[[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as Potent Antihyperglycemic Agents

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A series of [(ureidoethoxy)benzyl]-2,4-thiazolidinediones and [[(heterocyclylamino)alkoxy]-benzyl]-2,4-thiazolidinediones was synthesized from the corresponding aldehydes. Compounds from the urea series, exemplified by **16**, showed antihyperglycemic potency comparable with known agents of the type such as pioglitazone and troglitazone (CS-045). The benzoxazole **49**, a cyclic analogue of **16**, was a very potent enhancer of insulin sensitivity, and by modification of the aromatic heterocycle, an aminopyridine, **37**, was identified as a lead compound from SAR studies. Evaluation of antihyperglycemic activity together with effects on blood hemoglobin content, to determine the therapeutic index, was performed in 8-day repeat administration studies in genetically obese C57 Bl/6 ob/ob mice. From these studies, BRL 49653 (**37**) has been selected, on the basis of antihyperglycemic potency combined with enhanced selectivity against reductions in blood hemoglobin content, for further evaluation.

Introduction

Non-insulin-dependent diabetes mellitus (NIDDM) is a multifactorial disease characterized by insulin resistance in the liver and peripheral tissues[1] together with a pancreatic β-cell defect. Defective insulin action in the liver results in an increase in the basal rate of glucose output, thereby producing fasting hyperglycemia. The failure of insulin to adequately suppress hepatic glucose output postprandially together with a reduced rate of glucose disposal by peripheral tissues, particularly skeletal muscle, is responsible for the abnormal glycemic control after feeding. Insulin resistance, together with the hyperinsulinemia that is often present, may also play a role in the etiology of a wider spectrum of metabolic disorders such as obesity, hypertension, and atherosclerosis.[2]

The primary therapy for NIDDM is caloric restriction and aerobic exercise. These regimes increase insulin sensitivity,[3] but only a small percentage of patients adopt them with sufficient rigor to achieve a significant improvement in glycemic control. The most widely used oral pharmacological agents are members of the sulfonylurea class of antidiabetic drugs. These agents act by increasing insulin secretion, but they can also induce the adverse effects of severe hypoglycemia and weight gain.[4] In addition, both primary and secondary failure rates are high,[5] and there is no evidence that sulfonylureas successfully modify the macro- and microvascular complications of NIDDM.[4] Thus, pharmacological approaches that result in better glycemic control are required since such agents might be expected to lead to a reduction in the secondary complications.[6,7] Pharmacological intervention to enhance the biological activity of endogenous insulin (insulin sensitivity enhancers) represents an attractive and novel approach to the treatment of NIDDM. The pioneer compound ciglitazone (Figure 1) improves glycemic control in insulin resistant animal models of NIDDM by increasing insulin sensitivity.[8] Three further substituted benzyl-2,4-thiazolidinediones, pioglitazone,[9] troglitazone (CS-045),[10] and englitazone,[11] have been, or are being, progressed clinically.

We now report the synthesis and biological action of a series of potent antihyperglycemic agents based initially on considerations of CLog *P*, a calculated partition coefficient between octan-1-ol and water.[13] These compounds promote insulin action in a range of animal models of insulin resistance. The early lead series which satisfied the criterion for CLog *P* contained a urea or thiourea moiety, a modification that produced compounds having a 10-fold increase in potency when compared with ciglitazone. Cyclic analogues of the (thio)urea portion of these derivatives afforded compounds showing a further marked improvement in potency.

In toxicological studies, several antihyperglycemic 2,4-thiazolidinediones have been reported to adversely affect bone marrow function[14] and reduce packed red cell volume.[15] The impact on red cell parameters of our more potent antidiabetic compounds was assessed to determine selectivities to facilitate compound progression.

Chemistry

2,4-Thiazolidinediones **3** were generally prepared from the corresponding aryl aldehydes **1** by the procedure shown in Scheme 1. Knöevenagel condensation between the aldehyde and 2,4-thiazolidinedione in refluxing toluene, containing a catalytic amount of piperidinium acetate or benzoate, gave the benzylidenes **2**, which crystallized from the reaction mixture in high purity. In most cases, the olefinic bond of the benzylidene-2,4-thiazolidinedione **2** was reduced with hydrogen in 1,4-dioxane using 10% palladium on carbon as catalyst to give the benzyl-2,4-thiazolidinedione **3**. In the case of those substrates where poisoning of the catalyst became a problem, the reduction was effected by utilization of the magnesium–methanol electron transfer technique of Watt *et al.*[16]

The aldehydes **1** were prepared using one of the route exemplified in Schemes 2 and 3. Reaction of a 2-halogenoheterocycle with an appropriately substituted ω-al-

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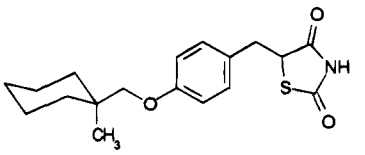
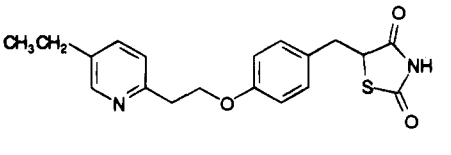
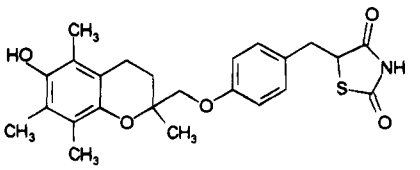


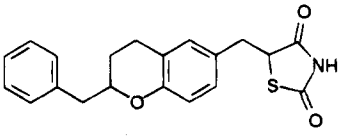
Ciglitazone (CLog *P* 3.57)[12]



Pioglitazone



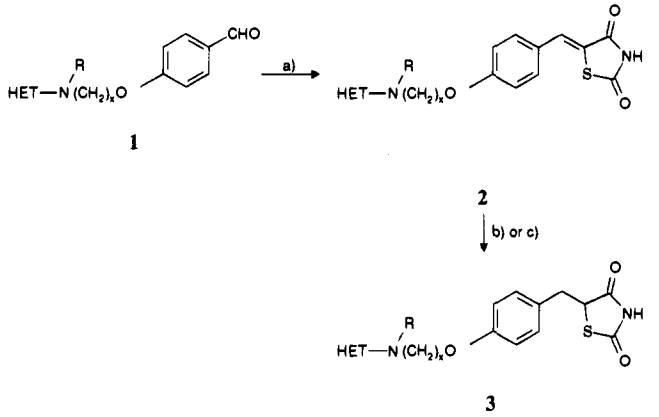
Troglitazone (CS-045)



Englitazone

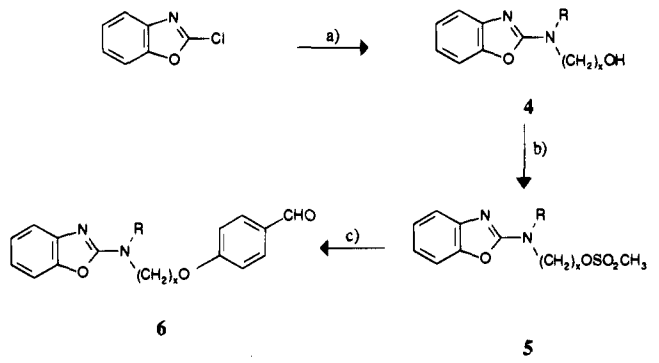
Figure 1.

Scheme 1[a]



[a] (a) 2,4-Thiazolidinedione, piperidine, acetic acid, toluene, reflux; (b) H_2, 10% Pd–C, dioxane; (c) Mg, methanol.

