Novel Thiazolidine-2,4-diones as Potent Euglycemic Agents

Bernard Hulin,* David A. Clark,* Steven W. Goldstein,* Ruth E. McDermott, Paul J. Dambek, Werner H. Kappeler, Charles H. Lamphere, Diana M. Lewis, and James P. Rizzi

Central Research, Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340. *Received December 16, 1991*

A new series of thiazolidine-2,4-diones was obtained by replacing the ether function of englitazone with various functional groups, i.e., a ketone, alcohol, or olefin moiety. These compounds lower blood glucose levels in the genetically obese and insulin-resistant ob/ob mouse. Appending an oxazole-based group at the terminus of the chain provided highly potent compounds.

Non-insulin-dependent diabetes mellitus (NIDDM) is a metabolic disorder characterized by hyperglycemia as well as insulin resistance and/or impaired insulin secretion.[1] In the United States 6 million people are diagnosed as non-insulin-dependent diabetics[2] and it has been estimated that an equal number of diabetics remain undiagnosed.[3] A large body of evidence from epidemiological[4] and clinical[5] studies points to a positive relationship between hyperglycemia and long-term organ complications such as neuropathy, nephropathy, retinopathy, and premature atherosclerosis and to the necessity for tight control of blood glucose levels in the early stages of the disease.[6]

Therapy for NIDDM has been aimed at improving glycemic control via a combination of diet, exercise, and oral agents.[7] The most commonly used agents are the sulfonylureas.[8] These compounds stimulate the secretion of insulin in response to glucose and may have extrapancreatic effects as well.[9] Because of the relatively high rate of primary and secondary failure and the high incidence of life-threatening hypoglycemic episodes,[10] new agents which do not stimulate insulin release are being investigated.[11]

In 1982, Takeda, Inc., reported a series of 5-substituted-2,4-thiazolidinediones as a new class of glucose-lowering agents.[12] In this and subsequent papers they showed that these compounds and in particular the prototype ciglitazone lower plasma glucose in animal models of NIDDM but not in nondiabetic animals.[13] Since that time, numerous reports have appeared reflecting efforts to discover more potent and better tolerated members of this class.[14]

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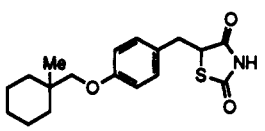
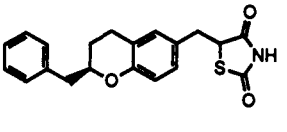
Our laboratories have recently disclosed a series of dihydrobenzopyran and dihydrobenzofuran thiazolidinediones, including englitazone, a compound undergoing clinical studies,[15] as well as a series of 5-benzyl-2,4-oxazolidinediones.[16] Here we report some studies aimed at the discovery of a second generation of 2,4-thiazolidinedione euglycemics with novel structural features and greatly improved potency.



Ciglitazone

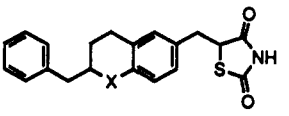


Englitazone

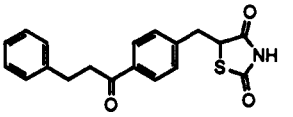
Biological Procedure

Measure of in Vivo Euglycemic Activity. The method used has been described previously[15,16] and is herein repeated for convenience. Six- to eight-week-old C57 BL/6J-ob/ob mice (obtained from Jackson Laboratories, Bar Harbor, ME) were housed five per cage under standard animal care practices. After a 1-week acclimation period, the animals were weighed and 25 μL of blood were collected via the retro-orbital sinus prior to any treatment. The blood sample was immediately diluted 1:5 with saline containing 2% sodium heparin and held on ice for glucose analysis. Animals were then dosed daily for 4 days with drug or vehicle. All drugs were administered by oral gavage, once daily, in a vehicle consisting of 0.25% (w/v) methylcellulose in water with no pH adjustment (0.1 mL of solution per 20 g of animal weight). Animals were bled 24 h after the fourth administration of drug or vehicle (via the retro-orbital sinus) for blood glucose levels. The weight of each animal was recorded on days 1 and 5 of the treatment. The freshly collected samples (125 μL in 330-μL tubes) were centrifuged for 2 min at 10000g at room temperature. A 50-μL sample was analyzed for glucose by the Abbott VP Super System Analyzer,[17] using the A-gent[17] glucose UV reagent system[18] (hexokinase method using 100, 300, and 500 mg/dL standards). Ciglitazone was dosed at 50 mg/kg as a positive control and results are reported in all tables as the percentage of glucose normalization compared to the standard ciglitazone-treated group (100% at 50 mg/kg) and the vehicle treated group (0%).

Table I. Euglycemic Activity of Ketones vs Ethers



1 X = O
2 X = CO



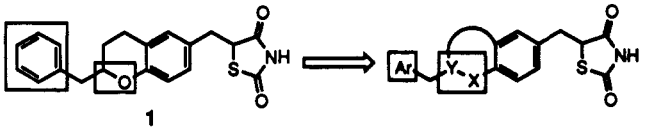
3

compd	% glucose normalization in ob/ob mouse (mg/kg)[a] 25	10	5
1[15]	91[b]	70[b]	48[b]
2	47[b]	54	39[b]
3	93[b]	81[c]	53[d]

[a] Normalization (100%) = ciglitazone effect at 50 mg/kg. [b] $p < 0.05$ when compared to vehicle control. [c] Average of 4 separate tests, ±20%. [d] Average of 2 separate tests, ±15%.

Results and Discussion

Our strategy for the discovery of novel potent euglycemics involved the search for a new sterically and biologically equivalent functional entity to replace the ether function found in ciglitazone and englitazone. It was thought that such an ether bioisostere[19] would allow us entry into a structurally novel class of compounds, while modification of the lipophilic "tail" part of englitazone might greatly improve the potency, as had been the case in the ether/thiazolidinedione[14d] and ether/oxazolidinedione[16] series of compounds.



1

The ether oxygen of the 2-benzylbenzopyran 1[14h,15] was replaced by sulfur, substituted nitrogen, and carbonyl groups. While the sulfur and nitrogen analogues were somewhat inferior in potency,[20] the analogous ketone 2 as well as the alicyclic ketone 3 possessed equivalent activity (Table I).

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(17) A registered trademark of Abbott Laboratories, Diagnostic Division. 820 Mission Street, So. Pasadena, CA 91030.

(18) A modification of the method of: Richterich, R.; Dauwalder, H. Assay of Blood-Glucose by Hexokinase/Glucose-6-Phosphate Dehydrogenase Method. *Schweiz. Med. Wochenscr.* 1971, *101*, 615.

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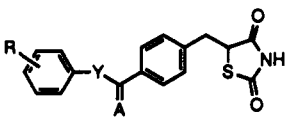
Table II. Euglycemic Activity of Ketone Analogues of **3**



compd				% glucose normalization in ob/ob mouse (mg/kg)[a]		
no.	R	A	Y	25	10	5
3	H	O	$(CH_2)_2$	93[b]	81[c]	53[d]
4	H	O	CH_2		0	
5	H	O	$(CH_2)_3$		26	
6	H	O	OCH_2		7	
7	4-OBn	O	$(CH_2)_2$		45[e]	
8	4-Ph	O	$(CH_2)_2$		71[b]	54
9	2-OMe	O	$(CH_2)_2$		0	
10	4-OMe	O	$(CH_2)_2$		50	
11	H	O	CH=CH (*E*)	99[b]	65[b]	23
12	4-OBn	O	CH=CH (*E*)	96[b]	57[b]	64[b]
13	2-OMe	O	CH=CH (*E*)		66[f]	50
14	2-Cl	O	CH=CH (*E*)		44[b]	65[b]
15	2-CF_3	O	CH=CH (*E*)		57[b]	39
16	2-Bn	O	CH=CH (*E*)		56[b]	
17	3-Cl	O	CH=CH (*E*)		4	
18	4-Br	O	CH=CH (*E*)		28	
19	4-COOEt	O	CH=CH (*E*)		4	
20	4-Ph	O	CH=CH (*E*)	65[g]	56	
21	2-OH	O	CH=CH (*E*)	0		
22	2-Me	O	CH=CH (*E*)		21	
23	4-CH_2OMe	O	CH=CH (*E*)	0		
24	4-OMe	O	CH=CH (*E*)		68[h]	0
25	4-NMe_2	O	CH=CH (*E*)		17	
26	H	H, OH	$(CH_2)_2$		89[h]	47[i]
27	H	H_2	$(CH_2)_2$	73[j]	77[k]	46

[a] Normalization (100%) = ciglitazone effect at 50 mg/kg. [b] $p < 0.05$ when compared to vehicle control. [c] Average of 4 separate tests, ± 20%. [d] Average of 2 separate tests, ±16%. [e] Average of 2 separate tests, ±13%. [f] Average of 2 separate tests, ±4%. [g] Average of 2 separate tests, ±6%. [h] Average of 2 separate tests, ±12%. [i] Average of 3 separate tests, ±47%. [j] Average of 2 separate tests, ±14%. [k] Average of 2 separate tests, ±23%.

It is also apparent that the tetralone **2** offers no potency advantage over the open-chain ketone **3**. In addition, in the benzopyran series, the stereogenicity at C-2 of the benzopyran ring of **1** has been shown to have little influence over its euglycemic potency.[15] Assuming the same lack of effect of C-2 in the tetralone **2**, the cyclic structure would present no distinct advantage over the simpler alicyclic analogue **3**. We therefore chose **3** as our new starting point. Close-in analogues of **3** were prepared in order to probe the following areas of the molecule: (a) the pendant phenyl ring; (b) the ethane linker; (c) the ketone function; (d) the "internal" phenyl ring. The results are shown in Table II.

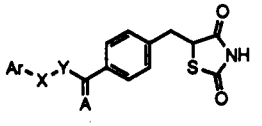
While several compounds generated in this analogue program have potency equivalent to **3**, no significant improvement was achieved. The ethane linker could not be shortened (**4**), lengthened (**5**), or incorporate an oxygen (**6**) without virtually complete loss of activity. Introduction of a double bond in this spacer, however, produced compounds with similar activity (**11**, **12**). Attempting to increase the potency by substitution on the pendant phenyl ring proved equally difficult and only equipotent compounds to **3** could be found (**7**–**25**). Manipulation of the carbonyl group of **3** gave interesting results. While the activity of the alcohol **26** (equivalent to **3**) was not unexpected, to our surprise, the methylene analogue **27** was also equipotent, indicating that the presence of an oxygen functionality, or indeed of any functionality, is not required at that position.

Our next step was to replace the phenyl tail by a heterocycle. The initial results are presented in Table III.

As was the case in the ether/thiazolidinedione[14e] and ether/oxazolidinedione[16] series, replacement of the phenyl group by a 4-linked oxazole leads to a remarkable jump in potency, as exemplified by **32** (CP-86,325). This effect appears to be specific to the 4-oxazole moiety: the analogous thiazole group displayed considerably weaker activity. In addition, introduction of a furan (**28**, **31**), pyridine (**33**, **34**), or benzothiazole (**29**) ring at the end of the ethane linker results in similar to or markedly lower activity than that of **3**. We thus proceeded to explore the structure–activity relationship (SAR) around **32**, further introducing fine modifications in all areas of the molecule except the oxazole ring which appears to be essential to ensure high potency. Table IV illustrates the influence of the substitution on the oxazole ring. While removal of the 5-methyl group lowers the activity, the 2-position is amenable to substitution. Indeed, the phenyl ring can be substituted with a 4-trifluoromethyl (**41**) or 3,5-dimethyl-4-methoxy (**44**) group, or replaced by a 4-methyl-2-furanyl group (**47**) with retention of the activity. These four compounds (**32**, **41**, **44**, **47**) have an ED_{50} (defined as the dose causing 50% normalization) close to or below 0.1 mg/kg, a considerable improvement over **3** and **1** (ED_{50} ca. 5 mg/kg).

