Studies on New Acidic Azoles as Glucose-Lowering Agents in Obese, Diabetic db/db Mice

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Bioisosteric substitution was used as a tool to generate several new structural alternatives to the thiazolidine-2,4-dione and tetrazole heterocycles as potential antidiabetic agents. Among the initial leads that emerged from this strategy, a family of acidic azoles, isoxazol-3- and -5-ones and a pyrazol-3-one, showed significant plasma glucose-lowering activity (17–42% reduction) in genetically obese, diabetic db/db mice at a dose of 100 mg/kg/day ×4. Structure–activity relationship studies determined that 5-alkyl-4-(arylmethyl)pyrazol-3-ones, which exist in solution as aromatic enol/iminol tautomers, were the most promising new class of potential antidiabetic agent (32–45% reduction at 20 mg/kg/d ×4). Included in this work are convenient syntheses for several types of acidic azoles that may find use as new acidic bioisosteres in medicinal chemistry such as the antidiabetic lead 5-(trifluoromethyl)pyrazol-3-one (hydroxy tautomer) and aza homologs of the pyrazolones, 1,2,3-triazol-5-ones (hydroxy tautomer) and 1,2,3,4-tetrazol-5-one heterocycles. log P and pK_a data for 15 potential acidic bioisosteres, all appended to a 2-naphthalenylmethyl residue so as to maintain a similar distance between the acidic hydrogen and arene nucleus, are presented. This new data set allows comparison of a wide variety of potential acid mimetics (pK_a 3.78–10.66; log P −0.21 to 2.76) for future drug design.

Non-insulin-dependent diabetes mellitus (NIDDM, type II diabetes) constitutes 90–95% of the approximately 6 million diagnosed diabetics in the United States.[1] NIDDM is characterized by hyperglycemia, the result of insulin resistance in peripheral tissues (muscle, fat), where insulin-stimulated uptake/utilization of glucose is blunted, and in liver, where insulin suppression of gluconeogenesis is insufficient.[2] Because most NIDDM subjects are obese (~80%) and exercise enhances tissue responsiveness to insulin, diet and exercise are first-line therapy for NIDDM patients.[3] However, due to difficulties inherent in lifestyle changes and the rapid reversal of the positive effects of exercise,[4] an increasing number of NIDDM patients receive oral hypoglycemic therapy to control blood glucose levels.[5] The most widely used hypoglycemic agents are various formulations of insulin and the sulfonylureas.[6] A major drawback with each of these therapies is the occurrence of potentially life-threatening hypoglycemia which is due to hyperinsulinemia. This problem has not been solved with the insulin-releasing sulfonylureas, although more than 30 years of research on this class of hypoglycemic agent has yielded many products, some with dramatically increased potency.[7] In addition, the hyperinsulinemia that can occur with these therapies is also associated with an elevated risk of cardiovascular disease,[8] a major killer of diabetics.[1] Consequently, a need exists for new therapeutic options which do not involve increased circulating insulin concentrations.[9]

Takeda scientists have described a promising new class of oral antidiabetic agents, 5-(4-substituted benzyl)thiazolidine-2,4-diones, represented by the prototype ciglitazone (Chart 1).[10a] In preclinical rodent models of obesity, insulin resistance, and hyperglycemia, thiazolidinediones ameliorate insulin resistance and normalize plasma glucose and insulin (where elevated) without causing a hypoglycemic state, even at very high doses.[10b] Since the disclosure of this class of compounds, many new derivatives have been reported with greatly increased in vivo potency,[11] but questions still remain concerning the efficacy and safety of these agents in humans.[12] To date no member of the thiazolidinedione class has reached any of the world markets.[13]

Recent efforts in these laboratories have focused on the discovery of structurally novel antihyperglycemic agents that would control hyperglycemia without causing hypoglycemia or insulin release and that would possess a wider safety margin than the glitazones. Perfluorocarbon-based tetrazole analogs (**1**, Chart 1) of ciglitazone demonstrated a ciglitazone-like antihyperglycemic profile in obese, insulin-resistant diabetic ob/ob and db/db mice,[14a] two genetic rodent models of NIDDM, without causing hypoglycemia in these animals or in normal rats.[14b] Unfortunately, the more effective and thoroughly characterized compound (**1**, $R_F = C_7F_{15}$) caused hepatomegaly and a sustained antihyperglycemic action, persisting for at least 4 days after withdrawal of its administration.[14b]

More recently, two different classes of naphthalene-based antihyperglycemic agents have been reported. 2-Naphthalenylthiazolidinediones **2** (Chart 1) were effective in the insulin tolerance test administered to db/db mice, and sulfonyl-linked thiazolidinedione **2** demonstrated comparable efficacy to ciglitazone in the db/db postprandial assay and in obese, insulin-resistant Zucker rats.[15] Certain 2-naphthalene-based oxathia-

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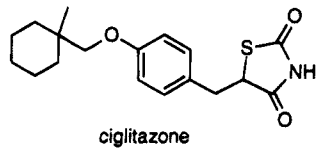
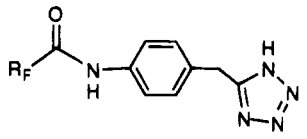
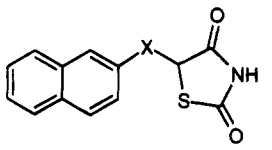
Chart 1. Antidiabetic Structures



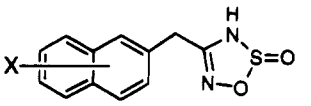
ciglitazone



1 (R_F = C_3F_7, C_7F_{15})



2 (X = SO_2, CH_2)



3 (X = Br, Cl)

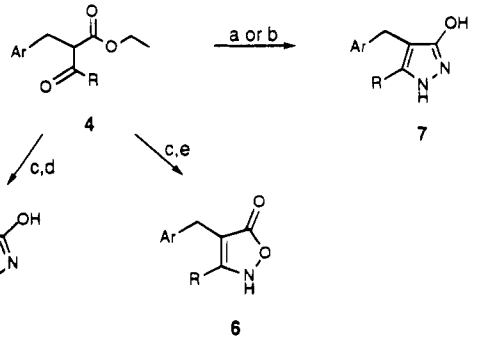
diazole *S*-oxides **3** (Chart 1) were found to be ~5–10-fold more potent than ciglitazone in the db/db postprandial assay. In this series, halogen substitution into C_1, C_5, or C_8 of the naphthalene markedly improved potency.[16] Like the glitazones, agents **1–3** did not cause overt hypoglycemia in diabetic or normal rodents, either acutely with very large doses or with prolonged administration. Importantly, 2-naphthalene-based agents **2** and **3** did not cause hepatomegaly in normal mice, unlike the perfluorocarbon-based agents **1** and many of the glitazones,[10a] nor did **2** or **3** show significant antihyperglycemic activity beyond 24 h after the last dose.

In this paper, we demonstrate the application of bioisosteric substitution as a tool for generating new antidiabetic lead structures, and synthetic and structure–activity relationship (SAR) studies on the resultant family of acidic azole leads (isoxazol-3- and 5-ones, pyrazol-3-ones) that established 5-alkyl-4-(arylmethyl)-pyrazol-3-ones (as aromatic hydroxyenol/iminol tautomers) as the most effective potential new antidiabetic agents. Included in this work are convenient syntheses for several types of acidic azoles, including 5-(trifluoromethyl)pyrazol-3-one (hydroxy tautomer), 1,2,3-triazol-5-one (hydroxy tautomer), and 1,2,3,4-tetrazol-5-one heterocycles that may find use as new acidic bioisosteres in medicinal chemistry. Measured pK_a and log *P* data obtained for seven of these new and eight previously suggested acidic bioisosteres, all appended to a 2-naphthalenylmethyl residue, provides a new data set for comparison of a wide variety of potential acid mimics (pK_a 3.78–10.66; log *P* -0.21 to 2.76) that should aid in future drug design.

