Novel 5-(3-Aryl-2-propynyl)-5-(arylsulfonyl)thiazolidine-2,4-diones as Antihyperglycemic Agents

Jay Wrobel,* Zenan Li, Arlene Dietrich, Michael McCaleb,[†] Brenda Mihan, Janet Sredy,[‡] and Donald Sullivan

*Wyeth-Ayerst Research, Inc., CN 8000, Princeton, New Jersey 08543-8000*

Novel 5-(3-aryl-2-propynyl)-5-(arylsulfonyl)thiazolidine-2,4-diones and 5-(3-aryl-2-propynyl)-5-(arylsulfanyl)thiazolidine-2,4-diones were prepared and evaluated as oral antihyperglycemic agents in the obese, insulin resistant db/db mouse model at 100 mg/kg and, if the analogue had sufficient potency, 20 mg/kg. The sulfonylthiazolidinediones, **2**, were more potent than the corresponding sulfanylthiazolidinedione congeners, **1**. With regard to substituent effects on the 3-propynyl phenyl ring (Ar′) of **2**, 4-halogen substitution generally resulted in the more potent analogues. Substituent effects on the phenylsulfonyl moiety (Ar) of **2** were less clear, although para-halogen substitution on Ar generally was preferable. 2-Pyridinesulfonyl derivatives (Ar = 2-pyridine in **2**) also had good potency. Several compounds from series **2** were effective at lowering glucose and insulin in the obese, insulin resistant ob/ob mouse at the 50 mg/kg oral dose. Compound **20** significantly improved the glucose tolerance of obese, insulin resistant Zucker rats at the 20 mg/kg dose level and had no effect on plasma glucose or on glucose tolerance in normal rats fasted for 18 h at the 100 mg/kg level.

Introduction

Type 2 diabetes is a metabolic disease caused, in part, by insulin resistance in peripheral tissues.[1] In turn, glucose metabolism is decreased in muscle and fat, and glucose output by liver rises. The sustained, high plasma glucose levels further result in a gradual progression of a number of complications, including neuropathy, nephropathy, retinopathy, and premature atherosclerosis. Treatment of type 2 diabetes usually consists of a regimen of diet and exercise, oral hypoglycemic agents, and, in severe cases, insulin. Recent results from the Diabetes Control and Complications Trial (DCCT) showed that intensive management to control euglycaemia in insulin-dependent diabetes mellitus (type 1) correlated with a reduction in diabetic complications.[2] Proper glycaemic control is, most likely, necessary for the control of diabetic complications in type 2 patients, as well; however, current therapies to reduce plasma glucose levels have inherent problems including compliance, ineffectiveness, and occurrences of hypoglycemic episodes with insulin and the sulfonylureas. Accordingly, there is a need for more effective, orally administered agents,[3] particularly ones that normalize both glucose and insulin levels.

In this regard, a number of arylmethylthiazolidinedione antihyperglycemic agents have been described in the last 15 years. The prototype, ciglitazone,[4,5] and more potent congeners[6−10] were active in animal models of insulin resistance and did not induce hypoglycaemia. Recently, troglitazone, a member of the class of arylmethylthiazolidinediones, has shown positive clinical results[11] and is now marketed in the US under the trade name Rezulin. More recently, Boehringer Mannheim has reported a number of α-arylsulfonyl carboxylic acids[12,13] and structurally related α-aryloxy carboxylic acids[14,15] that also normalized plasma glucose and insulin levels in animal models of type 2 diabetes. In addition, the α-arylsulfonylbutynoic acid BM 13.0907[12,13] was shown to increase glucose uptake and metabolism in rat adipocytes and to stimulate translocation of glucose transporters in this model. A new series of antihyperglycaemic α-aryloxy carboxylic acids, based on the Boehringer Mannheim work, was also recently disclosed.[16]
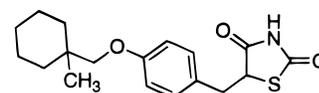

Ciglitazone
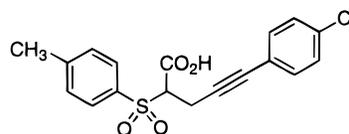
BM 13.0907
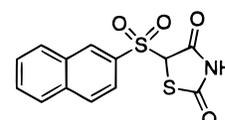
A
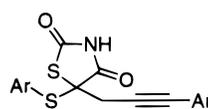
1
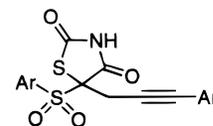
2

We were intrigued by the structural similarity between BM 13.0907 and (arylsulfonyl)thiazolidinediones, such as **A**,[17] which also lowered plasma glucose in the diabetic db/db mouse. Both compounds contained acidic

---

Scheme 1.[a] Synthesis of Precursors, Methods A−H

ArSH → Methods A or B → **4**

3

4 → Methods C, D or E → **5**

ArSH → Method F → **5**

3

**5** → Method G → **6**

Ar'I → Method H → Ar'—≡—CH₂Br **8**

7
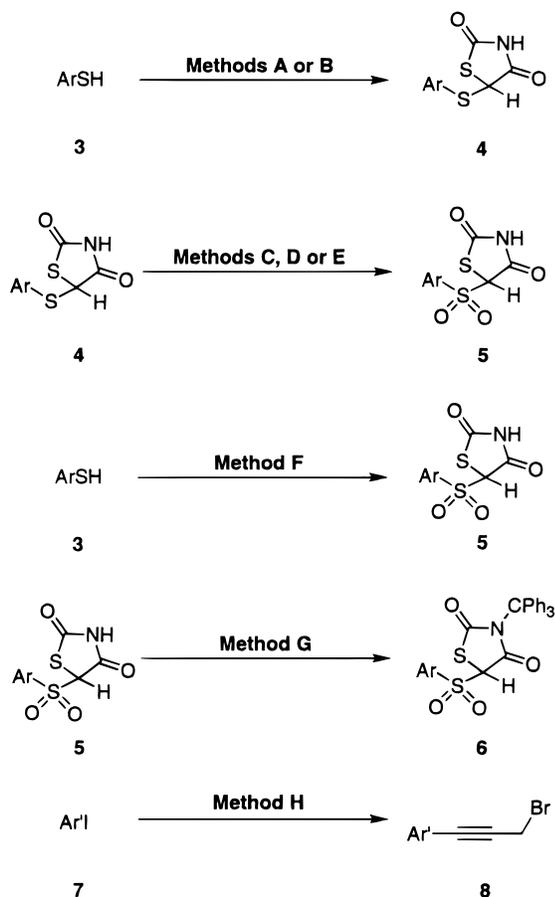
[a] Method A: TMS₂NLi/5-bromothiazolidine-2,4-dione/THF. Method B: Na₂CO₃/5-bromothiazolidine-2,4-dione/H₂O. Method C: H₂O₂/HOAc/Δ. Method D: oxone/MeOH. Method E: MCPBA/CHCl₃. Method F: (1) H₂O₂/aq NaOH/EtOH, (2) 5-bromothiazolidine-2, 4-dione/DMF. Method G: Ph₃CCl/TEA/CH₂Cl₂. Method H: (1) propargyl alcohol/(Ph₃P)₂Cl₂Pd/CuI/Et₂NH, (2) PBr₃/Pyr/Et₂O.

Scheme 2.[a] Synthesis of Target Compounds, Methods I−M

4 → Method I or J → **1**

6 → Method K → **2**

5 → Method L or M → **2**

[a] Method I: ≥2 equiv of NaH/**8**/THF. Method J: ≥2 equiv of *n*-BuLi/**8**/THF. Method K: (1) ≥1 equiv of NaH/**8**/THF. (2) TFA/CH₂Cl₂. Method L: ≥2 equiv of NaH/**8**/THF. Method M: ≥2 equiv of *n*-BuLi/**8**/THF.

C), oxone (method D), or MCPBA (method E). An alternative, but generally less satisfactory, preparation of (arylsulfonyl)thiazolidinediones **5** (method F) involved oxidation of aryl thiols **3** with hydrogen peroxide to the arylsulfinic acid, treatment with base to provide the arylsulfinate, and alkylation of the sulfinate with 5-bromothiazolidine-2, 4-dione. The thiazolidinedione nitrogen of compounds **5** could be protected with trityl chloride to form the trityl derivatives **6** (method G).