Scheme 2[a]

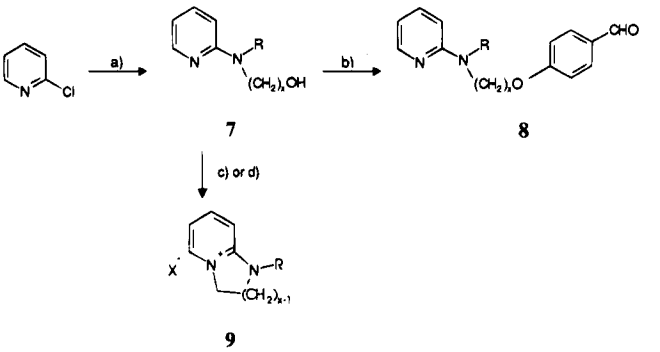


[a] (a) $RNH(CH_2)_xOH$, Et_3N, THF, room temperature; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (c) 4-hydroxybenzaldehyde, NaH, DMF, 80 °C.

kylamino alcohol gave the heterocyclic amino alcohols **4** in good yield (80–95%). Conversion of the alcohols to their methylsulfonyl esters **5** and reaction with the anion of 4-hydroxybenzaldehyde in *N,N*-dimethylformamide then gave the aldehydes **6** (Scheme 2).

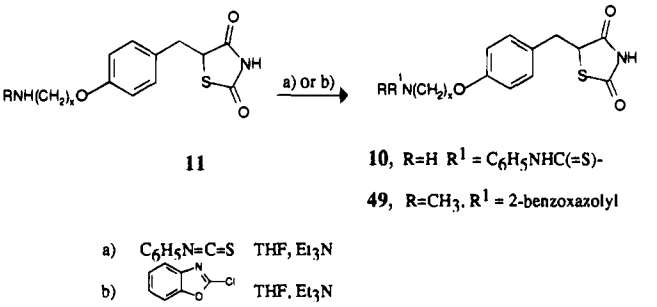
For those aldehydes containing a nucleophilic nitrogen atom (*e.g.*, **8**), reaction of the anion of the amino alcohol **7** with 4-fluorobenzaldehyde in *N,N*-dimethylformamide was employed (Scheme 3). Attempts to prepare the methanesulfonyl or halogen derivatives of **7**, as described in Scheme 2, gave predominantly **9**, the product of intramolecular cyclization, on exposure to base.

Scheme 3[a]



[a] (a) $RNH(CH_2)_xOH$, 120 °C; (b) 4-fluorobenzaldehyde, NaH, DMF, 80–120 °C; (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C and then 4-hydroxybenzaldehyde, NaH, DMF, 80 °C; (d) Ph_3P, CCl_4 and then 4-hydroxybenzaldehyde, NaH, DMF, 80 °C.

Scheme 4



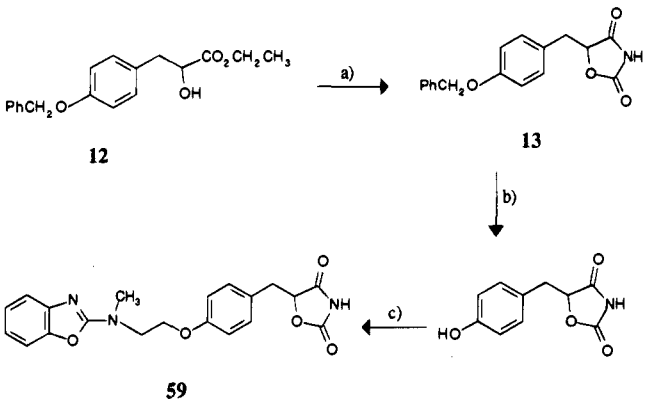
The thiourea **10** was prepared by reaction of amine **11** (R = H) with phenyl isothiocyanate (Scheme 4). It was subsequently found possible to react **11** (R = CH_3) with, for example, 2-chlorobenzoxazole to give **49**. Aldehydes used for the synthesis of ureas **16–22** (Table 1) were prepared from their corresponding alcohols[17] using the above fluoride displacement procedure (Scheme 3).

Treatment of ethyl 2-hydroxy-3-[(4-benzyloxy)phenyl]-propanoate (**12**)[18] with urea in the presence of alkoxide gave the 2,4-oxazolidinedione **13**. Debenzylation of **13** afforded the phenol which, on alkylation with mesylate **5**, gave the oxygen isostere **59** (Scheme 5).

Results and Discussion

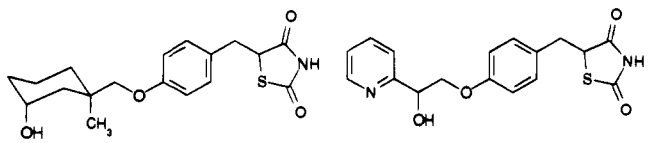
Antihyperglycemic activity was determined in genetically obese C57 Bl/6 ob/ob mice. This animal model of NIDDM is insulin resistant, hyperinsulinemic, and

Scheme 5[a]



[a] (a) Urea, CH_3ONa, CH_3OH, C_2H_5OH, reflux; (b) 10% Pd–C, H_2, 1,4-dioxane; (c) NaH (2 equiv), mesylate **5**, DMF, 80 °C.

glucose intolerant. Compound was administered in the diet for 8 days, and antihyperglycemic efficacy was assessed using an oral glucose tolerance test. The minimally effective dose of the prototype agent ciglitazone in this test procedure was 3000 μmol kg^{-1} of diet. In dog, rat, and man, several metabolic oxidation products of the cyclohexane ring of ciglitazone are formed.[19] One of these, AD 4743, showed more potent antihyperglycemic activity than ciglitazone in genetically obese and diabetic kk (kkA^y) mice.[19] The increased activity of AD 4743 may be related to increased bioavailability as a result of the greater hydrophilicity of this molecule or, for example, to a fortuitous incorporation of an additional functionality that enhances receptor binding. An investigation of compounds whose CLog *P* values were lower than that of ciglitazone (CLog *P* 3.57) and closer to that of AD 4743 (CLog *P* 1.48) was initiated. This approach was reinforced by a class of compounds, exemplified by **14** (CLog *P* −0.38), the potency of which was claimed to be 2 orders of magnitude greater than that of ciglitazone.[20]



AD 4743 (CLog *P* 1.48) **14** (CLog *P*-0.38)

We proposed that insertion of an amino linker in the alkoxy chain would lower the lipophilicity of such molecules. The results of initial studies led to a series of urea analogues (Table 1) having CLog *P* values intermediate between those of ciglitazone and AD 4743. Several of these compounds (**15**, **16**, **18**, and **22**) showed increased potency compared to ciglitazone and had potency similar to pioglitazone[9] and CS-045[10] (Table 1).

Substitution in the phenyl ring of the urea **16**, to give **17** and **19**–**21**, gave a reduction or complete loss of antihyperglycemic activity. The replacement of ureas and thioureas by bioisosteres is well documented.[21] In this series, replacement of the urea moiety in **18** by *N*-cyanoguanidine, to give **23**, resulted in loss of antihyperglycemic activity.

Cyclic analogues of thiourea **15** (CLog *P* 1.21) and urea **16** (CLog *P* 1.37), while increasing CLog *P* values above those sought originally, gave the very potent 2-aminobenzothiazole **47** (CLog *P* 2.81) and 2-aminobenzoxazole **49** (BRL 48482, CLog *P* 2.12) (Table 2). The minimally effective dose of **47** in the ob/ob mouse is 10 μmol kg^{-1} of diet, and that of **49** is 3 μmol kg^{-1} of diet. These two compounds are representative of a series of extremely potent heterocyclylamino-linked analogues which demonstrate activity at least 300 times greater than that of ciglitazone.