Table V shows the activity of various reduction products

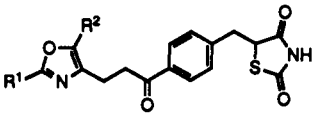
Table III. Euglycemic Activity of Ketones and Alcohols Equipped with Heterocyclic Tails



compd				% glucose normalization in ob/ob mouse (mg/kg)[a]		
no.	A	Ar	X–Y	10	5	2.5
28	O	2-furyl	CH=CH (*E*)	65[b]		
29	O	2-benzothiazolyl	CH=CH (*E*)	0		
30	O	5-methyl-2-phenyl-4-oxazolyl	CH=CH (*E*)	59	100[b]	
31	O	2-furyl	CH_2—CH_2	24		
32	O	5-methyl-2-phenyl-4-oxazolyl	CH_2—CH_2	100[b]	100[b]	88[c]
33	H, OH	2-pyridyl	CH_2—CH_2	13		
34	O	5-ethyl-2-pyridyl	CH_2—CH_2	41	0	
35	O	2-phenyl-4-thiazolyl	CH_2—CH_2		91[b]	48[b]
36	O	4-methyl-2-phenyl-5-thiazolyl	CH_2—CH_2		75[b]	33[d]
37	O	2-methyl-4-phenyl-5-thiazolyl	CH_2—CH_2		61[b]	0

[a] Normalization (100%) = ciglitazone effect at 50 mg/kg. [b] $p < 0.05$ when compared to vehicle control. [c] Average of 2 tests, ±12%. [d] Average of 2 tests, ±1%.

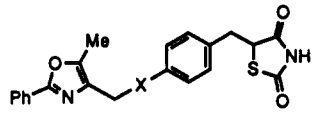
Table IV. Effect of Substitution of the Oxazole Ring on Euglycemic Activity



compd			% glucose normalization in ob/ob mouse (mg/kg)[a]			
no.	R^1	R^2	1	0.5	0.25	0.1
32	Ph	Me	100[b]	97[c]	88[d]	83[e]
38	Ph	H		30	52[f]	
39	4-OMe-Ph	Me	95[b]	43[b]		
40	4-Me-Ph	Me	47[g]	47[h]	15[i]	
41	4-CF_3-Ph	Me	86[b]	69[b]	81[b]	88[b]
42	4-Me-Ph	H		0	15[j]	
43	4-OH-Ph	Me	0			
44	4-OMe-3,5-Me_2-Ph	Me	100[b]	100[b]		75[b]
45	4-OH-3,5-Me_2-Ph	Me	100[b]	30		
46	2-furyl	Me	61[b]			
47	2-(5-methylfuryl)	Me		68[b]	87[b]	47
48	2-thienyl	Me	84[b]	71[b]	27	
49	2-naphthyl	Me	39[k]			

[a] Normalization (100%) = ciglitazone effect at 50 mg/kg. [b] $p <$ 0.05 when compared to vehicle control. [c] Average of 3 separate tests, ±5%. [d] Average of 3 separate tests, ±13%. [e] Average of 5 separate tests, ±30%. [f] Average of 2 separate tests, ±3%. [g] Average of 3 separate tests, ±31%. [h] Average of 2 separate tests, ±32%. [i] Average of 2 separate tests, ±1%. [j] Average of 2 separate tests, ±10%. [k] Average of 2 separate tests, ±20%.

Table V. Euglycemic Activity of Ketone Reduction Products



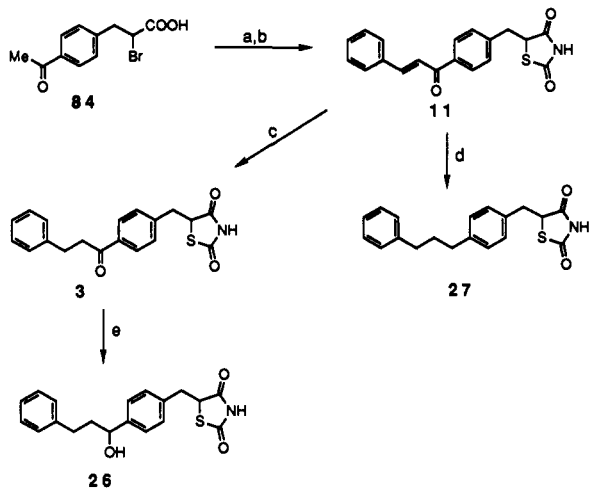
compd		% glucose normalization in ob/ob mouse (mg/kg)[a]			
no.	X	0.5	0.25	0.1	0.05
50	CH_2CHOH	100[b]	85[c]	93[b]	72[b]
51	CH=CH	84[d]	74[e]	29[b]	
52	$(CH_2)_2$	37			

[a] Normalization (100%) = ciglitazone effect at 50 mg/kg. [b] $p <$ 0.05 when compared to vehicle control. [c] Average of 4 separate tests, ±12%. [d] Average of 2 separate tests, ±8%. [e] Average of 2 separate tests, ±3%.

of the ketone function of **32**. The alcohol is fully active, the olefin **51** is also very potent although somewhat less so than **32**, and the hydrocarbon **52** is clearly inferior. Changing the central phenyl ring into a 2,4-disubstituted thiophene led to compounds generally less active (Table VI). Interestingly, in this group of compounds the olefin **59** was more potent than the corresponding ketone **57**, a reversal of the potency order seen between **32** and its corresponding olefin **51**.

With the ED_{50} comfortably below 0.5 mg/kg, we proceeded to search for new isosteres of the ketone function in order to expand the scope of this study. As shown in Table VII, all sulfides, sulfones, amides, and sulfonamides examined were comparatively inactive. The oxime **72** showed a 10-fold drop in potency. It is unclear whether this compound is converted in vivo to the ketone **32**.[21]

Scheme I[a]



[a] (a) Thiourea, sulfolane, 110 °C, then 2 N HCl, 110 °C; (b) benzaldehyde, NaOMe, ethanol; (c) triethylsilane (1 equiv), trifluoroacetic acid, 0 °C; (d) triethylsilane (3 equiv), trifluoroacetic acid, 0 °C to room temperature; (e) sodium borohydride, methanol.

Finally, Table VIII examines the activity of the α,β-unsaturated thiazolidinediones. The parent compound **75**, as well as the thiophene analogue **82**, appears to have comparable activity to **32**, while all other analogues prepared showed reduced activity at 1 mg/kg. However, the insolubility of these compounds makes any precise analysis difficult.

In summary, we have shown that the ether linkage of englitazone could be adequately replaced by carbonyl, carbinol, or olefin groups and that high potency could be obtained by appending the 5-methyl-2-aryl-4-oxazolyl tail. Based on its remarkable in vivo potency (50–100-fold improvement over englitazone), CP-86,325 (**32**) was selected for clinical studies.

Chemistry

Each compound in this paper was prepared according to one of the standard methods described in the schemes below. Table IX contains analytical data and shows which method was used for each individual compound.

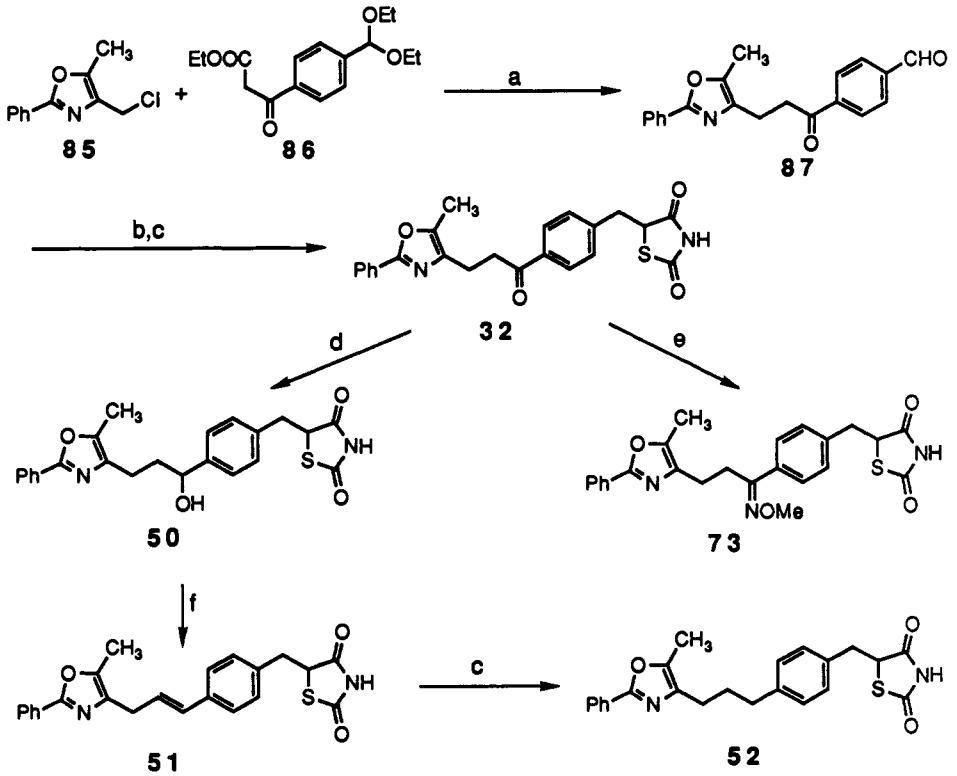
All phenethyl ketones were synthesized by aldol condensation[22] followed by reduction to the saturated ketone, the alcohol, or the alkane (Scheme I). The heterocycle-substituted ethyl ketones were prepared by alkylation of keto ester **86** followed by decarboxylation/deprotection and conversion of the aldehyde to the thiazolidinedione by the standard procedure[15] (Scheme II). The amides and sulfonamides were put together by straightforward coupling reactions (Scheme III).

The shortened-chain and oxygen-inserted compounds **4** and **6** were prepared according to Schemes IV and V, respectively. The sulfides were synthesized by alkylation of 4-bromothiophenol followed by formylation and conversion of the aldehyde to the thiazolidinedione, and the sulfones were obtained by *m*-chloroperbenzoic acid oxidation (Scheme VI). The thiophene compounds were prepared in a similar fashion to the phenyl analogues (Scheme VII), the aldehyde function being introduced at a later stage in the synthesis. All saturated thiazolidinediones are racemic compounds. All secondary alcohols (e.g., **50**) are mixtures of the four possible isomers.

(21) See, for example: (a) Sternson, L. A. Species Variation in the Metabolism of Acetophenone Oxime by Hepatic Enzymes. *Pharmacology* **1975**, *13*, 234. (b) Hucker, B.; Michniewic, B. M.; Rhodes, R. E. Phenylacetone Oxime–An Intermediate in the Oxidative Deamination of Amphetamine. *Biochem. Pharmacol.* **1971**, *20*, 2123–2128.

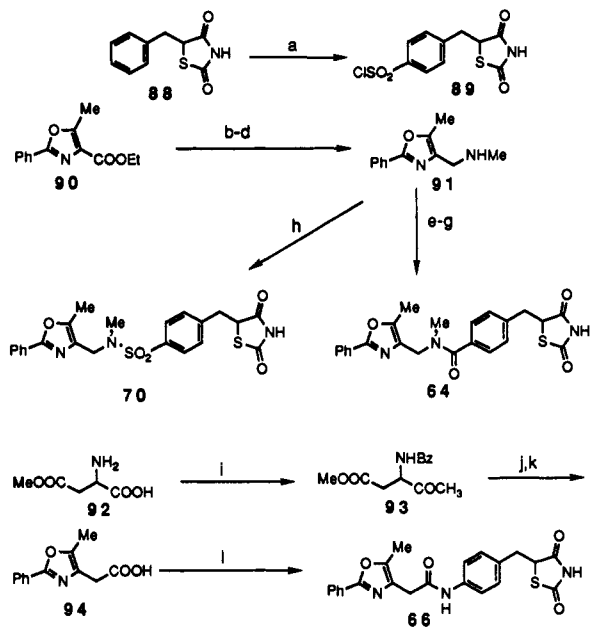
(22) Nielsen, A. T.; Houlihan, W. J. The Aldol Condensation. *Org. React.* **1968**, *16*, 1–444.

Scheme II[a]



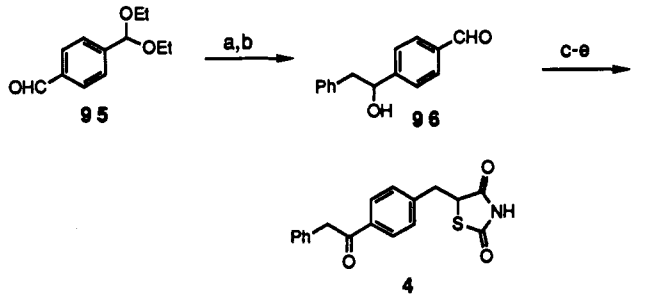
[a] (a) Sodium hydride, THF, then NaOH, then 1 N HCl; (b) 2,4-thiazolidinedione, piperidine, ethanol, reflux; (c) H_2, Pd–C; (d) sodium borohydride, 2-propanol; (e) methoxyamine hydrochloride, pyridine, ethanol; (f) *p*-toluenesulfonic acid, toluene, reflux.