The 3-arylprop-2-ynyl bromides **8** were prepared from commercially available aryl iodides **7** and propargyl alcohol using a two-step process (method H) involving palladium/copper-catalyzed Castro−Stevens type coupling followed by conversion of the 3-arylprop-2-ynyl alcohols to the bromides **8** with PBr₃.

Target compounds **1** and **2** were prepared according to methods I−M in Scheme 2. The dianion of **4** could be prepared using either sodium hydride (method I) or *n*-butyllithium (method J) and these dianions could be reacted with the 3-arylprop-2-ynyl bromides **8**. Alkylation occurred exclusively on carbon to afford the (arylsulfanyl)thiazolidinediones **1**. Similarly, the dianion of **5** could be generated with either *n*-butyllithium or sodium hydride (method L or M) and reacted with **8** to afford the C-alkylated product **2** exclusively. Alternatively, the N-protected thiazolidinediones **6** could be alkylated with **8** using sodium hydride as base, and the trityl protecting groups could be removed to provide the target thiazoladinediones **2**. All compounds were racemic, and none were resolved or synthesized enantiomerically pure during the course of this study.

residues adjacent to an α-arylsulfonyl moiety. However, compound **A** lacked the 3-arylpropynyl chain of BM 13.0907. We envisioned that replacement of the carboxylic acid function of BM 13.0907 with a more lipophilic thiazolidinedione ring would lead to compounds of general structure **2** that would possibly have enhanced bioavailability and therefore greater antidiabetic potency. Our objective, therefore, was to find potent analogues of **2** using an empirical structure−activity approach. In the course of the investigation, some of the sulfanylthiazolidinedione precursors of **2**, that is, compounds **1**, were also shown to have antidiabetic activity, and their data are also reported here.

Chemistry

The (arylsulfanyl)- and (arylsulfonyl)thiazolidinediones **1** and **2** were synthesized according to the methods in Schemes 1 and 2. Precursor (arylsulfanyl)thiazolidinediones **4** were best prepared from reaction of 5-bromothiazolidine-2,4-dione[17] with aryl thiols **3** using either lithium (bis)trimethylsilylamide in THF (method A) or sodium carbonate in water (method B). Oxidation of **4** to the (arylsulfonyl)thiazolidinediones **5** could be accomplished using several different oxidation procedures, including hydrogen peroxide/acetic acid (method

Results and Discussion

The antidiabetic activity of analogues of **1** and **2** was assessed orally in the db/db mouse,[18] a model of type 2 diabetes. These mice are obese, are glucose intolerant, and have fasting hyperglycemia sometimes accompanied

Table 1. (Arylsulfanyl)thiazolidindiones

| | | | | | | db/db mouse % decrease, glucose[b] | |
| | | | | | | 100 | 20 |
compd	Ar	Ar′	synthesis methods	formula	mp (°C)	(mg/kg/day)	(mg/kg/day)
9	4-methylphenyl	4-chlorophenyl	A, H, I	$C_{19}H_{14}ClNO_2S_2$	108−109	27	nt
10	phenyl	4-chlorophenyl	B, H, I	$C_{18}H_{12}ClNO_2S_2$	87−88	a	nt
11	4-fluorophenyl	4-chlorophenyl	B, H, I	$C_{18}H_{11}ClFNO_2S_2$	116−117	a	nt
12	2-pyridyl	4-chlorophenyl	A, H, I	$C_{17}H_{11}ClN_2O_2S_2$	124−125	a	nt
13	2-quinolyl	4-chlorophenyl	A, H, I	$C_{21}H_{13}ClN_2O_2S_2$	163−165	a	nt
14	4-chlorophenyl	4-chlorophenyl	B, H, J	$C_{18}H_{11}Cl_2NO_2S_2$	146−147	24	nt
15	2-(6-methyl)pyridyl	4-chlorophenyl	A, H, J	$C_{18}H_{13}ClN_2O_2S_2$	147−148	a	nt
BM 13.0907						30	nt
A						21	nt
ciglitazone[c]						32[d]	a

[a] Less than 15% decrease at dose tested. [b] All values for the drug-treated groups, other than a or nt (not tested), are significant vs vehicle-treated mice: $p < 0.05$. [c] Reference standard. [d] Mean of 38 experiments.

by hyperinsulinemia.[18] Traditional hypoglycemic agents, the sulfonylureas, which exert their effect primarily through stimulation of insulin release, are not effective in this model, even at high doses.[19] Analogues from series **1** and **2** were evaluated for 4 days in the db/db mouse at 100 mg/kg/day and, if sufficient potency was seen, at 20 mg/kg/day (see Tables 1 and 2 for results). In this assay, plasma glucose levels of the drug-treated group were measured relative to a vehicle-treated control group. A 50−60% decrease in the plasma glucose levels generally is a reduction that normalizes plasma glucose (i.e. treated animals with this decrease have the same plasma glucose levels as nondiabetic controls).

A quick examination of Tables 1 and 2 reveals that the sulfonylthiazolidinediones were much more potent as antihyperglycemic agents than the corresponding sulfanylthiazolidinediones. Most of the compounds in Table 1 were not effective at 100 mg/kg with the exception of two analogues, **9** and **14**, that had modest potency. Therefore, most of our effort was directed toward the sulfonylthiazolidinediones series in Table 2. The reference compounds, BM 13.0907 and sulfonylthiazolidinedione **A**, were approximately equipotent to ciglitazone in the db/db mouse (Table 1).

The compounds in Table 2 varied mostly in the substituents attached to the phenyl rings of Ar and Ar′, although there were several congeners where Ar was a pyridyl group. More than 80% of the analogues in Table 2 showed a statistically significant drop in plasma glucose at the 100 mg/kg dose, and almost one-half of the compounds normalized glucose at this dose. Approximately one-fifth of the analogues showed a statistically significant glucose drop at the 20 mg/kg dose.

With regard to substituent effects on the 3-propynyl phenyl ring (Ar′), 4-halogen substitution generally resulted in the more potent analogues. For example, examination of the phenylsulfonyl series (Ar = phenyl), 4-halophenyl analogues, **20** (4-Cl), **27** (4-F), and **36** (4-Br) normalized plasma glucose, while **21** (unsubstituted), **29** (4-methyl) and **45** (4-methoxy) were much less potent. The position of the halogen on the phenyl ring was also crucial since 2-chloro and 3-chloro analogues (**46** and **50**, respectively) had less activity than the

4-chloro compound **20**. 4-Trifluoromethyl (**40**) and 4-trifluoromethoxy (**57**) also appeared to be good substituents. Disubstitution on Ar′ did not enhance potency, although there were only a few examples, e.g. 3,5-bis-CF₃ **49**) and 3,4-difluoro (**58**).

Substituent effects on the phenylsulfonyl moiety (Ar) of **2** were less clear. Generally, as previously discussed for Ar′, 4-halogen substitution on Ar was preferable. For example, in the Ar′ = 4-chlorophenyl series, compounds **17** (4-F), **24** (4-Cl) and **26** (4-Br) normalized plasma glucose at 100 mg/kg. The 4-methyl (**16**), 4-methoxy (**32**), and 3-methyl (**43**) congeners were less effective, although these analogues did have good potency at this dose. In general, however, the substituent on Ar had less of an impact than the same substituent on Ar′. The substituted phenylsulfonyl compounds were also more potent than 2-naphthylsulfonyl analogues (**19** and **33**).

Several 2-pyridinesulfonyl derivatives (Ar = 2-pyridine) were prepared. Two analogues in particular, **18** and **56**, normalized plasma glucose at 100 mg/kg and showed robust activity at the 20 mg/kg dose. However, substitution of a methyl group onto the 6-position of the pyridine ring (**61**) greatly diminished potency. Likewise, the 2-quinoline derivative **60** was not nearly as effective as the two 2-pyridine analogues.