Replacement of the benzothiazole and benzoxazole rings of **47** and **49** by 2-oxazole (**24**–**25**), 2-thiazole (**26**–**31**), 2-pyrimidine (**32**–**35**), pyrazine (**36**), and 2-pyridine (**37**–**45**) led to a number of compounds with potent antihyperglycemic activity in the ob/ob mouse screen (Table 2). However, replacement of the 2-pyridyl moiety of **37** by a 4-pyridyl group, to give **46**, reduced antihyperglycemic activity significantly. This result is similar to that observed in the pioglitazone series.[22]

The unsubstituted 2-pyridyl compound **37** (BRL 49653, CLog *P* 1.32) is one of the most potent compounds of this class, with a minimally effective dose of 3 μmol kg^{-1} of diet. While the CLog *P* values of AD 4743, the urea **16**, and BRL 49653 are comparable, a 100-fold difference in potencies was observed. This suggests that, contrary to our original postulate, hydrophilicity is not an important criterion for the enhanced potency of these compounds.

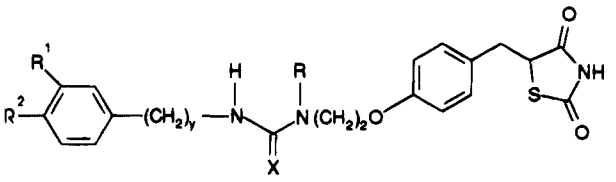
Introduction of substituents into the pyridyl ring of **37**, giving **38**–**45**, led to compounds with decreased potency. The thiazole ring of **26** was amenable to both methyl and phenyl substitution, **27** and **31** demonstrating much improved activity when compared to the parent compound. In contrast, **33**, the 4-phenyl-substituted analogue of the pyrimidine **32**, showed a decrease in potency.

Variations in the spatial separation of the thiazolidinedione and heterocycle were achieved by altering the length of either the linking chain, to give **52** and **53** (Table 3), or the methylene of the benzyl moiety, to give **61** and **62** (Table 4). Both strategies resulted in compounds with poor antihyperglycemic potency, suggesting that the optimum linkage between the thiazolidinedione and heterocycle is that represented by **49**. Replacement of the ether oxygen link by sulfur (**54**) reduced potency (Table 3). Modification of the chain by alkyl (**55** and **57**) or phenyl (**56**) branching or introduction of a hydroxyl group (**58**) into the chain all gave poorly active or inactive compounds (Table 4).

Modification of the 2,4-thiazolidinedione by replacement of sulfur with oxygen (**59**) and selenium (**60**) gave compounds which retained potency, although not at the level shown by **49**, while replacement with methylene to give the succinimide **63** abolished activity (Table 4). Methylation of the imide nitrogen of the 2,4-thiazolidinedione gave **64** which showed good activity only at high dose; this activity may be a result of metabolic demethylation.[8]

Removal of the substituent from the exocyclic nitrogen atom, as in the secondary amines **34** and **50**, or increased bulk of the group at this position, as in **48** and **51**, also reduced potency. Similarly, acylation of the exocyclic nitrogen, to give **35**, led to reduced activity. The benzylidene precursors, **65** and **66**, of the two potent compounds **49** and **37**, respectively, show moderate antihyperglycemic activity. Chemical shift analysis of the position of the benzylidene protons of **65** and **66** (at

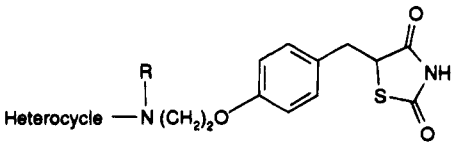
Table 1. Substituted Ureas and Thioureas



compound						% reduction in area under glucose tolerance curve (AUC) at μmol kg^{-1} of diet[a]				
no.	R	R^1	R^2	y	X	3000	1000	300	100	30
15	H	H	H	0	S		43***		10*	IA
16	H	H	H	0	O		58***		21**	
17	H	H	F	0	O		IA			
18	CH_3	H	H	0	O			27***		
19	H	H	Cl	0	O			IA		
20	H	Cl	Cl	0	O			IA		
21	H	H	OCH_3	0	O			IA		
22	CH_3	H	H	1	O			41**		IA
23	CH_3	H	H	0	N=CN			IA		
		ciglitazone				41**		IA		
		pioglitazone				63***	62***	35**	IA	
		CS-045				48***		20*	IA	

[a] IA indicates no significant activity at that dose. Significance of reductions in area under glucose tolerance curves: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, by Student's *t*-test.

Table 2. Modified Heterocycles



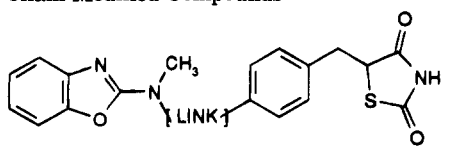
compound			% reduction in area under glucose tolerance curve (AUC) at μmol kg^{-1} of diet[b]				
no.	heterocycle	R	300	100	30	10	3
24	4,5-dimethyl-2-oxazolyl	$-CH_3$			33***	16*	IA
25	5-phenyl-2-oxazolyl	$-CH_3$			22*	20**	
26	2-thiazolyl	$-CH_3$		58***		IA	
27	4-methyl-2-thiazolyl	$-CH_3$			53***	28**	14*
28	4,5-dimethyl-2-thiazolyl	$-CH_3$			47***	IA	
29	4-phenyl-2-thiazolyl	$-CH_3$		34*	IA		
30	5-CH_3-4-Ph-2-thiazolyl	$-CH_3$		37***	20***	IA	
31	4-CH_3-5-Ph-2-thiazolyl	$-CH_3$		39**		27**	33***
32	2-pyrimidinyl	$-CH_3$		43***		18**	18**
33	4-Ph-2-pyrimidinyl	$-CH_3$				IA	
34	2-pyrimidinyl	-H			15**		
35	2-pyrimidinyl	$-COCH_3$			19**		
36	2-pyrazinyl	$-CH_3$		46***		IA	
37	2-pyridyl	$-CH_3$	61***	56***	41***	31***	17*
38	3-chloro-2-pyridyl	$-CH_3$	40***		15**		
39	4-methyl-2-pyridyl	$-CH_3$	41***		34***		IA
40	5-chloro-2-pyridyl	$-CH_3$	44***		IA		
41	5-methyl-2-pyridyl	$-CH_3$	35***	19**	18*		
42	5-amino-2-pyridyl	$-CH_3$			IA		
43	5-nitro-2-pyridyl	$-CH_3$			IA		
44	6-methyl-2-pyridyl	$-CH_3$	33***		IA		
45	6-methoxy-2-pyridyl	$-CH_3$	35***		IA		
46	4-pyridyl	$-CH_3$		13**		IA	
47	2-benzothiazolyl	$-CH_3$	66***	51**		36*	IA
48	2-benzothiazolyl	$-CH_2Ph$	56***	IA			
49	2-benzoxazolyl	$-CH_3$	42***	57***	52***	41***	22**
50	2-benzoxazolyl	-H		44***	IA		
51	2-benzoxazolyl	$-CHMe_2$		20**			

[a] See footnote a in Table 1.

