be complete after ca. 3 min (no further addition of HCl required). The mixture was stirred for an additional 50 min and poured into 800 mL of ice–water resulting in the formation of a precipitate. The mixture was cooled in an ice bath for an additional 4 h and filtered, and the solids were washed with additional water. After drying, **6d** (4.87 g, 98%) was obtained as a colorless solid: mp 190–191 °C; $[\alpha]_D$ = +95° (c = 1, methanol), [lit. mp 187–190 °C, $[\alpha]_D$ = +99° (c = 0.26, DMF)].[7] Anal. ($C_{17}H_{17}NO_4S$) C, H, N, S.

(3*R*-*cis*)-3-(Acetyloxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (1f). A solution of (3*R*-*cis*)-3-(acetyloxy)-7-chloro-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one monohydrochloride (**1h**, 170 mg, 0.36 mmol, see ref 1 for preparation) was neutralized in ether by washing with with saturated $NaHCO_3$. The ether solution of the free base was then concentrated and the residue redissolved in acetic acid (10 mL). Catalyst was then added (80 mg of 10% Pd/C), and the mixture was shaken overnight under 30 psi of hydrogen gas at room temperature. The mixture was then filtered through Celite and the filtrate, plus washes, was washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. The residue was dissolved in ether and treated with HCl-saturated ether. The resulting white precipitate was filtered and dried to yield 0.13 g (83%) of the desired product: mp 63–65 °C; $[\alpha]_D$ = +117.2° (c = 1, MeOH); ^1H NMR (CD_3OD) δ 7.45 (m, 3 H), 7.35 (m, 1 H), 7.25 (d, 2 H), 6.90 (d, 2 H), 5.05 (d, 1 H), 4.30 (m, 2 H), 3.80 (m, 4 H), 3.65 (m, 1 H), 3.45 (m, 1 H), 3.00 (m, 8 H), 1.85 (s, 3 H); ^{13}C NMR (CD_3OD) δ 20.35, 37.94, 44.05, 45.34, 51.53, 55.74, 56.46, 73.19, 114.71, 123.76, 128.88, 129.95, 130.67, 130.96, 132.63, 135.51, 141.38, 160.41, 171.07, 171.79. Anal. ($C_{23}H_{29}N_2O_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

Acknowledgment. Analytical data were supplied by the Bristol-Myers Squibb Analytical Research and Development Department.

Studies on Antidiabetic Agents. 11.[1] Novel Thiazolidinedione Derivatives as Potent Hypoglycemic and Hypolipidemic Agents[2]

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In the course of further chemical modification of the novel antidiabetic pioglitazone (AD-4833, U-72, 107), a series of 5-[4-(2- or 4-azolylalkoxy)benzyl- or -benzylidene]-2,4-thiazolidinediones was prepared and evaluated for hypoglycemic and hypolipidemic activities in insulin-resistant, genetically obese, and diabetic KKA^y mice. Replacement of the 2-pyridyl moiety of pioglitazone by a 2- or 4-oxazolyl or a 2- or 4-thiazolyl moiety greatly enhanced in vivo potency. The corresponding 5-benzylidene-type compounds, in which a methine was used as a linker between the benzene ring and the thiazolidinedione ring, also had potent biological activity. Among the compounds synthesized, 5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione (18) exhibited the most potent activity, more than 100 times that of pioglitazone. The synthesis and structure–activity relationships for this novel series of derivatives are detailed.

Introduction

Insulin resistance is a characteristic feature of non-insulin-dependent diabetes mellitus (NIDDM), in particular when it is associated with obesity. This insulin-resistant state at the peripheral tissue level causes impaired glucose utilization leading to hyperglycemia.[3] Therefore, amelioration of insulin resistance with a drug would provide a novel and useful means of treating NIDDM. With regard to this concept[3,4] few drugs have, however, been studied, and exercise and calorimetric restriction are still the fundamental modes of treating NIDDM patients. It has been reported that sulfonylureas, the most commonly used oral hypoglycemics, potentiate insulin action in peripheral tissues by increasing the number of insulin receptors;[5] however, their main mechanism of action actually involves insulin secretion. This insulin secretion can bring about undesired effects such as induction of hypoglycemia.

In 1982, we reported a series of 5-(4-alkoxybenzyl)-2,4-thiazolidinediones[6a] as novel antidiabetic agents which were shown to effectively reduce insulin resistance or potentiate insulin action in genetically diabetic and/or obese animals. Ciglitazone, a prototypical compound of the series (Chart I), was shown to normalize hyperglycemia, hyper-

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(4) Reaven, G. M. Therapeutic Approaches to Reducing Insulin Resistance in Patients with Noninsulin-Dependent Diabetes Mellitus. *Am. J. Med.* **1983**, *74* (Suppl. 1A), 109–112.

(5) Gavin, J. R., III Dual Actions of Sulfonylureas and Glyburide. Receptor and Post-Receptor Effects. *Am. J. Med.* **1985**, *79* (Suppl. 3B), 34–42.

