N, Cl	>300
17b	2, 1	Ph	CH_2O(4-ClPh)	7 (A)	144−145	$C_{20}H_{20}NO_3Cl$	C, H, N	>300
22b	1, 1	*t*-Bu	CH_2O(4-ClPh)	24 (A)	109−111	$C_{17}H_{22}NO_3Cl$	C, H, N, Cl	>300
23b	1, 1	*c*-hexyl	CH_2O(4-ClPh)	22 (A)	128−130	$C_{19}H_{24}NO_3Cl$	C, H, N, Cl	>300
25b	1, 1	3,4-diClPh	CH_2O(4-ClPh)	14 (A)	106−108	$C_{19}H_{16}NO_3Cl_3$	C, H, N	>300
26b	1, 1	4-(MeO)Ph	CH_2O(4-ClPh)	10 (A)	117	$C_{20}H_{20}NO_4Cl$	C, H, N, Cl	>300
27b	1, 1	4-Cl-3-CF_3Ph	CH_2O(4-ClPh)	27 (A)	88.5−90.5	$C_{20}H_{16}NO_3Cl_2F_3$	C, H, N, Cl	300
28b	1, 1	4-FPh	CH_2O(4-ClPh)	13 (A)	76−78	$C_{19}H_{17}NO_3ClF$	C, H, N, Cl	>300
29b	1, 1	2-naphthyl	CH_2O(4-ClPh)	16 (A)	145	$C_{23}H_{20}NO_3Cl$	C, H, N	>300
31b	1, 1	4-biphenyl	CH_2O(4-ClPh)	20 (A)	157−158	$C_{25}H_{22}NO_3Cl$	C, H, N, Cl	>300
32b	1, 1	*c*	CH_2O(4-ClPh)	24 (A)	118−120	$C_{27}H_{24}NO_3Cl$	C, H, N, Cl	>300
33b	1, 1	*d*	CH_2O(4-ClPh)	13 (A)	137−139	$C_{25}H_{20}NO_3Cl$	C, H, N, Cl	>300
34b	1, 1	4-pyridyl	CH_2O(4-ClPh)	11 (A)	140−143	$C_{18}H_{17}N_2O_3Cl$	C, H, N, Cl	100
35b	1, 1	3-pyridyl	CH_2O(4-ClPh)	13 (A)	138−140	$C_{18}H_{17}N_2O_3Cl$	C, H, N, Cl	300
37b	1, 1 (diMe)	4-ClPh	CH_2O(4-ClPh)	13 (A)	117−119	$C_{21}H_{21}NO_3Cl_2$	C, H, N, Cl	100
40	1, 1	4-ClPh	H	99 (E)	91−92	$C_{12}H_{12}NOSCl$	C, H, N, S, Cl	300
41	2, 1	4-ClPh	H	85 (E)	97−99	$C_{13}H_{14}NOSCl$	C, H, N, S, Cl	>300
42	1, 1	4-ClPh	CH_2O(4-ClPh)	18 (F)	132−132.5	$C_{19}H_{17}NOSCl_2$	C, H, N, Cl	>300
43	1, 1	4-ClPh	CH_2O(4-ClPh)	13 (F)	100−102	$C_{19}H_{17}NOSCl_2$	C, H, N, Cl	10
44a		OH	H	41 (A)	162	$C_{13}H_{15}NO_3$	C, H, N	>300
44b		H	OH	37 (A)	175	$C_{13}H_{15}NO_3$	C, H, N	>300

[a] Analytical results were within ±0.4% of the theoretical value. [b] Lowest concentration (μM) tested in the L6 myocyte in vitro assay at which glucose utilized was greater than or equal to 140% of control (see Biological Methods). [c] R = 2-(9,10-dihydrophenanthrenyl). [d] R = 2-dibenzofuranyl.

Scheme 3. General Synthesis of Tetrahydropyrrolo[2,1-*b*]oxa(thia)zol-5(6*H*)-ones



Scheme 4. General Synthesis of 3-Oxa(thia)zolidinyl Analogues[a]



[a] Conditions: (a) EtOH or CH_3CN or benzene and concentrate; (b) R1COCl or R1NCO or R1NCS or $R1SO_2Cl$, Et_3N or pyridine; (c) for hydrochloride, Et_3N, EtOH; (d) Boc-protected amide, TFA, aldehyde, CH_3CN.

pounds in mild acid readily converted to **44a** and **44b**; in fact the trace of acid in commercial $CDCl_3$ readily effected these conversions in less than 3 h. Therefore, **6a** and **6b** could not practically be utilized as a general intermediate.

Most of the substituted tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-ones (**3a**−**39**) and tetrahydropyrrolo[2,1-*b*]-thiazol-5(6*H*)-ones (**40**−**43**) in Table 1 were readily synthesized from appropriate amino alcohols or amino thiols and keto acids in one step via a condensation as shown in Scheme 3, usually in excellent yields. All amino alcohols and keto acids utilized in this paper are either commercially available or were prepared by known literature methods. In most cases, near-quantitative yields of 1,2-amino alcohols resulted from the stirring of a methanolic solution of the appropriate epoxide with an excess of ammonia in a steel bomb overnight. The keto acids were prepared either via Friedel−Crafts acylation or via decarboxylation of an alkylation product of malonic acid. To prepare the tetrahydropyrrolo[2,1-*b*]thiazol-5(6*H*)-ones, optimal yields were obtained if the free base of the relevant amino thiol was freshly prepared or the amino thiol was prepared in situ via a deprotection of a *t*-BOC-protected amino thiol.

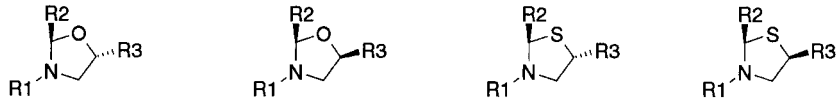
The monocyclic tetrahydrooxazoles **47a**−**56b** and tetrahydrothiazoles **57**−**61b** were synthesized by conjugating the unpurified imine of the appropriate amino alcohol or amino thiol with an aldehyde and the appropriate acid chloride, isocyanate, isothiocyanate, or sulfonyl chloride (Scheme 4). All of the derivatives in Tables 1 and 2 are racemates with the exception of **25a-(2*R*)** and **25a(2*S*)** which were prepared from optically pure 1,2-amino alcohols.

The isoxazole derivatives **62a**−**k**, **63a**−**b**, and **64a** were synthesized via a cyclization of hydroximinoyl chloride with a propargylic alcohol (Scheme 5).[20] Isoxazole **65** was synthesized via a Mitsunobu coupling of *p*-chlorophenol with **62a**. Isoxazole **66** was synthesized via alkylation of **62a** with methyl iodide. Isoxazole **67** was prepared via hydrolysis of isoxazole **62d** (Scheme 6).