7.74 and 7.73 ppm, respectively) confirms *Z*-geometry about the double bond.[23]

A number of the more potent analogues, **31**, **32**, **37**, and **49**, were tested for their ability to reduce blood hemoglobin content after 8 days of administration (in the diet) to the C57 Bl/6 ob/ob mouse. In addition, the effects of a low-potency thiazolidinedione, CS-045 (troglitazone), on blood hemoglobin content were determined also. At doses higher than those required to improve glycemic control, all compounds significantly reduced blood hemoglobin. In the case of CS-045, the no-significant-effect dose level on blood hemoglobin was

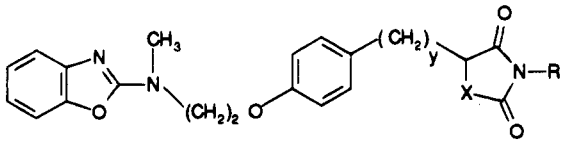
Table 3. Chain-Modified Compounds

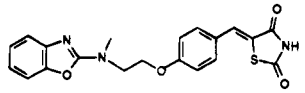
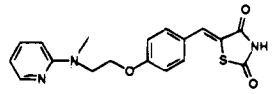


compound		% reduction in area under glucose tolerance curve (AUC) at μmol kg^{-1} of diet[a]			
no.	link	300	100	30	10
52	-$(CH_2)_3O$-	32*	IA		
53	-$(CH_2)_4O$-	25*		IA	
54	-CH_2CH_2S-		20**		
55	-$CH_2CH(CH_3)O$-	IA			
56	-$CH_2CH(C_6H_5)O$-			IA	
57	-$CH(CH_3)CH_2O$-	38***	IA		
58	-$CH_2CH(OH)CH_2O$-		IA		

[a] See footnote a in Table 1.

Table 4. Modified 2,4-Thiazolidinediones



compound				% reduction in area under glucose tolerance curve (AUC) at μmol kg^{-1} of diet[a]				
no.	X	y	R	1000	300	100	30	10
59	O	1	H	52***	41***	23**	IA	
60	Se	1	H			45**		IA
61	S	0	H	IA				
62	S	2	H			IA		
63	CH_2	1	H		IA			
64	S	1	CH_3	42***		IA		
65					30***			
66					47***		IA	

[a] See footnote a in Table 1.

Table 5. Selectivities of Potent 2,4-Thiazolidinediones

compound	antihyperglycemic potency dose (μmol kg^{-1} of diet) producing approx 25% reduction in area under glucose tolerance curve	no-significant-effect dose level on blood hemoglobin (μmol kg^{-1} of diet)	selectivity ratio
31	3	<300	<100
32	10	100	10
37	3	300	100
49	3	30	10
CS-045	400	600	1.5

only 1.5 times greater than the minimally effective antihyperglycemic dose level (Table 5). For **32** and **49**, the therapeutic margin was increased to 10, while for **37**, a dose level 100-fold greater than the minimally effective antihyperglycemic dose level had no significant effect on blood hemoglobin. **31**, although having equivalent antihyperglycemic potency to **37**, reduced blood hemoglobin significantly at a dose 100-fold greater than the minimally effective antidiabetic dose level.

In conclusion, we have discovered potent antihyperglycemic activity in a series of [[(heterocyclylamino)-alkoxy]benzyl]-2,4-thiazolidinediones. **37** (BRL 49653) is one of the most potent of these compounds and, in addition, has enhanced selectivity with respect to reductions in blood hemoglobin concentration.

Experimental Section

Melting points were recorded on a Büchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Erba analyzer, and all values are within ±0.4% of calculated values. ^{1}H NMR spectra were recorded using a Jeol GX 270 MHz or a Bruker AMX 400 MHz spectrometer as solutions in either $CDCl_3$ or DMSO-d_6 using tetramethylsilane as internal standard. Chemical shifts are expressed as δ (ppm) values for protons relative to the internal standard; all compounds gave spectra consistent with their assigned structures. The analytical data and the preparative procedures for compounds **15**–**66** are recorded in Table 6.

Biological Procedures. Determination of Antihyperglycemic Activity. C57 Bl/6 ob/ob mice were obtained at 9–10 weeks of age from Harlan Olac Ltd., Oxon, U.K. They were maintained at 26 ± 2 °C on a 12 h light/12 h dark cycle. Mice were provided with powdered RM3 diet (Special Diet Services, Witham, Essex, U.K.) and water *ad libitum*. Compounds were administered by dietary admixture for 8 days. Diets supplemented with compound were stored at 4 °C, and mice were provided with fresh food each day. None of the compounds tested caused significant changes in body weight gain during the treatment period. Six to eight mice were used in each treatment group. After 8 days of compound administration, mice were fasted for 5 h from 08.00 h. A blood sample (10 μL) was taken for glucose analysis from the cut tip of the tail. Glucose (3 g/kg of body wt, 10 mL/kg of body wt) was then administered by oral gavage. Additional blood samples (10 μL) for glucose analysis were taken at 45, 90, and 135 min after glucose administration. Blood samples were added to 1 mL of hemolysis reagent (50 mg/L digitonin, 100 mg/L maleimide). The glucose concentration in the hemolyzed sample was determined spectrophotometrically with hexokinase/glucose-6-phosphate dehydrogenase,[24] using a Ciba-Corning 550 express clinical chemistry analyzer.

Antihyperglycemic activity is defined as the percentage of reduction in the area under the blood glucose versus time curve (AUC) relative to control animals. The AUC was calculated trigonometrically using the trapezoid rule.[25] A dose of compound that produces an approximate 25–30% reduction in the area under the blood glucose versus time curve is defined as the minimally effective antihyperglycemic dose. This results in a glucose tolerance profile equivalent to that of normoglycemic (+/?) lean littermates.

Estimation of Blood Hemoglobin Content. The hemoglobin content of blood was determined by measurement of the absorbance at 576 nm of hemolyzed blood (10 μL taken at the start of the glucose tolerance test) after 8 days of treatment with compound.

Synthesis of Benzaldehydes 1. 4-[2-(Methyl-2-pyridinylamino)ethoxy]benzaldehyde (Fluoride Displacement Method). To a stirred solution of 2-(methyl-2-pyridinylamino)ethanol (15.2 g, 100 mmol) in dry dimethylformamide (500 mL) was added sodium hydride (4.4 g, 110 mmol, 60% dispersion in oil) portionwise under nitrogen at room temperature. The mixture was stirred at room temperature until the vigorous reaction ceased, and a solution of freshly distilled 4-fluorobenzaldehyde (13.6 g, 110 mmol) in dry dimethylformamide (100 mL) was added dropwise over 15 min. The reaction mixture was stirred at room temperature for 18 h; the mixture was added carefully to iced water (1.5 L) and extracted with ethyl acetate (4 × 1 L). The combined organic phase was washed exhaustively with water, dried ($MgSO_4$), filtered, and evaporated. The residual oil was chromatographed on silica gel in 1% methanol–dichloromethane to give 4-[2-(methyl-2-pyridinylamino)ethoxy]benzaldehyde (12.3 g, 48%) as an oil which solidified on standing: mp 58–62 °C; ^{1}H