Several of the more potent compounds from series **2** were further evaluated in another diabetic model, the genetically obese hyperglycemic ob/ob mouse.[18] This model exhibits many of the metabolic abnormalities of type 2 diabetes including obesity, hyperglycemia, abnormal insulin secretion, hyperinsulinemia, and insulin resistance. The analogues from series **2** were administered orally for 4 days at 50 or 100 mg/kg/day (see Table 3). In this assay, plasma glucose and insulin levels of the drug-treated group were measured relative to a vehicle-treated control group. A 40−60% decrease in plasma glucose levels and a 70−90% decrease in plasma insulin levels were equivalent to the levels of nondiabetic animals. As in the previous model, the (arylsulfonyl)thiazolidinediones outperformed the reference standards, ciglitazone and BM 13.907. The four analogues tested at the 50 mg/kg dose showed a robust response at lowering both glucose and insulin levels. Compounds **24** (Ar = 4-chlorophenyl, Ar′ = 4-chlorophe-

Table 2. (Arylsulfonyl)thiazolidinediones
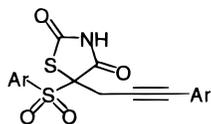
compd	Ar	Ar'	synthesis methods	formula	mp (°C)	db/db mouse % decrease, glucose[b] 100 (mg/kg/day)	20 (mg/kg/day)
16	4-methylphenyl	4-chlorophenyl	A, C, G, H, K	$C_{19}H_{14}ClNO_4S_2$	172–174	35	nt
17	4-fluorophenyl	4-chlorophenyl	A, C, H, L	$C_{18}H_{11}ClFNO_4S_2$	176–177	79	31
18	2-pyridyl	4-chlorophenyl	A, E, H, L	$C_{17}H_{11}ClN_2O_4S_2$	140–141	55	38
19	2-naphthyl	4-chlorophenyl	A, C, H, L	$C_{22}H_{14}ClNO_4S_2$	190–191	20	nt
20	phenyl	4-chlorophenyl	B, D, H, L	$C_{18}H_{12}ClNO_4S_2$	92–93	52	21
21	phenyl	phenyl	B, D, H, L	$C_{18}H_{13}NO_4S_2$	130–131	*a*	nt
22	4-methylphenyl	phenyl	A, C, H, L	$C_{19}H_{15}NO_4S_2$	143–145	43	23
23	4-chlorophenyl	phenyl	B, C, H, L	$C_{18}H_{12}ClNO_4S_2$	144–146	36	nt
24	4-chlorophenyl	4-chlorophenyl	B, C, H, L	$C_{18}H_{11}Cl_2NO_4S_2$	172–173	70	18
25	4-fluorophenyl	phenyl	B, C, H, L	$C_{18}H_{12}FNO_4S_2$	135–141	26	nt
26	4-bromophenyl	4-chlorophenyl	B, D, H, L	$C_{18}H_{11}BrClNO_4S_2$	171–175	69	*a*
27	phenyl	4-fluorophenyl	B, D, H, L	$C_{18}H_{12}FNO_4S_2$	171–172	58	*a*
28	4-methylphenyl	4-fluorophenyl	A, C, H, L	$C_{19}H_{14}FNO_4S_2$	154–156	65	*a*
29	phenyl	4-methylphenyl	A, C, H, L	$C_{19}H_{15}NO_4S_2$	168–169	*a*	nt
30	4-methylphenyl	4-methylphenyl	A, C, H, L	$C_{20}H_{17}NO_4S_2$	195–196	28	nt
31	4-bromophenyl	phenyl	B, D, H, L	$C_{18}H_{12}BrNO_4S_2$	172–176	43	*a*
32	4-methoxyphenyl	4-chlorophenyl	B, D, H, L	$C_{19}H_{14}ClNO_5S_2$	134–136	45	*a*
33	2-naphthyl	phenyl	A, C, H, L	$C_{22}H_{15}NO_4S_2$	174–177	24	nt
34	4-methoxyphenyl	phenyl	B, D, H, L	$C_{19}H_{15}NO_5S_2$	142–143	21	nt
35	4-methylphenyl	4-(trifluoromethyl)phenyl	A, C, H, L	$C_{20}H_{14}F_3NO_4S_2$	78–80	36	*a*
36	phenyl	4-bromophenyl	B, D, H, L	$C_{18}H_{12}BrNO_4S_2$	81–83	53	*a*
37	4-methylphenyl	4-methoxyphenyl	A, C, H, L	$C_{20}H_{17}NO_5S_2$	80–82	*a*	nt
38	4-methylphenyl	4-bromophenyl	A, C, H, L	$C_{19}H_{14}BrNO_4S_2$	161–162	51	23
39	3-methylphenyl	phenyl	B, D, H, L	$C_{19}H_{15}NO_4S_2$	128–130	48	*a*
40	phenyl	4-(trifluoromethyl)phenyl	B, D, H, L	$C_{19}H_{12}F_3NO_4S_2 \cdot 0.53H_2O$	80–81	59	*a*
41	4-fluorophenyl	4-fluorophenyl	B, C, H, L	$C_{18}H_{11}F_2NO_4S_2$	177–181	57	25
42	4-chlorophenyl	4-fluorophenyl	B, C, H, L	$C_{18}H_{11}ClFNO_4S_2$	171–173	54	*a*
43	3-methylphenyl	4-chlorophenyl	B, D, H, L	$C_{19}H_{14}ClNO_4S_2$	136–138	33	nt
44	4-methylphenyl	3-chlorophenyl	A, C, H, L	$C_{19}H_{14}ClNO_4S_2$	70–72	30	nt
45	phenyl	4-methoxyphenyl	B, D, H, L	$C_{19}H_{15}NO_5S_2 \cdot 0.71H_2O$	161–162	25	nt
46	phenyl	2-chlorophenyl	B, D, H, L	$C_{18}H_{12}ClNO_4S_2$	162–163	*a*	nt
47	4-methylphenyl	2-chlorophenyl	A, C, H, L	$C_{19}H_{14}ClNO_4S_2$	160–161	30	nt
48	phenyl	3,5-bis(trifluoromethyl)phenyl	B, D, H, L	$C_{20}H_{11}F_6NO_4S_2$	226–229	54	21
49	4-methylphenyl	3,5-bis(trifluoromethyl)phenyl	A, C, H, L	$C_{21}H_{13}F_6NO_4S_2$	207–209	22	nt
50	phenyl	3-chlorophenyl	B, D, H, L	$C_{18}H_{12}ClNO_4S_2$	107–108	*a*	nt
51	4-fluorophenyl	4-bromophenyl	B, C, H, L	$C_{18}H_{11}BrFNO_4S_2$	155–157	70	*a*
52	4-chlorophenyl	4-bromophenyl	B, D, H, L	$C_{18}H_{11}BrClNO_4S_2$	160–161	68	*a*
53	4-fluorophenyl	4-(trifluoromethyl)phenyl	B, C, H, L	$C_{19}H_{11}F_4NO_4S_2$	143–145	52	*a*
54	4-chlorophenyl	4-(trifluoromethyl)phenyl	B, D, H, L	$C_{19}H_{11}ClF_3NO_4S_2$	144–145	37	nt
55	4-bromophenyl	4-fluorophenyl	B, D, H, L	$C_{18}H_{11}BrFNO_4S_2$	186–188	64	*a*
56	2-pyridyl	4-fluorophenyl	A, E, H, L	$C_{17}H_{11}FN_2O_4S_2$	92–94	67	36
57	4-fluorophenyl	4-(trifluoromethoxy)phenyl	B, C, H, L	$C_{19}H_{11}F_4NO_5S_2$	133–135	56	*a*
58	4-fluorophenyl	3,4-difluorophenyl	B, C, H, L	$C_{18}H_{10}F_3NO_4S_2$	130–133	33	nt
59	4-fluorophenyl	4-(methylthio)phenyl	B, C, H, L	$C_{19}H_{14}FNO_4S_3$	74–76	*a*	nt
60	2-quinolyl	4-chlorophenyl	F, H, L	$C_{21}H_{13}ClN_2O_4S_2$	191–192	nt	*a*
61	6-methyl-2-pyridyl	4-chlorophenyl	F, H, M	$C_{18}H_{13}ClN_2O_4S_2$	104–106	*a*	*a*
62	2-pyridyl	3,5-bis(trifluoromethyl)phenyl	A, E, H, M	$C_{19}H_{10}F_6N_2O_4S_2$	150–152	nt	*a*

a Less than 15% decrease at dose tested. *b* All values from drug-treated mice, other than *a* or nt (not tested), are significant vs vehicle-treated mice: $p < 0.05$.

Table 3

compd	dose (mg/kg/day)	4 day ob/ob mouse % decrease, glucose[b]	% decrease, insulin[b]
20	100	40	65
24	50	47	56
26	50	36	69
28	50	30	30
56	50	44	54
BM 13.0907	50	*a*	54
ciglitazone[c]	100	43	39

a Less than 15% decrease at dose tested. *b* All values from drug treated-mice, other than *a*, are significant vs vehicle-treated mice: $p < 0.05$. *c* Reference standard.

nyl) and **56** (Ar = 2-pyridyl, Ar'= 4-fluorophenyl) caused a near normalization of these levels.