Chemistry

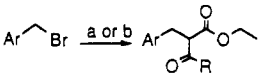
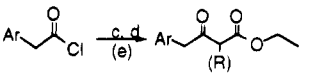
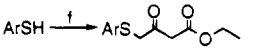
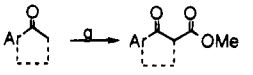
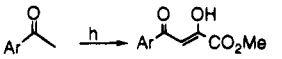
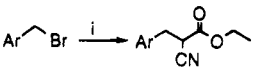
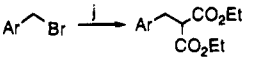
The majority of the acidic azoles (Tables 2–4) were synthesized by condensation of branched *β*-keto esters (**4**, Scheme 1) with hydroxylamine at basic pH[17a] or hydrazine. Acidification of the hydroxylamine reactions provided either isoxazol-3- or -5-one isomers as the major product, depending on the nature of the workup conditions.[17b] For example, pouring the crude reaction mixture onto cold, concentrated aqueous HCl (or acetic acid saturated with HCl(g)[17c] gave mainly the isoxazol-3-one isomers **5**. Alternatively, addition of acetic acid to the same reaction mixture gave the thermodynamically favored isoxazol-5-one isomers, **6**.[18] Reaction of

Scheme 1. Representative Synthetic Procedures for Azoles **11–13** and Analogs[a]



[a] (a) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; (b) NH_2NH_2, DME or toluene, reflux; (c) $NH_2OH{\cdot}HCl$, 1 N NaOH, THF, 0 °C, 1.5 h; (d) concentrated HCl, 0 °C; (e) acetic acid, 0 °C.

Scheme 2. Routes to Acidic Azole Precursors[a]

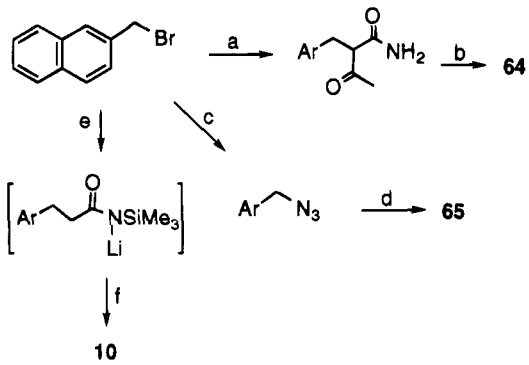
Compound	Precursor Route	Reagents/conditions
11-13, 18, 19	A	
31-43, 47-54		
56-59		
16, 17, 21	B	
22-24, 25	C	
27, 28	D	
14, 15, 29, 30	E	
20, 44, 45	F	
8, 46	G	
60, 62, 63		

[a] (a) NaOEt, $RCOCH_2CO_2Et$, EtOH, reflux; (b) NaH, $RCOCH_2CO_2Et$, DME, reflux; (c) Meldrum's acid, pyridine, 0 °C, then 2 N HCl; (d) EtOH, reflux, (e) K_2CO_3, MeI, acetone, reflux; (f) methyl 4-chloroacetoacetate, Hünig's base, (**22–24**) or ethyl 2-chloroacetoacetate, Et_3N (**25**), CH_2Cl_2, room temperature; (g) LDA (2 equiv) THF, −78 °C, $CH_3OC(O)CN$; (h) NaH, MeOH, benzene, 0 °C, then aryl ketone and dimethyl oxalate; (i) ethyl cyanoacetate, NaH, DMF, 0 °C, then arylmethyl bromide, reflux; (j) diethyl malonate, NaH, DME, 0 °C then arylmethyl bromide, reflux.

β-keto esters **4** with hydrazine in refluxing ethanol gave pyrazolones **7**. Azoles **5** and **7** exist (NMR, IR (KBr or solution)) as the aromatic enol/iminol tautomers except where noted in Tables 2–4. Isoxazol-5-ones **6** exhibited a solvent-dependent equilibrium between $N_2(H)$ (NMR, DMSO) and $C_4(H)$ (NMR, $CDCl_3$) tautomers.[19] Accordingly, analogs **11–13**, **16–19**, **21–28**, **31–43**, and **47-68** were prepared and displayed similar properties.[20]

Synthesis of the branched *β*-keto ester starting materials[21] for the azoles were derived from 1,3-dicarbonyl anion addition to an arylmethylbromide (precursor route A, Scheme 2). Aprotic reaction conditions are preferred for the perfluorocarbon analogs **38–40**, since protic conditions generated hemiketal products at the perfluoroacyl carbon which were then very slow to cyclize with

Scheme 3. Synthetic Routes to Acidic Azoles **10**, **64**, and **65**[a]



[a] (a) Acetoacetamide, NaH, DMF–DME, 80 °C; (b) MsN_3, Et_3N, CH_3CN, room temperature, 3 h, then NaOMe, MeOH, room temperature, 15 h, then 2.5 N HCl, 0 °C; (c) NaN_3 (excess), CH_3CN, room temperature; (d) chlorocarbonyl isocyanate, toluene, 60 °C, then H_2O; (e) *N*-(trimethylsilyl)acetamide, BuLi (2 equiv), THF, 0 °C then arylmethyl bromide, 0 °C; (f) BuLi (1 equiv), 0 °C, dimethyl oxalate, 0 °C, then 1 N HCl.

hydrazine.[22] Alternatively, condensation of 2,3-dihydro-1,4-benzodioxin-6-carboxaldehyde with ethyl acetoacetate under a Dean–Stark trap gave a mixture of (*E*)- and (*Z*)-α-acetylpropenoic esters which were reduced with sodium borohydride in pyridine (see **55**, Experimental Section).[23] Linear β-keto ester starting materials[24] were prepared via routes B and C (Scheme 2).

Regiospecific C-acylation of ketone enolates with Mander's reagent[25] (route D) provided the precursors[21] to conformationally constrained pyrazolones **27** and **28**. Condensation of 2-acetylnaphthalene with dimethyl oxalate gave methyl butenoate **14**[26] (route E). Ester **14** was hydrolyzed to the known acid **15**[27] and reacted with hydrazine to give carbomethoxy substituted pyrazole **29**. Saponification of **29** gave **30**.

Reaction of ethyl α-cyano-3-(2-naphthalenyl)propionate (route F) with excess hydrazine gave amino-substituted pyrazolone **44** along with unexpected products hydrazinopyrazolone **45** and the reduction product **20**. Trituration of the crude mixture ($CHCl_3$–EtOH, warm) gave the insoluble pyrazolone **45** (10%). Chromatography of the solute on silica gel (elution with 7% MeOH/$CHCl_3$) gave the analog **20** (9%) and desired **44** (15%).[28]

Hydrolysis and decarboxylation of diethyl 2-(naphthalenylmethyl)malonate[29] (route G) gave propionic acid **8**,[30] whereas reaction with hydrazine gave hydroxy-substituted pyrazolone **46**. Treatment of the malonate with sodium ethoxide, followed by benzyl azide according to Begtrup and Pederson,[31] gave triazolone **62**. Alkylation of **62** with MeI gave inner salt **63**. Reaction of **63** with 3-fluorobenzoyl chloride (115 °C, 20 h) afforded the 3-fluorobenzoate ester of **60**.[31] Saponification of this ester gave **60**. Similarly, reaction of dimethyl methylmalonate anion (Na, EtOH) with benzyl azide, followed by alkylation with 2-(bromomethyl)-naphthalene and debenzylation/saponification gave isomeric triazolone **61**. NOE experiments performed on **61** and **63** confirmed that alkylation of N_1-benzyl-1,2,3-triazol-5-ones (e.g., **62**) occurred at N_3 rather than N_2 to give (ultimately) the isomers **60** and **61**.[32]

A new synthesis of the 4-substituted 1,2,3-triazol-5-one heterocycle was developed.[33] Reaction of α-acetyl-3-(2-naphthalenyl)propionamide (Scheme 3) with methanesulfonyl azide in the presence of triethylamine and water in acetonitrile[34] effected diazotization and deacetylation to give the α-diazoamide derivative. Exposure of the crude diazoamide to sodium methoxide followed by acidification gave 4-(2-naphthalenylmethyl)-1,2,3-triazol-5-one, **64**. The 1,2,3-triazolones **60**–**62** and **64** all exist spectroscopically as the aromatic enol tautomer, similar to isoxazol-3-one **11** and pyrazol-3-one **13** and related analogs.