Table 6. Analytical Data and Preparation Method

compd	prep method	mp (°C)	formula	anal.[a]	yield[b] (%)
15	3	132–133	$C_{19}H_{19}N_3O_3S_2$	C,H,N	33
16	1[c]	178–179	$C_{19}H_{19}N_3O_4S$	C,H,N	17
17	1[c]	172–173	$C_{19}H_{18}FN_3O_4S$	C,H,N	15
18	1[c]	147–148	$C_{20}H_{21}N_3O_4S$	H,N,C[d]	31
19	1[c]	169–170	$C_{19}H_{18}ClN_3O_4S$	C,H,N[e]	8
20	1[c]	199–201	$C_{19}H_{17}Cl_2N_3O_4S$	C,H,N	27
21	1[c]	174–175	$C_{20}H_{21}N_3O_5S$	C,H,N	10
22	1[c]	foam	$C_{21}H_{23}N_3O_4S$	C,N,H[f]	38
23	3	foam	$C_{21}H_{21}N_5O_3S$	C,N,H[g]	11
24	2[c]	foam	$C_{18}H_{21}N_3O_4S$	C,H,N	26
25	2[c]	200	$C_{22}H_{21}N_3O_4S$	C,H,N	46
26	2[c]	186	$C_{16}H_{17}N_3O_3S_2$	C,H,N	30
27	2[c]	foam	$C_{17}H_{19}N_3O_3S_2$	C,H,N	41
28	2[c]	177	$C_{18}H_{21}N_3O_3S_2$	C,H,N	18
29	2[c]	foam	$C_{22}H_{21}N_3O_3S_2$	C,H,N	17
30	2[c]	foam	$C_{23}H_{23}N_3O_3S_2$	C,H,N	65
31	2[c]	174	$C_{23}H_{23}N_3O_3S_2$	C,H,N	55
32	1[c]	150–151	$C_{17}H_{18}N_4O_3S$	C,H,N	21
33	1[c]	170–172	$C_{23}H_{22}N_4O_3S$	C,H,N	45
34	1[c]	173	$C_{16}H_{16}N_4O_3S$	C,H,N	51
35	*h*	137	$C_{18}H_{18}N_4O_4S$	C,H,N	24
36	2[c]	175–177	$C_{17}H_{18}N_4O_3S$	C,H,N	2
37	2[c]	153–155	$C_{18}H_{19}N_3O_3S$	C,H,N	72
38	1[c]	110–111	$C_{18}H_{18}ClN_3O_3S$	C,H,N,Cl	7
39	2[c]	foam	$C_{19}H_{21}N_3O_3S$	N,C,H[i]	9
40	2[c]	foam	$C_{18}H_{18}ClN_3O_3S$	C,H,N	16
41	1[c]	176–177	$C_{19}H_{21}N_3O_3S$	N,C,H[j]	32
42	1	240–244	$C_{18}H_{20}N_4O_3S{\cdot}2HCl$	C,H,N	27
43	3	149–151	$C_{18}H_{18}N_4O_5S$	C,H,N	39
44	2[c]	137–138	$C_{19}H_{21}N_3O_3S$	C,H,N	22
45	2[c]	>270	$C_{19}H_{20}N_3O_4SNa$	C,H,N	18
46	2[c]	260–261	$C_{18}H_{19}N_3O_3S$	C,H,N	15
47	1[c]	167–168	$C_{20}H_{19}N_3O_3S_2$	C,H,N	11
48	1[c]	foam	$C_{26}H_{23}N_3O_3S_2$	C,H,N	35
49	1[k]	147–149	$C_{20}H_{19}N_3O_4S$	C,H,N	61
50	1[c]	202–203	$C_{19}H_{17}N_3O_4S$	C,H,N	60
51	1[k]	foam	$C_{22}H_{23}N_3O_4S$	C,H,N	33
52	1[k]	171–173	$C_{21}H_{21}N_3O_4S$	C,H,N	50
53	1[k]	112	$C_{22}H_{23}N_3O_4S$	C,H,N	64
54	2	159–160	$C_{20}H_{19}N_3O_3S_2$	C,H,N	19
55	1	foam	$C_{21}H_{21}N_3O_4S$	C,H,N	9
56	2[c]	85–90	$C_{26}H_{23}N_3O_4S$	C,H,N	42
57	1[k]	152–156	$C_{21}H_{21}N_3O_4S$	C,H,N	21
58	1	152	$C_{21}H_{21}N_3O_5S$	C,H,N	20
59	6	173–174	$C_{20}H_{19}N_3O_5$	C,H,N	63
60	4	97–99	$C_{20}H_{19}N_3O_4Se$	C,H,N	51
61	4	>260	$C_{19}H_{16}N_3O_4SNa$	C,H,N	23
62	4	151–154	$C_{21}H_{21}N_3O_4S$	C,H,N	72
63	7	163–164	$C_{21}H_{21}N_3O_4$	C,H,N	16
64	5	118–120	$C_{21}H_{21}N_3O_4S$	C,H,N	91
65		227–229	$C_{20}H_{17}N_3O_4S$	C,H,N	95
66		196–197	$C_{18}H_{17}N_3O_3S$	C,H,N	96

[a] C,H,N analysis within ±0.4% of theory unless specified otherwise. [b] Yields quoted are for final stage. [c] Aldehyde prepared by fluoride displacement method. [d] C requires 59.98, observed 59.46. [e] N requires 10.00, observed 9.51. [f] H requires 5.57, observed 4.90. [g] H requires 5.00, observed 4.57. [h] Prepared by acylation of **34**. [i] C requires 61.38, observed 60.84; H requires 11.31, observed 10.82. [j] C requires 61.38, observed 60.92; H requires 11.31, observed 10.83. [k] Aldehyde prepared by mesylate displacement method.

NMR ($CDCl_3$) δ 3.10 (3H, s), 4.00 (2H, t), 4.25 (2H, t), 6.55 (2H, t), 7.05 (2H, d), 7.45 (1H, m), 7.90 (2H, d), 8.20 (1H, d), 9.90 (1H, s).

The starting material for the above reaction was prepared as follows: A mixture of 2-chloropyridine (11.4 g, 100 mmol) and 2-(methylamino)ethanol (100 mL) was heated under nitrogen to 120 °C, with stirring, for 15 h. The mixture was cooled to room temperature and added to iced water (200 mL), and the solution was extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were washed with brine (2 × 500 mL), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residual oil was vacuum distilled to give 2-(methyl-2-pyridinylamino)ethanol (9.58 g, 63%): bp 110–116 °C (1.0–1.5 mmHg); ^1H NMR ($CDCl_3$) δ 3.10 (3H, s), 3.6–3.85 (4H, m), 5.25 (1H, s, exchanges with D_2O), 6.6 (2H, m), 7.40 (1H, t), 8.10 (1H, d).

4-[2-(2-Benzoxazolylmethylamino)ethoxy]benzaldehyde (Mesylate Displacement Method). To a stirred solution of 4-hydroxybenzaldehyde (1.22 g, 10 mmol) in dry dimethylformamide (20 mL) under nitrogen was added sodium hydride (0.44 g, 11 mmol, 60% dispersion) portionwise at room temperature. When hydrogen evolution ceased, a solution of 2-(2-benzoxazolylmethylamino)ethanol methylsulfonyl ester (2.7 g, 10 mmol) in dry dimethylformamide (20 mL) was added dropwise. The mixture was heated to 80 °C and stirred at this temperature for 18 h. After cooling to room temperature, the solution was poured into iced water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed exhaustively with saturated brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 4-[2-(2-benzoxazolylmethylamino)ethoxy]benzaldehyde (2.52 g, 85%): mp 96–98 °C (ethanol); ^1H NMR ($CDCl_3$) δ 3.25 (3H, s), 3.95 (2H, t), 4.40 (2H, t), 6.90–7.40 (6H, m), 7.85 (2H, d), 9.90 (1H, s).

The starting material for the above reaction was prepared as follows: A solution of 2-chlorobenzoxazole (15.4 g, 100 mmol) in dry tetrahydrofuran (70 mL) was added dropwise to an ice-cooled, stirred solution of 2-(methylamino)ethanol (8.15 g, 110 mmol) in dry tetrahydrofuran (100 mL) containing triethylamine (10 mL) with protection from atmospheric moisture. The mixture was stirred at 0 °C for 1 h and at room temperature for a further 2 h. The solid was removed by filtration and washed with tetrahydrofuran (50 mL), and the combined organic solutions were evaporated under reduced pressure. Chromatography of the residue on silica gel in dichloromethane gave 2-(2-benzoxazolylmethylamino)ethanol (15.1 g, 85%): mp 62–63 °C; ^1H NMR ($CDCl_3$) δ 3.12 (3H, s), 3.4–4.0 (4H, m), 4.70 (1H, s, exchanges with D_2O), 6.8–7.4 (4H, m).