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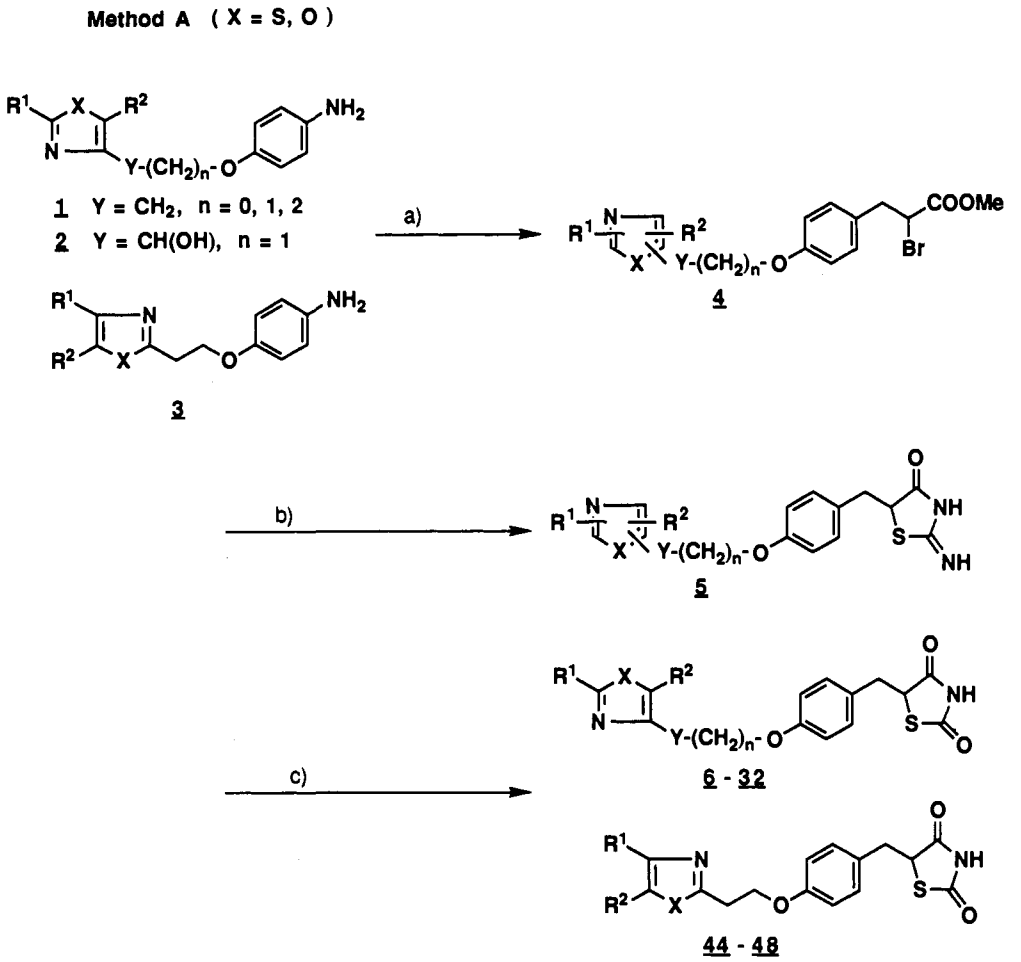
Scheme I[a]

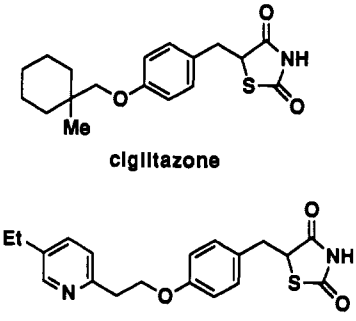


[a] (a) Aqueous HBr, $NaNO_2$ then CH_2=CHCOOMe, Cu_2O; (b) $(NH_2)_2CS$, NaOAc; (c) aqueous HCl.

insulinemia, and hypertriglyceridemia in various insulin-resistant animal models without altering normoglycemia in nondiabetic animal models.[6b,c] Since our discovery of ciglitazone, many other structurally analogous thiazolidinediones have been reported,[7] and drug development along this line is becoming one of the major concerns in the field of antidiabetic agents.[8]

In a previous paper,[9] we reported on the potent hypo-

Chart I



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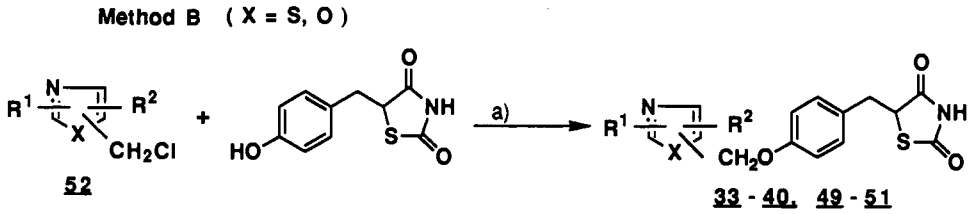
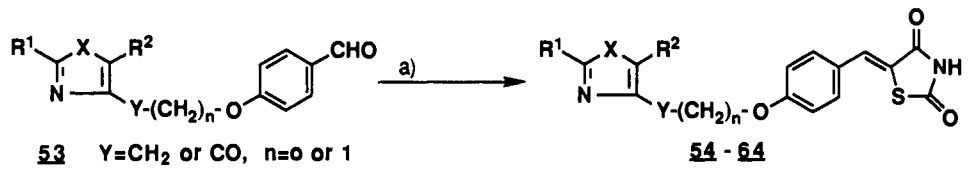
Scheme II[a]



[a] (a) NaH.