Compound **20** (Ar = phenyl, Ar'= 4-chlorophenyl) was further evaluated in a third animal model of insulin resistance, the obese Zucker rat. Compound **20** significantly improved the glucose tolerance of these animals at the 20 mg/kg dose level (Figure 1). Furthermore, **20** at 100 mg/kg had no effect on plasma glucose nor on glucose tolerance in normal rats fasted for 18 h (data not shown).

In summary, novel 5-(3-aryl-2-propynyl)-5-(arylsulfonyl)thiazolidine-2,4-diones and 5-(3-aryl-2-propynyl)-5-(arylsulfanyl)thiazolidine-2,4-diones were evaluated as antihyperglycemic agents. Three different animal models of insulin resistance were used in this evaluation. Half of the sulfonylthiazolidinediones (**2**) prepared normalized plasma glucose at the 100 mg/kg dose in the obese, insulin resistant db/db mouse model, and these analogues were more potent than the corresponding sulfanylthiazolidinedione congeners (**1**). Several compounds from series **2** were also effective at lowering glucose and insulin in the obese, insulin resistant ob/
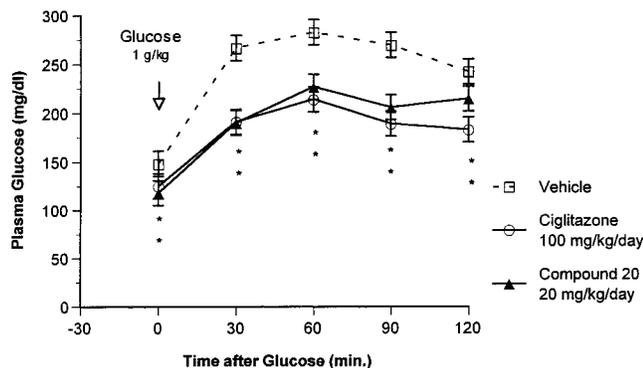
Figure 1. Effect of **20** on SCGTT in fasted Zucker rats. Compounds (po, 4 days) or vehicle (2% Tween 80/saline) were administered 1 h prior to a subcutaneous administration of D-glucose. Blood samples were collected from the tail tip of unanesthetized rats, and plasma glucose levels were determined by an Abbott VP analyzer. $N = 5$ rats per group. *$p < 0.05$ vs vehicle group using Dunnett's two-tailed *t*-test.

ob mouse. One compound (**20**) was tested in the obese Zucker rat and was active at 20 mg/kg. Finally, these compounds appear to ameliorate insulin resistance and normalize plasma glucose levels but have little or no effect on plasma glucose in normal rodents.

Experimental Section

Chemistry. Melting points were determined on an Electrothermal capillary melting point apparatus and are not corrected. Proton magnetic resonance (¹H NMR) spectra were recorded at 200 (Varian XL-200), 300 (VXR-300), or at 400 MHz (Bruker AM-400 or VXR-400). Infrared spectra were obtained on either a Beckman Accu Lab 2 or a Perkin-Elmer model 781 spectrophotometer as KBr pellets, as thin films on sodium chloride plates, or as solutions in chloroform and are reported as reciprocal centimeters (cm⁻¹). Electron impact (EI, IE = 70 eV) and chemical ionization (CI, isobutane reagent gas) mass spectra were recorded on a Finnigan model 8230 spectrometer. Fast atom bombardment (FAB) were recorded on a Kratos MS50. Analyses (C, H, N) were carried out on a modified Perkin-Elmer model 240 CHN analyzer. Analytical results for elements were within $\pm$ 0.4% of the theoretical values. Flash chromatography was carried out according to the procedure of Still.[20] Thin layer analyses were done on E. Merck silica gel 60 F-254 plates of 0.25 mm thickness. 2-Methyl-6-mercaptopyridine was prepared according to the procedure of Dunn et al.[21] All commercial reagents and solvents were used as received unless otherwise noted.

Method A. 5-(Toluene-4-sulfanyl)thiazolidine-2,4-dione (4, Ar = 4-Methylphenyl). To a solution of 5-bromothiazolidine-2,4-dione[17] (5.0 g, 25.5 mmol) and *p*-thiocresol [(**3**, Ar = 4-methylphenyl), 3.17 g, 25.5 mmol] in dry THF (200 mL) at -78 °C was added lithium bis(trimethylsilyl)amide (1.0 M in hexanes, 56 mL, 56 mmol) dropwise. After 30 min the reaction mixture was warmed to room temperature. After an additional hour, 2 N HCl was added to pH = 1. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 300 mL). The combined organic phase was dried (MgSO₄), concentrated, and flash chromatographed (3:2 petroleum ether:ethyl acetate) to provide the title compound as a white solid (4.4 g, 72%): mp 124–126 °C; NMR (CDCl₃) δ 8.08 (s, 1H, N*H*), 7.48 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.18 (d, $J = 8.7$ Hz, 2H, Ar*H*), 5.32 (s, 1H, C*H*); MS (EI) 239 (MI, 90), 196 (18), 123 (100).

Method A. 5-(Pyridine-2-sulfanyl)thiazolidine-2,4-dione (4, Ar = 2-Pyridyl). To a solution of 5-bromothiazolidine-2,4-dione[17] (28.24 g, 0.144 mol) and 2-mercaptopyridine [(**3**, Ar = 2-pyridyl), 16.0 g, 0.144 mol] in dry THF (200 mL) at -78 °C was added lithium bis(trimethylsilyl)amide (1.0 M in hexanes, 317 mL, 0.317 mol) dropwise over a 40 min period.

After 30 min the reaction mixture was warmed to room temperature. After an additional 3 h, 10% HCl was added to pH = 1. The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 500 mL). The combined organic phase was washed with water (500 mL) and brine (500 mL), dried (MgSO₄), and concentrated to provide the title compound as a green solid (30.45 g, 93%): mp 118–120 °C; NMR (DMSO-d_6) δ 12.35 (s, 1H, N*H*), 8.39 (d, $J = 5.3$ Hz, 1H, Pyr*H*), 7.69 (dd, $J = 7.3$, 8.3 Hz, 1H, Pry*H*), 7.42 (d, $J = 8.3$ Hz, 1H, Pyr*H*), 7.19 (dd, $J = 5.3, 7.3$ Hz, 1H, Pyr*H*), 6.31 (s, 1H, C*H*); MS (EI) 226 (MI, 12), 155 (10), 79 (100). Anal. (C₈H₆N₂O₂S₂) C, H, N.

Method B. 5-(4-Fluorophenylsulfanyl)thiazolidine-2,4-dione (4, Ar = 4-Fluorophenyl). 5-Bromothiazolidine-2,4-dione[17] (15.0 g, 76.5 mmol) was added to a 0 °C, mechanically stirred solution of 4-fluorothiophenol [(**3**, Ar = 4-fluorophenyl), 9.8 g, 76.5 mmol], sodium carbonate (27.75 g, 262 mmol) and water (120 mL). After 16 h, the reaction mixture was diluted with water (500 mL), acidified with concentrated HCl to pH = 1 and filtered. The resultant solid was washed with water and petroleum ether and dried in vacuo to provide the title compound as a white solid (14.05 g, 75%): mp 99–100 °C; NMR (DMSO-d_6) δ 12.14 (s, 1H, N*H*), 7.66 (t, $J = 8.0$ Hz, 2H, Ar*H*), 7.29 (t, $J = 8.5$ Hz, 2H, Ar*H*), 6.05 (s, 1H, C*H*); MS (EI) 243 (MI, 100), 200 (30), 128 (60), 127 (50). Anal. (C₉H₆FNO₂S₂) C, H, N.

Method C. 5-(4-Fluorophenylsulfonyl)thiazolidine-2,4-dione, (5, Ar = 4-Fluorophenyl). A 30% hydrogen peroxide solution (50.4 mL, 0.489 mol) was added dropwise over a 1 h, 20 min period to a mechanically stirred solution of 5-(4-fluorophenylsulfanyl)thiazolidine-2,4-dione [(**4**, Ar = 4-fluorophenyl), 11.9 g, 48.9 mmol] in glacial acetic acid (457 mL) at 60 °C. After an additional 3 h, the reaction mixture was cooled to ambient temperatures and concentrated. The residue was partitioned between water and ethyl acetate. The ethyl acetate layer was dried (MgSO₄) and concentrated to provide the title compound as a white solid (10.9 g, 81%): mp 190–196 °C; NMR (DMSO-d_6) δ 12.78 (broad s, 1H, N*H*) 8.00 (m, 2H, Ar*H*), 7.58 (t, $J = 8.9$ Hz, 2H, Ar*H*), 6.70 (s, 1H, C*H*); MS (CI) 276 (M + H, 100). Anal. (C₉H₆FNO₄S₂) C, H, N.