Methanesulfonyl chloride (11.5 g, 100 mmol) was added dropwise to a stirred solution of 2-(2-benzoxazolylmethylamino)ethanol (19.2 g, 107 mmol) in dry pyridine with protection from atmospheric moisture. The mixture was stirred at room temperature for 3 h and poured into iced water (500 mL), and the solution was extracted with dichloromethane (3 × 250 mL). The combined organic phase was washed with saturated sodium bicarbonate solution (250 mL) and saturated brine (250 mL), dried ($MgSO_4$), filtered, and evaporated. 2-(2-Benzoxazolylmethylamino)ethanol methylsulfonyl ester (18.2 g, 69%), mp 97–98 °C, was obtained following crystallization from isopropyl alcohol: ^1H NMR ($CDCl_3$) δ 3.0 (3H, s), 3.25 (3H, s), 3.90 (2H, t), 4.30 (2H, t), 6.90–7.40 (4H, m).

Synthesis of Benzylidene-2,4-thiazolidinediones 2. (*Z*)-5-[[4-[2-(2-Benzoxazolylmethylamino)ethoxy]phenyl]methylene]-2,4-thiazolidinedione (65). A solution of 4-[2-(2-benzoxazolylmethylamino)ethoxy]benzaldehyde (1.6 g, 5.4 mmol) and 2,4-thiazolidinedione (0.63 g, 5.4 mmol) in toluene containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean–Stark water trap for 2 h. The solution was cooled in a refrigerator overnight and filtered and the precipitate washed with ether and dried under vacuum to give **65** (2.03 g, 96%): mp 227–229 °C; ^1H NMR (DMSO-d_6) δ 3.23 (3H, s), 3.92 (2H, t), 4.34 (2H, t), 6.95–7.40 (6H, m), 7.53 (2H, d), 7.74 (1H, s, benzylidene proton), 12.5 (1H, br s, exchanges with D_2O). Anal. ($C_{20}H_{17}N_3O_4S$) C,H,N.

(*Z*)-5-[[4-[2-(Methyl-2-pyridinylamino)ethoxy]phenyl]methylene]-2,4-thiazolidinedione (66). Reaction of 4-[2-(methyl-2-pyridinylamino)ethoxy]benzaldehyde (2.85 g, 11 mmol) with 2,4-thiazolidinedione (1.30 g, 11 mmol) in toluene (60 mL), as described above, gave **66** (3.72 g, 95%): mp 196–197 °C (toluene); ^1H NMR (400 MHz, DMSO-d_6) δ 3.10 (3H, s), 3.92 (2H, t), 4.23 (2H, t), 6.57 (1H, q), 6.65 (1H, d), 7.10 (2H, d), 7.49–7.55 (3H, m), 7.73 (1H, s, benzylidene proton), 8.10 (1H, m), 12.5 (1H, br s). Anal. ($C_{18}H_{17}N_3O_3S$) C,H,N.

Synthesis of Benzyl-2,4-thiazolidinediones 3. 5-[[4-[2-Benzoxazolylmethylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (49) (Method 1). A solution of **65** (1.5 g, 3.8 mmol) in dry 1,4-dioxane (80 mL) was hydrogenated in the presence of 10% palladium on charcoal (2.0 g) at 18 °C

and atmospheric pressure until hydrogen uptake ceased. The solution was filtered though Celite, the filter pad was washed with dry 1,4-dioxane (100 mL), and the combined filtrates were evaporated to dryness under reduced pressure. The resulting oil was chromatographed on silica gel in 2% methanol in dichloromethane to give **49** (0.93 g, 61%) as a colorless solid: mp 147–149 °C (following recrystallization from methanol); ^{1}H NMR (DMSO-d_6) δ 3.1–3.5 (2H, m), 3.3 (3H, s), 3.95 (2H, t), 4.25 (2H, t), 4.5 (1H, m), 6.8–7.4 (8H, m), 12.2 (1H, br s, exchanges with D_2O). Anal. ($C_{20}H_{19}N_3O_4S$) C,H,N.

5-[[4-[2-(Methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (37) (Method 2). To a stirred suspension of **66** (1.0 g, 2.5 mmol) in methanol (70 mL) at room temperature was added magnesium turnings (100 mg). A further quantity of preactivated magnesium turnings (50 mg; activated with a crystal of iodine in methanol) was added, and the mixture was stirred and warmed until the reaction started (as evidenced by hydrogen evolution). Magnesium (900 mg) was added portionwise over a 2 h period. On completion of the addition, the mixture was stirred at room temperature for a further 2 h. The reaction mixture was added to iced water (150 mL), the pH adjusted to 7.5–8.0 using 10% aqueous hydrochloric acid, and the solution extracted with dichloromethane (3 × 150 mL). The combined organic extracts were washed with water (300 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residual gum was chromatographed on silica gel in 2% methanol–dichloromethane to give **37** (0.61 g, 62%) as a colorless solid: mp 153–155 °C (following recrystallization from methanol); ^{1}H NMR (DMSO-d_6) δ 2.9–3.4 (2H, m), 3.1 (3H, s), 3.9 (2H, t), 4.15 (2H, t), 4.8 (1H, m), 6.5–6.85 (2H, m), 6.8 (2H, d), 7.2 (2H, d), 7.5 (1H, m), 8.1 (1H, d), 12.05 (1H, br s, exchanges with D_2O). Anal. ($C_{18}H_{19}N_3O_3S$) C,H,N.

***N''*-Cyano-*N*-[2-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]ethyl]-*N*-methyl-*N'*-phenylguanidine (23) (Method 3).** 5-[[4-[2-(Methylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (2.0 g, 7.1 mmol), *N*-cyano-*N'*-phenylthiourea sodium salt (from phenyl isothiocyanate (1.25 g) and sodium cyanate (0.58 g)), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.4 g, 7.1 mmol) in dry dimethylformamide were stirred at room temperature for 110 h. The mixture was added to water (300 mL) and extracted with ethyl acetate (3 × 100 mL), and the combined organic extracts were washed with hydrochloric acid (2 × 100 mL, 2 M) and saturated brine (100 mL), dried ($MgSO_4$), filtered, and evaporated. Chromatography of the residue on silica gel eluting with 2% methanol in dichloromethane as eluant gave **23** (320 mg, 14%) as a foam: mp 91 °C (softens), 110–112 °C (collapses); ^{1}H NMR (DMSO-d_6) δ 3.05 (3H, s), 300–3.45 (2H, m), 3.80 (2H, t), 4.20 (2H, t), 4.85 (1H, m), 6.95 (2H, d), 7.05 (3H, m), 7.25 (2H, d), 7.30 (2H, t), 9.2 (1H, s, exchanges with D_2O), 12.0 (1H, br s, exchanges with D_2O). MH^+ – 424.

The starting material for the above reaction was prepared as follows: Methanesulfonyl chloride (27.2 g, 18.4 mL, 236 mmol) was added dropwise to an ice-cooled solution of phenylmethyl (2-hydroxyethyl)methylcarbamate (45.2 g, 216 mmol) and triethylamine (24 g, 236 mmol) in dichloromethane (150 mL) over 30 min. The resulting mixture was stirred at 0 °C for 2 h and then at room temperature overnight. Following dilution with dichloromethane (150 mL) and filtration, the filtrate was washed with water (2 × 200 mL) and saturated brine (200 mL), dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure to give phenylmethyl [2-[(methylsulfonyl)oxy]ethyl]methylcarbamate as an oil (58 g, 93%): ^{1}H NMR ($CDCl_3$) δ 2.85 (3H, s), 3.05 (2H, s), 3.60 (2H, t), 5.25 (2H, s), 7.40 (5H, s).