Scheme III[a]



[a] (a) 2,4-Thiazolidinedione, piperidine.

glycemic and hypolipidemic activity of pioglitazone (AD-4833, U-72, 107) in insulin-resistant animal models such as KKA^y mice[10] and Wistar fatty rats.[11] The structure–activity relationship (SAR) studies on pioglitazone and related compounds revealed that the presence of a pyridyl ring on the *p*-alkoxy chain of the benzyl moiety potentiated biological activities and that location of the pyridine nitrogen α to the oxyethyl chain was a very important factor for the activity.[1,9a] These findings led us to the syntheses of other heterocyclic analogues of pioglitazone having the ring nitrogen at the same relative position. This report details some SAR studies on this series.

Chemistry

Most of the 5-benzyl-2,4-thiazolidinediones in Tables I and II were synthesized starting from 4-[(2- or 4-)oxazolyl- or -thiazolylalkoxy]aniline derivatives **1–3** by the general procedure described in previous papers.[1,6a,9a] Meerwein arylation of the aniline derivatives gave the 3-aryl-2-bromopropionates **4**, which were then treated with thiourea to afford the iminothiazolidinones **5**. Acid hydrolysis of **5** gave the desired 2,4-thiazolidinediones **6–32** and **44–48** in good yield (method A, Scheme I).

The requisite 4-(4-azolylalkoxy)aniline derivatives **1** were prepared by condensation of 4-azolyl alcohols with *p*-fluoronitrobenzene followed by reduction as described in the synthesis of the 4-[2-(substituted 2-pyridyl)ethoxy]-benzyl derivatives.[9a] The 2-(2-oxazolyl)ethoxy analogues **3** were also obtained by reduction of the corresponding nitro compounds, which were synthesized by cyclization of α-[3-(4-nitrophenoxy)propionyl]amino ketones with $POCl_3$. Coupling of 4-(bromoacetyl)azoles with *p*-acetamidophenol followed by $NaBH_4$ reduction and alkaline hydrolysis afforded the anilines **2** bearing a hydroxy group on the 4-ethoxy chain.

O-Alkylation of 5-(4-hydroxybenzyl)-2,4-thiazolidinedione with (2- or 4-chloromethyl)azoles **52** provided a simpler method for the preparation of 5-(2- or 4-azolylmethoxy)benzyl derivatives and was used as the general synthetic procedure for compounds **33–40** and **49–51** (method B, Scheme II).

Compound **41** possessing a hydroxymethyl group at the 5-position on the oxazole ring was obtained by bromination of **18** with NBS followed by hydrolysis (see Experimental Section). Oxidation of **30** and **31** was effected by DMSO–Ac_2O to give the corresponding 2-oxoethyl derivatives **42** and **43**, respectively.

The 5-benzylidene-2,4-thiazolidinediones **54–64** were obtained by Knoevenagel condensation of the benzaldehydes **53** with 2,4-thiazolidinedione using piperidine as base (method C, Scheme III). The starting benzaldehydes **53** were readily prepared by the method described in the previous paper.[1] The 2-oxoethyl derivatives **63** and **64** were reduced with $NaBH_4$ to the corresponding hydroxy compounds **65** and **66**, respectively.

2- or 4-functionalized oxazoles and thiazoles used in methods A–C above were prepared following the procedure reported previously by Meguro et al.[12] The derivatives in Tables I–III are simple racemates or racemic mixtures of diastereomers, and no attempts at optical resolution have been carried out.

Biological Procedures

The biological activities of the compounds prepared were tested using genetically obese and diabetic KKA^y mice[10] (8–11-week-old). After being fed a laboratory chow (CE-2, Clea Japan Inc., Tokyo, Japan) for 3 d, the mice were

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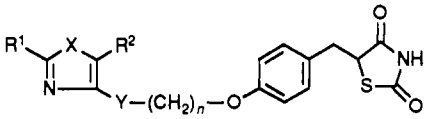
(12) Meguro, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. Studies on Antidiabetic Agents. VII. Synthesis and Hypoglycemic Activity of 4-Oxazoleacetic Acid Derivatives. *Chem. Pharm. Bull.* **1986**, *34*, 2840–2851.