Results and Discussion

Clavamycin D **(1)**, (hydroxymethyl)clavam (**2**), and (+)-*trans*-2-[(4-chlorophenoxy)methyl]-7α-(4-chlorophenyl)tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one **(3)** increased glucose utilization by L6 myocytes (see Table 1) and lowered blood glucose levels in vivo in diabetic obese *ob/ob* mice (see Table 4). As the β-lactams **1** and **2** and the γ-lactam **3** each have an oxidized 2-methyl substituent attached to the ring, the requirement of this substituent for activity was explored. In the tetrahydropyrrolo-

Table 2. Physical and in Vitro Properties of Tetrahydrooxa(thia)zole Analogues

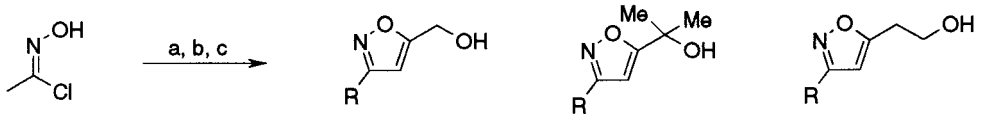


45, 46, 47-56a **47-56b** **57-61a** **61b**

entry	R1	R2	R3	% yield (method G)	mp (°C)	formula	anal.[a]	140% at (μM)[b]
45	C(=S)NHMe	4-ClPh	H	31	138−140	$C_{11}H_{13}N_2OSCl$	C, H, N, Cl, S	>300
46	C(=O)NHMe	4-ClPh	H	62	97	$C_{11}H_{13}N_2O_2Cl$	C, H, N, Cl	>300
47a	C(=O)CH_3	4-ClPh	CH_2O(4-ClPh)	29	104−106	$C_{18}H_{17}NO_3Cl_2$	C, H, N, Cl	100
47b	C(=O)CH_3	4-ClPh	CH_2O(4-ClPh)	26	80−83	$C_{18}H_{17}NO_3Cl_2$	C, H, N, Cl	100
48a	C(=O)CH_3	4-MeOPh	CH_2O(4-ClPh)	53	115−117	$C_{19}H_{20}NO_4Cl$	C, H, N, Cl	>300
48b	C(=O)CH_3	4-MeOPh	CH_2O(4-ClPh)	29	104−106	$C_{19}H_{20}NO_4Cl$	C, H, N, Cl	>300
49a	C(=O)CH_3	3,4-diClPh	CH_2O(4-ClPh)	39	84−88	$C_{18}H_{16}NO_3Cl_3$	C, H, N, Cl	30
49b	C(=O)CH_3	3,4-diClPh	CH_2O(4-ClPh)	33	oil	$C_{18}H_{16}NO_3Cl_3$	C, H, N, Cl	30
50a	C(=O)CH_3	3-CF_3, 4-ClPh	CH_2O(4-ClPh)	33	75−78	$C_{19}H_{16}NO_3Cl_2F_3$	C, H, N	30
50b	C(=O)CH_3	3-CF_3, 4-ClPh	CH_2O(4-ClPh)	24	85−87	$C_{19}H_{16}NO_3Cl_2F_3$	C, H, N	30
51a	C(=O)$CH(CH_3)_2$	3,4-diClPh	CH_2O(4-ClPh)	36	139−141	$C_{20}H_{20}NO_3Cl_3$	C, H, N, Cl	30
51b	C(=O)$CH(CH_3)_2$	3,4-diClPh	CH_2O(4-ClPh)	37	(oil)	$C_{20}H_{20}NO_3Cl_3$	C, H, N	30
52a	C(=O)Ph	3,4-diClPh	CH_2O(4-ClPh)	39	oil	$C_{23}H_{18}NO_3Cl_3$	C, H, N, Cl	>300
52b	C(=O)Ph	3,4-diClPh	CH_2O(4-ClPh)	25	oil	$C_{23}H_{18}NO_3Cl_3$	C, H, N, Cl	300
53a	SO_2CH_3	4-ClPh	CH_2O(4-ClPh)	21	140−142	$C_{17}H_{17}NO_4SCl_2$	C, H, N, Cl, S	30
53b	SO_2CH_3	4-ClPh	CH_2O(4-ClPh)	29	85−7	$C_{17}H_{17}NO_4SCl_2$	C, H, N, Cl, S	100
54a	C(=O)OCH_3	3,4-diClPh	CH_2O(4-ClPh)	23	88−90	$C_{18}H_{16}NO_4Cl_3$	C, H, N, Cl	300
54b	C(=O)OCH_3	3,4-diClPh	CH_2O(4-ClPh)	20	89−92	$C_{18}H_{16}NO_4Cl_3$	C, H, N, Cl	30
55a	C(=O)NHPh	3,4-diClPh	CH_2O(4-ClPh)	32	94−96	$C_{23}H_{19}N_2O_3Cl_3$	C, H, N	30
55b	C(=O)NHPh	3,4-diClPh	CH_2O(4-ClPh)	12	99−101	$C_{23}H_{19}N_2O_3Cl_3$	C, H, N, Cl	30
56a	SO_2CH_3	3,4-diClPh	CH_2O(4-ClPh)	27	oil	$C_{18}H_{17}N_2O_3Cl_3$	C, H, N, Cl	30
56b	SO_2CH_3	3,4-diClPh	CH_2O(4-ClPh)	33	oil	$C_{17}H_{16}NO_4SCl_3$	C, H, N, Cl, S	30
57	C(=O)Me	4-ClPh	H	62	oil	$C_{11}H_{12}NOSCl$	C, H, N	>300
58	C(=O)NHMe	4-ClPh	H	94	117−118	$C_{11}H_{13}N_2OSCl$	C, H, N, Cl, S	300
59	C(=S)NHMe	4-ClPh	H	44	138−140	$C_{11}H_{13}N_2S_2Cl$	C, H, N	300
60	SO_2CH_3	4-ClPh	H	68	73−74	$C_{10}H_{12}NO_2S_2Cl$	C, H, N, Cl, S	300
61a	C(=O)CH_3	4-ClPh	CH_2O(4-ClPh)	26	126−128	$C_{18}H_{17}NO_2SCl_2$	C, H, N, S	300
61b	C(=O)CH_3	4-ClPh	CH_2O(4-ClPh)	42	105−106.5	$C_{18}H_{17}NO_2SCl_2$	C, H, N, Cl, S	30

[a] Analytical results were within ±0.4% of the theoretical value. [b] Lowest concentration (μM) tested in the L6 myocyte in vitro assay at which glucose utilized was greater than or equal to 140% of control (see Biological Methods).