A new, one-pot procedure was utilized for the synthesis of the 3-hydroxypyrrole-2,4-dione heterocycle,[35] **10**. The dianion of *N*-(trimethylsilyl)acetamide[36] was treated sequentially with 2-(bromomethyl)naphthalene, butyllithium, and dimethyl oxalate. Acidification, followed by column chromatography on silica gel and recrystallization, gave **10** in low yield (Scheme 3). Exposure of 2-naphthalenylmethyl azide[37] to chlorocarbonylisocyanate in toluene[38] followed by addition of water gave tetrazol-5-one **65** (IR ($CHCl_3$): 1725 cm^{-1} (s), Scheme 3). Reaction of 2-(cyanomethyl)naphthalene[39] with sodium azide and ammonium chloride (5 equiv each, DMF, 135 °C) gave the tetrazole **9**.

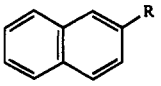
SAR Results and Discussion

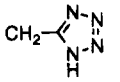
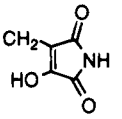
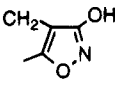
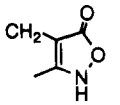
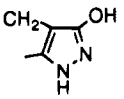
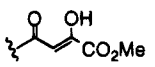
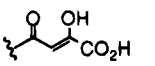
Similar to the glitazones, agents **1**–**3** have in common an acidic azole bound to a lipophilic aryl moiety. Since thiazolidinediones[40] and tetrazoles,[41] as well as other acidic azoles,[42,43] appear to function as carboxylic acid mimetics in vivo, we surveyed a number of acidic entities that were similarly postulated as potential carboxylic acid bioisosteres in the medicinal chemistry literature.[42] The acidic moieties were appended to the 2-naphthalene ring so as to maintain the four-atom distance between the acidic hydrogen and the arene nucleus, analogous to the situation in the glitazones, compounds **2** and the N_2(H) tautomer of tetrazoles **1**.

The results (Table 1) demonstrate that in this case, the application of acidic isostere replacement was successful as a tool for generating new lead structures for our antidiabetic program. Particularly attractive for further study were the family of acidic azoles **11**–**13**. Not only were isoxazol-3-one **11** and pyrazol-3-one **13** the most effective glucose-lowering compounds initially screened in the db/db postprandial assay, because **11**-**13** are related via a common synthetic intermediate (β-keto ester **4**, Scheme 1), independent variation of β-keto ester substituents at C_2 (Ar) and C_4 (R) could be translated into concomitant SAR results for these distinct azole series.

A preliminary SAR study indicated that the activity of azoles **11**–**13** was specific to these structures. For example, regioisomeric compounds **16** and **17**, in which the C_4, C_5 substituents (R_1, R_2, Table 2) of **11** and **13** are transposed, were inactive, as were the 1-naphthyl isomers of **12** and **13** (**18**, **19**). Independently substituting hydrogen for methyl at R_2 (**20**) or at R_1 with 2-naphthalenylmethyl at R_2 (**21**) abolished activity in the pyrazole series. Broader structural changes, such as hydrogen at R_1 coupled with insertion of sulfur into the bridge between naphthyl and azole (**22**) or in combinations with benzoheterocycle (**23**–**25**) or adamantyl substitution for 2-naphthyl (**26**), also were unsuccessful. Likewise several conformationally restricted acidic pyrazoles showed no significant activity at high doses (**27**–**30**, Table 2).

Table 1. Effects of 2-Naphthyl-Substituted Acids on Plasma Glucose in db/db Mice



no.[a]	R	Syn[b] method	% Yield[c]	mp(°C)	pKa[d]	Log P[e]	db/db Dose (mg/kg)	db/db % Δ[f] [Glucose]
8	$(CH_2)_2CO_2H$	G[29]	20	133-135[g]	6.52	1.09	100	NA
9		h	43	155-158[i]	5.77	0.72	20	NA
10		j	3	184-187.5	5.08	-0.1	20	NA
11		A[k]	26	169-171	7.89	2.14	100 20	-48±4* -25±6*
12		A[k]	20	91-94[l]	6.02	0.58	100	-17±3
13		A[k]	78	240-244	10.33	2.76	100 20	-42±1* -31±3*
14		E	94	104-106	7.62	2.3	100	-37±5*
15		E	40	173-175[m] (dec)	3.78	2.23	100	-28±3*
	ciglitazone				7.8[n]	3.61[n]	100	-28±9*[o]

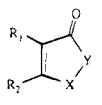
[a] Analyses (C, H, N) were within ±0.4% of theoretical values unless otherwise indicated. [b] Letters refer to routes in Scheme 2. Numbers are references to known intermediates. [c] Yields are for analytically pure material obtained in the last step and are not optimized. [d] Apparent pK_a values (average of two runs) were measured by potentiometric titration in dioxane–water (1:1). See Experimental Section. [e] log *P* values (average of at least two runs) were obtained from the manual shake flask (octanol–H_2O) method. See Experimental Section. [f] Groups of db/db mice ($N = 4–6$) were administered either drug or vehicle (Tween 80/saline) once daily po × 4 days. Values (mean ± SE) are the percent change in plasma glucose concentration of drug treated mice relative to vehicle controls at the given dose (mg/kg); NA = not active, generally less than −15% change; *$p < 0.05$ compared to vehicle control. [g] Analysis for 0.15 hydrate; lit.[30] mp 137–138 °C. [h] See text. [i] Analysis for 0.125 hydrate. [j] See Scheme 3 and text. [k] See Scheme 1. [l] The analysis for 0.25 hydrate. [m] Literature[27] mp 169–177 °C dec. [n] Literature[43a] pK_a 7.65; log *P* 3.57. [o] Mean ± SD from 43 experiments.

We therefore narrowed the focus of the SAR by varying only the R_2 (methyl) substituent of azoles **11–13**. The results of this study (Table 3) revealed that for consistent activity in the db/db mouse and reliable synthesis over a broad range of substituents (which enabled a more thorough evaluation of SAR), the pyrazolone heterocycle was preferred over either of the isoxazolones. In the homologous series of C_5-alkylpyrazolones, optimum activity resided with methyl (**13**) and ethyl (**31**) derivatives. Further increases in the chain length (**33**), branching (**35**), or inclusion of oxygen for methylene (**36**) markedly diminished activity. In contrast, in the perfluoroalkyl series (**38–40**) only trifluoromethyl (**38**) was active, but this compound appears to be the most potent analog (Table 3).

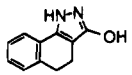
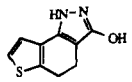
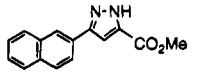
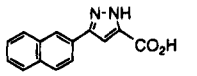
With R_2 optimized, variation of the aryl component at R_1 was investigated (Table 4). Halogen substitution in the naphthalene ring attenuated antihyperglycemic potency (compare **11–13** vs **47–49** and **38** vs **50**). These results are in contrast with the significant improvement in potency resulting from halogen substitution at C_1 or C_5 of the naphthalenylmethyl oxathiadiazole **3**[16a] (Chart 1) and suggests separate in vivo binding sites or a different mode of action by these two series. However, like **3**, pyrazolone antihyperglycemic activity was not limited to the 2-naphthalenylarene. The results in Table 4 demonstrate that a variety of benzoheterocycles (**55–58**) show significant activity in the fed db/db mouse. Even unsubstituted phenyl showed activity, provided R_2 on the pyrazolone was CF_3 (compare **51** vs **53**, Table 4); however, these compounds do not show more potent activity than 2-naphthalenyl analog **38**.