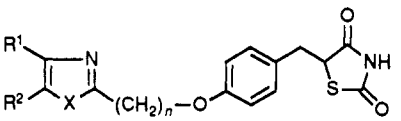
Table I. Physical Data and Yield of 5-[4-(4-Azolylalkoxy)benzyl]-2,4-thiazolidinediones



entry	R^1	R^2	X	Y	n	prep method[a]	yield[b] (%)	mp (°C)	formula	anal.[c]
6	H	Me	S	CH_2	1	A	20	185–186	$C_{16}H_{16}N_2O_3S_2$	C,H,N
7	Me	H	S	CH_2	1	A	21	142–143	$C_{16}H_{16}N_2O_3S_2$	C,H,N
8	Et	H	S	CH_2	1	A	40	148–149	$C_{17}H_{18}N_2O_3S_2$	C,H,N
9	*i*-Pr	H	S	CH_2	1	A	34	107–108	$C_{18}H_{20}N_2O_3S_2$	C,H,N
10	cyclohexyl	H	S	CH_2	1	A	26	289–291	$C_{21}H_{23}N_2O_3S_2Na$	C,H,N
11	Ph	H	S	CH_2	1	A	41	113–114	$C_{21}H_{18}N_2O_3S_2$	C,H,N
12	Me	H	O	CH_2	1	A	22	184–185	$C_{18}H_{16}N_2O_4S$	C,H,N
13	Pr	H	O	CH_2	1	A	11	87–88	$C_{18}H_{20}N_2O_4S$	C,H,N
14	Me	Me	O	CH_2	1	A	46	200–201	$C_{17}H_{18}N_2O_4S$	C,H,N
15	Me	Et	O	CH_2	1	A	31	189–190	$C_{18}H_{20}N_2O_4S$	C,H,N
16	cyclohexyl	H	O	CH_2	1	A	13	269–271	$C_{21}H_{23}N_2O_4SNa \cdot {}^1/_2H_2O$	C,H,N
17	Ph	H	O	CH_2	1	A	29	109–110	$C_{21}H_{18}N_2O_4S$	C,H,N
18	Ph	Me	O	CH_2	1	A	52	116–117	$C_{22}H_{20}N_2O_4S$	C,H,N
19	Ph	Et	O	CH_2	1	A	21	109–111	$C_{23}H_{22}N_2O_4S$	C,H,N
20	Ph	Me	O	CH_2	2	A	34	130–131	$C_{23}H_{22}N_2O_4S$	C,H,N
21	cyclohexyl	Me	O	CH_2	1	A	27	273–275	$C_{22}H_{25}N_2O_4SNa$	C,H,N
22	2-furyl	Me	O	CH_2	1	A	21	114–115	$C_{20}H_{18}N_2O_5S$	C,H,N
23	2-thienyl	Me	O	CH_2	1	A	32	144–145	$C_{20}H_{18}N_2O_4S_2$	C,H,N
24	4-(MeO)C_6H_4	Me	O	CH_2	1	A	51	167–168	$C_{23}H_{22}N_2O_5S$	C,H,N
25	3,4-$(MeO)_2C_6H_3$	Me	O	CH_2	1	A	29	167–168	$C_{24}H_{24}N_2O_6S$	C,H,N
26	3-(Me)C_6H_4	Me	O	CH_2	1	A	37	99–100	$C_{23}H_{22}N_2O_4S$	C,H,N
27	3-(MeS)C_6H_4	Me	O	CH_2	1	A	31	161–162	$C_{23}H_{22}N_2O_4S_2$	C,H,N
28	2-(Cl)C_6H_4	Me	O	CH_2	1	A	23	93–94	$C_{22}H_{19}N_2O_4SCl$	C,H,N
29	4-(OH)C_6H_4	Me	O	CH_2	1	A	45	213–214	$C_{22}H_{20}N_2O_5S$	C,H,N
30	Me	Me	O	CH(OH)	1	A	32	214–215	$C_{17}H_{18}N_2O_5S$	C,H,N
31	Ph	Me	O	CH(OH)	1	A	50	165–166	$C_{22}H_{20}N_2O_5S$	C,H,N
32	cyclohexyl	Me	O	CH(OH)	1	A	19	oil	$C_{22}H_{26}N_2O_5S$	C,H,N
33	Me	H	S	CH_2	0	B	40	181–182	$C_{15}H_{14}N_2O_3S_2$	C,H,N
34	Ph	H	S	CH_2	0	B	41	164–165	$C_{20}H_{16}N_2O_3S_2$	C,H,N
35	3-Py	H	S	CH_2	0	B	13	205–206	$C_{19}H_{15}N_3O_3S_2$	C,H,N
36	Me	H	O	CH_2	0	B	28	192–193	$C_{15}H_{14}N_2O_4S$	C,H,N
37	Pr	H	O	CH_2	0	B	36	114–115	$C_{17}H_{18}N_2O_4S$	C,H,N
38	Ph	H	O	CH_2	0	B	47	188–189	$C_{20}H_{16}N_2O_4S$	C,H,N
39	Ph	Me	O	CH_2	0	B	79	162–163	$C_{21}H_{18}N_2O_4S$	C,H,N
40	2-furyl	Me	O	CH_2	0	B	50	194–196	$C_{19}H_{16}N_2O_5S$	C,H,N
41	Ph	CH_2OH	O	CH_2	1	Ex	21	98–99	$C_{22}H_{20}N_2O_5S$	C,H,N
42	Me	Me	O	C=O	1	Ex	48	161–162	$C_{17}H_{16}N_2O_5S$	C,H,N
43	Ph	Me	O	C=O	1	Ex	81	168–169	$C_{22}H_{18}N_2O_5S$	C,H,N

[a] A, B = general method, Ex = experimental procedure described. [b] Overall yield based on 1 or 2 (method A), 52 (method B). [c] Compounds gave satisfactory analyses (±0.4%).