Scheme 5. General Synthesis of the Isoxazoles[a]



62a-k **63a, b** **64a**

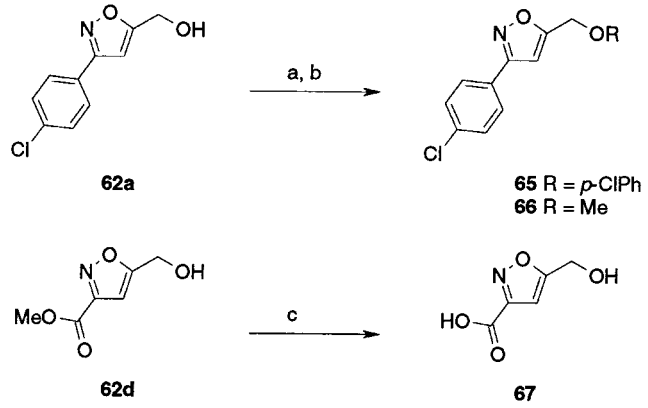
62-4a R = *p*-ClPh
62-3b R = *p*-(PhO)Ph
62c R = COMe
62d R = COOMe
62e R = Ph
62f R = (3,4-diCl)Ph
62g R = (2,4-diCl)Ph
62h R = *p*-(CF_3)Ph
62i R = Me
62j R = Bn
62k R = *t*Bu

[a] Conditions: (a) Et_3N, CH_2Cl_2, propargylic alcohol; (b) Et_3N, CH_2Cl_2, 2-methyl-3-butyn-2-ol; (c) Et_3N, CH_2Cl_2, 3-butyn-1-ol.

[2,1-*b*]oxazol-5(6*H*)-ones, the 2-substituent CH_2XAr, where X is either oxygen or sulfur, increased the in vitro potency of this series in effecting glucose utilization (compare **3**, **11a**, and **12a** to **4**−**10** in Table 1).

Although the 2-substituent in **3a** is trans to the 8-(4-chlorophenyl) group, whereas the corresponding substituents in **1**, **2**, and **43** are cis-disposed, the global minimal structures of these biologically active molecules are predicted by molecular modeling to be quite similar.[21] In each, the 2-aryloxymethyl (or hydroxymethyl) substituent was predicted to be nearly coplanar to the tetrahydrooxa(thia)zole ring and the 2-hydrogens to be perpendicular to this ring. In the inactive isomers **3b** and **42**, the 2-aryloxymethyl (or hydroxymethyl) substituent was predicted to be nearly perpendicular to the tetrahydrooxa(thia)zole ring and the 2-hydrogens to be approximately planar to this ring. To examine the validity of these predictions, X-ray structures of **25a-**

Scheme 6. Synthesis of Other Isoxazoles[a]

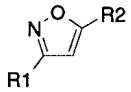


62a **65** R = *p*-ClPh, **66** R = Me

62d **67**

[a] Conditions: (a) DIAD, Ph_3P, THF, 4-chlorophenol; (b) NaH, DMF, MeI; (c) 1 N NaOH, EtOH.

Table 3. Physical and in Vitro Properties of Isoxazole Analogues



entry	R1	R2	% yield (method)	mp (°C)	formula	anal.[a]	140% at (μM)[b]
62a	4-ClPh	CH_2OH	97 (H)	99	$C_{10}H_8NO_2Cl$	C, H, N, Cl	100
62b	4-(PhO)Ph	CH_2OH	75 (H)	95	$C_{16}H_{13}NO_3$	C, H, N	30
62c	COMe	CH_2OH	6 (H)	oil	$C_6H_7NO_3$		>300
62d	COOMe	CH_2OH	68 (H)	oil	$C_7H_9NO_4$		>300
62e	Ph	CH_2OH	52 (H)	52−53.5	$C_{10}H_9NO_2$		>300
62f	2,4-diClPh	CH_2OH	45 (H)	114	$C_{10}H_7NO_2Cl_2$	C, H, N, Cl	300
62g	3,4-diClPh	CH_2OH	50 (H)	106−108	$C_{10}H_7NO_2Cl_2$		30
62h	4-(CF_3)Ph	CH_2OH	38 (H)	98−100	$C_{11}H_8NO_2F_3$	C, H, N	100
62i	Me	CH_2OH	27 (H)	oil	$C_5H_7NO_2$		>300
62j	Bn	CH_2OH	11 (H)	oil	$C_{11}H_{11}NO_2$		>300
62k	*t*-Bu	CH_2OH	63 (H)	35−37.5	$C_8H_{13}NO_2$		>300
63a	4-ClPh	$C(Me)_2OH$	54 (H)	98	$C_{12}H_{12}NO_2Cl$		100
63b	4-(PhO)Ph	$C(Me)_2OH$	58 (H)	82−83	$C_{18}H_{17}NO_3$	C, H, N	30
64a	4-ClPh	CH_2CH_2OH	63 (H)	65	$C_{11}H_{10}NO_2Cl$	C, H, N	100
65	4-ClPh	CH_2O(4-ClPh)	83 (I)	143	$C_{16}H_{11}NO_2Cl_2$	C, H, N	>300
66	4-ClPh	CH_2OMe	67 (J)	54−55	$C_{11}H_{10}NO_2Cl$	C, H, N, Cl	100
67	CO_2H	CH_2OH	73 (H)	135−136.5	$C_5H_5NO_4$		>300

[a] Analytical results were within ±0.4% of the theoretical value. [b] Lowest concentration (μM) tested in the L6 myocyte in vitro assay at which glucose utilized was greater than or equal to 140% of control (see Biological Methods).

Table 4. In Vivo Activity of Selected Compounds in a Model of Diabetes, the *ob*/*ob* Mouse[a]

	% efficacy				
	day 1		day 3		
entry	2 h	4 h	2 h	4 h	8 h
1[b]	63**	63*			
2[c]	66**	86**	53*	23	44*
3a[c]	31*	46*	14	−15	−26
4	21	7	23	28	11
11a	−17	−20	−19	−8	−28
15	−8	11	−3	−1	−4
16a	−29	−6	2	−25	−3
17a	42*	29	10	50	54*
19	25	29	45**	50**	3
24a	3	45*	18	−16	−28
25a	0	36	70**	80**	78*
26a	−12	3	−5	−27	12
28a	−2	19	67**	60*	38
29a	21	37*	49**	62**	39
31a	16	17	20	35*	7
32a	31*	38**	51*	56*	45*
33a	−25	−43	8	16	7
34	−18	−2	13	31	25
35a	22	20	1	22	35
39	9	−18	55*	−3	−37
29b	−6	−11	13	7	8
40	16	2	57*	64**	68**
42	28	14	−11	9	11
43	9	3	44	48	35
47b	10	0	42*	54**	54**
49a	8	26	69**	70**	61**
51	15	−11	25	6	1
51b	32	21	20	24	6
53a	−10	18	11	55**	22
53b	−12	−4	35	59**	29
54b	13	40	25	19	−9
62a	−3	−1	61*	53	34
62b	14	15	56**	14	24
62h	14	52*	6	48**	50*
63b	6	−2	61*	60	55*

[a] All compounds dosed orally with a dose of 300 μmol/kg, except where noted. [b] Orally dosed at 15.86 μmol/kg. [c] Orally dosed at 200 μmol/kg. *p < 0.05; **p < 0.01.

(2*R*) and **42** were obtained, and these experimental structures are consistent with those postulated.