Scheme III[a]



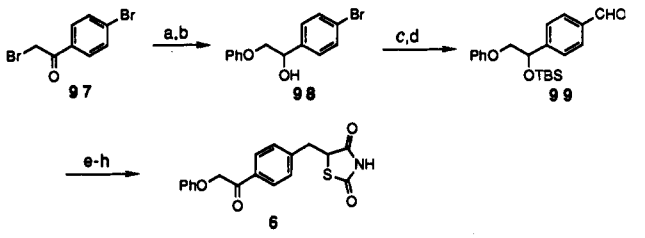
[a] (a) Chlorosulfonic acid; (b) $LiAlH_4$, ether; (c) PDC, CH_2Cl_2; (d) $MeNH_2$, $MgSO_4$, ether then $NaBH_4$, methanol; (e) 4-carboxybenzaldehyde, *i*-BuOCOCl, Et_3N, CH_2Cl_2; (f) 2,4-thiazolidinedione, NaOAc, 140 °C; (g) H_2, Pd–C, THF; (h) **89**, *i*-Pr_2EtN, CH_2Cl_2; (i) BzCl, pyridine, then Ac_2O, 90 °C; (j) $POCl_3$, toluene, reflux; (k) 1 N NaOH, reflux; (l) 5-(4-aminobenzyl)thiazolidine-2,4-dione, ClCOOEt, Et_3N, CH_2Cl_2.

Scheme IV[a]



[a] (a) BnMgBr, ether, −30 °C; (b) $HClO_4$, THF; (c) 2,4-thiazolidinedione, NaOAc, 140 °C; (d) Na(Hg), methanol; (e) H_2CrO_4, ether.

Scheme V[a]

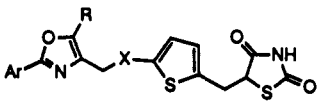


[a] (a) Phenol, K_2CO_3, acetone; (b) $NaBH_4$, *i*-PrOH, CH_2Cl_2; (c) *t*-$BuMe_2SiCl$, imidazole, DMF; (d) *n*-BuLi, DMF, THF; (e) 2,4-thiazolidinedione, NaOAc, 140 °C; (f) Na(Hg), methanol; (g) $HClO_4$, THF; (h) H_2CrO_4, ether.

Experimental Section

Melting points were taken using a Thomas Hoover apparatus and are uncorrected. Elemental analyses were carried out by the Analytical Department of Pfizer Central Research and results obtained for specified elements are within ±0.4% of the theoretical values unless otherwise denoted. ^1H NMR spectra of deuteriochloroform or DMSO-d_6 solutions (internal standard TMS, δ 0 or the solvent was utilized as an internal standard and deuterium lock) were recorded on Varian A-60, Bruker AM-250, or Varian XL-300 spectrometers. Low resolution and high resolution mass spectra were obtained on Finnigan 4510 and AEI MS-30 instruments, respectively. Compounds analyzed by high resolution mass spectroscopy (HRMS) were >95% pure, as determined by proton NMR and thin-layer chromatography. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer.

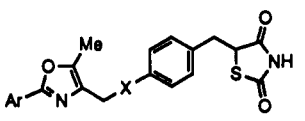
Table VI. Euglycemic Activity of Thiophene Analogues of **32**



compd				% glucose normalization in ob/ob mouse (mg/kg)[a]				
no.	X	R	Ar	5	2.5	1	0.5	0.25
53	CH_2CHOH	Me	Ph	100[b]		23		
54	CH_2CO	Me	Ph	100[b]	99[b]	37		
55	CH_2CO	Me	4-Cl-Ph		100[b]	51[b]		
56	CH_2CO	H	4-Me-Ph		0	10		
57	CH_2CO	Me	4-Me-Ph			100[b]	27	
58	CH_2CO	Me	4-CF_3-Ph			78[c]	27[d]	
59	CH=CH	Me	4-Me-Ph		90[b]	98[e]	73[b]	64[f]

[a] Normalization (100%) = ciglitazone effect at 50 mg/kg. [b] $p < 0.05$ when compared to vehicle control. [c] Average of 2 separate tests, ±22%. [d] Average of 2 separate tests, ±27%. [e] Average of 2 separate tests, ±2%. [f] Average of 2 separate tests, ±3%.

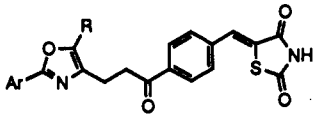
Table VII. Euglycemic Activity of Various Ketone Isosteres



compound			% glucose normalization in ob/ob mouse (mg/kg)[a]			
no.	X	Ar	5	2.5	1	0.5
60	CH_2S	Ph				0
61	CH_2SO_2	Ph	69[b]		11	
62	CH_2SO_2	2-naphthyl	0	0		
63	NHCO	Ph	50[b]	49		
64	NMeCO	Ph	83	0		
65	NPhCO	Ph	23			
66	CONH	Ph	64[b]	16		
67	CONMe	Ph	9			
68	CONEt	Ph	25			
69	$NHSO_2$	Ph	0			
70	$MeNSO_2$	Ph	9			
71	$PhNSO_2$	Ph		32		
72	$CH_2C(NOH)$	Ph	100[b]		99[b]	0
73	$CH_2C(NOMe)$	Ph	100[b]		0	
74	$CH_2C(NOBn)$	Ph	17			

[a] Normalization (100%) = ciglitazone effect at 50 mg/kg. [b] $p <$ 0.05 when compared to vehicle control.

Table VIII. Euglycemic Activity of Unsaturated Thiazolidinediones

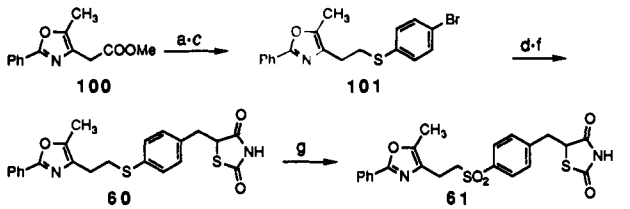


compd			% glucose normalization in ob/ob mouse (mg/kg)[a]		
no.	Ar	R	1	0.5	0.1
75	Ph	Me	84[b]	81[b]	43
76	4-OMe-Ph	Me	62[b]		
77	4-Me-Ph	Me	0	27	
78	4-CF_3-Ph	Me	58[b]	28[c]	
79	4-Me-Ph	H	53[b]		
80	2-furyl	Me	55		
81	2-(5-methylfuryl)	Me	76[b]	1	
82	2-thiophenyl	Me	100[b]		
83	2-naphthyl	Me	90[b]	38[d]	

[a] Normalization (100%) = ciglitazone effect at 50 mg/kg. [b] $p <$ 0.05 when compared to vehicle control. [c] Average of 2 separate tests, ±28%. [d] Average of 2 separate tests, ±11%.

5-(4-Acetylbenzyl)thiazolidine-2,4-dione. A mixture of 2-bromo-3-(4-acetylphenyl)propanoic acid[23] (84, 89 g, 0.33 mol), thiourea (50 g, 0.66 mol), and sulfolane (100 mL) was heated to 110 °C for 5 h. Then 2 N HCl (165 mL) was added and the mixture was heated to 110 °C overnight. After cooling, the solution was diluted with ice–water (700 mL), and the solid was collected, washed with water, and dried (77 g, 94%, mp 170.5–171.5 °C): ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.55 (s, 3 H), 3.25 (dd, J = 14, 9 Hz, 1 H), 3.50 (dd, J = 14, 4 Hz, 1 H), 4.95 (dd, J = 9, 4 Hz, 1 H), 7.40 (d, J = 8 Hz, 2 H), 7.85 (d, J = 8 Hz, 2 H), 12.05 (br s, 1 H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 26.6, 36.9, 52.0, 128.2, 129.5, 171.3, 175.4, 222.0.

Scheme VI[a]



[a] (a) $LiAlH_4$, ether; (b) Ph_3P, CBr_4, ether; (c) 4-bromothiophenol, NaH, THF; (d) BuLi, DMF, THF; (e) 2,4-thiazolidinedione, piperidine, ethanol; (f) Na(Hg), methanol; (g) *m*-CPBA, CH_2Cl_2.

(*E*)-5-[4-(3-Phenyl-2-propenoyl)benzyl]thiazolidine-2,4-dione (11). To a slurry of 5-(4-acetylbenzyl)thiazolidine-2,4-dione (1.0 g, 4.0 mmol) and benzaldehyde (0.41 mL, 4.0 mmol) in ethanol (10 mL) was added sodium methoxide (4.8 mmol, 0.26 g). The solution was heated to reflux for 1.5 h and then cooled, diluted with water (60 mL), acidified with 2 N HCl, and extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed with water (50 mL), dried over sodium sulfate, and concentrated. The residue was recrystallized from 2-propanol to give the title product as a pale yellow solid (0.33 g, 24%, mp 147–149 °C): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.24 (dd, J = 14.1, 9.5 Hz, 1 H), 3.45 (dd, J = 14.1, 4.0 Hz, 1 H), 4.57 (dd, J = 9.5, 4.0 Hz, 1 H), 7.37 (d, J = 8.3 Hz, 2 H), 7.41–7.43 (m, 3 H), 7.51 (d, J = 15.7 Hz, 1 H), 7.63–7.66 (m, 2 H), 7.82 (d, J = 15.7 Hz, 1 H), 7.98 (d, J = 8.3 Hz, 2 H), 8.71 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.5, 52.7, 121.8, 128.5, 129.0, 129.1, 129.6, 130.7, 134.8, 137.6, 145.2, 169.8, 173.7, 190.1; IR (KBr) ν (cm^{-1}) 770, 1155, 1220, 1330, 1570, 1590, 1660, 1710 (s), 1725, 1750, 3060, 3200; MS (EI) *m/e* 337 (M^+), 221, 193, 178, 131, 118, 103, 90, 77, 51. Anal. ($C_{19}H_{15}NO_3S$) C, H, N.

5-[4-(3-Phenylpropionyl)benzyl]thiazolidine-2,4-dione (3). To an ice-cooled solution of 11 (2.0 g, 5.9 mmol) in trifluoroacetic acid (20 mL) was added triethylsilane (0.95 mL, 5.9 mmol). The mixture was stirred for 25 min at 0 °C and then diluted with water (50 mL) and extracted with ether (2 × 40 mL). The combined extracts were washed with water (2 × 40 mL) and 5% sodium bicarbonate (2 × 40 mL), dried over sodium sulfate, and concentrated. The residue was triturated with hexane to give **3** as a pale yellow solid (1.65 g, 82%, mp 119–121 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.95 (t, J = 7.5 Hz, 2 H), 3.20 (dd, J = 14, 9

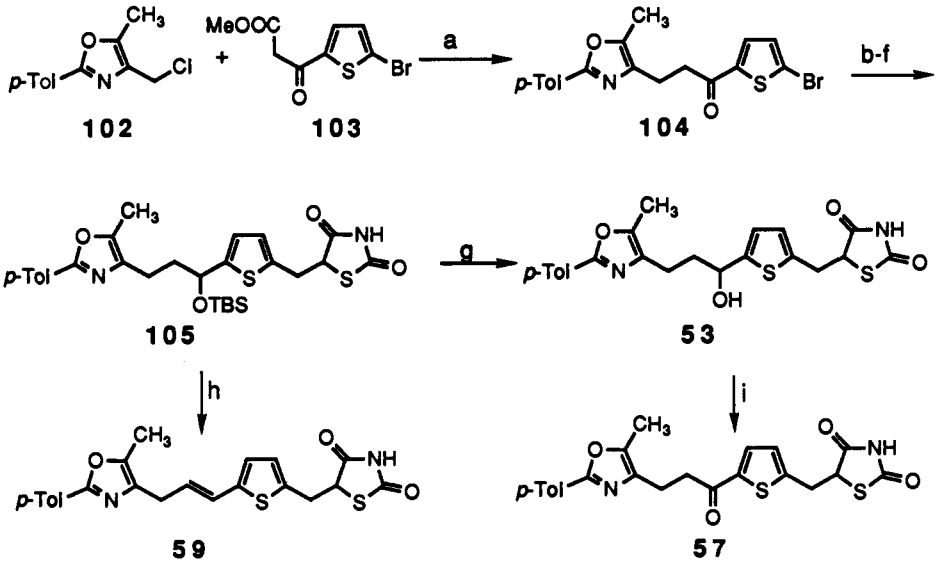
(23) Cleland, G. H. *p*-Acetyl-α-bromohydrocinnamic Acid. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 21–23.