Table II. Physical Data and Yield of 5-[4-(2-Azolylalkoxy)benzyl]-2,4-thiazolidinediones



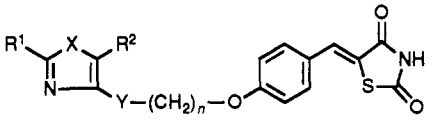
entry	R^1	R^2	X	n	prep method[a]	yield[b] (%)	mp (°C)	formula	anal.[c]
44	*i*-Bu	Me	O	2	A	27	123–124	$C_{20}H_{24}N_2O_4S$	C,H,N
45	cyclohexyl	Me	O	2	A	24	175–176	$C_{22}H_{26}N_2O_4S$	C,H,N
46	Ph	Me	O	2	A	34	261–262	$C_{22}H_{18}N_2O_4SNa$	C,H,N
47	Ph	Et	O	2	A	30	248–250	$C_{23}H_{21}N_2O_4SNa$	C,H,N
48	Me	Ph	O	2	A	21	168–169	$C_{22}H_{20}N_2O_4S$	C,H,N
49	Ph	H	S	1	B	49	164–165	$C_{20}H_{18}N_2O_3S_2$	C,H,N
50	2-benzothiazolyl			1	B	35	184–185	$C_{18}H_{14}N_2O_3S_2$	C,H,N
51	2-benzoxazolyl			1	B	33	188–189	$C_{18}H_{14}N_2O_4S$	C,H,N

[a] A, B = general method. [b] Overall yield based on 3 (method A) or 52 (method B). [c] Compounds gave satisfactory analyses (±0.4%).

divided into experimental groups of five mice each according to their blood glucose levels. The test compounds were given as a dietary admixture at 0.005% or 0.001% in the CE-2 powdered diet. The mice were fed the experimental diet and water ad libitum for 4 d. Blood samples were taken from the orbital vein. Blood glucose was determined using the glucose oxidase method[13] and plasma triglyceride using a commercially available assay kit (Cleantech TG-S, Iatron Laboratories Inc., Tokyo, Japan).

(13) Werner, W.; Rey, H. G.; Wielinger, H. Über die Eigenschaften eines neuen Chromogens für die Blutzuckerbestimmung nach der GOD/POD-Methode. *Fresenius' Z. Anal. Chem.* **1970**, *252*, 224–228.

Table III. Physical Data and Yield of 5-[4-(4-Azolylalkoxy)benzylidene]-2,4-thiazolidinediones



entry	R^1	R^2	X	Y	n	prep method[a]	yield[b] (%)	mp (°C)	formula	anal.[c]
54	Me	H	S	CH_2	1	C	82	215–216	$C_{16}H_{14}N_2O_3S_2$	C,H,N
55	Ph	H	S	CH_2	1	C	91	210–211	$C_{21}H_{18}N_2O_3S_2$	C,H,N
56	Ph	Me	O	CH_2	1	C	95	214–215	$C_{22}H_{18}N_2O_3S$	C,H,N
57	Ph	Et	O	CH_2	1	C	72	175–176	$C_{23}H_{20}N_2O_3S$	C,H,N
58	4-(Cl)C_6H_4	Me	O	CH_2	1	C	91	214–215	$C_{22}H_{17}ClN_2O_3S$	C,H,N
59	3-(MeS)C_6H_4	Me	O	CH_2	1	C	67	185–186	$C_{23}H_{20}N_2O_4S_2$	C,H,N
60	1-Me-cyclohexyl	Me	O	CH_2	1	C	51	172–175	$C_{23}H_{26}N_2O_4S$	C,H,N
61	2-thienyl	Me	O	CH_2	1	C	48	221–222	$C_{20}H_{16}N_2O_4S_2$	C,H,N
62	Ph	Me	O	CH_2	0	C	81	225–226	$C_{21}H_{16}N_2O_4S$	C,H,N
63	Ph	Me	O	C=O	1	C	76	244–245	$C_{22}H_{18}N_2O_5S$	C,H,N
64	Me	Me	O	C=O	1	C	63	234–235	$C_{17}H_{14}N_2O_5S$	C,H,N
65	Ph	Me	O	CH(OH)	1	Ex	98	252–253	$C_{22}H_{18}N_2O_5S$	C,H,N
66	Me	Me	O	CH(OH)	1	Ex	98	223–224	$C_{17}H_{18}N_2O_5S$	C,H,N

[a] C = general method, Ex = experimental procedure described. [b] Yield from 53 (method C). [c] Compounds gave satisfactory analyses (±0.4%).