Simultaneously, the effect of changing the ring sizes of the bicyclic system was explored. Although the lactam ring can contain four, five, or six atoms and retain in vitro activity (compare compounds **2**, **3**, and **17**), expansion of the tetrahydrooxazole ring to six atoms resulted in loss of activity in the analogues tested (compare **3** and **20**). Whether the lack of activity of **20** is due to the nonplanarity of the 2-substituent or due to an unfavorable steric interaction resulting from the extra ring atom has not been established.

These data suggest that a pharmacophore of a five-atom heterocyclic ring with an aryloxy(or hydroxy)-methyl group is required for in vitro activity. As a consequence, compounds with a five-atom heteroaromatic ring substituted with an oxidized methyl group were investigated for activity in the L6 myocyte screen and in the *ob*/*ob* mouse. The compounds initially investigated for activity were 5-substituted-3-alkoxy(or hydroxymethyl)isoxazoles. The isoxazoles **62c** and **62d** were expected to be the most potent. However, 5-aryl-substituted-3-(hydroxymethyl)isoxazoles, exemplified by **62a**, **62b**, and **62g,** proved to be superior in enhancing glucose utilization in L6 myocytes (see Table 3). The effects of the aryl substituent on the SAR of the isoxazoles were similar to those seen within the tetrahydropyrrolo[2,1-*b*]oxaxol-5(6*H*)-ones (discussed below). The in vivo profile of the isoxazoles was improved by adding two methyl groups to the hydroxymethyl side chain, as exemplified by **63b** (see Table 4).

It appeared likely that the conformation necessary for biological activity of the lactam ring was quite flexible as β-lactams (**1** and **2**), γ-lactams (e.g., **3**), and δ-lactams all possessed in vitro activity. As a consequence, monocyclic derivatives, exemplified by **45**−**61**, were prepared (see Table 2) as a mixture of two readily separable isomers. Molecular modeling suggested that in each isomer, the aryl(*R*) group would be perpendicular to the plane of the tetrahydrooxazole ring to relieve allylic strain with the *N*-acetyl moiety, whereas the 2-substituent would lie approximately within this plane (X-ray structures of **49a** and **49b** were obtained—their experimental structures are consistent with those predicted). Thus, both isomers would fit our minimal model for activity, and indeed in many cases both isomers increased glucose utilization in L6 myocytes. Replacement of the acyl moiety of **49a** and **49b** presented an opportunity to quickly explore diverse substituents in similar proximity to the position of the methyls of **37a**−

39a. The reported compounds (**45**−**61a**) are examples of structural diversity in this region. As in the tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-ones, it was necessary to have a 2-substituent CH_2XAr (where X is either oxygen or sulfur) for optimal in vitro potency of this series in affecting glucose utilization. If this substituent is present, all compounds have similar potency in the L6 myocyte assay (see **49a**, **49b**, **53a**, **53b**, **55a**, **55b**). Collectively these data suggest that the acetyl of **49a** does not interact with the compound's unknown target site.

To further the SAR of the tetrahydropyrrolo[2,1-*b*]-oxazol-5(6*H*)-ones, the effect of different substituents at the 7α-position was explored. Of the compounds tested, the presence of a six-membered ring, especially a substituted aromatic ring, was desirable for enhancement of glucose utilization. Substitution of an aromatic group in the para or meta-position afforded compounds with slightly increased in vitro and in vivo potency (compare **24a** to **3a**, **16a**, **25a**, and others). The addition of a phenoxy group at the para-position allowed in vitro and in vivo activity to be seen without a 2-substituent CH_2XAr (compare **4** to **15** and **19**). It was disappointing that **16a** was not hypoglycemic orally, although it was very efficacious via ip administration (data not shown). The clog *P* values of the aromatic substituted tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-ones were in the range of 4.0−6.5. It has been noted by Lipinski and others that clog *P* values of above 5.0 may lead to problems of absorption.[22,23] However, the in vivo potency of this series is not simply correlated to clog *P*, as **32a** has a higher clog *P* than **16a** (6.5 vs 6.2) and is hypoglycemic upon oral dosing.

Although the in vitro potency of this series of compounds was not markedly affected by electronic effects, the in vivo potency was significantly affected. Compounds in which the aromatic ring was substituted with electron-donating substituents were less efficacious in vivo than those substituted with electron-withdrawing substituents (i.e., compare **25a** and **28a** with **26a**).

Without a 2-substituent, the tetrahydrothiazole derivatives were more potent in vitro and more efficacious in vivo than the tetrahydrooxazole derivatives (compare **3** and **40**). However, the addition of a C2-oxidized methyl substituent, while causing an increase in in vitro potency, did not have a significant effect on in vivo potency (compare **40** to **43**).

Of the insulin-sensitizing agents described above, five compounds (**25a(2*S*)**, **40**, **49a**, **62a**, and **63b**) were selected initially for further pharmacological profiling. **25a(2*S*)**, **40**, **49a**, **62a**, and **63b** enhanced insulin sensitivity in vitro by a mechanism distinct from that of the thiazolidinediones. Troglitazone induces preadipocyte differentiation and is an agonist of PPARγ receptors,[16] whereas **25a(2*S*)**, **40**, **49a**, **62a**, and **63b** had no affect on this process or receptor. The in vivo mechanism of **25a(2*S*)**, **40**, **49a**, **62a**, **63b**, and other members of this novel class of insulin-sensitizing agents is unknown. The isoxazoles **62a** and **63b** were less potent (ED_{50} values greater than 200 μmol/kg) in the *ob/ob* diabetic animal model than the other candidates.

On the basis of both in vivo efficacy and preliminary toxicity evaluation, **25a(2*S*)** (SDZ PGU 693) was selected for further pharmacological study. In L6 myocytes in vitro, **25a(2*S*)** stimulated glucose utilization with an EC_{50} value of 6.8 μM. **25a(2*S*)** enhanced 2-deoxyglucose uptake in 3T3-L1 adipocytes under both basal and insulin-stimulated conditions. In vivo, **25a(2*S*)** significantly improved glucose metabolism in diabetic and insulin-resistant animals. In obese, hyperglycemic *ob/ob* mice, oral administration of **25a(2*S*)** for 3 days effectively reduced glucose levels with a dose of 4 mg/kg/day producing 50% efficacy. The efficacy and potency of **25a(2*S*)** in this model was equal to or greater than that of troglitazone and metformin (Figure 1). The duration of action of **25a(2*S*)** was at least 8 h (see Table 4). In obese, insulin-resistant cynomolgus monkeys, 21-day treatment with **25a(2*S*)** substantially increased insulin sensitivity (S_I, +71 ± 21%, $p < 0.05$) as determined by the Bergman minimal model[24] while reducing basal (−36 ± 11%, $p < 0.05$) and glucose-stimulated (−35 ± 11%, $p < 0.05$) insulin levels during an intravenous glucose tolerance test.[25] The results of these pharmacological studies suggest that **25a(2*S*)** may provide a novel approach to improving glucose disposal in type 2 diabetic patients.