Method D. 5-(Benzenesulfonyl)thiazolidine-2,4-dione, (5, Ar = Phenyl). A solution of 5-(benzenesulfanyl)thiazolidine-2,4-dione [(**4**, Ar = phenyl), 10.0 g, 41.8 mmol] in methanol (105 mL) was added to a mechanically stirred suspension of oxone (51.4 g, 83.6 mmol) in water (210 mL) at 0 °C. The suspension was immediately warmed to room temperature. After 3.5 h, the reaction was diluted with water (1.5 L) and the solid was filtered. The solid was washed with water and dried in vacuo to provide the title compound as a white solid (8.31 g, 73%): mp 130–133 °C; NMR (CDCl₃) δ 8.07 (s, 1H, N*H*), 7.98 (d, $J = 7.2$ Hz, 2H, Ar*H*), 7.78 (t, $J = 7.5$ Hz, 1H, Ar*H*), 7.67 (t, $J = 8.1$ Hz, 2H, Ar*H*), 5.44 (s, 1H C*H*); MS (EI) 225 (MI, 24), 182 (18), 153 (12), 110 (100).

Method E. 5-(Pyridine-2-sulfonyl)thiazolidine-2,4-dione (5, Ar = 2-Pyridyl). *m*-Chloroperbenzoic acid (25.7 g, 146 mmol) was added portionwise over 30 min to a stirred suspension of 5-(pyridine-2-sulfanyl)thiazolidine-2,4-dione [(**4**, Ar = 2-pyridyl), 15.0 g, 66.3 mmol] in chloroform (600 mL) at room temperature. After 18 h, more *m*-chloroperbenzoic acid (4.65 g, 26.4 mmol) was added, and the reaction mixture was stirred an additional 6 h. The reaction mixture was cooled in an ice bath, and the resultant solid (18.7 g) was filtered. A 10 g portion of the resultant solid was purified by flash chromatography (9:1 CH₂Cl₂:acetonitrile) to provide the title compound as a white solid (4.18 g, 46%): mp 129–131 °C; NMR (DMSO-d_6) δ 12.00 (broad s, 1H, N*H*), 8.85 (d, $J = 4.0$ Hz, 1H, Pyr*H*), 8.23 (dd, $J = 6.1$, 7.9 Hz, 1H, Pyr*H*), 8.12 (d, $J = 7.9$ Hz, 1H, Pyr*H*), 7.85 (dd, $J = 4.0$, 6.1 Hz, 1H, Pyr*H*), 6.79 (s, 1H, C*H*); MS (EI) 258 (MI, 8), 215 (55), 123 (22), 78 (100).

Method F. 5-(Quinoline-2-sulfonyl)thiazolidine-2,4-dione, (5, Ar = 2-Quinolyl). A 30% aqueous hydrogen peroxide solution (10 0.7 mL, 104 mmol) was added dropwise to a stirred solution of 2-quinolinethiol [(**3**, Ar = 2-quinolyl),

8.0 g, 49.6 mmol] in 2.5% aqueous NaOH (229 mL) and ethanol (229 mL). After 1 h the reaction mixture was concentrated to provide a white solid (8.34 g) which contained mainly sodium 2-naphthalenesulfinate. A 7.0 g portion of this compound ($\leq$32.5 mmol) was added to a solution of 5-bromothiazolidine-2,4-dione[17] (6.38 g, 32.5 mmol) in dry DMF (53 mL), and the resultant solution was stirred at room temperature for 4 h. The DMF was removed in vacuo, and water (400 mL) was added to the residue. The water phase was extracted with ethyl acetate (2 × 400 mL), and the combined ethyl acetate phase was dried (brine) and concentrated. The crude product was flash chromatographed (gradient: 98:2 to 97:3 CH_2Cl_2:2-propanol) to provide the title compound as a yellow solid (1.1 g, 9%): mp 168−169 °C; NMR (DMSO-d_6) δ 12.9 (broad s, 1H, N*H*), 8.85 (d, J = 8.8 Hz, 1H, Ar*H*), 8.24 (d, J = 8.1 Hz, 1H, Ar*H*), 8.16 (d, J = 8.7 Hz, 2H, Ar*H*), 8.02 (dd, J = 6.9, 8.3 Hz, 1H, Ar*H*), 7.89 (dd, J = 6.9, 8.1 Hz, 1H, Ar*H*), 6.95 (s, 1H, C*H*); MS (EI) 308 (MI, 10), 265 (8), 145 (18), 129 (100), 128 (75). Anal. ($C_{12}H_8N_2O_4S_2$) C, H, N.

Method G. *N*-(Triphenylmethyl)-5-(toluene-4-sulfonyl)thiazolidine-2,4-dione, (6, Ar = 4-Methylphenyl). Triphenylmethyl chloride (2.67 g, 9.58 mmol) was added to a stirred, room-temperature solution of 5-(toluene-4-sulfonyl)-thiazolidine-2,4-dione [(5, Ar = 4-methylphenyl), 1.30 g, 4.79 mmol], triethylamine (0.67 mL, 4.79 mmol), and dichloromethane (6.5 mL). After 1 h, water (300 mL) was added and the organic material was extracted with ethyl acetate (2 × 200 mL). The combined extracts were dried (brine, $MgSO_4$), concentrated, and purified by flash chromatography (4:1 petroleum ether:ethyl acetate) to provide the title compound as a white solid (1.1 g, 45%): mp 105−110 °C; NMR (CDCl₃) δ 7.85 (d, J = 8.3 Hz, 2H, Ar*H*), 7.48 (d, J = 8.1 Hz, 6H, CPh₃*H*), 7.38 (d, J = 8.3 Hz, 2H, Ar*H*), 7.23 (m, 9H, CPh₃*H*), 5.13 (s, 1H, C*H*), 2.46 (s, 3H, C*H₃*).

Method H. [3-(4-Chlorophenyl)prop-2-ynyl]Bromide (8, Ar′ = 4-Chlorophenyl). A suspension of *p*-iodochlorobenzene [(7, Ar′ = 4-chlorophenyl), 7.15 g, 30.0 mmol], propargyl alcohol (1.75 mL, 30 mmol), dichlorobis(triphenylphosphine)-palladium(II) (0.21 g, 0.3 mmol), copper(I) iodide (29 mg, 0.15 mmol), and diethylamine (50 mL) was stirred under a N₂ atmosphere at room temperature, and dissolution occurred within 20 min. After 5 h, the diethylamine was removed, and the crude product was partitioned between water and ether. The ether phase was dried (brine), concentrated, and flash chromatographed (4:1 petroleum ether:ethyl acetate) to provide 3-(4-chlorophenyl)prop-2-yn-ol (4.09 g, 82%). This compound (3.47 g, 20.83 mmol) was suspended in dry ether (12 mL), and pyridine (0.42 mL) was added. The reaction mixture was cooled in an ice bath, and a solution of phosphorus tribromide (1.0 mL, 10.42 mmol) in dry ether (6 mL) was added dropwise over a 15 min period. The reaction mixture was then stirred at room temperature for 2.5 h and cooled in an ice bath, and crushed ice was added. The reaction mixture was added to water (200 mL) and extracted with ether (200 mL). The ether phase was washed with water, saturated aqueous NaHCO₃, and brine. The extract was concentrated and purified by flash chromatography (9:1 petroleum ether:ethyl acetate) to provide the title compound as a white solid (3.38 g, 86%): mp 41−43 °C; NMR (CDCl₃) δ 7.37 (d, J = 8.7 Hz, 2H, Ar*H*), 7.27 (d, J = 8.7 Hz, 2H, Ar*H*), 4.16 (s, 2H, C*H₂*).