Table IX. Analytical Data and Preparation

compd	formula	mp (°C)	prep method[a]	anal.	compd	formula	mp (°C)	prep method[a]	anal.
2	$C_{21}H_{18}NO_3SNa \cdot {}^1/_2H_2O$	288–289	A	C,H,N	**43**	$C_{23}H_{20}N_2O_5S \cdot {}^1/_2H_2O$	218–219	H	C,H,N
3	$C_{19}H_{17}NO_3S$	119–121	A	C,H,N	**44**	$C_{26}H_{25}N_2NaO_5S$	225–235	A	C,H,N
4	$C_{18}H_{15}NO_3S$	145–146	D	C,H,N	**45**	$C_{25}H_{23}N_2NaO_5S \cdot 2H_2O$	150–200	H	C,H,N
5	$C_{20}H_{19}NO_3S \cdot {}^1/_4H_2O$	138–140	A	C,H,N	**46**	$C_{21}H_{18}N_2O_5S \cdot {}^1/_3C_4H_8O_2$	155–156	A	C,H,N
6	$C_{18}H_{15}NO_4S$	170–174	E	C,H,N	**47**	$C_{22}H_{20}N_2NaO_5S$	208–210	A	HRMS
7	$C_{26}H_{23}NO_4S \cdot H_2O$	97–101	B	C,H,N	**48**	$C_{21}H_{18}N_2O_4S_2 \cdot {}^1/_4H_2O$	157–158	A	C,H,N
8	$C_{25}H_{21}NO_3S \cdot {}^1/_2H_2O$	99–100	B	C,H,N	**49**	$C_{27}H_{22}N_2O_4S$	188–189	A	C,H,N
9	$C_{20}H_{18}NNaO_4S$	269 dec	B	C,H,N	**50**	$C_{23}H_{21}N_2NaO_4S$	268–272	B	C,H,N
10	$C_{20}H_{18}NNaO_4S \cdot {}^1/_2H_2O$	272–274	B	C,H,N	**51**	$C_{23}H_{19}N_2NaO_3S \cdot H_2O$	285 dec	B	C,H,N
11	$C_{19}H_{15}NO_3S$	147–149	B	C,H,N	**52**	$C_{23}H_{22}N_2O_3S$	98–99	B	C,H,N
12	$C_{26}H_{21}NO_4S \cdot {}^1/_2H_2O$	240 dec	B	C,H,N	**53**	$C_{21}H_{19}N_2NaO_4S_2$	206–210	G	HRMS
13	$C_{20}H_{17}NO_4S \cdot H_2O$	gum	B	C,H,N	**54**	$C_{21}H_{18}N_2O_4S_2$	164–166	G	C,H,N
14	$C_{19}H_{14}ClNO_3S \cdot {}^1/_4H_2O$	193–196	B	C,H,N	**55**	$C_{21}H_{17}ClN_2O_4S_2$	147–149	G	HRMS
15	$C_{20}H_{13}NNaO_3S \cdot {}^1/_2H_2O$	251–254	B	C,H,N	**56**	$C_{21}H_{18}N_2O_4S_2 \cdot {}^1/_2C_2H_4Cl_2$	151–153	G	C,H,N
16	$C_{26}H_{21}NO_3S \cdot {}^1/_2H_2O$	135–136	B	C,H,N	**57**	$C_{22}H_{20}N_2O_4S_2 \cdot {}^1/_2H_2O$	158–160	G	C,H,N
17	$C_{19}H_{14}ClNO_3S \cdot {}^1/_4H_2O$	162.5–164	B	C,H,N	**58**	$C_{22}H_{17}F_3N_2O_4S_2$	157–159	G	C,H,N
18	$C_{19}H_{13}BrKNO_3S$	>250	B	C,H,N	**59**	$C_{22}H_{19}N_2NaO_3S_2$	245–250	G	C,H,N
19	$C_{22}H_{19}NO_5S \cdot {}^1/_4H_2O$	173	B	C,H,N	**60**	$C_{22}H_{19}N_2NaO_3S_2$	268–270	F	C,H,N
20	$C_{25}H_{19}NO_3S \cdot {}^1/_4H_2O$	198.5–200	B	C,H,N	**61**	$C_{22}H_{20}N_2O_5S_2$	foam	F	HRMS
21	$C_{19}H_{15}NO_4S$	150–153	B	C,H,N	**62**	$C_{26}H_{22}N_2O_5S_2$	77–80	F	HRMS
22	$C_{20}H_{17}NO_3S \cdot H_2O$	115–120	B	C,H,N	**63**	$C_{22}H_{19}N_3O_4S \cdot H_2O$	101–103	C	C,H,N
23	$C_{21}H_{18}NNaO_4S \cdot {}^3/_4H_2O$	282–286	B	C,H,N	**64**	$C_{23}H_{21}N_3O_4S \cdot H_2O$	75–78	C	C,H,N
24	$C_{20}H_{17}NO_4S \cdot {}^1/_4H_2O$	177–180	B	C,H,N	**65**	$C_{28}H_{23}N_3O_4S$	95–98	C	HRMS
25	$C_{21}H_{19}N_2NaO_3S \cdot H_2O$	284–286	B	C,H,N	**66**	$C_{22}H_{19}N_3O_4S \cdot {}^1/_2H_2O$	201–202	C	C,H,N
26	$C_{19}H_{18}NNaO_3S \cdot {}^3/_4H_2O$	249–254	A	C,H,N	**67**	$C_{23}H_{21}N_3O_4S \cdot {}^3/_4H_2O$	75–77	C	C,H,N
27	$C_{19}H_{19}NO_2S$	84–86	A	C,H,N	**68**	$C_{24}H_{23}N_3O_4S \cdot {}^1/_2H_2O$	68.5–70	C	C,H,N
28	$C_{17}H_{12}KNO_4S \cdot {}^1/_4H_2O$	270–275	B	C,H,N	**69**	$C_{21}H_{19}N_3O_5S_2$	120–122	C	HRMS
29	$C_{20}H_{14}N_2O_3S_2 \cdot {}^1/_2H_2O$	200–204	B	C,H,N	**70**	$C_{22}H_{21}N_3O_5S_2 \cdot {}^1/_4H_2O$	83–84	C	C,H,N
30	$C_{23}H_{18}N_2O_4S \cdot {}^1/_4H_2O$	190–192	B	C,H,N	**71**	$C_{28}H_{25}N_3O_5S_2$	68–71	C	C,H,N
31	$C_{17}H_{15}NO_4SNa \cdot {}^1/_4H_2O$	265–270	B	C,H,N	**72**	$C_{23}H_{21}N_3O_4S$	202–205	B	C,H,N
32	$C_{23}H_{20}N_2O_4S$	145–146	B	C,H,N	**73**	$C_{24}H_{23}N_3O_4S \cdot {}^1/_2H_2O$	138–140	B	C,H,N
33	$C_{18}H_{17}N_2NaO_3S \cdot {}^3/_2H_2O$	125–130	A	C,H,N	**74**	$C_{30}H_{27}N_3O_4S$	175–177	B	C,H,N
34	$C_{20}H_{20}N_2O_3S$	168–169	A	C,H,N	**75**	$C_{23}H_{18}N_2O_4S$	224–225	B	C,H,N
35	$C_{22}H_{18}N_2O\ S_2$	139–142	A	C,H,N	**76**	$C_{24}H_{20}N_2O_5S$	223–224	A	C,H,N
36	$C_{23}H_{20}N_2O_3S_2$	118–120	A	C,H,N	**77**	$C_{24}H_{20}N_2O_4S$	250–251	A	C,H,N
37	$C_{23}H_{19}N_2NaO_3S_2$	210–220 dec	A	C,H,N	**78**	$C_{24}H_{17}F_3N_2O_4S$	244–245	A	C,H,N
38	$C_{22}H_{18}N_2O_3S_2$	151–155	A	C,H,N	**79**	$C_{23}H_{18}N_2O_4S$	220–223	A	C,H,N
39	$C_{24}H_{22}N_2O_5S$	173–174	A	C,H,N	**80**	$C_{21}H_{16}N_2O_5S$	237–238	A	C,H,N
40	$C_{24}H_{22}N_2O_4S$	240–242	A	C,H,N	**81**	$C_{22}H_{18}N_2O_5S \cdot {}^1/_3H_2O$	236–238	A	C,H,N
41	$C_{24}H_{19}F_3N_2O_4S$	244–245	A	C,H,N	**82**	$C_{21}H_{16}N_2O_4S_2$	237–238	A	C,H,N
42	$C_{23}H_{20}N_2O_4S$	143–144	A	C,H,N	**83**	$C_{27}H_{20}N_2O_4S$	221–222	A	C,H,N

[a] Method A is shown in Scheme I; method B is shown in Scheme II; method C is shown in Scheme III; method D is shown in Scheme IV; method E is shown in Scheme V; method F is shown in Scheme VI; method G is shown in Scheme VII; method H, demethylation of **42** or **44** with HBr, AcOH.

Scheme VII[a]



[a] (a) NaH, THF, then NaOH, then HCl; (b) $NaBH_4$, ethanol; (c) *t*-$BuMe_2SiCl$, imidazole, DMF; (d) *n*-BuLi, DMF, THF; (e) 2,4-thiazolidinedione, NaOAc, 140 °C; (f) Na(Hg), methanol; (g) $HClO_4$, THF; (h) 6 N HCl, THF; (i) PDC, CH_2Cl_2.

Hz, 1 H), 3.55 (dd, J = 14, 4 Hz, 1 H), 4.95 (dd, J = 9, 4 Hz, 1 H), 7.15 (m, 1 H), 7.25 (m, 4 H), 7.45 (d, J = 8 Hz, 2 H), 7.95 (d, J = 8 Hz, 2 H), 12.1 (br s, 1 H). Anal. ($C_{19}H_{17}NO_3S$) C, H, N.

5-[4-(3-Phenylpropyl)benzyl]thiazolidine-2,4-dione (27). A solution of 11 (2.0 g, 5.9 mmol) in trifluoroacetic acid (20 mL), cooled to 0 °C, was treated with triethylsilane (2.8 mL, 18 mmol). After 25 min at 0 °C and 25 min at room temperature, the solution was diluted with water (60 mL) and extracted with ether (2 × 50 mL). The combined extracts were washed with water (2 × 50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated, leaving a brown oil. The product was isolated by flash chromatography (hexanes/ethyl acetate, 5:1) as a solid (1.11 g, 58%, mp 84–86 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (quin, J = 7.6 Hz, 2 H), 2.71 (t, J = 6.7 Hz, 2 H), 2.73 (t, J = 6.9 Hz, 2 H), 3.13 (dd, J = 13.9, 10.2 Hz, 1 H), 3.58 (dd, J = 14.0, 3.7 Hz, 1 H), 4.56 (dd, J = 10.0, 3.7 Hz, 1 H), 7.22–7.35 (m, 8 H), 7.38 (t, J = 7.7 Hz, 1 H), 9.61 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.95, 35.14, 35.56, 38.36, 53.83, 125.95, 128.49, 128.59, 129.05, 129.21, 133.46, 141.83, 171.72, 175.42; IR (KBr) ν (cm^{-1}) 1170, 1340, 1700 (s), 1740, 3200 (br). Anal. ($C_{19}H_{19}NO_2S$) C, H, N.

5-[4-(1-Hydroxy-3-phenylpropyl)benzyl]thiazolidine-2,4-dione (26). To an ice-cooled solution of **3** (1.65 g, 4.9 mmol) in methanol (35 mL) was added sodium borohydride (0.19 g, 4.9 mmol). The solution was stirred for 2 h at room temperature and then quenched with 1 N HCl, diluted with water (100 mL), and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated, leaving **26** as an oil (1.6 g, 97%). The sodium salt was prepared by combining the product (1.6 g, 4.7 mmol) and sodium methoxide (0.26 g, 4.7 mmol) in methanol (15 mL) and concentrating the solution to a yellow solid (mp 249–254 °C): ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.86–1.88 (m, 2 H), 2.55–2.73 (m, 3 H), 3.67 (dd, J = 13.9, 3.3 Hz, 1 H), 4.19 (dd, J = 10.6, 3.4 Hz, 1 H), 4.50 (t, J = 6.1 Hz, 1 H), 7.15–7.28 (m, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.62, 31.93, 40.93, 58.68, 71.51, 125.57, 125.69, 128.23, 128.42, 138.48, 142.11, 143.97, 181.59, 190.65; IR (KBr) ν (cm^{-1}) 700, 1240, 1330, 1550, 1570 (s), 1670, 3360; MS (EI) m/e 281, 176, 105, 91, 77, 60. Anal. ($C_{19}H_{18}NNaO_3S\cdot{}^3/_4H_2O$) C, H, N.