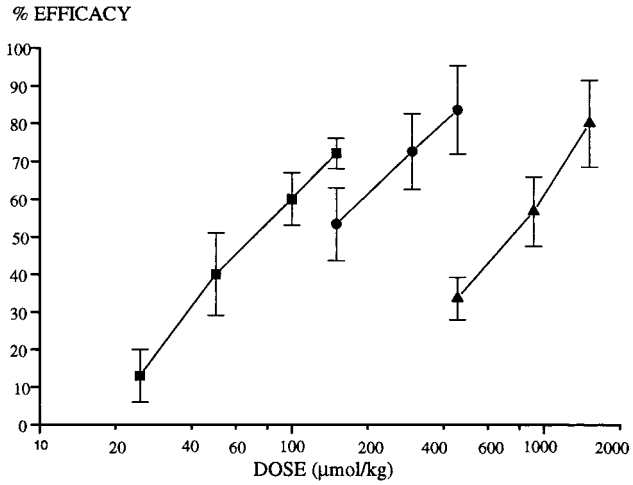


Figure 1. Efficacy of glucose lowering by **25a(2*S*)** (SDZ PGU 693; squares), troglitazone (circles), or metformin (triangles) in *ob/ob* mice. Compounds were given orally for 3 days. Data depicted represent blood glucose concentrations at 2 h postdose on day 3 ($N = 6-18$ mice/group).

Experimental Section

Chemistry. All melting points (mp) were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Bruker AC 300-MHz spectrometer. Chemical shifts were recorded in ppm (δ) and are reported relative to the solvent peak or TMS. Mass spectra were run on a Finnigan Mat 4600 spectrometer. Elemental analyses were performed on a CHNS-O EA 1108 elemental analyzer produced by Carlo Erba and the data for C, H, and N are within 0.4% of theoretical values unless otherwise indicated. Thin-layer chromatography (TLC) was carried out on Macherey-Nagel Polygram Sil G/U_{254} plates. Column chromatography separations were carried out using Merck silica gel 60 (mesh 230−400). Reagents and solvents were purchased from common suppliers and were utilized as received. All reactions were conducted under a nitrogen atmosphere. Yields were of purified product and were not optimized. All starting materials were commercially available unless otherwise indicated. All keto acids and amino alcohols which were not commercially available were made by the methods reported in the literature, and were consistent with the reported physical properties.

General Procedures for the Preparation of 3−67: Method A. (+)-*trans*-2-[(4-Chlorophenoxy)methyl]-7α-(3,4-dichlorophenyl)tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (25a) and (+)-*cis*-2-[(4-Chlorophenoxy)methyl]-7α-(3,4-dichlorophenyl)tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (25b). In a round-bottom flask equipped with a Dean−Stark water separator, a mixture of 3-(3,4-dichlorobenzoyl)propionic acid (24.5 g, 99.5 mmol), 3-(4-chlorophenoxy)-2-hydroxypropylamine (20.0 g, 99.5 mmol), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.1 g) in toluene (1 L) was heated to reflux for 16 h. The mixture was cooled and concentrated in vacuo. The crude residue was separated via column chromatography on silica gel (∼750 g) eluting with CH_2Cl_2−methanol (99.5:0.5, ∼5 L) to afford two products. The first product to elute from the column was concentrated in vacuo and recrystallized from CH_2Cl_2/diethyl ether to yield **25a** (18.1 g, 44%) as white crystals: mp 126−127.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.09 (m, 1H), 2.51−2.64 (m, 2H), 2.80 (m, 1H), 3.15 (dd, J = 11.5, 8.2 Hz, 1H), 3.91 (dd, J = 10.2, 4.2 Hz, 1H), 4.05 (m, 2H), 4.37 (m, 1H), 6.83 (d, J = 9.0 Hz, 2H), 7.22 (d, J = 9.0 Hz, 2H), 7.33 (dd, J = 8.3, 2.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H); MS (DCI, NH_3) *m*/*z* (rel intensity) 416 (26), 415 (19), 414 (79), 413 (27), 412 (100), 380 (31), 378 (60). Anal. ($C_{19}H_{16}NO_3Cl_3$) C, H, N, Cl.

The second product to elute was concentrated in vacuo and recrystallized from CH_2Cl_2/diethyl ether to yield **25b** (5.60 g, 14%) as white crystals: mp 106−108 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (m, 1H), 2.50−2.68 (m, 2H), 2.80 (m, 1H), 2.96 (dd, 1H), 3.75−3.85 (m, 2H), 4.37 (dd, 1H), 4.46 (m, 1H), 6.62 (d, 2H), 7.20 (d, 2H), 7.33 (dd, 1H), 7.40 (d, 1H), 7.55 (d, 1H); MS (DCI, NH_3) *m*/*z* (rel intensity) 416 (29), 415 (21), 414 (89), 413 (27), 412 (100). Anal. ($C_{19}H_{16}NO_3Cl_3$) C, H, N, Cl.

Method B. (+)-*trans*-2-(Hydroxymethyl)-7α-4-(chlorophenyl)tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (6a) and (+)-*cis*-2-(Hydroxymethyl)-7α-4-(chlorophenyl)tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (6b). Following the general procedure of method A from 1-amino-2-hydroxybut-3-ene (0.91 g, 10.5 mmol) and 3-(4-chlorobenzoyl)propionic acid (2.12 g, 10 mmol) was obtained 1.13 g of a mixture of bicyclic alkenes which were used as they were. Ozone was passed through a solution of the alkenes (1.49 g, 5.66 mmol) in CH_2Cl_2 (15 mL) and 4.5 mL of a 2.5 N solution of NaOH in MeOH at −78 °C until the solution became blue (∼0.5 h). The mixture was diluted with diethyl ether (50 mL), washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was filtered through silica gel eluting with 5% methyl *tert*-butyl ether in CH_2Cl_2. The filtrate was concentrated to afford 1.28 g of a mixture of two esters.

To a mixture of the esters (1.88 g, 6.38 mmol) in MeOH (50 mL) at 0 °C was added an excess of $NaBH_4$ (600 mg). The mixture was stirred overnight and then concentrated to a paste. The residue was partitioned between water (20 mL) and ethyl acetate (30 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was subjected to chromatography, eluting with a 19:1 mixture of CH_2Cl_2−2-propanol, to afford after concentration 183 mg (11%) of **6a**: mp 115−117 °C; ^{1}H NMR (C_6D_6) δ 1.76 (m, 1H), 2.09−2.47 (m, 4H), 3.16−3.38 (m, 3H), 3.95 (dd, 1H), 4.22 (1H, m), 7.15 (d, 2H), 7.22 (d, 2H); MS (DCI, NH_3) *m*/*z* (rel intensity) 270 (30), 269 (16), 268 (100). Anal. ($C_{13}H_{14}NO_3Cl$) C, H, N.