Comparison of pK_a and log *P* data obtained for the collection of potential acidic isosteres in Table 1 indicate these compounds cover a broad range of values at each parameter (pK_a 3.78–10.33; log *P* −0.1 to 2.76), but only

Table 2. Exploratory SAR of Azoles **11–13**



A = naphthalenylmethyl
B = naphthalenylthiomethyl
C = benzothiazol-2yl-thiomethyl
D = adamantyl
E = benzimidazol-2yl-thio

no.[a]	R_1	R_2	X	Y[b]	Synthetic[c] Method	% Yield[d]	mp(°C)	db/db Dose (mg/kg)	% Δ [Glucose][e]
16	Me	2-A	O	NH	B	23	161-164[f]	100	NA
17	Me	2-A	NH	NH	B	91	205-207	20	NA
18	1-A	Me	NH	O	A	34	122-124	20	NA
19	1-A	Me	NH	NH	A	85	165-166 (dec)[g]	20	NA
20	2-A	H	NH	NH	F	6	189-191[h]	27	NA
21	H	2-A	NH	NH	B[58]	59	230-233 (dec)	100	NA
22	H	2-B	NH	O	C	27	87.5-89.5	100	NA
23	H	C	NH	NH	C	68	190-193	100	NA
24	H	C	NH	O	C	13	82-85[i]	100	NA
25[i]	E	Me	NH	NH	C	59	248-250	100	NA
26	H	1-D	NH	NH	A[k]	52	180 (dec)	20	NA
27					D[56]	66	211-213	100	NA
28					D[57]	66	219-220[j]	100	NA
29					E[26]	14	179.5-181.5	100	NA
30					E[27]	51	>225[m]	100	NA

[a,c,d,e] See footnotes *a*, *b*, *c*, and *f*, respectively, Table 1. [b] Except for **21**,[55] all compounds listed as NH exist as the iminol tautomer by ^{1}H NMR (DMSO-d_6) and IR (KBr). [f] Analysis for 0.25 hydrate. [g] Analysis for hydrate. [h] Analysis for 0.3 hydrate. [i] Analysis for 0.25 hydrate. [j] Synthesized by Dr. Peter H. L. Wei). [k] Ethyl 3-(1-adamantyl)-3-oxopropionate purchased from Aldrich. [l] Analysis for hydrate. [m] Analysis for 0.1 ethyl acetate (NMR).

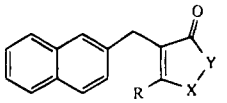
hydroxyisoxazole **11**, hydroxypyrazole **13**, and the enolic butenoates **14** and **15** showed significant glucose-lowering activity in db/db mice. These actives cover the entire range of pK_a values found in Table 1 and considerably narrow the range in log *P* (2.14-2.76), but none of the compounds closely matched ciglitazone in both physicochemical parameters (see Table 1). From the SAR, the set of analogs with the best activity were pyrazolones **13**, **31**, and **38**. Pyrazolones **13** and **31** are reasonably close to ciglitazone in log *P*,[44] but they are 100-1000-fold less acidic,[45] whereas trifluoromethyl-substituted pyrazolone **38** (pK_a = 7.03, log *P* 2.51) irradicates this difference and appears to be the closest novel structure to ciglitazone overall. While it is unclear in which direction CF_3 modulates pyrazolone lipophilicity in vivo,[46] the marked increase in heterocycle acidity induced by CF_3, apparently due to a strong electronegative inductive effect, is measurable and unambiguous.

In the desire to find a more potent compound than **38** and in order to further assess the relative influence of acidity on pyrazolone in vivo activity, several additional analogs were synthesized containing other C_5 substituents that have comparable group electronegativity values to CF_3[47] (**41**, **43–46**, Table 3). Of these only amino analog **44** showed significant glucose-lowering activity but, unlike CF_3, NH_2 substantially decreased pyrazolone acidity (pK_a (**44**) = 10.66) and diminished antihyperglycemic potency relative to **38** or **13**. Conversely, hydroxyl substitution (**46**) markedly increased pyrazolone acidity (pK_{a1} = 3.95; pK_{a2} = 6.8, Table 3), but this substitution destroyed in vivo activity. Thus it appears there is no discernable correlation between pyrazolone acidity and in vivo activity, but several factors could mask any such trend and would account for these and the other SAR results obtained in Tables 1–3.

First, it is apparent that the C_5 position of the pyrazolone ring is sterically sensitive (compare **11**, **31**, **38** vs **35**, **36**), and this overides any acidity contributions (e.g., from phenyl, **41**, 4-nitrophenyl, **43**, or extended perfluoroalkyl chains, **39**, **40**). Second, the lipophilicity range of active compounds is quite narrow (Δlog *P* 0.62), and this parameter too can overide acidity through hindrance of oral absorption (e.g., **8–10**, **12**, **45–46**).[48] It is also possible that a specific tautomeric form of the heterocycle is required for in vivo activity, since all of the active azoles (e.g., **11**, **13**, **31**, **38**, **44**) exist in solution as the hydroxy aromatic tautomer while inactive analogs such as **12**, **45**, and **46** do not.[49] In addition, polar functionalities such as amino and hydroxyl could participate in hydrogen bond donor/acceptor interactions not available to CH_3, C_2H_5, or CF_3 groups. Because contributions from some or all of these factors confound interpretation of the SAR results, we sought an alternative way to increase azole acidity.

Substitution of nitrogen for carbon in the azole backbone was expected to increase azole group electronegativity and consequently increase heterocycle acidity without causing the extreme perturbations in lipophilicity or steric demand like the C5-substituent changes on the pyrazolones. Preferred compounds containing three and four contiguous nitrogen atoms, aza homologs of the pyrazolones, were synthesized (**60**, **61**, **64**, **65**, Table 5) and did show the expected trend. A steady decline of a little more than 1 log unit in acidity for each deleted carbon was accompanied by ~0.5 unit decrease in log *P*.[50] The result was that triazolones **60**, **61**, and **64** filled the existing gap in pK_a between pyrazolones **13** and **38** and maintained the heteroaromatic ring by preferring to adopt enolic structures in solution.[31,33] In contrast, tetrazolone **65** adopts the keto form exclusively in solution and is the strongest acid of the homologous azolones synthesized, but lipophilicity for this compound is out of the acceptable range.[48] Despite the favorable range of pK_a and log *P* of the 1,2,3-triazolones, none of these azoles (nor the intermediates **62** and **63**) showed glucose-lowering activity in the db/db mouse. It can be argued that, with the exception of triazolone **60**, the results in Table 5 are consistent with the steric (**62–65**), aromatic (**65**), or acidic proton–arene distance (**61**) requirements previously noted in the pyrazolone series. Compound **60**, however, seems to compare favorably in every respect with the other active azoles **11**, **13**, **31**, and **38**. We conclude that other considerations, such as pharmacokinetic or pharmodynamic properties of these azoles in db/db mice, must account for the activity differences observed.