1-[4-(Diethoxymethyl)phenyl]ethanol (106). 4-(Diethoxymethyl)benzaldehyde (104 g, 0.5 mol) was dissolved in ether (300 mL) and the resulting solution cooled to −75 °C. With vigorous stirring, methyllithium (390 mL of a 1.4 M ether solution, 0.55 mol) was added at a rate which maintained the temperature below −60 °C. The reaction mixture was allowed to warm to room temperature, poured into ice–water (500 mL), and stirred for 10 min, and the layers were separated. The aqueous layer was extracted with ether (500 mL). The combined organic layers were washed with water (500 mL) and brine (500 mL), dried over magnesium sulfate, and concentrated to yield a viscous yellow oil (110 g, 98%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.2 (t, J = 8 Hz, 6 H), 1.4 (d, J = 7 Hz, 3 H), 2.6 (br s, 1 H), 3.5 (q, J = 8 Hz, 4 H), 4.8 (q, J = 7 Hz, 1 H), 5.4 (s, 1 H), 7.4 (m, 4 H).

4-(Diethoxymethyl)acetophenone. 106 (223 g, 1.0 mol) and manganese dioxide (480 g, 5.5 mol) were combined in toluene (2.5 L) and the resulting dark suspension was heated to reflux for 18 h, cooled to room temperature, and filtered over diatomaceous earth with ethyl acetate wash. The filtrate was concentrated to yield an oil which was distilled to give the title product (134 g, 60%, bp 113–115 °C at 0.2–0.7 mmHg): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.2 (t, J = 8 Hz, 6 H), 2.6 (s, 3 H), 3.6 (q, J = 8 Hz, 4 H), 5.6 (s, 1 H), 7.6 (d, J = 9 Hz, 2 H), 8.0 (d, J = 9 Hz, 2 H).

Ethyl 2-[4-(Diethoxymethyl)benzoyl]acetate (86). Sodium hydride (32.4 g, 1.35 mol) was added to ice-cooled ether (400 mL), followed immediately by diethyl carbonate (96 g, 0.81 mol). After stirring for 25 min at room temperature, a solution of 4-(diethoxymethyl)acetophenone (120 g, 0.54 mol) and ethanol (1 mL) in ether (300 mL) was added over 25 min at room temperature. The mixture was slowly heated to reflux and kept at reflux for 6 h. The reaction mixture was cooled to room temperature and then slowly poured into a cold (0 °C) mixture of 10% HCl (500 mL) and ether (500 mL). The aqueous layer was separated and extracted with ether (500 mL), and the organic layers were combined, washed with water (500 mL) and brine (500 mL), dried over magnesium sulfate, and concentrated to yield the product as a viscous oil (158 g, 99%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.2 (t, J = 8 Hz, 6 H), 3.6 (q, J = 8 Hz, 4 H), 4.0 (s, 2 H), 4.2 (q, J = 7 Hz, 2 H), 5.6 (s, 1 H), 7.6 (d, J = 8 Hz, 2 H), 8.0 (d, J = 8 Hz, 2 H).

4-[3-(5-Methyl-2-phenyl-4-oxazolyl)propionyl]benzaldehyde (87). Sodium hydride (3.4 g, 0.14 mol) was combined with 250 mL of THF and cooled to 0 °C. With stirring, a solution of **86** (41.5 g, 0.14 mol) in THF (250 mL) was added portionwise over 0.5 h, maintaining the temperature below 25 °C. After stirring for an additional 0.5 h at room temperature, (5-methyl-2-phenyl-4-oxazolyl)methyl chloride (**85**)[24] (26 g, 0.13 mol) was added, and the mixture was heated to reflux for 48 h, cooled, and concentrated. The residue was taken up in a mixture of acetic acid (360 mL) and concentrated HCl (90 mL), heated to reflux for 5 h, cooled to room temperature, diluted with water (600 mL), and extracted with 1:1 ethyl acetate/ether (2 × 1 L). The organic layers were combined, washed with water (1 L) and brine (1 L), dried over magnesium sulfate, and concentrated. The residue was purified by flash chromatography (ether/chloroform, 1:19) and the product isolated as an oil which solidified on standing (34 g, 85%, mp 76–80 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3 H), 3.0 (t, J = 6 Hz, 2 H), 3.45 (t, J = 6 Hz, 2 H), 7.4 (m, 3 H), 7.9 (m, 4 H), 8.1 (m, 2 H), 10.1 (s, 1 H).

5-[[4-[3-(5-Methyl-2-phenyl-4-oxazolyl)propionyl]phenyl]methylene]thiazolidine-2,4-dione (75). **87** (16 g, 50 mmol), thiazolidine-2,4-dione (11.7 g, 0.10 mol), and piperidine (0.85 g, 10 mmol) were combined in ethanol (300 mL), and the mixture was refluxed for 24 h, cooled to 0 °C, and diluted with ether (600 mL). After stirring for 1 h at 0 °C, the precipitate was filtered and triturated with warm (40–50 °C) acetic acid (0.15 L). The resulting slurry was cooled to room temperature and diluted with ether (0.3 L) and the product was collected (14.2 g, 71%, mp 224–225 °C). Anal. ($C_{23}H_{18}N_2O_4S$) C, H, N.

5-[4-[3-(5-Methyl-2-phenyl-4-oxazolyl)propionyl]benzyl]thiazolidine-2,4-dione (32). **75** (14.2 g) was hydrogenated in THF (800 mL) in the presence of palladium on carbon (10 g) in a Parr shaker at 50 psi and room temperature for 24 h. The catalyst was recovered by filtration over diatomaceous earth with THF wash. The combined filtrate/wash was concentrated to a gum which was crystallized by trituration with 1:1 hexane/ethyl acetate (250 mL) (11.4 g, 81%, mp 145–146 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 2.9 (t, J = 7 Hz, 2 H), 3.22 (dd, J = 14, 10 Hz, 1 H), 3.35 (t, J = 7 Hz, 2 H), 3.5 (dd, J = 14, 4 Hz, 1 H), 4.5 (dd, J = 10, 4 Hz, 1 H), 7.3 (d, J = 8 Hz, 2 H), 7.4 (m, 3 H), 7.9 (m, 4 H), 8.32 (br s, 1 H); MS (EI) m/e 420 (M$^+$, 2), 186 (100); UV λ_{max} = 253 nm (MeOH). Anal. ($C_{23}H_{20}N_2O_4S$) C, H, N.

5-[4-[3-(5-Methyl-2-phenyl-4-oxazolyl)-1-hydroxypropyl]benzyl]thiazolidine-2,4-dione (50). **32** (0.70 g) was suspended in 2-propanol (50 mL). Sodium borohydride (0.15 g) was added and the mixture was stirred for 2 h, concentrated to low volume, diluted with water (50 mL), and extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated, and the residue was chromatographed on silica gel (hexanes/ethyl acetate, 1:1, 1% acetic acid) to yield **50** as a solid (0.32 g, 46%, mp 50–55 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.92 (m, 2 H), 2.24 (s, 3 H), 2.48 (t, J = 7.8 Hz, 2 H), 3.11 (dd, J = 14, 9.6 Hz, 1 H), 3.39 (dd, J = 14.2, 4.0 Hz, 1 H), 4.56 (m, 1 H), 4.87 (dd, J = 8.8, 3.6 Hz, 1 H), 5.29 (m, 1 H), 7.19 (d, J = 7.2 Hz, 2 H), 7.29 (d, J = 7.3 Hz, 2 H), 7.43–7.48 (m, 3 H), 7.87–7.90 (m, 2 H). Anal. ($C_{23}H_{21}N_2NaO_4S$) C, H, N.

5-[4-[3-(5-Methyl-2-phenyl-4-oxazolyl)-1-propenyl]benzyl]thiazolidine-2,4-dione (51). A solution of **50** (7.3 g, 17 mmol) and p-toluenesulfonic acid hydrate (1.0 g, 5.3 mmol) in toluene (150 mL) was heated to reflux overnight. The solution was diluted with ethyl acetate (150 mL), washed with water (2 × 150 mL) and brine (150 mL), dried over sodium sulfate, and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 3:2) and obtained as a gummy solid (3.5 g, 50%). The product was dissolved in ethyl acetate (150 mL)

(24) Goto, Y.; Yamazaki, M.; Hamana, M. Studies on Azole Compounds. III. Reactions of Oxazole-*N*-Oxides with Phosphoryl Chloride and Acetic Anhydride. *Chem. Pharm. Bull.* **1971**, *19*, 2050–2057.

and sodium 2-ethylhexanoate (1.5 g, 3.7 mmol) was added in ethyl acetate (50 mL). The sodium salt was collected and washed with ether (2.6 g, mp 288 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.36 (s, 3 H), 2.65 (dd, J = 13.8, 10.5 Hz, 1 H), 3.38 (t, J = 6 Hz, 2 H), 4.13 (dd, J = 10.4, 3.3 Hz, 1 H), 6.2 (dt, J = 16, 6 Hz, 1 H), 6.47 (d, J = 16.2 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 7.46–7.50 (m, 3 H), 7.89–7.92 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.95, 28.99, 39.67, 58.02, 125.48, 125.88, 126.72, 126.23, 127.50, 129.07, 129.11, 130.03, 130.51, 134.16, 135.03, 138.95, 144.21, 158.39, 180.58; IR (KBr) ν (cm^{-1}) 1240, 1330, 1550, 1570 (s), 1670; MS (EI) m/e 404 (M$^+$), 288, 173, 105. Anal. ($C_{23}H_{19}N_2NaO_3S\cdot H_2O$) C, H, N.

5-[4-[3-(5-Methyl-2-phenyl-4-oxazolyl)propyl]benzyl]thiazolidine-2,4-dione (52). A solution of **51** (0.5 g, 1.2 mmol) in ethyl acetate (40 mL) containing 5% palladium on charcoal (0.45 g) was hydrogenated at 40 psi in a Parr apparatus overnight. The catalyst was filtered over diatomaceous earth, the solvent was evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate, 3:2). **52** was obtained as a white solid (0.40 g, 80%, mp 98–99 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (quin, J = 7.6 Hz, 2 H), 2.27 (s, 3 H), 2.50 (t, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.7 Hz, 2 H), 3.05 (dd, J = 14.0, 9.9 Hz, 1 H), 3.48 (dd, J = 14.1, 3.8 Hz, 1 H), 4.46 (dd, J = 9.9, 3.9 Hz, 1 H), 7.12 (*AB*, J = 9.0 Hz, 1 H), 7.14 (*AB*, J = 9.0 Hz, 1 H), 7.38–7.44 (m, 3 H), 7.95–7.98 (m, 2 H), 9.73 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 25.2, 30.4, 34.9, 38.3, 53.6, 126.0, 126.6, 127.8, 128.7, 129.0, 129.1, 129.8, 133.3, 135.7, 141.6, 143.5, 159.4, 171.0, 174.8; IR (KBr) ν (cm^{-1}) 720, 1130, 1340, 1700 (s), 1750, 2950; MS (EI) m/e 406 (M$^+$), 174, 173, 172, 145, 117, 105, 104, 77, 70. Anal. ($C_{23}H_{22}N_2O_3S$) C, H, N.

5-[4-[3-(5-Methyl-2-phenyl-4-oxazolyl)-1-(methoxyimino)propyl]benzyl]thiazolidine-2,4-dione (73). **32** (0.10 g, 0.24 mmol), methoxyamine hydrochloride (50 mg, 0.60 mmol), and pyridine (2 mL) were combined in ethanol (3 mL) and the mixture was stirred at room temperature for 18 h and then concentrated. The residue was taken up in ethyl acetate (7.5 mL), washed with cold 18% HCl (5 mL), and brine (5 mL) and concentrated to yield **73** as a white solid which was recrystallized from ethyl acetate/hexanes (mp 138–140 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3 H), 2.64 (t, J = 7 Hz, 2 H), 2.99 (t, J = 7 Hz, 2 H), 3.10 (dd, J = 14, 9 Hz, 1 H), 3.35 (dd, J = 14, 4 Hz, 1 H), 3.88 (s, 3 H), 4.88 (dd, J = 9, 4 Hz, 1 H), 7.22 (d, J = 8 Hz, 2 H), 7.46–7.48 (m, 3 H), 7.55 (d, J = 8 Hz, 2 H), 7.86–7.90 (m, 2 H). Anal. ($C_{24}H_{23}N_3O_4S\cdot{}^1/_2H_2O$) C, H, N.

5-Benzylthiazolidine-2,4-dione (88). A solution of 5-(phenylmethylene)thiazolidine-2,4-dione (25 g, 0.12 mol) in THF (750 mL) and acetic acid (250 mL) was hydrogenated in a Parr shaker over 10% Pd–C (25 g of 50% wt water). The catalyst was removed by filtration over diatomaceous earth and the solvent evaporated. The solid was recrystallized from ethanol/water (1:2) and obtained as pale grey crystals (15 g, 60%, mp 101–103 °C).