Also eluted was **6b** (385 mg, 23%): mp 144−146 °C; ^{1}H NMR (C_6D_6) δ 1.72 (m, 1H), 2.17−2.47 (m, 4H), 3.15 (m, 1H), 3.20 (m, 1H), 3.27 (m, 1H), 3.88 (dd, 1H), 4.19 (m, 1H), 7.17 (d, 2H), 7.21 (d, 2H); MS (DCI, NH_3) *m*/*z* (rel intensity) 285 (29), 270 (30), 268 (100). Anal. ($C_{13}H_{14}NO_3Cl$) C, H, N.

Method C. 2-*trans*-2-[[7α-(4-Chlorophenyl)hexahydro-5-oxopyrrolo[2,1-*b*]oxazol-2-yl]methoxy]acetic Acid, Methyl Ester (9a). Ozone was passed through a solution of 2-*trans*-7α-(4-chlorophenyl)tetrahydro-2-[(2-propenyloxy)methyl]pyrrolo[2,1-*b*]oxazol-5(6*H*)-one (**8a**) (2.33 g, 7.59 mmol) in CH_2Cl_2 (15 mL) and 4.5 mL of a 2.5 N solution of NaOH in MeOH at −78 °C until the solution became blue (∼0.5 h). The mixture was diluted with diethyl ether (50 mL), washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was filtered through silica gel eluting with 20% methyl *tert*-butyl ether in CH_2Cl_2. The major fraction was concentrated to afford **9a** (1.74 g, 68%) as a colorless oil: ^{1}H NMR (C_6D_6) δ 1.78 (m, 1H), 2.30−2.43 (m, 3H), 2.78 (m, 1H), 3.43 (s, 2H), 3.44 (s, 3H), 3.90−3.96 (m, 3H), 4.09 (m, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H). Anal. ($C_{16}H_{18}NO_5Cl$) C, H, N, Cl.

2-*trans*-7α-(4-Chlorophenyl)tetrahydro-2-[(2-hydroxyethoxy)methyl]pyrrolo[2,1-*b*]oxazol-5(6*H*)-one (10a). To a solution of the ester **9a** (1.17 g, 3.45 mmol) in MeOH (50 mL) at 0 °C was added an excess of $NaBH_4$ (600 mg). The mixture was stirred overnight and then concentrated to a paste. The residue was partitioned between water (20 mL) and ethyl acetate (30 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated. The residue was subjected to chromatography, eluting with a 19:1 mixture of CH_2Cl_2−MeOH, to afford after concentration of the major fraction and recrystallization from ethyl acetate/hexanes **10a** (560 mg, 45%) as white crystals: mp 91−93 °C; ^{1}H NMR ($CDCl_3$) δ 2.20 (m, 1H), 2.58−2.66 (m, 2H), 2.78 (m, 1H), 3.01 (dd, J = 11.3, 8.1 Hz, 1H), 3.38 (dd, J = 11.3, 3.0 Hz, 1H), 3.53 (m, 1H), 3.59−3.79 (m, 3H), 4.05 (dd, J = 11.3, 3.5 Hz, 1H), 4.17 (m, 1H), 7.39 (m, 4H); MS (DCI, NH_3) *m*/*z* (rel intensity) 331 (20), 329 (65), 314 (33), 312 (100). Anal. ($C_{15}H_{18}NO_4Cl$) C, H, N, Cl.

Method D. 2-*trans*-*N*-(4-Chlorophenyl)-*N*-[[7α-(4-chlorophenyl)hexahydro-5-oxopyrrolo[2,1-*b*]oxazol-2-yl]methyl]acetamide (14a). To a solution of 2-*trans*-7α-(4-chlorophenyl)tetrahydro-2-[[(4-chlorophenyl)amino]methyl]pyrrolo-[2,1-*b*]oxazol-5(6*H*)-one (**13a**) (0.42 g, 1.1 mmol) in THF (10 mL) was added triethylamine (16 μL, 1.1 mmol) followed by acetyl chloride (8 μL, 1.1 mmol). The mixture was stirred at room temperature for 72 h and was partitioned between ethyl acetate (15 mL) and water (15 mL). After separation, the organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography, eluting with ethyl acetate−hexanes (2:1) to afford after concentration of the lower R_f major component **14a** (170 mg, 37%): mp 65−67 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.06 (m, 1H), 2.33 (m, 1H), 2.44 (m, 1H), 2.75 (m, 1H), 3.02 (dd, J = 11.5, 7.9 Hz, 1H), 3.63 (dd, J = 11.5, 5.4 Hz, 1H), 3.70−3.92 (m, 2H), 4.21 (m, 1H), 7.16−7.43 (m, 8H); MS (DCI, NH_3) *m*/*z* (rel intensity) 438 (25), 437 (11), 436 (40), 422 (15), 421 (62), 420 (26), 419 (100). Anal. ($C_{22}H_{20}N_2O_3Cl_2$) C, H, N, Cl.

Method E. (±)-7α-(4-Chlorophenyl)tetrahydropyrrolo-[2,1-*b*]thiazol-5(6*H*)-one (40). Sodium hydroxide (8.8 g) in methanol (20 mL) was added to a saturated solution of cystamine hydrochloride (25.0 g, 220 mmol) in anhydrous methanol (75 mL). The mixture was stirred for 15 min, filtered, and concentrated. A mixture of the residue, toluene (500 mL), 3-(4-chlorobenzoyl)propionic acid (30.0 g, 141 mmol), and *p*-toluenesulfonic acid (1.25 g) was refluxed for 1 h using a Dean−Stark trap. The solution was cooled to room temperature, and then diethyl ether was added (300 mL). The solution was decanted. The solution was washed with water (200 mL), 0.2 N HCl (200 mL), and water (200 mL) and then dried ($MgSO_4$) and concentrated under reduced pressure to approximately 50 mL. To the mixture was added hexane (30 mL). Crystallization occurred, and the filtered crystals were dried in vacuo to yield **40** (35.6 g, 99.5% theoretical yield) as white crystals: mp 91−92 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (m, 1H), 2.61−2.78 (m, 3H), 2.93−3.06 (m, 2H), 3.21 (m, 1H), 4.40 (m, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H); MS (DCI, NH_3) *m*/*z* (rel intensity) 273 (36), 271 (100), 256 (18), 254 (52). Anal. ($C_{12}H_{12}NSOCl$) C, H, N.

Method F. (+)-*cis*-2-[(4-Chlorophenoxy)methyl]-7α-(3,4-dichlorophenyl)tetrahydropyrrolo[2,1-*b*]thiazol-5-(6*H*)-one (42) and (+)-*trans*-2-[(4-Chlorophenoxy)methyl]-7α-(3,4-dichlorophenyl)tetrahydropyrrolo[2,1-*b*]thiazol-5(6*H*)-one (43). To a stirred mixture of di-*tert*-butyl dicarbonate (35.1 g, 161 mmol) in CH_2Cl_2 (320 mL) was added aqueous 2 N NaOH (161 mL, 322 mmol) followed by 3-(4-chlorophenoxy)-2-hydroxypropylamine (32.4 g, 161 mmol). The

mixture was stirred until clear (2 h), washed with water (200 mL), 2 N HCl (150 mL), 10% $NaHCO_3$ (150 mL), and brine (150 mL), dried ($MgSO_4$), and concentrated in vacuo to yield *N*-(*tert*-butoxycarbonyl)-3-(4-chlorophenoxy)-2-hydroxypropylamine as a white solid which was used without additional purification.