The maximum decreases in blood glucose and plasma triglyceride levels were calculated as percentage change from the control value. Effective dose to reduce blood glucose and plasma triglyceride levels by 25% (ED_{25}) was determined using data from an experiment in which three different doses were used. The doses were selected according to the potency of compound. The dosages of test compounds (mg/kg/d) were calculated from food intake and body weight. ED_{25} (mg/kg/d) was then derived by linear regression analysis of the data.

Results and Discussion

We have already reported a thiazole derivative **67** (Table IV) with an oxyethyl chain at the 5-position of the thiazole ring.[6a] Detailed pharmacological evaluation of this compound revealed that **67** was slightly less active than ciglitazone (Table IV). A sharp increase in activity was, however, observed on shifting the side chain from the 5- to the 4-position of the thiazole ring, i.e. from β to α to the ring nitrogen, as seen in compounds **6** and **7**. This finding parallels that observed in the case of the 3-pyridyl- and 2-pyridylethoxy compounds reported previously.[9a] On the basis of this general trend between structure and activity, we focused our synthetic efforts on the preparation of various 5-(4-alkoxybenzyl)-2,4-thiazolidinediones bearing 4-oxazolyl and 4-thiazolyl moieties.

The 4-oxazolyl and 4-thiazolyl derivatives synthesized possessed, on the whole, superior activities over the compounds which had been studied previously. No significant difference was observed between the activities of the oxazole and thiazole derivatives (**7** vs **12**; **11** vs **17**; **33** vs **36**; **34** vs **38**; etc.).

Variation of the distance between the benzene ring and the azole ring showed that two-carbon units were the most effective for eliciting the activities (**7** > **33**; **18** > **39** > **20**; **11** > **34**; etc.), as was the case with the phenylalkoxy or pyridylalkoxy derivatives.[6a,9a]

Among the compounds with two-carbon units (**12–19** and **21–29**), introduction of a methyl group at the 5-position of the oxazole ring potentiated the activity, whereas an ethyl group was not as effective, indicating that a methyl moiety was optimal (**14** > **12** and **15**; **18** > **17** and **19**).

The effect of a substituent at the 2-position was studied for both the two-carbon (**6–19**, **21–29**) and one-carbon unit (**33–40**) compounds. For those bearing alkyl groups, the number of carbon atoms present in the substituent seems to be unrelated to the activities (**7** vs **8** and **9**; **12** vs **13**; **36** vs **37**; etc.); however, conversion of the 2-alkyl group to a cycloalkyl group tended to increase the activity (**7**, **8** and **9** vs **10**; **12** and **13** vs **16**; **14** vs **21**). Compound **21**, in particular, showed very potent activity, being about 42–155 times more potent than ciglitazone. Compounds with an aryl or a heteroaryl group showed superior activities to those with an alkyl or a cycloalkyl group as can be seen in **11**, **17–19**, **22**, **23**, **34**, **35**, **38**, **39**, **40**, etc. Introduction of substituent(s) into the 2-phenyl group of **18**, an extremely active compound having a potency some 277–620 times that of ciglitazone, did not enhance activity but even resulted in a decrease in activity in some cases (e.g. **24** and **25**).

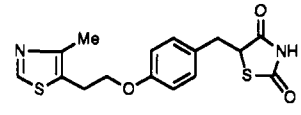
Considering the structure–activity relationships mentioned above, it seems that the 2-position of the oxazole ring might play an important role in hydrophobic binding in the drugs active site. It seems likely that a phenyl group would fit best into the hydrophobic pocket of the binding site, and a cyclohexyl group would seem next best.

Derivatives of **18** hydroxylated at the 5-methyl (**41**) and on the 2-phenyl ring (**29**) showed only reduced activities. In contrast, compounds **30–32** having a hydroxy group on the ethoxy chain, which were expected to have the same effect as in the previous study with the 2-pyridylethoxy series,[9a] exhibited activities either stronger than or comparable to those of the parent compounds (**14** vs **30**, **18** vs **31**, **21** vs **32**). These facts support the suggestion obtained from the previous study,[9a] that a steric effect rather than a net increase in hydrophilicity of the molecule is the more important factor to consider when trying to rationalize how the hydroxy group induces favorable biological activity.

The activity of the oxo derivatives **42** and **43** seem to be slightly lower than those of the hydroxy derivatives (**42** vs **30**, **43** vs **31**); however, these activities were at quite a high level.