A solution of 4-hydroxybenzaldehyde (24.7 g, 233 mmol) in dry dimethylformamide (100 mL) was added dropwise to a stirred suspension of sodium hydride (8.8 g, 220 mmol, 60% dispersion) in dry dimethylformamide (200 mL), under nitrogen, and the resulting suspension was stirred at room temperature for 1 h. Phenylmethyl [2-[(methylsulfonyl)oxy]ethyl]methylcarbamate (58 g, 200 mmol) in dry dimethylformamide (200 mL) was added dropwise over 1 h and the resulting mixture was warmed to 80 °C and maintained at this temperature for 18 h. The cooled reaction mixture was added to iced water (700 mL) and the solution extracted with ethyl acetate (3 × 500 mL). The organic extracts were washed with water (6 × 500 mL) and saturated brine (2 × 500 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give an oil. The crude product was subjected to flash chromatography on silica gel (500 g) eluting with ethyl acetate–hexane (1:1) to give phenylmethyl [2-(4-formylphenoxy)ethyl]methylcarbamate (39.8 g, 63%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.10 (3H, s), 3.70 (2H, t), 4.20 (2H, partially resolved t), 5.20 (2H, s), 6.85 (2H, d), 7.35 (5H, s), 7.85 (2H, d), 9.90 (1H, s).

A mixture of the above aldehyde (39.5 g, 126 mmol), 2,4-thiazolidinedione (14.75 g, 126 mmol), and a catalytic amount of piperidinium benzoate in toluene (300 mL) was boiled under reflux in a Dean–Stark apparatus for 5 h to give the theoretical amount of water. The solution was cooled, and the product was collected by filtration, washed with diethyl ether, and dried under vacuum to give (*Z*)-phenylmethyl [2-[4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenoxy]ethyl]methylcarbamate (43 g, 83%): mp 160–163 °C; ^{1}H NMR (DMSO-d_6) δ 3.00 (3H, s), 3.65 (2H, t), 4.20 (2H, t), 5.15 (2H, s), 7.10 (2H, d), 7.40 (5H, s), 7.55 (2H, d), 7.80 (1H, s), 11.5–12.5 (1H, br s).

The above benzylidene compound (18 g, 44 mmol) in 1,4-dioxane (500 mL) was reduced under hydrogen at normal temperature and pressure in the presence of 10% palladium on carbon (18 g) for 24 h. After this time, a further portion of catalyst (17 g) was carefully added and the hydrogenation was continued for a further 48 h. The reaction mixture was filtered through Arbocel, the filter bed was washed with dioxane (500 mL), and the combined filtrates were evaporated to give phenylmethyl[2-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]ethyl]methylcarbamate (16.2 g, 90%) as a low-melting foam: ^{1}H NMR ($CDCl_3$) δ 3.10 (3H, s), 3.00–3.80 (4H, m), 4.15 (2H, partially resolved t), 4.52 (1H, dd), 5.23 (2H, s), 6.90 (2H, br d), 7.25 (2H, d), 7.50 (5H, s), 9.86 (1H, br s).

The above carbamate (16 g, 39 mmol) in ethanol (130 mL) was treated with hydrochloric acid (130 mL, 6 M), and the mixture was boiled under reflux overnight. After cooling to room temperature, the solution volume was reduced to 100 mL under vacuum, the residual solution was washed with ethyl acetate (2 × 100 mL) and filtered, and the pH was adjusted to 7.5 using 2.5 M sodium hydroxide solution. The resultant white solid was collected and dried under vacuum at 50 °C to give 5-[[4-[2-(methylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (5.3 g, 49%): mp 221–222 °C; ^{1}H NMR (DMSO-d_6, TFA-*d*) δ 2.70 (3H, s), 2.65–3.2 (2H, m), 3.35 (2H, t), 4.25 (2H, t), 4.8 (1H, m), 6.90 (2H, d), 7.25 (2H, d), 8.85 (1H, br s, exchanges with D_2O), 11.80 (1H, br s, exchanges with D_2O).

5-[4-[2-(2-Benzoxazolylmethylamino)ethoxy]phenyl]-2,4-thiazolidinedione Sodium Salt (61) (Method 4). A solution of lithium diisopropylamide (3.52 mL, 7 mmol, 2 M solution in heptane) in dry tetrahydrofuran (10 mL) was cooled to –78 °C under an atmosphere of dry nitrogen, and trimethylsilyl chloride (1.43 mL, 12 mmol) was added slowly with stirring. A solution of methyl 4-[2-(2-benzoxazolylmethylamino)ethoxy]benzeneacetate (2.18 g, 6.4 mmol) in dry tetrahydrofuran was added dropwise, and the mixture was stirred at –78 °C for 2 h. *N*-bromosuccinimide (1.18 g, 6.6 mmol) was added, and the mixture was allowed to warm to room temperature overnight. The solvent was evaporated; the residue was suspended in water (150 mL) and extracted with diethyl ether (2 × 150 mL). The combined ether layers were washed with water (3 × 300 mL) and brine (300 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residual oil was dissolved in methoxyethanol (25 mL); thiourea (0.73 g, 9.6 mmol) and sodium acetate (0.53 g, 6.5 mmol) were added and the mixture was heated at 100 °C for 18 h. Hydrochloric acid (5 mL, 6 M) was added, and the mixture was heated at reflux for 5 h. Water (200 mL) was added, and the mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with water (3 × 200 mL) and brine (1 × 200 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel in 1% methanol–dichloromethane. The product (0.60 g, 1.6 mmol), obtained as a foam, was dissolved in

methanol (3.5 mL) at 0 °C, and sodium hydride (64 mg, 1.6 mmol, 60% dispersion) was added. The mixture was stirred for 5 min, diluted with dry diethyl ether (15 mL), and stirred for a further 15 min. The solid was filtered, washed with diethyl ether, and dried under vacuum at 90 °C to give **61** as its sodium salt (0.53 g, 20%): mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 3.30 (3H, s), 3.85 (2H, t) 4.25 (2H, t), 4.95 (1H, s), 6.80 (2H, d), 7.00 (1H, t), 7.20 (3H, m), 7.30 (1H, d), 7.40 (1H, d). Anal. ($C_{19}H_{16}N_3O_4SNa$) C,H,N.

The starting material for the above reaction was prepared as follows: To a solution of methyl 4-hydroxybenzeneacetate (3.32 g, 20 mmol) in dry dimethylformamide (50 mL) at room temperature under an atmosphere of nitrogen was added sodium hydride (0.88 g, 22 mmol, 60% dispersion), and this mixture was stirred at room temperature for 30 min. 2-(2-Benzoxazolylmethylamino)ethanol methylsulfonyl ester (5.4 g, 20 mmol) in dry dimethylformamide (50 mL) was added, and the mixture was heated to 80 °C and maintained at this temperature overnight. After cooling, the mixture was added to water (1.5 L) and the aqueous solution was extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed with water (4 × 1 L) and saturated brine (1 × 1 L), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give methyl 4-[2-(2-benzoxazolylmethylamino)ethoxy]-benzeneacetate (4.38 g, 65%) as a gum: ^{1}H NMR ($CDCl_3$) δ 3.20 (3H, s), 3.55 (2H, s), 3.70 (3H, s), 3.80 (2H, t), 4.10 (2H, t), 6.70–7.40 (8H, m).