To a solution of triphenylphosphine (84.5 g, 322 mmol) in THF (320 mL) at 0 °C was added diisopropyl azodicarboxylate (63.4 mL, 322 mmol), and the mixture was stirred for 30 min. Crude *N*-(*tert*-butoxycarbonyl)-3-(4-chlorophenoxy)-2-hydroxypropylamine and thioacetic acid (23.0 mL, 322 mmol) in THF (160 mL) was added dropwise, and the mixture was allowed to warm to room temperature overnight. The mixture was concentrated, and the residue was extracted with diethyl ether (2 × 100 mL). The combined ether layer was dried and concentrated, and the residue was subjected to column chromatography with 20% methyl *tert*-butyl ether−hexanes as the eluant. The major fraction was concentrated to yield (19.8 g, 34%) the *N*-(*tert*-butoxycarbonyl)-3-(4-chlorophenoxy)-2-mercaptopropylamine, acetic acid thioester as an oil.

NH_4OH (15 N) (7.3 mL, 110 mmol) was added to a solution of *N*-(*tert*-butoxycarbonyl)-3-(4-chlorophenoxy)-2-mercaptopropylamine, acetic acid thioester (19.7 g, 54.9 mmol) in methanol (500 mL); the mixture was stirred for 16 h. The reaction mixture was concentrated to a paste, poured into a cold solution of 3 N HCl (13 mL), and extracted with diethyl ether (2 × 150 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The *N*-(*tert*-butoxycarbonyl)-3-(4-chlorophenoxy)-2-mercaptopropylamine was purified by column chromatography on silica gel (150 g) using ethyl acetate−hexane (15:85) yielding (17.5 g, ∼100%) a clear oil.

In a round-bottom flask equipped with a Dean−Stark water separator, a mixture of *N*-(*tert*-butoxycarbonyl)-3-(4-chlorophenoxy)-2-mercaptopropylamine (5.00 g, 15.7 mmol), 3-(4-chlorobenzoyl)propionic acid (3.35 g, 15.7 mmol), and trifluoroacetic acid (30 mL) in toluene (100 mL) was stirred for 30 min at room temperature and then heated to reflux for 1 h. The mixture was cooled, diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified via column chromatography on silica gel eluting with 20% diethyl ether−hexane (1:5) to afford two products. After concentration and recrystallization of the first product to elute, **42** was isolated as white crystals (1.15 g, 18%): mp 132−132.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (m, 1H), 2.70 (m, 2H), 2.79 (m, 1H), 3.13 (dd, J = 12.4, 6.0 Hz, 1H), 3.90 (m, 3H), 4.52 (dd, J = 12.6, 0.6 Hz, 1H), 4.37 (m, 1H), 6.83 (d, 2H), 7.22 (d, 2H), 7.39 (m, 4H); MS (DCI, NH_3) *m*/*z* (rel intensity) 413 (70), 412 (21), 411 (100), 396 (26), 394 (33). Anal. ($C_{19}H_{16}NOCl_2$) C, H, N, Cl.

The second fraction was concentrated and also recrystallized from hexanes−diethyl ether to afford **43** as white crystals (0.85 g, 13%): mp 100−102 °C; ^{1}H NMR ($CDCl_3$) δ 2.26 (m, 1H), 2.64−2.75 (m, 3H), 2.84 (dd, J = 12.4, 7.4 Hz, 1H), 3.65 (dd, J = 9.5, 7.8 Hz, 1H), 3.89 (dd, J = 9.5, 5.7 Hz, 1H), 4.16 (m, 1H), 4.73 (dd, J = 12.4, 7.9 Hz, 1H), 6.62 (d, 2H), 7.18 (d, 2H), 7.34−7.43 (m, 4H); MS (DCI, NH_3) *m*/*z* (rel intensity) 413 (72), 412 (24), 411 (100), 396 (74), 395 (22), 394(99), 136 (28). Anal. ($C_{19}H_{16}NOCl_2$) C, H, N, Cl

Method G. 1-[5-[(4-Chlorophenoxy)methyl]-2-(3,4-dichlorophenyl)-3-oxazolidinyl]-*trans*-ethanone (49a) and 1-[5-[(4-Chlorophenoxy)methyl]-2-(3,4-dichlorophenyl)-3-oxazolidinyl]-*cis*-ethanone (49b). A mixture of 3,4-dichlorobenzaldehyde (10.0 g, 57 mmol) and 3-(4-chlorophenoxy)-2-hydroxypropylamine (11.5 g, 57 mmol) in benzene (500 mL) was heated at reflux with a Dean−Stark trap for 4 h. The mixture was cooled and concentrated to afford a crude hydroxylimine (20.5 g, ∼100%) which was used as is in aliquots.

Acetyl chloride (0.60 mL, 84 mmol) was added to a solution of the hydroxylimine (3.0 g, 84 mmol) and pyridine (0.70 mL, 84 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 8 h, diluted in ethyl acetate (100 mL), washed with water and brine, dried ($MgSO_4$), and concentrated. The two products were separated via column chromatography eluting with ethyl acetate−hexanes (3:1). The first product to elute was concentrated and crystallized from hexanes−CH_2Cl_2 to afford **49a** as white crystals (1.30 g, 39%): mp 84−8 °C; ^{1}H NMR (CD_3SOCD_3, 100 °C) δ 2.01 (s, 3H), 3.80 (m, 1H), 3.88 (m, 1H), 4.13−4.19 (m, 2H), 4.64 (m, 1H), 6.32 (s, 1H), 6.97 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 8.3 Hz, 1H), 7.59−7.61 (m, 2H); MS (DCI, NH_3) *m*/*z* (rel intensity) 421 (27), 420 (19), 419 (75), 418 (31), 417 (100), 402 (26), 400 (35), 385 (29). Anal. ($C_{18}H_{16}NO_3Cl_3$) C, H, N, Cl.

The second product to elute was concentrated and crystallized from hexanes−CH_2Cl_2 to afford **49b** as an oil (1.10 g, 33%): ^{1}H NMR (CD_3SOCD_3, 100 °C) δ 1.98 (s, 3H), 3.58 (m, 1H), 4.13 (m, 1H), 4.17 (dd, J = 11.0, 5.1 Hz, 1H), 4.25 (dd, J = 11.0, 3.6 Hz, 1H), 4.55 (m, 1H), 6.15 (s, 1H), 6.96 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H), 7.40 (dd, J = 8.3, 2.0 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H); MS (DCI, NH_3) *m*/*z* (rel intensity) 421 (27), 420 (20), 419 (85), 418 (26), 417 (100), 402 (34), 401 (12), 400 (43), 385 (29), 383 (51), 365 (31). Anal. ($C_{18}H_{16}NO_3Cl_3$) C, H, N, Cl.