4-[(2,4-Dioxothiazolidin-5-yl)methyl]benzenesulfonyl Chloride (89). Chlorosulfonic acid (5 mL) was cooled to 0 °C and **88** (9.6 mmol, 2.0 g) was added portionwise. The reaction mixture was stirred at room temperature for 0.5 h and poured into ice (25 g). The solution was extracted with methylene chloride (2 × 50 mL), the combined organic layers were dried over sodium sulfate, and the solvent was removed to afford the product which was used without further purification.

Ethyl 5-Methyl-3-oxo-2-phenyloxazole-4-carboxylate Hydrochloride (107). To a solution of ethyl 2-(hydroxyimino)-3-oxobutyrate[25] (340 g, 2.2 mol) in acetic acid (550 mL) was added benzaldehyde (290 mL, 2.8 mol). The mixture was cooled to 0 °C and dry HCl was bubbled into the stirred reaction mixture at a moderate rate for 2 h. The mixture was diluted with 3 volumes of ether and filtered to yield 620 g of wet ether product which was immediately bottled and stored at refrigerator temperature.

Ethyl 5-Methyl-2-phenyloxazole-4-carboxylate (90). **107** (210 g) was dissolved in ethanol (1 L) and methanol (120 mL) and hydrogenated in a Parr shaker over 10% Pd–C (14 g) at 50 psi for 3 h, by which time uptake of hydrogen was complete. The catalyst was filtered over diatomaceous earth with methanol wash, and the solvent was removed to yield the product as an oil (67 g, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J = 7 Hz, 3 H), 2.70 (s, 3 H), 4.42 (q, J = 7 Hz, 2 H), 7.42–7.45 (m, 3 H), 8.05–8.08 (m, 2 H).

5-Methyl-2-phenyloxazole-4-methanol (108). A slurry of $LiAlH_4$ (11 g, 0.29 mol) in ether (300 mL) was cooled to 0 °C and a solution of **90** (67 g, 0.29 mol) in ether (300 mL) was added over 30 min, maintaining the temperature at 0–10 °C. The reaction was stirred for 1 h at room temperature and then diluted with THF (200 mL) and carefully quenched with water (11 mL), 1 N NaOH (11 mL), and again water (33 mL). The mixture was stirred for 15 min, diluted with THF (200 mL), and filtered over diatomaceous earth and the filtrate was concentrated to yield the title product as a solid (46 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.46 (br, 1 H), 4.64 (s, 2 H), 7.43–7.46 (m, 3 H), 8.00–8.03 (m, 2 H).

5-Methyl-2-phenyloxazole-4-carboxaldehyde (109). To a solution of **108** (20 g, 0.11 mol) in dichloromethane (500 mL) was added pyridinium dichromate (120 g, 0.32 mol). The slurry was stirred for 7 h, diluted with ether (1 L), and filtered over diatomaceous earth and the filtrate was concentrated to yield the product as a solid (14 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (s, 3 H), 7.45–7.48 (m, 3 H), 8.02–8.06 (m, 2 H), 10.0 (s, 1 H).

***N*-Methyl-*N*-[(5-methyl-2-phenyl-4-oxazolyl)methyl]amine (91).** **109** (2.0 g, 11 mmol) was dissolved in ether (50 mL), magnesium sulfate (2.0 g) was added, and the mixture was cooled to 0 °C and saturated with gaseous methylamine. The mixture was stirred for 15 min at 0°C and then at room temperature for 3 h and filtered and the filtrate was concentrated. The residue was taken up in methanol (50 mL) and cooled to 0 °C and sodium borohydride (2.2 g, 58 mmol) was added. The mixture was stirred at 0 °C for 15 min and then at room temperature for 18 h. It was then diluted with 2 volumes of water and extracted with ethyl acetate (2 × 150 mL). The combined extracts were washed with water (2 × 150 mL) and brine (150 mL) and concentrated to yield the product as an oil (1.5 g, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 2.45 (s, 3 H), 7.38–7.41 (m, 3 H), 7.94–7.98 (m, 2 H).

4-[*N*-Methyl-*N*-[(5-methyl-2-phenyl-4-oxazolyl)]methylaminocarbonyl]benzaldehyde (110). To an ice-cooled solution of 4-carboxybenzaldehyde (1.1 g, 7.4 mmol) and triethylamine (1.0 mL, 7.4 mmol) in THF (50 mL) were added isobutyl chloroformate (0.96 mL, 7.4 mmol) and after 30 min a solution of **91** (1.5 g, 7.4 mmol) in THF (30 mL). The mixture was stirred for 30 min at 0 °C and then at room temperature overnight. Water was added followed by 1 N NaOH and the mixture was extracted with ethyl acetate (2×). The combined extracts were washed with water and brine, dried over magnesium sulfate, and concentrated to an oil. The product was purified by flash chromatography (hexanes/ethyl acetate, 1:3) and obtained as an oil (0.52 g, 21%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 1.5 H), 2.48 (s, 1.5 H), 3.05 (s, 3 H), 4.24 (s, 1 H), 4.62 (s, 2 H), 7.37–7.42 (m, 3 H), 7.56 (d, J = 8 Hz, 1 H), 7.80–7.98 (m, 5 H), 9.98 (s, 1 H).

***N*-Methyl-*N*-[(5-methyl-2-phenyl-4-oxazolyl)methyl]-4-[(2,4-dioxothiazolidin-5-ylidene)methyl]benzamide (111).** A mixture of **110** (0.52 g, 1.6 mmol), 2,4-thiazolidinedione (0.27 g, 2.3 mmol), and sodium acetate (0.38 g, 4.7 mmol) was heated to 140 °C for 2 h and then triturated in water, and the resulting solid was collected, washed with water, and dried (0.61 g, 90%, mp 95–98 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3 H), 2.95 (s, 3 H), 4.32 (br s, 1 H), 4.58 (br s, 1 H), 7.48–7.55 (m, 5 H), 7.62–7.75 (m, 3 H), 7.93–7.96 (m, 2 H); MS (EI) m/e 433 (M$^+$), 201 (100), 193, 172, 117, 105, 104.

***N*-Methyl-*N*-[(5-methyl-2-phenyl-4-oxazolyl)methyl]-4-[(2,4-dioxothiazolidin-5-yl)methyl]benzamide (64).** A solution of 111 (0.30 g, 0.69 mmol) in THF (80 mL) and acetic acid (25 mL) was hydrogenated over 10% Pd–C sulfur-resistant catalyst (0.80 g) in a Parr shaker at 50 psi for 2 h. The catalyst was filtered, the solvent was evaporated, and the product was purified by flash chromatography (hexanes/ethyl acetate, 1:3) and obtained as a solid (81 mg, 27%, mp 75–78 °C); IR (KBr) ν (cm^{-1}) 1610, 1700 (s), 1750, 3200 (br); MS (EI) m/e 435 (M$^+$), 313, 202, 201, 172. Anal. ($C_{23}H_{21}N_3O_4S\cdot H_2O$) C, H, N.

***N*-Methyl-*N*-[(5-methyl-2-phenyl-4-oxazolyl)methyl]-4-[(2,4-dioxothiazolidin-5-yl)methyl]benzenesulfonamide (70).**

(25) Adkins, H.; Reeve, E. W. A Synthesis of *dl*-Threonine. *J. Am. Chem. Soc.* **1938**, *60*, 1328–1331.

To an ice-cooled solution of **91** (0.59 g, 1.9 mmol) in dichloromethane (20 mL) was added a solution of **89** (0.39 g, 1.9 mmol) in dichloromethane (10 mL) followed by diisopropylethylamine (0.40 mL, 2.3 mmol). The solution was stirred at 0 °C for 15 min and then at room temperature overnight. The solution was diluted with dichloromethane, washed with 1 N HCl, 5% sodium bicarbonate (2×), and brine, dried over magnesium sulfate, and concentrated to a yellow solid which was purified by flash chromatography (chloroform/methanol, 20:1) and obtained as a white solid (0.45 g, 50%, mp 83–84 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.81 (s, 3 H), 3.13 (dd, J = 14.1, 9.4 Hz, 1 H), 3.46 (dd, J = 14.1, 3.9 Hz, 1 H), 4.43 (dd, J = 9.4, 4.0 Hz, 1 H), 7.34 (d, J = 8.3 Hz, 2 H), 7.39–7.42 (m, 3 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.87–7.90 (m, 2 H), 9.49 (br s); IR (KBr) ν (cm^{-1}) 1160, 1340, 1705, 1760, 3210 (br); MS (EI) m/e 471 (M^+), 201, 172. Anal. ($C_{22}H_{21}N_3O_5S_2 \cdot {}^1/_4H_2O$) C, H, N.

Methyl 3-Benzamido-4-oxovalerate (93). L-Aspartic acid β-methyl ester hydrochloride (**92**) (5.0 g, 27 mmol) was partially dissolved in pyridine (15 mL) and the mixture cooled to 0 °C. Benzoyl chloride (3.1 mL, 27 mmol) was then added dropwise and stirring was continued for 1.5 h at 0 °C and 0.5 h at room temperature. Acetic anhydride (10 mL) was added and the mixture was heated to 90 °C for 2 h and then diluted with water (15 mL) and heating was continued for 15 min. The mixture was cooled, acidified with excess dilute HCl, and extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed with 2 N HCl (50 mL), water (50 mL), saturated sodium bicarbonate (3 × 50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate, and concentrated to yield a thick oil (4.3 g) which was used directly in the next step.

Methyl 2-(5-Methyl-2-phenyl-4-oxazolyl)acetate (112). Phosphorus oxychloride (20 mL) was added to a solution of the crude **93** (4.3 g) in toluene (80 mL) and the mixture was heated to reflux for 4 h, cooled to room temperature, and poured into ice/water (200 mL). The resulting mixture was adjusted to pH 7.5 with potassium carbonate and extracted with ether (2 × 100 mL). The combined organic layers were combined, washed with water (100 mL) and brine (100 mL), and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 2:1) as an oil (1.1 g, 18%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.3 (s, 3 H), 3.5 (s, 2 H), 3.7 (s, 3 H), 7.1–7.4 (m, 3 H), 7.7–7.9 (m, 2 H).

2-(5-Methyl-2-phenyl-4-oxazolyl)acetic Acid (94). **112** (1.1 g, 4.8 mmol) was slurried in 1 N NaOH (15 mL) and heated to gentle reflux for 0.5 h. The resulting solution was cooled to 0–5 °C and acidified with 6 N HCl. The precipitate was collected and dried (0.82 g, 80%, mp 120.5–124.5 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3 H), 3.50 (s, 2 H), 7.40–7.45 (m, 3 H), 7.85–7.90 (m, 2 H), 12.4 (br s, 1 H).

5-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)acetamido]benzyl]thiazolidine-2,4-dione (66). **94** (0.40 g, 1.8 mmol) was dissolved in dichloromethane (5 mL) and cooled to 0–5 °C. Triethylamine (0.22 mL) was added dropwise followed by ethyl chloroformate (0.31 mL). After 15 min of stirring at 0 °C, a solution of 5-(4-aminobenzyl)thiazolidine-2,4-dione[12] (0.71 g, 3.2 mmol) and triethylamine (0.24 mL) in dichloromethane (15 mL) was added. The cold bath was removed and the solution was stirred at room temperature overnight. The solvent was removed and the residue was partitioned between 2 N HCl (25 mL) and ethyl acetate (25 mL). The aqueous layer was extracted with additional ethyl acetate (25 mL) and the combined organic layers were washed with water (30 mL), saturated sodium bicarbonate (30 mL), and brine (30 mL), dried over sodium sulfate, and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 2:1) as a solid (0.43 g, 55%, mp 201–202 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (s, 3 H), 3.07 (dd, J = 14.2, 9.2 Hz, 1 H), 3.33 (dd, 1 H), 3.60 (s, 2 H), 4.95 (dd, J = 9.1, 4.3 Hz, 1 H), 7.18 (d, J = 8.5 Hz, 2 H), 7.49–7.51 (m, 3 H), 7.56 (d, J = 8.5 Hz, 2 H), 7.89–7.93 (m, 2 H), 10.20 (s, 1 H), 12.0 (br s, 1 H); IR (KBr) ν (cm^{-1}) 720, 1520, 1545, 1660, 1680 (s), 1755; MS (EI) m/e 421 (M^+), 174, 173, 172, 106, 104, 70. Anal. ($C_{22}H_{19}N_3O_4S \cdot {}^1/_2H_2O$) C, H, N.