Method I. 5-[3-(4-Chlorophenyl)prop-2-ynyl]-5-(toluene-4-sulfanyl)thiazolidine-2,4-dione (9). Sodium hydride (80% dispersion in mineral oil, 0.63 g, 21.1 mmol) was added to a solution of 5-(toluene-4-sulfanyl)thiazolidine-2,4-dione [(4, Ar = 4-methylphenyl), 1.75 g, 8.44 mmol] in dry THF (9 mL) at 0 °C under a dry N₂ atmosphere. After 10 min, a solution of [3-(4-chlorophenyl)prop-2-ynyl] bromide [(8, Ar′ = 4-chlorophenyl), 1.94 g, 8.44 mmol] in dry THF (9 mL) was added over a 30 min period. After 2.5 h, the reaction mixture was concentrated and dilute aqueous HCl was added (85 mL). The organics were extracted with ethyl acetate (2 × 85 mL), and the extracts were dried (brine), concentrated, purified by flash chromatography (98:2 CH_2Cl_2:2-propanol), and triturated with petroleum ether to provide the title compound as a white solid

(1.25 g, 38%): mp 108−109 °C; NMR (DMSO-d_6) δ 12.27 (s, 1H, N*H*), 7.46 (d, J = 8.5 Hz, 2H, Ar*H*, Ar′*H*), 7.39 (d, J = 8.7 Hz, 1H, Ar′*H*), 7.27 (d, J = 7.9 Hz, 1H, Ar*H*), 3.48 (d, J = 17.3 Hz, 1H, C*H₂*), 3.32 (d, J = 17.3 Hz, 1H, C*H₂*), 2.34 (s, 3H, C*H₃*); MS (EI) 387 (MI, 5), 389 (2), 124 (85), 91 (100). Anal. Calcd for $C_{19}H_{14}ClNO_2S_2$: C, H, N.

Method J. 5-[3-(4-Chlorophenyl)prop-2-ynyl]-5-(4-chlorophenylsulfanyl)thiazolidine-2,4-dione (14). *n*-Butyllithium (2.5 M in hexanes, 12.3 mL, 30.8 mmol) was added to a solution of 5-(4-chlorophenylsulfanyl)thiazolidine-2,4-dione [(4, Ar = 4-chlorophenyl), 4.0 g, 15.4 mmol] in dry THF (195 mL) at −78 °C under a dry N₂ atmosphere over a 40 min period. After an additional 30 min, a solution of [3-(4-chlorophenyl)prop-2-ynyl] bromide [(8, Ar′ = 4-chlorophenyl), 3.53 g, 15.4 mmol] in dry THF (65 mL) was added over a 12 min period. After 10 min, the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was added to saturated aqueous ammonium chloride (1 L) and extracted with ethyl acetate (800 mL). The extracts were dried (brine), concentrated, and purified by flash chromatography (4:1 petroleum ether:ethyl acetate) to provide the title compound as a white solid (2.58 g, 41%): mp 144−146 °C: NMR (DMSO-d_6) δ 12.37 (s, 1H, N*H*), 7.59 (d, J = 8.5 Hz, 2H, Ar*H*), 7.56 (d, J = 8.7 Hz, 2H, Ar*H*), 7.46 (d, J = 8.5 Hz, 2H, Ar′*H*), 7.40 (d, J = 8.3 Hz, 2H, Ar′*H*), 3.52 (d, J = 17.3 Hz, 1H, C*H₂*), 3.35 (d, J = 17.3 Hz, 1H, C*H₂*); MS (EI) 407, 409, 411 (MI, 5), 364, 366 (8), 264 (30), 193 (40), 149 (100), 143 (20). Anal. Calcd for $C_{18}H_{11}Cl_2NO_2S_2$: C, H, N.

Method K. 5-[3-(4-Chlorophenyl)prop-2-ynyl]-5-(toluene-4-sulfonyl)thiazolidine-2,4-dione (16). Sodium hydride (80% dispersion in mineral oil, 93 mg, 3.10 mmol) was added to a solution of *N*-(triphenylmethyl)-5-(toluene-4-sulfonyl)thiazolidine-2,4-dione [(6, Ar = 4-methylphenyl), 1.06 g, 2.07 mmol] in dry DMF (9 mL) at 0 °C under a dry N₂ atmosphere. After 20 min, [3-(4-chlorophenyl)prop-2-ynyl] bromide [(8, Ar′ = 4-chlorophenyl), 0.52 g, 2.27 mmol] was added, and the reaction mixture was stirred an additional 20 min at 0 °C. Saturated aqueous NH₄Cl (60 mL) was added, followed by water (60 mL). After 10 min of stirring, the solid was filtered, washed with water, and triturated with petroleum ether to provide *N*-(triphenylmethyl)-5-[3-(4-chlorophenyl)prop-2-ynyl]-5-(toluene-4-sulfonyl)thiazolidine-2,4-dione as a gray solid (1.16 g, 90%): mp 221−223 °C; NMR (CDCl₃) δ 7.80 (d, J = 8.2 Hz, 2H, Ar*H*), 7.45 (d, J = 7.5 Hz, 6H, CPh₃*H*), 7.35 (d, J = 8.2 Hz, 2H, Ar*H*), 7.14 (m, 11H, Ar′*H*, CPh₃*H*), 6.98 (d, J = 8.5 Hz, 2H, Ar′*H*), 3.29 (d, J = 16.7 Hz, 1H, C*H₂*), 3.12 (d, J = 16.7 Hz, 1H, C*H₂*), 2.46 (s, 3H, C*H₃*). Trifluoroacetic acid (0.32 mL, 4.07 mmol) was added to a room temperature, stirred suspension of this compound (1.29 g, 1.94 mmol) in CH_2Cl_2 (2 mL). Dissolution occurred immediately. After 1 h, the reaction mixture was added to water (200 mL) and extracted with ethyl acetate (200 mL). The ethyl acetate phase was washed with water and brine and then concentrated. The crude product was purified by flash chromatography (95:5 CH_2Cl_2:2-propanol) and then triturated in petroleum ether to provide the title compound as a off-white solid (0.52 g, 64%): mp 172−174 °C; NMR (CDCl₃) δ 8.00 (s, 1H, N*H*) 7.85 (d, J = 8.3 Hz, 2H, Ar*H*), 7.41 (d, J = 8.3 Hz, 2H, Ar*H*), 7.26 (s, 4H, Ar′*H*), 3.65 (d, J = 17.1 Hz, 1H, C*H₂*), 3.33 (d, J = 17.1 Hz, 1H, C*H₂*), 2.49 (s, 3H, C*H₃*); MS (CI) 420 (M + H, 58), 422 (M + H, 24), 265 (40), 267 (26), 157 (100). Anal. Calcd for $C_{19}H_{14}ClNO_4S_2$: C, H, N.

Method L. 5-[3-(4-Chlorophenyl)prop-2-ynyl]-5-(4-fluorobenzenesulfonyl)thiazolidine-2,4-dione (17). Sodium hydride (80% dispersion in mineral oil, 0.55 g, 18.2 mmol) was added to a solution of 5-(4-fluorophenylsulfonyl)thiazolidine-2,4-dione [(5, Ar = 4-fluorophenyl), 2.0 g, 7.27 mmol] in dry THF (12 mL) at 0 °C under a dry N₂ atmosphere. After 1.5 h, a solution of [3-(4-chlorophenyl)prop-2-ynyl] bromide [(8, Ar′ = 4-chlorophenyl), 1.67 g, 7.27 mmol] in dry THF (12 mL) was added over a 25 min period. After 20 h, the reaction mixture was concentrated and dilute aqueous HCl was added (100 mL). The organics were extracted with ethyl acetate (3 × 100 mL), and the extracts were dried (brine), concentrated,

purified by flash chromatography (97:3 CH$_2$Cl$_2$:methanol), and triturated with petroleum ether to provide the title compound as a white solid (0.99 g, 32%). The solid was further purified by recrystallization from ethanol: water: mp 176−177 °C; NMR (DMSO-d_6) δ 13.0 (broad s, 1H, NH), 8.02 (m, 1H, ArH), 7.59 (t, J = 8.9 Hz, 1H, ArH), 7.45 (d, J = 8.5 Hz, 1H, Ar′H), 7.35 (d, J = 8.5 Hz, 1H, Ar′H), 3.66 (d, J = 17.5 Hz, 1H, CH_2), 3.50 (d, J = 17.3 Hz, 1H, CH_2); MS (−DCI) 422 (M − H, 22), 424 (M − H, 16), 263 (100), 265 (40). Anal. Calcd for C$_{18}$H$_{11}$ClFNO$_4$S$_2$: C, H, N.