Potent antidiabetic activity was also found in the 5-[4-(2-azolylalkoxy)benzyl]-2,4-thiazolidinediones (Table II), which have the oxyethyl chain α to the azole ring nitrogen. In particular, those having a bulky group at the 4-position of the ring had superior activities as can be seen in **44–47** and **49**. On the other hand, compound **48** with only a small substituent (Me) at the 4-position did not show any noticeable activities at the doses employed. These facts as well as the findings with **18** and its analogues clearly

Table IV. Hypoglycemic and Hypolipidemic Activities of 2,4-Thiazolidinediones

	hypoglycemic activity[a]			hypolipidemic activity[a]		
	dose (%)			dose (%)		
	0.001	0.005	ED_{25}[b]	0.001	0.005	ED_{25}[b]
6		52****			45***	
7	17	42****[c]	4	15	52***	4
8		55****			37***	
9		56****			45****	
10	43****		0.8	33**		3
11	39****	52****	0.5	54****	63****	0.3
12	13	37****	5	20	42***	3
13	29**	52****	2	26***	65****	2
14	27*	55****	2	10	56****	3
15	15***	46****	3	0	45***	5
16	31***		1	14		9
17	41****	58****	0.3	51****	68****	0.5
18	55****	59****	0.05	67****	66****	0.09
19	49****	55****	0.3	55****	79****	0.6
20		21***			29**	
21	51****	52****	0.2	58****	71****	0.6
22	50****	50****	0.4	41****	69****	0.9
23	50****	51****	0.09	41****	72****	0.3
24	53****	55****	0.3	63****	72****	0.6
25	52****		0.5	54****		0.6
26	49****		0.05	61****		0.06
27		52****			67****	
28	52****			57****		
29	22***			26****		
30	55****	51****	0.2	52****	62****	0.5
31	54****	58****	0.05	62****	81****	0.1
32		49****			67****	
33		19			30	
34	11**	28***	6	3	32*	8
35		25**			30**	
36		19**			1	
37		12			29*	
38	16**	48****	3	12	51***	4
39	23***	41****	3	17**	44****	5
40		43****			35***	
41		31***			39**	
42		39***			27***	
43		52****			67****	
44		53****			43***	
45		54****			51****	
46		54****			60****	
47		46****			51****	
48		18*			7	
49		48****			44**	
50		43***			43**	
51		35**			24	
54		34**			5	
55	49***	57****	0.6	44****	57****	1.3
56	55****		0.4	65****		0.2
57		54****			59****	
58		54****			58****	
59		52****			58****	
60		24****			9	
61		55****			57****	
62		37***			40***	
63		45****			51****	
64		33****			29	
65	36****	56****	0.9	54***	60****	0.3
66	26****	59****	2.2	37*	61****	0.8
67						
	(0.02%)	(0.01%)		(0.02%)	(0.01%)	
	31**	15*	40	25*	8	40
ciglitazone			31			25
pioglitazone hydrochloride			6			6

[a] Maximum reductions in blood glucose and plasma triglyceride levels in KKA^y mice at a dosage of 0.001 or 0.005% in the diet were calculated as percentage reduction with respect to the control value. [b] Effective dose (mg/kg/d) of 25% reduction, estimated from dose–response curve at three doses. [c] Statistically significant at (*) $p < 0.05$, (**) $p < 0.02$, (***) $p < 0.01$, (****) $p < 0.001$.

suggest that a structure having a bulky group (e.g. phenyl) and an oxyalkyl chain at the α and α' positions, respectively, of the oxazole or thiazole ring is favorable for activity. Judging from the activities of compounds **50** and **51**, benzoxazole and benzothiazole would also seem to fit well into the binding site.

A series of 5-benzylidene-2,4-thiazolidinediones were prepared on the basis of our previous findings in the pyridylalkoxy series.[1] Most compounds exhibited potent hypoglycemic and hypolipidemic activities, showing the effectiveness of the methine moiety as a linker between the benzene and the thiazolidinedione rings. The potency shown was slightly low compared to that shown by the corresponding methylene counterparts, but a similar SAR was observed. Concerning the substituent at the 2-position of the azole ring, an aryl group was superior to an alkyl or cycloalkyl group. Compounds hydroxylated on the ethoxy chain were equipotent, and the oxo derivatives were slightly less potent than the parent compound.

In summary, extremely potent antidiabetic activites were attained in a series of 5-[4-[2-(4-oxazolyl)ethoxy]benzyl- or -benzylidene]-2,4-thiazolidinediones. Compound **18**, the most potent compound in this series, did not alter plasma glucose in normal rats, which suggests that this series of compounds possess the same biological profile as ciglitazone. Further pharmacological evaluation is now in progress in order to select a compound for clinical use.

Experimental Section

Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses (C, H, and N) were carried out by the Analytical Department of the Takeda Chemical Industries, Ltd. ^{1}H NMR spectra of deuteriochloroform or DMSO-d_6 solutions (internal standard TMS, δ 0) were recorded on a Varian EM-390 or a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Hitachi IR-215 spectrometer. All compounds exhibited ^{1}H NMR, IR, and analytical data consistent with the proposed structures. Column chromatography was done with E. Merck silica gel 60 (0.063–0.200 mm).