Method I. 3-(4-Chlorophenyl)-5-(hydroxymethyl)isoxazole (62a). *N*-Chlorosuccinimide (51.2 g, 383 mmol) was added to a solution of 4-chlorobenzaldoxime (52.1 g, 335 mmol) in dimethylformamide (800 mL) at 0−5 °C. After stirring overnight at room temperature, the solution was added to ethyl acetate (800 mL). The solution was washed with 1:1 saturated sodium chloride−water (2 × 800 mL) and water (2 × 800 mL), dried ($MgSO_4$), and concentrated to yield the hydoximinoyl chloride as a white solid.

Triethylamine (51 mL, 370 mmol) was added to a mixture of the crude chloride and propargyl alcohol (25 mL, 430 mmol) in CH_2Cl_2 (800 mL) at 0 °C at a rate such that the temperature did not rise (30 min). The mixture warmed to room temperature overnight. The mixture was washed with water, dried ($MgSO_4$), and concentrated. The residue was recrystallized twice from CH_2Cl_2−hexane (4:1, 800 mL of solution each time) to afford **62a** as white crystals (42.4 g, 60% based on oxime). Recrystallization of the mother liquor afforded another crop of crystals (26.7 g, 37%): mp 99 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (bs, 1H), 4.83 (s, 2H), 6.55 (s, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H); MS (DCI, NH_3) *m*/*z* (rel intensity) 229 (33), 227 (100), 212 (20), 210 (55). Anal. ($C_{10}H_8NO_2Cl$) C, H, N, Cl.

Method J. 5-(4-Chlorophenoxymethyl)-3-(4-chlorophenyl)isoxazole (65). Diethyl azodicarboxylate (790 μL, 5.02 mmol) in THF (1 mL) was added over 15 min to a stirred solution at 0 °C of the alcohol **62a** (1.00 g, 4.78 mmol), 4-chlorophenol (615 mg, 4.78 mmol), and triphenylphosphine (1.32 g, 5.02 mmol) in THF (10 mL). The mixture was allowed to warm to room temperature overnight. To the mixture was added hexane (15 mL), followed by filtration, and the solids were washed with hexane. The combined filtrates was concentrated. The residue was filtered through silica (CH_2Cl_2 eluant), concentrated, and recrystallized from aqueous ethanol to yield **65** as white crystals (1.28 g, 83%): mp 143 °C; ^{1}H NMR ($CDCl_3$) δ 5.19 (s, 2H), 6.62 (s, 1H), 6.92 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H); MS (DCI, NH_3) *m*/*z* (rel intensity) 229 (33), 227 (100), 212 (20), 210 (55). Anal. ($C_{16}H_{11}NO_2Cl_2$) C, H, N.

Method K. 3-(4-Chlorophenyl)-5-(methoxymethyl)-isoxazole (66). NaH (60% in mineral oil) (1.20 g, 40 mmol) was washed with hexane. DMF (15 mL) was carefully added. To this mixture at 0 °C was added a solution of the alcohol **62a** (3.20 g, 15 mmol) in DMF (5 mL). The mixture was stirred at room temperature for 90 min, methyl iodide (4.26 g, 30 mmol) was added, and stirring was continued overnight. The mixture was poured into water and extracted with ether (2 × 40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Recrystallization of the residue from petroleum ether afforded **66** as white crystals (2.23 g, 67%): mp 54−55 °C; ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H), 4.60 (s, 2H), 6.55 (s, 1H), 7.42 (d, J = 8.5 Hz, 2H),

7.78 (d, J = 8.5 Hz, 2H); MS (DCI, NH_3) m/z (rel intensity) 243 (36), 241 (100), 226 (26), 224 (72). Anal. ($C_{11}H_{10}NO_2Cl$) C, H, N, Cl.

Biological Procedures. (1) In Vitro Stimulation of Glucose Utilization in L6 Myocytes. Rat L6 myoblasts (American type Culture Collection) were maintained in Dulbecco's modified Eagle's medium (DMEM, containing 5 mM glucose and 10% calf serum supplement) and were plated in 96-well microtiter plates at a density of 3000 cells/well. Cells were used in experiments once they had differentiated, on the 11th or 13th day following plating. L6 cells were treated with the test compound and serum-free DMEM containing 15 mM glucose for 20 h. The test compound was dissolved in DMSO (the final concentration of DMSO in the serum-free testing media (1%) had no effect on glucose utilization). The compound was tested in quadruplicate in each experiment at a final concentration of 3, 10, 30, 100, and 300 μM. Glucose utilization was assessed by measurement of glucose remaining in the media using a glucose oxidase assay (Ciba-Corning #S1004B).

A statistical analysis of the screening of 1508 random compounds of the Sandoz compound library[19] determined that an enhancement of glucose utilization of 40% was ~2.33 standard deviations from the mean. In Tables 1−3 the lowest concentrations at which compounds effected an enhancement of glucose utilization of greater than or equal to 40% from the control values are indicated. The maximum enhancement of glucose utilization was approximately 80% over control. The maximum efficacy of SDZ PGU 693 is the same as the maximal effect of insulin, metformin, or troglitazone.

(2) In Vivo Hypoglycemic Activity. Adult male C57BL *ob/ob* mice (Jackson Lab., Bar Harbor, ME) were housed 4/cage in hanging wire-bottom cages with standard laboratory conditions and a 12:12-h light−dark cycle (lights off 6 a.m.). Food (Purina Rodent Chow) and water were available ad libitum. For blood sampling the mice were placed in a restrainer and a drop of blood was obtained by a nick in the tip of the tail. Blood glucose concentrations were determined in 10 μL of blood using a YSI 27 (Yellow Springs Instruments, OH) analyzer. The protocol for compound evaluation was as follows: Fed mice were distributed into groups of 6 and matched for blood glucose levels on day 0. The animals were dosed (po) in the morning of days 1−3 with vehicle (carboxymethylcellulose (CMC, 0.5%) with Tween-80 (0.2%)) or compound. Blood glucose concentrations were monitored 2 and 4 h postdose on day 1 and at 2, 4, and 8 h postdose on day 3. Results are expressed as absolute blood glucose concentrations (in mg/dL) and as % efficacy, i.e., the ability of the compound to normalize glycemia (100 mg/dL), calculated with the formula: % efficacy = $\{1 - ([\text{glucose}]_{\text{compound}} - 100)/([\text{glucose}]_{\text{vehicle}} - 100)\} \times 100$. Animals that displayed glycemia of less than 150 mg/dL on day 0 (basal) were considered not to be diabetic and were excluded from the study. Statistical significance (*$p < 0.05$, **$p < 0.01$) is given versus the appropriate condition in vehicle-treated animals.

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Supporting Information Available: Complete X-ray crystallographic data of **3a**, **42**, **49a**, and **49b** (37 pages). Ordering information is given on any current masthead page.

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