Table 3. Effects of Alkyl Substitution on Plasma Glucose in db/db Mice



no.[a]	R	X	Y[b]	synthetic[c] method	% yield[d]	mp (°C)	db/db dose (mg/kg)	db/db %Δ [glucose][e]
31	Et	NH	NH	A	60	145–147	20	−32 ± 4*
							5	NA
32	Et	O	NH	A	16	133–135	20	NA
					44	35–38	20	−24 ± 8
33	*n*-Pr	NH	NH	A				
34	*n*-Pr	O	NH	A	13	118–120	20	NA
35	*i*-Pr	NH	NH	A	89	143–145[f]	100	−30 ± 4*
							20	−15 ± 4
36	$MeOCH_2$	NH	NH	A	88	156–156[g]	100	−39 ± 3*
							20	NA
37	$MeOCH_2$	NH	O	A	60	88–90[h]	100	NA
							20	−45 ± 4*
38[i]	CF_3	NH	NH	A	70	165–167	5	−16 ± 3
39	C_2F_5	NH	NH	A	8	162–164	100	NA
40	C_3F_7	NH	NH	A	11	165–166	100	NA
41	Ph	NH	NH	A	4	170–171	100	NA
42	Ph	NH	O	A	17	123–125	100	NA
43	4-NO_2Ph	NH	NH	A	49	235–237	100	NA
44[j]	NH_2	NH	NH	F	32	215.5–217.5 dec[k]	73	−27 ± 8*
45	NH_2NH	NH	NH	F	10	194–195 dec	100	NA
46[l]	OH	NH	NH	G	71	246–248[m]	100	NA
ciglitazone							100	−28 ± 9* [n]

[a,c,e,n] See footnotes *a*, *b*, *f*, and *o*, respectively, Table 1. [b] Except for **45**[49] and **46**,[49] all compounds listed as NH exist as the iminol tautomer by ^{1}H NMR (DMSO-d_6) and IR (KBr). [d] Yields are for analytically pure material obtained from the last step (Scheme 1) and are not optimized. [f] Analysis for 0.25 hydrate. [g] Analysis for 0.2 hydrate. [h] Analysis for 0.167 hydrate. [i] pK_a, 7.03; log *P*, 2.51. [j] pK_a, 10.66; log *P*, 1.44. [k] Analysis for 0.25 hydrate. [l] pK_{a1}, 3.95; pK_{a2}, 6.81; log *P*, −0.21. [m] Analysis for dihydrate.

In summary, we have demonstrated the successful application of bioisosteric substitution as a tool for generating new lead structures in the antidiabetic/insulin resistance area, where alternatives to thiazolidine-2,4-diones and tetrazoles are scarce.[51] Concurrent SAR investigations of the resultant family of acidic azole leads revealed that 5-alkyl-4-(arylmethyl)pyrazol-3-ones, which exist in solution as hydroxy–aromatic (enol/iminol) tautomers, are the most effective potential new class of antidiabetic agent.[52] SAR results, together with measured pK_a and log *P* data enabled the rational design of several acidic azoles, including 1,2,3-triazol-5-ones, 1,2,3,4-tetrazol-5-one, and the antidiabetic lead 5-(trifluoromethyl)pyrazol-3-one heterocycles that may find use as new acidic bioisosteres in medicinal chemistry.

The measured log *P* and pK_a data presented for 15 potential acidic bioisosteres, all appended to a 2-naphthalenylmethyl residue so as to maintain a four-atom distance between the acidic proton and the arene nucleus, provides a useful new data set for comparison of a wide variety of potential acid surrogates (pK_a 3.78–10.66; log *P* −0.21 to 2.76) that should aid in future drug design.

Continued SAR investigations on the pyrazolones have allowed the discovery of a potent series of antihyperglycemic (4-substitutedbenzyl)-5-(trifluoromethyl)-pyrazoles[53a] and pyrazolones[53b] in db/db mice. Details of these studies will be reported in the near future.

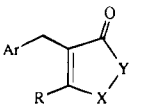
Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR spectra were recorded on a Varian XL-200, Varian VXR-300, or Bruker AM-400 instrument. IR spectra were recorded on a Perkin-Elmer diffraction grating or Perkin-Elmer 784 spectrophotometers. Mass spectra were recorded on a LKB-9000S, Kratos MS 50, or Finnigan 8230 mass spectrometers. Elemental analyses were obtained with a Perkin-Elmer 2400 elemental analyzer, and all compounds were within 0.4% of theoretical value unless otherwise noted. All reactions were carried out under inert atmosphere (N_2 or Ar). HPLC purifications were carried out on a Waters Prep 500 or Prep 500A instruments. "Standard aqueous workup" involves separation of an organic phase, washing it with saturated aqueous NaCl solution, drying over anhydrous $MgSO_4$, filtration, and concentration in vacuo on a rotary evaporator.

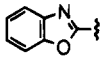
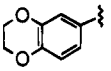
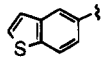
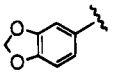
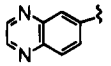
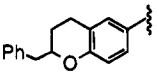
1*H*-3-Hydroxy-4-(2-naphthalenylmethyl)pyrrole-2,5-dione (10). To an ice-cold solution of *N*-(trimethylsilyl)-acetamide (7.11 g, 54.3 mmol) in THF (150 mL) was added a solution of butyllithium in pentane (10M, 11.9 mL, 119 mmol). The mixture was stirred for 0.5 h at 0 °C, when a solution of 2-(bromomethyl)naphthalene (10 g, 45 mmol) in THF (100 mL) was added. The reaction mixture was packed in ice and allowed to warm gradually to room temperature with stirring overnight. The reaction mixture was recooled in ice, butyllithium was added (10 M, 5.4 mL), stirring continued for 0.3 h, and then a solution of dimethyl oxalate (5.9 g, 50 mmol) in THF (70 mL) was added dropwise. The reaction was left to warm to ambient temperature and stirred overnight. Upon recooling the mixture in ice, 1 N HCl was added and the product was extracted with ethyl acetate. Following standard aqueous workup, the crude product was chromatographed on silica gel (Merck silica 60, elution with hexane–ethyl acetate (1:1 + 0.5% acetic acid) and recrystallized from toluene–ether mixture, which gave 0.30 g (1.2 mmol) of the title compound as a bright yellow solid: IR (KBr) ν (cm^{-1}) 3300, 1790, 1710, 1675, 1510, 1425, 1385, 1350, 1280, 1270, 1220, 1045, 985, 960, 900, 880, 810, 785, 755, 730, 665, 630; ^{1}H NMR(400 MHz, DMSO-d_6) δ 3.67 (s, 2H), 7.36 (dd, 1H, J = 8.4 and 1.7 Hz), 7.45 (m, 2H), 7.66 (s, 1H), 7.83 (m, 3H), 10.4 (s, 1H), 12.1 (s, broad, 1H); MS (EI) *m/z* 253 (M$^+$).

5-Methyl-4-(2-naphthalenylmethyl)-2*H*-isoxazol-3-one (Tautomer, 11). To a slurry of sodium hydride (2.17 g,

Table 4. Effects of Aryl Substitution on Plasma Glucose in db/db Mice



A = 2-naphthalenyl

no.[a]	Ar	R	X	Y[b]	Synthetic[c] Method	% Yield[d]	mp(°C)	db/db Dose (mg/kg)	db/db % Δ [Glucose][e]
47	(1-Br)A	Me	NH	NH	A[59]	58	189-191	20	-20±6
48	(1-Br)A	Me	O	NH	A[59]	37	197.5-199.5	20	NA
49	(1-Br)A	Me	NH	O	A[59]	58	149.5-151 (dec)	20	NA
50	(5-Br)A	CF_3	NH	NH	f	5	172-181 (dec)	20	-22±2*
51	Ph	Me	NH	NH	f	47	224.5-225.5	100	NA
52	Ph	Me	O	NH	f	45	119-121	100	NA
53	Ph	CF_3	NH	NH	A[60]	40	149-150	100 20	-33±2* -18±4
54		CH_3	NH	NH	A	10	257-258[g]	53	NA
55		Me	NH	NH	h	56	254-256	20	-21±6*
56		CF_3	NH	NH	A	21	188-189[i]	20	-29±14*
57		CF_3	NH	NH	A	59	196-197	20	-38±2*
58		CF_3	NH	NH	A	64	266-268	20	-27±5*
59[j]		CF_3	NH	NH	A	44	178-180	100	NA

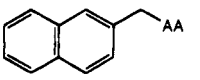
[a,c,d,e,*] See footnotes, Table 1. [b] All compounds listed as NH exist as the iminol tautomer by ^1H NMR, (DMSO-d_6) and IR (KBr). [f] Ethyl 2-benzylacetoacetate purchased from Aldrich. [g] Analysis for 0.25 hydrate. [h] β-Keto ester from borohydride/pyridine reduction of α-acetyl propenoates, see text. [i] Analysis for 0.0625 toluene (NMR). [j] Racemic material.