1-[4-(Diethoxymethyl)phenyl]-2-phenylethanol (113). A solution of terephthalaldehyde mono(diethyl acetal) (**95**) (16 g, 75 mmol) in ether (200 mL) was cooled to −30 °C and benzylmagnesium bromide (56 mL of a 2 M solution, 0.11 mol) was added dropwise, keeping the temperature below −20 °C. After 1 h at −20 °C the mixture was warmed to 0 °C, poured into saturated ammonium chloride (300 mL), and extracted with ether (2 × 300 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, and concentrated. The crude product was plug-filtered through silica gel using hexane/ether (2:1) as a solvent. The product was obtained as an oil (15.7 g, 69%). Crystallization in cold hexane gave the pure compound as a white solid, mp 48–50 °C.

4-(1-Hydroxy-2-phenylethyl)benzaldehyde (96). **113** (8.9 g, 30 mmol) was dissolved in THF (300 mL) and 3.5% perchloric acid (180 mL) and the solution was stirred at room temperature overnight. The mixture was concentrated to ca. 150 mL and extracted with ethyl acetate (2 × 300 mL). The combined organic layers were washed with water (250 mL), saturated sodium bicarbonate, and brine, dried over magnesium sulfate and concentrated to a colorless syrup (6.9 g, 100%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.6 (s, 1 H), 2.9 (d, J = 7 Hz, 2 H), 4.9 (t, J = 7 Hz, 1 H), 7.1–7.2 (m, 5 H), 7.3 (d, J = 8 Hz, 2 H), 7.7 (d, J = 8 Hz, 2 H), 10.0 (s, 1 H).

5-[[4-(1-Hydroxy-2-phenylethyl)phenyl]methylene]thiazolidine-2,4-dione (114) was prepared by condensation with 2,4-thiazolidinedione as described above for **111**. Yield: 7.5 g (75%). Mp 203–205 °C.

5-[4-(1-Hydroxy-2-phenylethyl)benzyl]thiazolidine-2,4-dione (115). To a suspension of **114** (7.0 g, 21 mmol) in methanol (750 mL) was added 3% sodium amalgam (42 g), and the mixture was stirred overnight and then filtered over diatomaceous earth and concentrated. The residue was purified by plug filtration through silica gel (600 g) using hexanes/ethyl acetate (1:1) with 2.5% AcOH as solvent. The product was dissolved in ethyl acetate, washed with saturated sodium bicarbonate, water, and brine, dried over magnesium sulfate, and concentrated to a light yellow gum (4.0 g, 57%).

5-[4-(1-Oxo-2-phenylethyl)benzyl]thiazolidine-2,4-dione (4). An aqueous chromic acid solution was prepared by dissolving sodium dichromate (10 g) in water (30 mL), adding concentrated sulfuric acid (13.6 g) at 0 °C, and diluting with water to a total volume of 50 mL. **115** (1.1 g, 3.3 mmol) was dissolved in ether (30 mL) and the oxidizing reagent (4 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and after 2 h was diluted with ether (100 mL) and water (25 mL). The aqueous layer was extracted with ether (25 mL) and the combined organic phases were washed with water and brine, dried over magnesium sulfate, and concentrated to a gum. The product was purified by column chromatography on silica gel (100 g) using hexanes/ethyl acetate (2:1) with 2.5% acetic acid as eluent and crystallized from hexanes/ethyl acetate to give a white solid (0.27 g, 25%, mp 145–146 °C): ^{1}H NMR (sodium salt, 300 MHz, DMSO-d_6) δ 3.07 (dd, J = 14, 9 Hz, 1 H), 3.46 (dd, J = 14, 4 Hz, 1 H), 4.23 (dd, J = 9, 4 Hz, 1 H), 4.38 (s, 2 H), 7.24–7.32 (m, 5 H), 7.37 (d, J = 8 Hz, 1 H), 7.96 (d, J = 8 Hz, 1 H). Anal. ($C_{18}H_{15}NO_3S$) C, H, N.

1-(4-Bromophenyl)-2-phenoxyethanol (98). A mixture of phenol (1.4 g, 15 mmol), 4′-bromophenacyl bromide (**97**) (4.2 g, 15 mmol), and potassium carbonate (4.2 g, 30 mmol) in acetone (50 mL) was heated to reflux for 8 h. The solution was concentrated, diluted with water (50 mL), and extracted with ether (2 × 100 mL). The combined extracts were washed with 10% NaOH and brine, dried over magnesium sulfate, and concentrated. The crude product was dissolved in 2-propanol (25 mL) and dichloromethane (25 mL) and sodium borohydride (0.57 g, 15 mmol) was added at 0 °C. After 1 h water was added and the mixture was extracted with dichloromethane (2×). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated. The product was plug-filtered through silica gel with dichloromethane as solvent to give an oily solid (3.0 g, 68%) which was used directly in the next step.

1-Bromo-4-[1-[(*tert*-butyldimethylsilyl)oxy]-2-phenoxyethyl]benzene (116). A solution of **98** (2.9 g, 10 mmol), *tert*-butyldimethylsilyl chloride (1.9 g, 12.5 mmol), and imidazole (1.7 g, 25 mmol) in DMF (40 mL) was stirred at room temperature for 36 h. Sodium bicarbonate (10%) (150 mL) was added and the mixture was extracted with hexanes (2 × 200 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, and concentrated. The residue was purified

by plug-filtration through silica gel using 20% butyl chloride in hexanes as the solvent. The title product was obtained as a colorless oil (2.5 g, 61%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.4 (s, 3 H), 0.6 (s, 3 H), 1.45 (s, 9 H), 3.9 (d, J = 7 Hz, 2 H), 5.3 (t, J = 7 Hz, 1 H), 7.7 (*AB*, J = 9 Hz, 2 H), 7.9 (*AB*, J = 9 Hz, 2 H).

4-[1-[(*tert*-Butyldimethylsilyl)oxy]-2-phenoxyethyl]benzaldehyde (99). A solution of 116 (2.5 g, 6.1 mmol) in THF (25 mL) was cooled to −78 °C and treated with *n*-BuLi (3.35 mL of a 2 M solution in hexanes, 6.7 mmol). The solution was stirred at −78 °C for 1 h and then DMF (0.52 mL, 6.7 mmol) was added and the solution was stirred for another hour at −78 °C, quenched with 10% HCl, warmed to room temperature, and extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated. The product (2.0 g) was used in the next step without further purification.

5-[4-[1-[(*tert*-Butyldimethylsilyl)oxy]-2-phenoxyethyl]benzyl]thiazolidine-2,4-dione (117). 5-[4-[1-[(*tert*-Butyldimethylsilyl)oxy]-2-phenoxyethyl]phenylmethylene]thiazolidine-2,4-dione (118) was prepared by condensation with 2,4-thiazolidinedione as described above for 111. The crude product was dissolved in methanol (100 mL) and 3% sodium amalgam (20 g) was added. The mixture was stirred for 20 h, filtered through diatomaceous earth, and concentrated. The residue was taken up in ethyl acetate (500 mL), washed with cold 10% HCl and brine, dried over magnesium sulfate, and concentrated. The product was purified by plug filtration through silica gel using hexanes/ethyl acetate (2:1) as solvent and obtained as an oil (1.6 g, 55% for 3 steps): ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.2 (s, 3 H), 0.6 (s, 3 H), 0.95 (s, 9 H), 3.05 (dd, J = 14, 9 Hz, 1 H), 3.5 (dd, J = 9, 4 Hz, 1 H), 3.95 (d, J = 6 Hz, 2 H), 4.5 (dd, J = 9, 4 Hz, 1 H), 5.0 (t, J = 6 Hz, 1 H), 6.8–7.5 (m, 9 H).

5-[4-(1-Hydroxy-2-phenoxyethyl)benzyl]thiazolidine-2,4-dione (119). A solution of 117 (1.5 g, 3.1 mmol) in THF (50 mL) and 3.5% perchloric acid (30 mL) was stirred at room temperature overnight. It was then extracted with ethyl acetate (2×), and the combined extracts were washed with brine, dried over magnesium sulfate, and concentrated. The product was purified by plug filtration through silica gel using hexanes/ethyl acetate (2:1) as solvent and obtained as an oil (0.69 g, 64%).

5-[4-(1-Oxo-2-phenoxyethyl)benzyl]thiazolidine-2,4-dione (6) was prepared by chromic acid oxidation of 119 as described above for 4 and obtained as a solid (mp 170–174 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.35 (dd, J = 14, 9 Hz, 1 H), 3.54 (dd, J = 14, 4 Hz, 1 H), 5.07 (dd, J = 9, 4 Hz, 1 H), 5.60 (s, 2 H), 7.00 (m, 3 H), 7.32 (t, J = 8 Hz, 2 H), 7.50 (d, J = 8 Hz, 2 H), 8.03 (d, J = 8 Hz, 2 H). Anal. ($C_{18}H_{15}NO_4S$) C, H, N.

2-(5-Methyl-2-phenyl-4-oxazolyl)ethanol (120) was prepared by lithium aluminum hydride reduction of methyl 2-(5-methyl-2-phenyl-4-oxazolyl)acetate (100) (1.1 g) as described above for 108 and obtained as a solid (0.75 g, 78%, mp 58–60 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.75 (t, J = 6 Hz, 2 H), 3.95 (t, J = 6 Hz, 2 H), 7.42–7.45 (m, 3 H), 7.98–8.01 (m, 2 H).

4-(2-Bromoethyl)-5-methyl-2-phenyloxazole (121). To an ice-cooled solution of 120 (0.75 g, 3.7 mmol) and carbon tetrabromide (2.5 g, 7.4 mmol) in ether (30 mL) was added triphenylphosphine (1.9 g, 7.4 mmol). The mixture was stirred for 10 min at 0 °C and 3 h at room temperature and then filtered and concentrated. The residue was purified by plug filtration (silica gel, dichloromethane) and the product obtained as an oil which solidified on standing (0.34 g, 35%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3.05 (t, J = 7 Hz, 2 H), 3.66 (t, J = 7 Hz, 2 H), 7.39–7.42 (m, 3 H), 7.94–7.97 (m, 2 H).

4-[2-[(4-Bromophenyl)thio]ethyl]-5-methyl-2-phenyloxazole (101). To an ice-cooled suspension of sodium hydride (53 mg, 2.2 mmol) in THF (10 mL) were added 4-bromothiophenol (0.32 g, 1.7 mmol) and after 15 min a solution of 121 (0.34 g, 1.3 mmol) in THF (5 mL). The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The precipitate was filtered, and the filtrate was diluted with ethyl acetate, washed with brine, dried over magnesium sulfate, and concentrated. The product was purified by plug filtration (silica gel, hexanes/ether, 4:1) and obtained as a solid (0.42 g, 86%, mp 48–50 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 2.80 (t, J = 7 Hz, 2 H), 3.25 (t, J = 7 Hz, 2 H), 7.18 (d, J = 8 Hz, 2 H), 7.35 (d, J = 8 Hz, 2 H), 7.39–7.42 (m, 3 H), 7.92–7.96 (m, 2 H).

4-[[2-(5-Methyl-2-phenyl-4-oxazolyl)ethyl]thio]benzaldehyde (122) was prepared by transmetalation and formylation of 101 as described for **99** and obtained as a white solid (0.25 g, 70%, mp 77–79 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 2.86 (t, J = 7 Hz, 2 H), 3.33 (t, J = 7 Hz, 2 H), 7.34 (d, J = 8 Hz, 2 H), 7.37–7.40 (m, 3 H), 7.69 (d, J = 8 Hz, 2 H), 7.90–7.94 (m, 2 H), 9.82 (s, 1 H).

5-[[4-[[2-(5-Methyl-2-phenyl-4-oxazolyl)ethyl]thio]phenyl]methylene]thiazolidine-2,4-dione (123). A solution of 122 (0.25 g, 0.77 mmol), 2,4-thiazolidinedione (0.18 g, 1.55 mmol), and piperidine (14 mg, 0.16 mmol) in ethanol (10 mL) was heated to reflux for 24 h. The mixture was cooled, ether (10 mL) was added, and the precipitate was collected (0.16 g, 49%, mp 193–195 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3 H), 2.83 (t, J = 7 Hz, 2 H), 3.35 (t, J = 7 Hz, 2 H), 7.41–7.50 (m, 3 H), 7.69 (s, 1 H), 7.86–7.90 (m, 2 H).