Method L. 5-[3-(4-Chlorophenyl)prop-2-ynyl]-5-(pyridine-2-sulfonyl)thiazolidine-2,4-dione (18). Sodium hydride (80% dispersion in mineral oil, 0.32 g, 10.8 mmol) was added to a solution of 5-(pyridine-2-sulfonyl)thiazolidine-2,4-dione [(**5**, Ar = 2-pyridyl), 1.1 g, 4.30 mmol] in dry THF (7.5 mL) at 0 °C under a dry N$_2$ atmosphere. After 10 min, a solution of [3-(4-chlorophenyl)prop-2-ynyl] bromide [(**8**, Ar = 4-chlorophenyl), 0.99 g, 4.30 mmol] in dry THF (7.5 mL) was added, over a 30 min period. After 27 h at room temperature, the reaction mixture was quenched with saturated aqueous NH$_4$Cl (20 mL), water (120 mL) was added and the organics were extracted with ethyl acetate (2 × 150 mL). The extracts were dried (brine), concentrated, and purified by flash chromatography (gradient: 97:3 to 88:12 CH$_2$Cl$_2$:methanol) to provide the title compound as a yellow solid (0.63 g, 36%): mp 140−141 °C; NMR (DMSO-d_6) δ 13.2 (broad s, 1H, NH), 8.82 (dd, J = 0.6, 4.0 Hz, 1H, Pyr$H$), 8.23 (td, J = 1.6, 7.8 Hz, 1H, Pyr$H$), 8.15 (d, J = 7.9 Hz, 1H, Pyr$H$), 7.87 (ddd, J = 1.1, 5.3, 7.7 Hz, 1H, Pyr$H$), 7.45 (d, J = 8.5 Hz, 1H, Ar′H), 7.35 (d, J = 8.5 Hz, 1H, Ar′H), 3.88 (d, J = 17.2 Hz, 1H, CH_2), 3.74 (d, J = 17.2 Hz, 1H, CH_2); MS (+DCI) 407 (M + H, 50), 409 (M + H, 24), 264 (80), 266 (36), 144 (100). Anal. Calcd for C$_{17}$H$_{11}$ClN$_2$O$_4$S$_2$: C, H, N.

Method M. 5-[3-(4-Chlorophenyl)prop-2-ynyl]-5-(6-methylpyridine-2-sulfonyl)thiazolidine-2,4-dione (61). *n*-Butyllithium (2.5 M in hexanes, 2.77 mL, 6.93 mmol) was added to a solution of 5-(6-methylpyridine-2-sulfonyl)thiazolidine-2,4-dione, [(**5**, 6-methyl-2-pyridyl), 0.92 g, 3.38 mmol] in dry THF (30 mL) at −78 °C under a dry N$_2$ atmosphere over a 20 min period. A solution of [3-(4-chlorophenyl)prop-2-ynyl] bromide [(**8**, Ar′ = 4-chlorophenyl), 3.53 g, 15.4 mmol] in dry THF (10 mL) was added over a 20 min period. The reaction mixture was allowed to warm to room temperature. After 16 h, the reaction mixture was added to saturated aqueous ammonium chloride (80 mL) and extracted with ethyl acetate (2 × 300 mL). The extracts were washed with water, dried (brine), concentrated, and purified by flash chromatography (gradient 97:3 to 93:7 CH$_2$Cl$_2$: 2-propanol) to provide a sticky solid which was triturated with petroleum ether (90 mL): benzene (2 mL) to provide the title compound as an off-white solid (0.55 g, 39%): mp 104−106 °C; NMR (DMSO-d_6) δ 13.1 (broad s, 1H, NH), 8.10 (t, J = 7.8 Hz, 1H, py$H$), 7.95 (d, J = 7.7 Hz, 1H, py$H$), 7.71 (d, J = 7.7 Hz, 1H, py$H$), 7.45 (d, J = 8.8 Hz, 2H, ArH), 7.35 (d, J = 8.7 Hz, 2H, ArH), 3.86 (d, J = 17.4 Hz, 1H, CH_2), 3.72 (d, J = 17.4 Hz, 1H, CH_2), 2.57 (s, 3H, CH_3); MS (EI) 420 (MI, 3), 265 (12), 263 (38), 194 (25), 192 (70), 149 (40), 93 (100). Anal. Calcd for C$_{18}$H$_{13}$ClN$_2$O$_4$S$_2$: C, H, N.

Antihyperglycemic Assays. The procedure using db/db mice was as follows: on the morning of day l, 35 mice [male db/db (C57BL/KsJ), Jackson Laboratories, 3.3 to 5.5 months of age and body weight 35−60 g] were fasted for 4 h and weighed, and a baseline blood sample was collected from the tail-tip of each mouse without anesthesia, placed directly into a fluoride-containing tube, mixed, and maintained on ice. [In each individual experiment, ages of the mice were identical between treatment groups (i.e. groups were always age matched in any given experiment and the range of ages as indicated above was actually much narrower than indicated.] Food was then returned to the mice. The plasma was separated, and levels of glucose in plasma were determined by the Abbott VP analyzer. Because of the variable plasma glucose levels of the db/db mice, the five mice having the most extreme (i.e., highest or lowest) plasma glucose levels were excluded and the remaining 30 mice were randomly assigned into seven groups of equivalent mean plasma glucose level (vehicle control, ciglitazone, and five drug groups). Ciglitazone was used as a reference standard in all db/db experiments so that the responsiveness of the animals to a known compound could be ascertained as well as to have a comparator for the compounds of unknown activity. On the afternoon of days l, 2, and 3 the vehicle (0.2 mL of 2% Tween 80/saline w/v) or test drugs were administered (po) to the ad libitum fed mice. On the morning of day 4, the mice were weighed and fasted, but water was available ad libitum. Three hours later, a blood sample was collected, and then the mice were given the fourth administration of drug or vehicle. Blood samples were collected again from the unanesthetized mice at 2 and 4 h after drug administration. The plasma was separated, and levels of glucose in plasma were determined by the Abbott VP analyzer.

To assess drug activity, the percent change of the animal's plasma glucose level on day 4 (mean of the 2 and 4 h samples) from its respective level before drug administration (day l baseline sample) was determined as follows:

$$\frac{\text{mean of 2 and 4 h samples (day 4)}}{\text{baseline sample (day 1)}} \times 100$$

A 50−60% reduction of plasma glucose levels in the hyperglycemic db/db mice represented a normalization of glucose levels.

Analysis of variance followed by Dunnett's multiple comparison (one-sided) was used to estimate the degree of statistical significance of the difference between the vehicle control group and the individual drug-treated groups. A drug was considered active, at the specific dosage administered, if the difference between the plasma glucose levels of the control and treated groups have a $p < 0.05$.

The procedure using ob/ob mice was as follows: Mice (male (C57 Bl/6J) Jackson Laboratories, ages 2 to 3 months (40 to 50 g)) were used to assess the effects of compounds on both glucose and insulin lowering. In each study the ob/ob mice were from the same litter so they were age-matched and had similar body weights and levels of glycemia. Since the degree of glycemia does vary somewhat within the litter, the mice from the litter were randomized into different treatment groups by body weight (4 groups of 10 mice). (We used body weight instead of glycemia as a parameter since we found that body weight in this age of ob/ob mice is well correlated with glycemic state. From earlier studies we know that randomization by body weight yields tight plasma glucose values for each group.) The mice were housed five per cage and were maintained on normal rodent chow with water ad libitum. Mice received compound daily (morning) by gavage (suspended in 0.5 mL of 0.5% methyl cellulose) for 4 days. The dose given (Table 3) was calculated based on the fed weekly body weight and is expressed as active moiety. Control mice received vehicle only.

On the morning of day 4, 4 h after drug administration, blood was collected into sodium fluoride-containing tubes after decapitation under anesthesia. The plasma was isolated by centrifugation, and the concentration of glucose was measured enzymatically on an Abbott VP analyzer; plasma insulin was quantitated by radioimmunoassay.[22]

For each mouse, the percentage change in plasma glucose on day 4 was calculated relative to the mean plasma glucose of the vehicle treated mice. Analysis of variance followed by Dunnett's comparison test (one-tailed) were used to estimate the significant difference between the plasma glucose values from the control group and the individual compound treated groups. A compound was considered active if the difference in plasma glucose levels between control and treated groups have a $p < 0.05$.