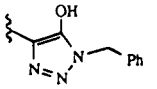
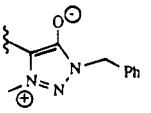
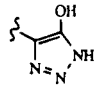
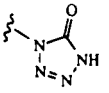
54.2 mmol, 60% oil dispersion) in THF (100 mL) cooled in an ice bath was added ethyl acetoacetate (neat, 5.9 g, 45 mmol) dropwise so as to control H_2 evolution. When gas evolution ceased, the mixture was allowed to warm to ambient temperature, a solution of 2-(bromomethyl)naphthalene (10 g, 45 mmol) in THF (125) mL was added, and the mixture was warmed to reflux for 15 h. The mixture was cooled in ice, quenched with 10% aqueous HCL solution, warmed to room temperature, diluted with ethyl acetate, and subjected to standard aqueous workup. the crude product was purified by HPLC (10% ethyl acetate/hexane) to give 11 g (41 mmol, 91%) of α-acetyl-3-(2-naphthalenyl)propionic acid ethyl ester as a pale yellow oil: IR ($CHCl_3$) υ (cm^{-1}) 1740, 1715; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.3 (d, 2H), 3.87 (t, 1H); MS (EI) *m/z* 270 (M^+).

A mixture of hydroxylamine hydrochloride (0.90 g, 13 mmol) and 1 N aqueous sodium hydroxide (13 mL), cooled in ice, was treated with a solution of α-acetyl-3-(2-naphthalenyl)propionic acid ethyl ester (3.5 g, 13 mmol) in THF (10 mL). After 1.5 h at ice temperature, a second equivalent of 1 N aqueous hydroxide solution was added and the mixture allowed to stir 1 h at 0 °C. The reaction mixture was then poured onto an ice-cold solution of glacial acetic acid saturated with anhydrous HCl(g). The mixture was allowed to warm to room temperature, diluted with water, and stirred for 1 h. The product was collected by suction filtration, washed with ether, and dried under vacuum to give the title compound as a white solid (0.80 g, 3.4 mmol): IR (KBr) ν (cm^{-1}) 3050, 2910, 2825, 2680, 2560, 1660, 1630, 1600, 1535, 1510, 1430, 1385, 1355, 1300, 1245, 1215, 1195, 945, 915, 890, 860, 830, 780, 755, 735, 700; ^1H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H), 3.73 (s, 2H), 7.35 (dd, 1H, J = 8.4, 1.6 Hz), 7.45 (m, 2H), 7.64 (s, 1H), 7.83 (m, 3H), 11.2 (s broad, 1H); MS (EI) *m/z* 239 (M^+).

4-(2-Naphthalenylmethyl)-3-methyl-5(2*H*)-isoxazolone (12). The procedure above for the synthesis of isoxazolone isomer **11** was followed except that the reaction was quenched by the addition of acetic acid to the cold mixture. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was poured onto aqueous saturated brine solution, extracted with ethyl acetate, and dried over $MgSO_4$. The crude product was dissolved in a minimum amount of warm dichloromethane, diluted with hexane until faintly turbid, and stored in a −10 °C freezer. The product was collected by filtration and dried under vacuum to give 0.490 g (2.05 mmol) of the title compound (from 2.76 g, 10.2 mmol of β keto ester) as a brown solid: IR ($CHCl_3$) ν (cm^{-1}) 3050, 3020, 3000, 1790, 1720 (broad), 1630, 1600, 1505, 1425, 1385, 1265, 1210, 1035, 1015, 870, 815; ^1H NMR (400 MHZ, DMSO-d_6) δ 2.1 (s, broad, 3H), 3.63 (s, 2H), 7.37 (dd, 1H, J = 8.4, 1.6 Hz), 7.46 (m, 2H), 7.67 (s, 1H), 7.84 (m, 3H), 11.99 (s, broad, 1H); MS (EI) *m/z* 239 (M^+).

Table 5. Effects of Additional Nitrogen Substitution into the Acidic Azole Backbone on Plasma Glucose in db/db Mice



no.[a]	AA	Synth[b] Method	% Yield[c]	mp(°C)	pKa[d]	Log P[e]	db/db Dose (mg/kg)	db/db % Δ [Glucose][f]
60		g	33	116-118[h]	9.11	2.12	20	NA
61		g	8	195-199 (dec)[i]	9.2	2.52	100	NA
62		g	36	176-177 (dec)			100	NA
63		g	81	117-120			100	NA
64		j	31	187 (dec)[k]	8.01	1.67	100	NA
65		j	27	168-170.5	6.36	0.79	100	NA

[a-f] See footnotes, Table 1. [g] See text. [h] Analysis for 0.08 ethyl acetate (NMR). [i] Analysis for 0.2 H_2O. [j] See Scheme 3. [k] Analysis for 0.09 ethyl acetate (NMR).

1,2-Dihydro-5-methyl-4-(2-naphthalenylmethyl)-3*H*-pyrazol-3-one (Tautomer, 13). A mixture of α-acetyl-3-(2-naphthalenyl)propionic acid ethyl ester (1.9 g, 7.0 mmol), hydrazine hydrate (0.34 mL, 7.0 mmol), and absolute ethanol (40 mL) were heated to reflux. After 15 min a white precipitate had formed. This material was collected on a Büchner funnel, washed with ether, and air-dried. The product (1.3 g, 5.5 mmol) was analytically pure as isolated: IR (KBr) ν (cm^{-1}) 2600 (broad), 1605, 1585, 1540, 1505, 1475, 1410, 1275, 1225, 1200, 1125, 1150, 920, 845, 805, 795, 780, 765, 745, 735; ^1H NMR (400 MHz, DMSO-d_6) δ 2.02 (s, 1H), 3.71 (s, 2H), 7.35 (dd, 1H, J = 6.8, 1.6 Hz), 7.42 (m, 2H), 7.59 (s, 1H), 7.79 (m, 3H), 10.4 (broad, 2H); MS (EI) *m/z* 238 (M^+).

2-Hydroxy-4-(2-naphthalenyl)-4-oxo-2-butenoic Acid Methyl Ester (14). A slurry of sodium hydride (4.70 g, 118 mmol, 60% oil dispersion) in benzene (150 mL) was cooled in ice, and methanol (4.80 mL, 118 mmol) was added dropwise. To this cold mixture was added dropwise a solution of 2-acetylnaphthalene (10 g, 59 mmol) and dimethyl oxalate (6.94 g, 58.8 mmol) in benzene (150 mL). The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with 1 N aqueous HCl solution, and following standard aqueous workup, the residue was dissolved in a minimum amount of warm methanol, diluted with Et_2O until turbid, and cooled in ice. The product (14.2 g, 55.2 mmol, combined two crops) precipitated as a yellow solid. It was collected by vacuum filtration and air-dried: IR (KBr) ν (cm^{-1}) 1750, 1630, 1440, 1430, 1355, 1315, 1285, 1270, 1250, 1195, 1130, 1120, 975, 875, 825, 780, 765, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.25 (s, 1H-(chloroform at 7.26), 7.58–7.68 (m, 2H), 7.89–8.05 (m, 5H), 8.56 (s, broad, 1H). MS (EI) m/z 256 (M^+).

4-[(2,3-Dihydro-1,4-benzodioxin-6-yl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one (Tautomer, 55). 2,3-Dihydro-1,4-benzodioxin-6-carboxaldehyde (12.5 g, 76.2 mmol), 8.80 mL (69.3 mmol) of ethyl acetoacetate, acetic acid (0.79 mL, 13.9 mmol), and piperidine (0.27 mL, 2.3 mmol) were combined in 250 mL of benzene, and the mixture was heated to reflux with azeotropic removal of water (Dean–Stark trap) for 15 h. The reaction mixture was cooled to room temperature, volatile materials were removed in vacuo on the rotary evaporator, and the residue was partitioned between ethyl acetate and 1 N aqueous HCl solution. The organic phase was separated, washed with saturated brine solution, dried over $MgSO_4$, and concentrated. The residue was filtered through a short silica gel pad with the aid of ethyl acetate and concentrated in vacuo, and the residue was distilled using a kugelrohr apparatus. The product, α-acetyl-3-(2,3-dihydro-1,4-benzodioxin-6-yl)propenoic acid ethyl ester, was obtained in quantitative yield, an ~1:1 mixture of *E* and *Z* double bond isomers, as a bright yellow oil, and was used directly in the next step: IR (film) ν (cm^{-1}) 1735, 1710, 1665, 1620, 1590, 1520; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s) and 2.38 (s, isomeric methyls), 7.41 and 7.51 (s, isomeric vinyl hydrogens); MS (EI) *m/z* 276 (M^+).