5-[4-[[2-(5-Methyl-2-phenyl-4-oxazolyl)ethyl]thio]benzyl]thiazolidine-2,4-dione (60) was prepared by sodium amalgam reduction of 123 as described for 117 and obtained as a solid (86 mg, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 2.83 (t, J = 7 Hz, 2 H), 3.10 (dd, J = 14, 9 Hz, 1 H), 3.30 (t, J = 7 Hz, 2 H), 3.43 (dd, J = 9, 4 Hz, 1 H), 4.46 (dd, J = 9, 4 Hz, 1 H), 7.12 (d, J = 8 Hz, 2 H), 7.29 (d, J = 8 Hz, 2 H), 7.42–7.44 (m, 3 H), 7.94–7.97 (m, 2 H). The compound was converted to its sodium salt as described for 51. Mp 268–270 °C. Anal. ($C_{22}H_{19}N_2NaO_3S_2$) C, H, N.

5-[4-[[2-(5-Methyl-2-phenyl-4-oxazolyl)ethyl]sulfonyl]benzyl]thiazolidine-2,4-dione (61). To an ice-cooled solution of 60 (53 mg, 0.13 mmol) in dichloromethane (5 mL) was added *m*-CPBA (58 mg, 0.28 mmol) in small portions. The mixture was allowed to warm to room temperature and stirred for 2 h, then diluted with dichloromethane, washed with 5% sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated, to yield the product as a white solid (27 mg, 47%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.95 (q, J = 6 Hz, 2 H), 3.10 (dd, J = 14, 9 Hz, 1 H), 3.36 (dd, J = 9, 4 Hz, 1 H), 3.56 (t, J = 6 Hz, 2 H), 4.40 (dd, J = 9, 4 Hz, 1 H), 7.34 (d, J = 8 Hz, 2 H), 7.40–7.44 (m, 3 H), 7.82 (d, J = 8 Hz, 2 H), 7.84–7.88 (m, 2 H); HRMS calcd 456.0814, found 456.0797.

Methyl 3-(2-Bromo-5-thienyl)-3-oxopropionate (103). To a suspension of sodium hydride (0.17 kg of a 60% dispersion, 4.2 mol) in THF (1 L) were added dimethyl carbonate (0.76 kg, 8.4 mol) and a solution of 2-acetyl-5-bromothiophene[26] (430 g, 2.1 mol) in THF (500 mL), the latter dropwise. The solution was stirred for 1 h and then poured into water, acidified to pH 2 with 6 N HCl, and extracted with ether (3×). The combined extracts were dried over magnesium sulfate and concentrated. The residue was distilled (bp 140–150 °C at 2 mmHg), and the oily distillate was washed with hexanes and dried to give the pure title compound (390 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3 H), 3.86 (s, 2 H), 7.09 (d, J = 4 Hz, 1 H), 7.45 (d, J = 4 Hz, 1 H).

5-Bromo-2-[3-(2-(4-methylphenyl)-5-methyl-4-oxazolyl)-propionyl]thiophene (104) was prepared by condensation of 4-(chloromethyl)-5-methyl-2-(4-methylphenyl)oxazole (102) and 103 followed by decarboxylation, as described for 87. The product was obtained as a brown solid (mp 119 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 2.34 (s, 3 H), 2.85 (t, J = 7.1 Hz, 2 H), 3.21 (t, J = 7.0 Hz, 2 H), 7.01 (d, J = 3.9 Hz, 1 H), 7.18 (d, J = 7.9 Hz, 2 H), 7.42 (d, J = 3.9 Hz, 1 H), 7.80 (d, J = 8.2 Hz, 2 H). Anal. C, H, N.

5-Bromo-2-[1-hydroxy-3-[2-(4-methylphenyl)-5-methyl-4-oxazolyl]propyl]thiophene (124). To a solution of 104 (120 g, 0.31 mol) in ethanol (1.9 L) was added sodium borohydride (8.0 g, 0.21 mol) by portions. After 1 h the solvent was removed, water was added, and the mixture was acidified to pH 1.5 with 6 N HCl and extracted with chloroform (3×). The combined extracts were washed, dried over magnesium sulfate, and concentrated, leaving a yellow gum which was used directly in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (m, 2 H), 2.30 (s, 3 H), 2.38 (s, 3 H), 2.68 (m, 2 H), 4.99 (dd, J = 8.0, 4.3 Hz, 2 H), 6.70 (d, J = 3.8 Hz, 1 H), 6.87 (d, J = 3.7 Hz, 1 H), 7.23 (d, J = 8.1 Hz, 2 H), 7.86 (d,

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J = 8.2 Hz, 2 H); MS (EI) m/e 392 (M^+), 201, 200, 188, 187 (100), 186, 119, 118, 91, 84, 70; IR ($CHCl_3$) ν (cm^{-1}) 1282, 1443, 1500, 1640, 2920.

5-[[5-[1-Hydroxy-3-[2-(4-methylphenyl)-5-methyl-4-oxazolyl]propyl]-2-thienyl]methyl]thiazolidine-2,4-dione (53) was prepared in 5 steps from **124** by the same sequence as that described for **119** and obtained as a white foam: ^1H NMR (300 MHz, $CDCl_3$) δ 2.13 (m, 2 H), 2.31 (s, 3 H), 2.38 (s, 3 H), 2.65 (m, 2 H), 3.39 (dd, J = 51.2, 8.8 Hz, 1 H), 3.59 (dd, J = 15.2, 3.8 Hz, 1 H), 4.50 (dd, J = 8.9, 3.7 Hz, 1 H), 5.01 (m, 1 H), 6.80 (m, 2 H), 7.24 (d, J = 7 Hz, 2 H), 7.88 (d, J = 6.6 Hz, 2 H); MS (EI) m/e 245, 201, 188, 187, 186, 141, 118; IR ($CHCl_3$) ν (cm^{-1}) 1700, 1750; HRMS calcd 428.0858, found 428.0749.

5-[[5-[3-[2-(4-Methylphenyl)-5-methyl-4-oxazolyl]-propionyl]-2-thienyl]methyl]thiazolidine-2,4-dione (57) was prepared by PDC oxidation of the alcohol **53**, as described above for **109** and obtained as a solid: mp 158–160 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 2.36 (s, 3 H), 2.87 (t, J = 6.9 Hz, 2 H), 3.24 (t, J = 6.8 Hz, 2 H), 3.45 (dd, J = 15.1, 8.1 Hz, 1 H), 3.66 (dd, J = 14.9, 4 Hz, 1 H), 4.53 (dd, J = 8, 4 Hz, 1 H), 6.90 (d, J = 3.4 Hz, 1 H), 7.20 (d, J = 7.8 Hz, 2 H), 7.56 (d, J = 3.5 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 2 H), 8.78 (br s, 1 H); MS (EI) m/e 440 (M^+), 200; IR (KBr) ν (cm^{-1}) 1670, 1700, 1750. Anal. ($C_{22}H_{20}N_2O_4S_2 \cdot {}^1/_2H_2O$) C, H, N.

5-[[5-[3-[2-(4-Methylphenyl)-5-methyl-4-oxazolyl]-1-propenyl]-2-thienyl]methyl]thiazolidine-2,4-dione (59). A solution of **105** (0.15 kg, 0.27 mol) in THF (600 mL) and 6 N HCl (600 mL) was stirred at room temperature for 45 min. The pH was adjusted to 5 with sodium bicarbonate and the solution was extracted with ethyl acetate (3×). The combined extracts were dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (30% ethyl acetate in hexanes) as an oil (42 g, 36%): ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 2.36 (s, 3 H), 3.28 (dd, J = 14.5, 8.8 Hz, 1 H), 3.36 (d, J = 6.7 Hz, 2 H), 3.55 (dd, J = 15.0, 3.8 Hz, 1 H), 4.45 (dd, J = 9.0, 3.8 Hz, 1 H), 6.11 (dt, J = 15.4, 7 Hz, 1 H), 6.47 (d, J = 15.4 Hz, 1 H), 6.69 (*AB*, J = 3.6 Hz, 1 H), 6.70 (*AB*, J = 3.7 Hz, 1 H), 7.20 (d, J = 7.9 Hz, 2 H), 7.84 (d, J = 8.2 Hz, 2 H), 9.0 (br s, 1 H); MS (EI) m/e 424 (M^+); IR ($CHCl_3$) ν (cm^{-1}) 1700. The product was converted to its sodium salt by the method described for **51**. Anal. ($C_{22}H_{19}N_2NaO_3S_2$) C, H, N.

5-[4-[3-[5-Methyl-2-(4-hydroxy-3,5-dimethylphenyl)-4-oxazolyl]propionyl]benzyl]thiazolidine-2,4-dione (45). A solution of **44** (105 mg, 0.21 mmol) in acetic acid (10 mL) and 48% HBr (5 mL) was heated to reflux for 1 h, cooled, poured into ice–water, and extracted with ethyl acetate. The combined extracts were washed with water, saturated sodium bicarbonate, water again, and brine, dried over magnesium sulfate, and concentrated (103 mg, 100%): ^1H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 6 H), 2.32 (s, 3 H), 2.86 (t, J = 7 Hz, 2 H), 3.15 (dd, J = 14, 9 Hz, 1 H), 3.30 (t, J = 7 Hz, 2 H), 3.47 (dd, J = 14, 4, Hz, 1 H), 4.49 (dd, J = 8, 4 Hz, 1 H), 7.23 (d, J = 8 Hz, 2 H), 7.56 (s, 2 H), 7.86 (d, J = 8.0 Hz, 2 H). The product was converted to its sodium salt as described for **26**: mp 230–240 °C. Anal. ($C_{25}H_{23}N_2NaO_5S \cdot 2H_2O$) C, H, N.

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Affinity of Human Growth Hormone-Releasing Factor (1–29)NH_2 Analogues for GRF Binding Sites in Rat Adenopituitary[1]

Pierrette Gaudreau,* Luce Boulanger, and Thierry Abribat

Neuroendocrinology Laboratory, Rm M-5226, Notre-Dame Hospital Research Center, 1560 Sherbrooke Street East, Montreal, Canada H2L 4M1. *Received September 24, 1991*

Previous research on growth hormone-releasing factor analogues has used pituitary cell culture assay systems to evaluate in vitro their biological activity. However, binding assay systems in which receptor affinity and peptide stability can be assessed independently have been lacking so far. Since we have recently develop a sensitive GRF binding assay with [^{125}I-Tyr^{10}]hGRF(1–44)NH_2, this method was applied to structure–affinity studies as a first step of screening GRF analogues. Acylation of the N-terminus of hGRF(1–29)NH_2 generally decreased its affinity (relative affinity to hGRF(1–29)NH_2 (RA), 26–85%). Replacement of the C-terminal carboxamide by a free carboxylic function decreased affinity likely by diminishing its proteolytic stability (RA, 57%). Removal of Tyr^1, Ser^9, Lys^{12}, Val^{13}, Gly^{15}, Gln^{16}, or Lys^{21} drastically decreased its affinity (RA, <3%). Multiple amino acid deletions in the segment 13–21 of hGRF(1–29)NH_2 also led to a loss of affinity as did replacing segment 13–15, 16–18, or 19–21 by an octanoyl moiety (RA, <1%). Removal of Asn^8, Gln^{24}, Asp^{25}, Ile^{26}, Met^{27}, and Ser^{28} or Arg^{29} had less effect on GRF receptor affinity (RA, 5–33%). Removal of Met^{27} or Ser^{28} only slightly affected hGRF(1–29)NH_2 affinity (RA, 62–78%). Altogether, these results indicate that the amino acids contained in the segment 13–21 are more important than those of 24–29 to insure high affinity receptor binding or to maintain an optimal conformation to allow GRF binding.

Introduction

Since the isolation and characterization of growth hormone (GH)-releasing factor (GRF),[2] a number of GRF analogues have been synthesized. Most[3-12] were designed to be potent agonists with potential clinical and zootechnical applications. Their structures were based upon that of hGRF(1–29)NH_2, the N-terminal portion of hGRF(1–44)NH_2, as this portion retains the full potency of the native 44 amino acid peptide to induce GH secretion in vitro and/or in vivo, in various species. Human GRF(1–29)NH_2 also possesses a high degree of sequence homology with porcine, bovine, and ovine GRF(1–29)NH_2 (≥93%) suggesting multiple applications, in various species, for a sole analogue.

* Author to whom correspondence and reprint requests should be sent.

(1) Symbols and abbreviations are in accord with the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature (*Eur. J. Biochem.* 1984, *158*, 9–37). All optically active amino acids are of the L configuration, unless otherwise specified. Additional abbreviations used are as follows: Ac, acetyl; desaminoTyr, 3-(4-hydroxyphenyl)propionic acid.

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