The procedure for subcutaneously administered glucose tolerance test (SCGTT) in the obese Zucker rat was as follows: male obese Zucker (fa/fa) rats weighing between 582 and 719 g (x = 644 ± 35 g) were studied. Animals were

randomized to three treatment groups of five animals each based on responses to a subcutaneously administered glucose load. Vehicle (2% Tween 80 in saline) or drugs (ciglitazone, 100 mg/kg or compound **20**, 20 mg/kg) were administered, po, once daily for 4 days. On the afternoon of day 3, food was removed and the animals were fasted overnight. One hour after drug administration on day 4, a 1 g/kg subcutaneous glucose load was administered. Blood was collected from the tail tip just prior to administration of glucose and 30, 60, 90, and 120 min after. Blood was collected in fluoride containing tubes and centrifuged at 10000g for 1 min to obtain plasma. Plasma glucose was determined using an Abbott VP auto analyzer. Treatment groups were compared to controls using a Dunnett's *T* test. Data are expressed as mean values.

Effects of compound **20** on basal plasma glucose and the disposition of a glucose load in fasted normal rats were determined as follows: male Sprague−Dawley rats (210−270 g) from Charles River were used in all studies. Rats were weighed and randomly assigned to one of three treatment groups [vehicle controls, tolbutamide (50 mg/kg)] as a reference or **20** (100 mg/kg) and fasted for 18 h prior to treatment. All rats had ad lib access to water.

Effects on basal plasma glucose: Following an 18 h fast, a blood sample (approximately 50 μL) was collected from the tail tip of each animal and placed into a fluoride-containing tube. The tube was immediately mixed and kept on ice until the plasma was separated by centrifugation. Vehicle or drugs were administered by oral gavage immediately after collection of the initial blood sample. Serial blood samples were collected similarly at $1/2$, 1, 2, and 4 h after vehicle or drug administration. Plasma glucose levels were determined using an Abbott VP autoanalyzer. Data are expressed as mean ± SEM.

Effects on disposition of a glucose load: Following an 18 h fast, vehicle or drugs were administered by oral gavage, and an SCGTT was performed as desribed above for Zucker rats.

References

(1) Kahn, C. R. Insulin Action, Diabetogenes, and the Cause of Type II Diabetes. *Diabetes* **1994**, *43*, 1066−1084.
(2) The Diabetes Control and Complications Trial Research Group: The Effect of Intensive Treatment of Diabetes on the Development and Progression of Longterm Complications in Insulin-Dependent Diabetes Melitus. *N. Engl. J. Med.* **1993**, *329*, 977−986.
(3) Witcher, J. W. Implications of the DCCT. A Pharmaceutical Industry Viewpoint and Commentary. *Diabetes Rev.* **1994**, *2*, 272−276.
(4) Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcylohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and its Derivatives. *Chem. Pharm. Bull.* **1982**, *30*, 3580−3600.
(5) Chang, A. Y.; Wyse, B. M.; Gilchrist, B. J.; Peterson, T.; Diani, R. Ciglitazone, a New Hypoglycemic Agent. 1. Studies in ob/ob and db/db Mice, Chinese Hamsters and Normal and Streptozotocin-Diabetic Rats. *Diabetes* **1983**, *32*, 830−838.
(6) Sohda, T.; Mizuno, K.; Momose, Y.; Ikeda, H.; Fujita, T.; Meguro, K. Studies on Antidiabetic Agents. 11. Novel Thiazolidinedione Derivatives as Potent Hypoglycemic and Hypolipidemic Agents. *J. Med. Chem.* **1992**, *35*, 2617−2626.
(7) Yu, M. M.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. Studies on Antidiabetic Agents. 10. Synthesis and Biological Activities of Pioglitazone and Related Compounds. *Chem. Pharm. Bull.* **1991**, *39*, 1440−1445.
(8) Clark, D. A.; Goldstein, S. W.; Volkmann, R. A.; Eggler, J. F.; Holland, G. F.; Hulin, B.; Stevenson, R. W.; Kreutter, D. K.; Gibbs, E. M.; Krupp, M. N.; Merrigan, P.; Kelbaugh, P. L.; Andrews, E. G.; Tickner, D. L.; Suleske, R. T.; Lamphere, C. H.; Rajeckas, F. J.; Kappeler, W. H.; McDermott, R. E.; Hutson, N. J.; Johnson, M. R. Substituted Dihydrobenzopyran and Dihydrobenzofuran Thiazolidine-2,4-diones as Hypoglycemic Agents. *J. Med. Chem.* **1991**, *34*, 319−325.
(9) Hulin, B.; Clark, D. A.; Goldstein, S. W.; McDermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, C. H.; Lewis, D. M.; Rizzi, J. P. Novel Thiazolidine-2,4-diones as Potent Euglycemic Agents. *J. Med. Chem.* **1992**, *35*, 1853−1864.
(10) Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. [[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as Potent Antihyperglycemic Agents. *J. Med. Chem.* **1994**, *37*, 3977−3985.
(11) Kumar, S.; Boulton, A. J. M.; Beck-Nielsen, H.; Berthezene, F.; Muggeo, M.; Persson, B.; Spinas, G. A.; Donoghue, S.; Lettis, S.; Stewart-Long, P.; for the Troglitazone study group Troglitazone, an Insulin Action Enhancer, Improves Metabolic Control in NIDDM Patients. *Diabetologia* **1996**, *30*, 701−709.
(12) Kuehnle, H. F.; Wolff, H. P.; Haring, H. U.; Wieland, O.; Strein, K. BM 13.0907. A New Oral Hypoglycemic Agent with an Effect on Insulin Resistance. *Arch. Pharmacol.* **1989**, *340*, (suppl. R40), Abstract 117.
(13) Obermaier-Kusser, B.; Muhlbacher, C.; Mushack, J.; Seffer, E.; Ermel, B.; Machicao, F.; Schmidt, F.; Haring, H. U. Further Evidence for a Two-Step Model of Glucose Transport Regulation. *Biochem. J.* **1989**, *261*, 699−705.
(14) Freund, P.; Wolff, H. P.; Kuehnle, H. F. (−)-BM 13.0913: A New Oral Antidiabetic Agent that Improves Insulin Sensitivity in Animal Models of Type II (non-insulin dependent) Diabetes Mellitus. *Metabolism* **1995**, *44*, 570−576.
(15) Heitzmann, T.; Neidlein, R.; Freund, P.; Strein, K. Pharmacokinetics of the New Oral Blood Glucose Lowering Agent (−)2-(4-tert-Butylphenoxy)-7-(4-chlorophenyl)-heptanoic Acid Sodium Salt in Mice, Rats and Dogs. *Araneim.-Forsch./Drug Res.* **1995**, *45(II)*,
(16) Sarges, R.; Hank, R. F.; Blake, J. F.; Bordner, J.; Bussolotti, D. L.; Hargrove, D. M.; Treadway, J. L.; Gibbs, E. M. Glucose Transport-Enhancing and Hypoglycemic Activity of 2-methyl-2-phenoxy-3-phenylpropanoic Acids. *J. Med. Chem.* **1996**, *39*, 4783−4803.
(17) Zask, A.; Jirkovsky, I.; Nowicki, J. W.; McCaleb, M. L. Synthesis and Antihyperglycemic Activity of Novel 5-(Naphthalenylsulfonyl)-2,4-thiazolidinediones. *J. Med. Chem.* **1990**, *33*, 1418−1423.
(18) Coleman, D. L.; Hummel, K. P. Studies with the Mutation, Diabetes in the Mouse. *Diabetologia* **1967**, *3*, 238−248.
(19) Tutwiler, G. F.; Kirsch, T.; Bridi, G. A Pharmacologic Profile of McN-3495 [N-(1-Methyl-2-pyrrolidinylidene)-N′-Phenyl-1-pyrrolidinecarboxamide], a New, Orally Effective Hypoglycemic Agent. *Diabetes* **1978**, *27*, 855−867.
(20) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(21) Dunn, A. D.; Norrie, R.; L'Hostis, J.; Marjot, S. The synthesis and some reactions of novel pyridine-2(1H)-thiones. *J. Prakt. Chem./Chem.-Ztg.* **1992**, *334*, 119−25.
(22) Heding, L. G. Determination of Total Serum Insulin (IRI) in Insulin-treated Diabetic Patients. *Diabetalogia* **1972**, *8*, 260−266.