The *E* and *Z* propenoic ester mixture (5.00 g, 19.5 mmol) was added to a solution of sodium borohydride (2.97 g, 7.86 mmol) in anhydrous pyridine at room temperature. The reaction was stirred at room temperature for 24 h. Pyridine was removed in vacuo on the rotary evaporator, and the residue was triturated with dichloromethane. The dichloromethane solution was decanted into ice-cold 0.5 N HCl solution with vigorous stirring, followed by standard aqueous workup to give 5.00 g (19.4 mmol, 99%) of pure α-acetyl-3-(2,3-dihydro-1,4-benzodioxin-6-yl)propanoic acid ethyl ester as

a colorless oil: IR (film) ν (cm^{-1}) 1740, 1715, 1590, 1500; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.05 (d, 2H, J = 7.6 Hz), 3.72 (t, 1H, J = 7.6 Hz); MS (EI) m/z 278 (M^+).

The title compound was prepared from the above β-keto ester (2.5 g, 9.7 mmol) and anhydrous hydrazine (0.76 mL, 24 mmol) in ethanol according to the procedure for compound **13**. The product precipitated from the ethanol and was collected on a suction funnel, washed with ethyl acetate and diethyl ether, and air-dried, which gave 0.61 g of the product as white solid: IR (KBr) ν (cm^{-1}) 2600 (broad), 1600 (broad), 1540 (broad), 1500, 1430, 1310, 1280, 1260, 1200, 1170, 1130, 1065, 915, 885, 790, 745; ^1H NMR (400 MHz, DMSO-d_6) δ 1.98 (s, 3H), 3.39 (s, 2H), 4.15 (s, 4H), 6.57–6.62 (m, 2H), 6.68 (d, 1H, J = 8.7 Hz); MS (EI) m/z 246 (M^+).

1,2-Dihydro-4-[(6-quinoxalinyl)methyl]-5-(trifluoromethyl)-3*H*-pyrazol-3-one (Tautomer, 58). A mixture of 6-methylquinoxaline (20.0 g, 0.139 mol, distilled prior to use [bp 119 °C (10 mmHg)], *N*-bromosuccinimide (29.7 g, 0.167 mol), azobisisobutyronitrile (catalytic amount), and carbon tetrachloride was refluxed for 2 h, at which time TLC (70:30 hexane–ethyl acetate) revealed the absence of starting material. The reaction mixture was allowed to stand at room temperature overnight, filtered, and concentrated in vacuo to give 35 g of crude product as a pale yellow solid. The material crystallized in an ice bath from dichloromethane to give 3.5 g of 6-(bromomethyl)quinoxaline[54] as a yellow solid. The mother liquor was concentrated in vacuo and treated with hot heptane on a steam bath (**caution**: prolonged heating on steam bath or use of a hot plate caused extensive decomposition, with evidence of bromine evolution) to provide an additional 12.7 g of the compound as white crystals (total yield = 15.5 g, 0.695 mol, 50%): MS (EI) m/z 222 (M^+).

A mixture of sodium hydride (3.6 g, 90 mmol, 60% oil dispersion) and 1,2-dimethoxyethane (125 mL) were cooled in ice. Ethyl 4,4,4-trifluoroacetoacetate (12 mL, 82 mmol) was added dropwise at a rate so as to control hydrogen evolution. The reaction mixture was then warmed to reflux temperature, and a solution of 6-(bromomethyl)quinoxaline (15.5 g, 69.5 mmol) in 125 mL of 1,2-dimethoxyethane was added. The reaction mixture was refluxed for 15 h, volatile materials were removed in vacuo on the rotary evaporator, and the residue was subjected to standard aqueous workup, followed by chromatography on silica gel (40 wt equiv), elution with 1:1 ethyl acetate–hexane + 1% acetic acid to give 11.0 g (33.7 mmol, 49%) of ethyl 6-quinoxolinyl-α-(trifluoroacetyl)propanoate, as a tan glass: IR (film) ν (cm^{-1}) 3200 (broad, enol), 1720, 1510. MS (EI) m/z 326 (M^+).

A mixture of the above β-keto ester (5.5 g, 17 mmol) and anhydrous hydrazine (0.78 mL, 25 mmol) in 300 mL of toluene were combined at 0 °C for 1 h and then brought to reflux for 48 h. The reaction mixture was cooled, and volatile materials were removed on a rotary evaporator. The residue was partitioned between ethyl acetate and 5 N HCl solution, followed by standard aqueous workup which gave 4.3 g of a tan solid. Recrystallization from hot ethanol gave the title compound as tan crystals: IR (KBr) ν (cm^{-1}) 3420, 3080, 2860, 2760, 2660, 1615, 1525, 1480, 1280, 1220, 1150, 1140, 1120, 1020, 995, 955, 915, 870, 830, 810, 780, 760, 750, 710, 685; ^1H NMR (400 MHz, DMSO-d_6) δ 4.0 (s, 2H), 7.66–7.71 (m, 2H), 8.02 (d, 1H, J = 8.5 Hz), 8.87 and 8.88 (AB q, 2H, J = 1.7 Hz), 10.95 (s, broad 1H), 12.96 (s, broad, 1H); MS (EI) m/z 294 (M^+).

1,2-Dihydro-4-(2-naphthalenylmethyl)-1,2,3-triazol-5-one (Tautomer, 64). A warm solution of acetoacetamide (13.7 g, 136 mmol) in dry DMF (35 mL) was added to a slurry of sodium hydride (5.43 g, 136 mmol, 60% oil dispersion) in dry 1,2-dimethoxyethane (DME, 150 mL) at room temperature. The mixture was warmed in a 60 °C oil bath until H_2 evolution ceased, whereupon a solution of 2-(bromomethyl)naphthalene (30.0 g, 136 mmol) in DME (300 mL) was added and the mixture heated to reflux for 15 h. The reaction mixture was cooled to room temperature, volatile materials were removed in vacuo on the rotary evaporator, and the residue was partitioned between ethyl acetate and 1 N aqueous HCl solution, followed by standard aqueous workup. The crude residue, essentially a 1:1 mixture of mono- and di-C-alkylated products, was dissolved in hot dichloromethane and left to stand at room temperature. The monoalkylated product, α-acetyl-3-(2-naphthalenyl)propionic acid amide (5.0 g, 21 mmol, 15%) crystallized from the mixture as a white solid: mp 145–147 °C; IR (KBr) ν (cm^{-1}) 3390, 3280, 1710, 1635; ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.27-3.40 (m, 2H AB portion of ABX, J_{ab} = 13.8 Hz), 3.78 (apparent t; X portion of ABX); MS (EI) m/z 241 (M^+).