5-[[4-[2-(2-Benzoxazolylmethylamino)ethoxy]phenyl]-methyl]-2,4-selenazolidinedione (60). A mixture of methyl 2-chloro-3-[4-[2-(2-benzoxazolylmethylamino)ethoxy]benzene]-propanoate[26] (1.94 g, 5 mmol), sodium acetate (0.41 g, 5 mmol), and selenourea (0.62 g, 5 mmol) in ethanol (20 mL) was heated under reflux for 18 h. After cooling and evaporation of solvent, the residue was dissolved in tetramethylenesulfone (15 mL); 6 M hydrochloric acid (5 mL) was added and the mixture heated at 110 °C for 5 h. After cooling and addition of iced water (50 mL), the mixture was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel in 2% methanol–dichloromethane to give **60** (1.13 g, 51%): mp 97–99 °C; ^{1}H NMR (DMSO-d_6) δ 3.1–3.4 (2H, m), 3.3 (3H, s), 3.9 (2H, t), 4.25 (2H, t), 4.65 (1H, m), 6.8–7.2 (8H, m), 12.5 (1H, br s). Anal. ($C_{20}H_{19}N_3O_4Se$) C,H,N.

5-[[4-[2-(2-Benzoxazolylmethylamino)ethoxy]phenyl]-methyl]-3-methyl-2,4-thiazolidinedione (64) (Method 5). **49** (1.59 g, 4.0 mmol) was dissolved in dry dimethylformamide (10 mL) containing potassium carbonate (0.55 g, 4.0 mmol), and the mixture was stirred at room temperature during the addition of methyl iodide (0.27 mL, 4.4 mmol). The mixture was stirred at room temperature for 2 h, diluted with water (300 mL), and extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were washed with water (2 × 300 mL) and brine (1 × 300 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chormatographed on silica gel in 1% methanol–dichloromethane to give **64** (1.25 g, 76%): mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (3H, s), 3.40 (3H, s), 3.0–3.5 (2H, m), 3.95 (2H, t), 4.25 (2H, t), 4.40 (1H, m), 6.80 (2H, d), 7.05 (1H, t), 7.15 (2H, d), 7.20–7.40 (3H, m). Anal. ($C_{21}H_{21}N_3O_4S$) C,H,N.

5-[[4-[2-(2-Benzoxazolylmethylamino)ethoxy]phenyl]-methyl]-2,4-oxazolidinedione (59) (Method 6). Sodium hydride (0.85 g, 21 mmol, 60% dispersion in oil) was added portionwise to a stirred solution of 5-[(4-hydroxyphenyl)-methyl]-2,4-oxazolidinedione (2 g, 10 mmol) in dry DMF (65 mL) under an atmosphere of nitrogen. After effervescence had ceased, 2-(2-benzoxazolylmethylamino)ethanol methylsulfonyl ester (2.73 g, 10 mmol) was added and the solution heated to 80 °C overnight. After cooling, the mixture was added to water (400 mL), neutralized (2 M HCl), and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with water (100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), and evaporated to dryness. Chromatography of the residue on silica gel in 1% methanol in dichloromethane gave **59** (2.13 g, 58%): mp 173–174 °C (methanol); ^{1}H NMR (DMSO-d_6) δ 2.9–3.15 (2H, m), 3.2 (3H, s), 3.85 (2H, t), 4.25 (2H, t), 5.2 (1H, m), 6.8–7.4 (8H, m), 11.7 (1H, br s, exchanges with D_2O). Anal. ($C_{20}H_{19}N_3O_5$) C,H,N.

The starting material for the above reaction was prepared as follows: A solution of **12**[27] (4.5 g, 15 mmol), urea (1.62 g, 27 mmol), and sodium methoxide (1.13 g, 21 mmol) in a mixture of methanol (4 mL) and ethanol (40 mL) was stirred for 2 h at room temperature and then refluxed for 3 h. After cooling, the mixture was added to hydrochloric acid (2 M, 250 mL) and extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was chromatographed on silica gel in 5% methanol in dichloromethane to give **13** (3.7 g, 82%): mp 140 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 2.9–3.3 (2H, m), 5.0 (1H, t), 5.05 (2H, s), 6.85–7.0 (2H, d), 7.1–7.25 (2H, d), 7.45 (5H, s), 7.2–7.7 (1H, br s, exchanges with D_2O).

A solution of **13** (4.7 g, 16 mmol) in dry 1,4-dioxane (70 mL) in the presence of 10% palladium on charcoal (0.25 g) was stirred under an atmosphere of hydrogen at ambient temperature until hydrogen uptake ceased. The solution was filtered through Celite, the filter pad was washed exhaustively with dioxane, and the combined filtrates were evaporated to dryness under vacuum. The residue was chromatographed on silica gel in 10% methanol in dichloromethane to give 5-[(4-hydroxyphenyl)methyl]-2,4-oxazolidinedione (2.98 g, 91%): mp 205 °C (methanol); ^{1}H NMR (DMSO-d_6) δ 2.8–3.2 (2H, m), 5.2 (1H, t), 6.65–6.75 (2H, d), 7.0–7.1 (2H, d), 9.5 (2H, br s, exchanges with D_2O).

3-[[4-[2-(2-Benzoxazolylmethylamino)ethoxy]phenyl]-methyl]-2,5-pyrrolidinedione (63) (Method 7). Diethyl [[4-[2-(2-benzoxazolylmethylamino)ethoxy]phenyl]methyl]-butanedioate (2.6 g, 5.7 mmol) in absolute ethanol (30 mL) was added to a solution of sodium ethoxide in ethanol, prepared from sodium (0.26 g, 11 mmol) in absolute ethanol (30 mL), at room temperature under nitrogen. Urea (0.38 g, 6.3 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The hot reaction mixture was filtered, the filter bed washed with hot ethanol (30 mL), the filtrate neutralized with glacial acetic acid, and the solvent removed under reduced pressure. The residue was chromatographed on silica gel in 60–80% ethyl acetate in hexane to give **63** (350 mg, 16%): mp 163–164 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ 2.25–3.10 (5H, m), 3.25 (3H, s), 3.85 (2H, t), 4.20 (2H, t), 6.80 (2H, d), 7.0 (1H, m), 7.10 (2H, d), 7.15 (1H, m), 7.25 (1H, d), 7.35 (1H, d), 11.10 (1H, br s, exchanges with D_2O). Anal. ($C_{21}H_{21}N_3O_4$) C,H,N.

The starting material for the above reaction was prepared as follows: Sodium hydride (0.3 g, 7.5 mmol, 60% dispersion in oil) was added to a solution of diethyl [(4-hydroxyphenyl)-methyl]butanedioate[28] (2.1 g, 7.5 mmol) in dry dimethylformamide (40 mL) with stirring at room temperature under nitrogen. The mixture was stirred for 30 min, and a solution of 2-(2-benzoxazolylmethylamino)ethanol methylsulfonyl ester (2.03 g, 7.5 mmol) in dry dimethylformamide (20 mL) was added. The solution was heated to 80 °C and maintained at this temperature overnight. After cooling, the mixture was poured into water (150 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with water (4 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel in 60% ethyl acetate in hexane to give diethyl [[4-[2-(2-benzoxazolylmethylamino)-ethoxy]phenyl]methyl]butanedioate (2.6 g, 76%) as a straw-colored oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (6H, t), 2.35–3.20 (5H, m), 3.40 (3H, s), 3.80–4.35 (8H, m), 6.80 (2H, d), 7.00–7.60 (6H, m).

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