The above β-keto amide (1.50 g, 6.22 mmol), methanesulfonyl azide (1.88 g, 15.5 mmol, prepared from methanesulfonyl chloride and sodium azide in acetone at room temperature),[34] triethylamine (2.2 mL, 15.8 mmol), and ~0.3 mL of H_2O[34] were combined in acetonitrile (25 mL) at room temperature until the complete disappearance of starting material by TLC (10% MeOH/$CHCl_3$: the product α-diazo amide is slightly more polar than starting material ($R_f \sim 0.5$) and fluoresces under a UV lamp). The reaction mixture was poured onto saturated, aqueous sodium bicarbonate solution and extracted with ethyl acetate and subjected to standard aqueous workup (**caution; the α-diazoamide decomposed when a water bath temperature of 70 °C was applied).** The crude diazoamide (IR (KBr) ν 2080, 1660, 1590 cm^{-1}) was carried on directly without purification by treatment with sodium methoxide solution in methanol (3 mL, 25 wt %). The mixture was stirred at room temperature for 15 h, poured onto cold (0 °C) 1 N aqueous HCl solution, and stirred for 1 h. The precipitate was collected and triturated with warm ethyl acetate which gave 0.43 g (1.91 mmol) of **64** as a yellow powder: IR (KBr) ν (cm^{-1}) 3400, 3180, 2935, 1580, 1550, 1385, 1175, 1160, 1150, 995, 980, 900, 840, 790, 740; ^1H NMR (400 MHz, DMSO-d_6) δ 4.0 (s, 2H), 7.38 (m, 1H), 7.42–7.5 (m, 2H), 7.67 (s, broad, 1H), 7.8–7.87 (m, 3H), 10.1 (s, broad, 1H), 13.5 (s, broad, 1H); MS (EI) m/z 225 (M^+).

1,4-Dihydro-1-(2-naphthalenylmethyl)tetrazol-5-one (65). To a solution of 2-(azidomethyl)naphthalene[37] (4.4 g, 24 mmol) in toluene (80 mL) was added chlorocarbonyl isocyanate (neat; tech grade, 5.8 mL ~ 72 mmol), and the mixture was heated in a 60 °C oil bath overnight. The reaction was cooled in ice and water added cautiously (vigorous gas evolution, exothermic). When gas evolution ceased, a white precipitate formed. Ethyl acetate and 1 N HCl solutions were added, and the mixture was stirred at room temperature for 1 h. The organics were separated, and during standard aqueous workup, the product crystallized from cold toluene–ethyl acetate mixture during concentration, providing 1.47 g (6.50 mmol) of **65** as white crystals: IR (KBr) ν (cm^{-1}) 3000, 2860, 2760, 1710, 1680, 1510, 1430, 1405, 1360, 1260, 1200, 1140, 1060, 1000, 960, 950, 890, 860, 820, 810, 735, 730, 725; ^1H NMR (400 MHz, DMSO-d_6) δ 5.25 (s, 2H), 7.44 (dd, 1H, J = 6.8 and 1.8 Hz), 7.5–7.56 (m, 2H), 7.83 (s, broad, 1H), 7.89–7.95 (m, 3H), 14 (s, broad, 1H); MS (DCI) m/z 227 ([M + H]$^+$).

pK_a Determinations. The apparent pK_as for selected compounds indicated in the tables were measured by potentiometric titration (in duplicate) in 1:1 dioxane–water using a Fisher Accumet pH meter model 630 and a Perkin-Elmer chart recorder model 56. Experimental conditions in all cases were as follows:

sample concentration	0.2 mM
solvent volume	30 mL
temperature	25 °C
titrant	0.1 N NaOH
flow rate	0.17 mL/min

A system conditioning and check was performed, in duplicate, to ensure accurate and reproducible results using as standards piperazine, allantoin, barbituric acid, and ciglitazone.

log *P* Determinations. All log *P* values listed in the tables are an average of at least two experiments. Generally, 1–2 mg of sample was added to a separatory funnel containing 1-2 mL of octanol and 5–10 mL of aqueous buffer (0.01 M $K_2HPO_4 \cdot 3H_2O$) at pH 7.4. The funnel was shaken for 1 min and then allowed to equilibrate over a 4 h period. The octanol and aqueous layers were then separated and centrifuged. Each solution was analyzed by reverse-phase HPLC. Samples from the octanol phase were diluted with acetonitrile–octanol mixture (9:1) before injection. Aqueous samples were injected directly. Chromatographic conditions were as follows:

column	Novapak C18 (3.9 × 150 mm)
particle size	4 mm
mobile phase	acetonitrile/0.01 M $NH_4H_2PO_3$; pH 3.5
flow rate	1 mL/min
wavelength	214 nm
injection size	10–100 mL

Note: For those samples with a high affinity for one phase, larger sample sizes were required to improve detection in both phases. Exceptions to the above chromatographic conditions were compound **14** (mobile phase buffer 0.05 M NH_4OAc; pH 2.65; column length 300 mm) and compound **15** (mobile phase buffer 0.05 M NH_4OAc; pH 2.95).

Postprandial db/db Mouse Assay. On the morning of day 1 (baseline), 35 male, db/db mice (C57BL/KsJ, Jackson Laboratories, 2–7 months of age and 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. Food was then returned to the mice. The plasma was separated, and the levels of glucose in the plasma were determined by an 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). On the afternoon of days 1, 2, and 3 the vehicle (0.2 mL of 2% Tween 80/saline w/v) or drugs (as suspensions in vehicle) were administered (po) to the ad libitum fed mice. On the morning of day 4, the food was removed from the cages; 3 h later, a blood sample was collected, and the mice were then given the fourth administration of drug or vehicle. Additional blood samples were collected at 2 and 4 h after drug administration and plasma glucose levels were determined.

To assess drug activity, the percent change of an animal's plasma glucose level on day 4 (mean of the 2- and 4-h values) from its level before drug administration (day 1 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 group and the individual groups.

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Supplementary Material Available: Experimental data for **9**, **17**, **23**, **44**, **60**, **62**, and **63** (7 pages). Ordering information is given on any current masthead page.

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(46) The measured log P of this compound is deceptive, since it indicates **38** is slightly less lipophilic than **13**. Conversely, the solubility and reverse-phase HPLC behavioral properties of these two compounds, in agreement with calculated log P values, suggest that **38** is significantly more lipophilic than **13**. Retention times on RP-HPLC (conditions: 40% acetonitrile, 60% pH 7.4 phosphate buffer; see Experimental Section) for **13** and **38** are 2.67 and 10.57 min, respectively. Solubility; **13** precipitates from refluxing ethanol, the conditions which form it, while pyrazolone **38** dissolves in hot hexane. Calculated log P values (MEDCHEM V3.54, Pamona College) are 2.78(**11**) and 4.16(**38**). Apparently, the discrepancy in log P values arises from the much greater acidity of **38** (100-1000-fold) relative to **13**, which produces a leveling effect when the two compounds are dispersed in octanol and pH 7.4 buffer (0.01 M K_2HPO_4) solutions.

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(48) Compounds **46** and **65** readily ionize and like all the active analogs, are freely soluble in 1% aqueous sodium bicarbonate solution, a property which can overcome possibly unfavorable lipophilicity. See: Dennis, M. J. Absorption Processes. In *Comprehensive Medicinal Chemistry*; Taylor, J. B., Ed.; Pergammon Press: Oxford, 1990; Vol. 5, pp 7–9.

(49) ^1H NMR of **44** in DMSO-d_6 indicates an ~85:15 ratio of tautomers, favoring the aromatic form. The minor component shows an ABX pattern and three exchangeable protons consistent with either a pyrazol-3-one or iminol structures. IR (KBr) does not show a carbonyl. **45**: IR (KBr) ν (cm^{-1}) 3260, 3190, 3170, 3025, 1685, 1650, 1610, 1535, 1450, 1335, 1305; NMR (400 MHz, DMSO-d_6) δ 3.16–3.38 (m, 2H, AB portion of an ABX, partially obscured by water peak), 3.48–3.53 (broadened singlet, 3H, overlapping X portion of ABX and 2H singlet) and broadened peaks at 3.85, 4.1, 9.0 and a sharp singlet at 9.9 sugest multiple tautomeric forms for this compound. **46**: IR (KBr) ν (cm^{-1}) 3500–2700 (broad), 1695, 1660, 1595; NMR (400 MHz, DMSO-d_6) δ 3.19–3.23 (m, 2H, broadened peaks overlapping with water signal, AB portion of an ABX), 3.56 (q, 1H, X portion of an ABX), 3.5 (s, broad, 1H) and 10.2 (broad, 1H) indicate this compound exists as the 5-hydroxy-2,4-dihydropyrazol-3-one tautomer.

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