Method A. 5-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione (18). A solution of $NaNO_2$ (16.8 g, 0.24 mol) in H_2O (30 mL) was added dropwise to a stirred and ice-cooled mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]aniline (65.0 g, 0.22 mol), aqueous HBr (47%, 151.5 g, 0.88 mol), MeOH (200 mL), and acetone (500 mL) below 5 °C. The whole was stirred at 5 °C for 30 min and methyl acrylate (117 mL, 1.32 mol) was added and the temperature was raised to 38 °C. Powdered Cu_2O (2.0 g, 0.014 mol) was added in small portions to the vigorously stirred mixture. After a N_2 gas evolution had ceased, the reaction mixture was concentrated in vacuo. The residue was diluted with H_2O, made alkaline with concentrated NH_4OH, and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give methyl 2-bromo-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionate as a crude oil (89.5 g, 92%): ^{1}H NMR ($CDCl_3$) δ 2.33 (3 H, s), 2.93 (2 H, t, J = 7 Hz), 3.15 (1 H, dd, J = 14, 7 Hz), 3.40 (1 H, dd, J = 14, 7 Hz), 3.65 (3 H, s), 4.21 (2 H, t, J = 7 Hz), 4.32 (1 H, t, J = 7 Hz), 6.81 (2 H, d, J = 9 Hz), 7.08 (2 H, d, J = 9 Hz), 7.4 (3 H, m), 7.98 (2 H, m).

A mixture of methyl 2-bromo-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionate (a crude oil, 38.6 g, 87 mmol), thiourea (6.6 g, 87 mmol), NaOAC (7.1 g, 87 mmol), and EtOH (350 mL) was stirred under reflux for 3 h and concentrated in vacuo. The residue was neutralized with aqueous $NaHCO_3$ and Et_2O (150 mL)–hexane (150 mL) was added. The whole was stirred at room temperature for 15 min, and the crystals were collected by filtration to give 2-imino-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-4-thiazolidinone (19.1 g, 54%): mp 212–213 °C (EtOH). Anal. ($C_{22}H_{21}N_3O_3S$) C, H, N.

A mixture of 2-imino-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]benzyl]-4-thiazolidinone (18.8 g, 46 mmol), 2 N HCl (200 mL), and EtOH (200 mL) was stirred under reflux for 12 h. The reaction mixture was concentrated in vacuo. The residue was diluted with H_2O, neutralized with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the title compound (18.0 g, 96%): mp 116–117 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.34 (3 H, s), 2.94 (2 H, t, J = 7 Hz), 3.02 (1 H, dd, J = 14, 9 Hz), 3.41 (1 H, dd, J = 14, 4 Hz), 4.18 (2 H, t, J = 7 Hz), 4.42 (1 H, dd, J = 9, 4 Hz), 6.80 (2 H, d, J = 9 Hz), 7.09 (2 H, d, J = 9 Hz), 7.4 (3 H, m), 7.95 (2 H, m). Anal. ($C_{22}H_{20}N_2O_4S$) C, H, N.

Method B. 5-[4-(2-Phenyl-4-oxazolylmethoxy)benzyl]-2,4-thiazolidinedione (38). A solution of 5-(4-hydroxybenzyl)-2,4-thiazolidinedione[6a] (9.4 g, 42 mmol) in DMF (80 mL) was treated with NaH (60% in oil, 3.4 g, 84 mmol) at room temperature for 30 min, and then a solution of 4-(chloromethyl)-2-phenyloxazole[14] (9.6 g, 50 mmol) in DMF (20 mL) was added. The whole was stirred at 70 °C for 1 h, poured into H_2O, and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the title compound (9.1 g, 47%): mp 188–189 °C (EtOH); ^{1}H NMR (d_6-DMSO) δ 3.03 (1 H, dd, J = 14, 9 Hz), 3.34 (1 H, dd, J = 14, 4 Hz), 4.88 (1 H, dd, J = 9, 4 Hz), 5.03 (2 H, s), 6.98 (2 H, d, J = 9 Hz), 7.18 (2 H, d, J = 9 Hz), 7.5 (3 H, m), 8.0 (2 H, m). Anal. ($C_{22}H_{18}N_2O_4S$) C, H, N.

Method C. 5-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene]-2,4-thiazolidinedione (56). A mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (40.3 g, 0.131 mol), 2,4-thiazolidinedione (23.0 g, 0.196 mol), piperidine (2.6 mL, 26 mmol), and EtOH (700 mL) was refluxed for 9 h. After cooling, the precipitated crystals were collected by filtration to give the title compound (42.6 g, 80%): mp 214–215 °C ($CHCl_3$–EtOH); ^{1}H NMR (d_6-DMSO) δ 2.35 (3 H, s), 2.94 (2 H, t, J = 6.5 Hz), 4.30 (2 H, t, J = 6.5 Hz), 7.07 (2 H, d, J = 9 Hz), 7.4–7.65 (5 H, m), 7.72 (1 H, s), 7.8–8.1 (2 H, m). Anal. ($C_{22}H_{18}N_2O_4S$) C, H, N.

5-[4-[2-[5-(Hydroxymethyl)-2-phenyl-4-oxazolyl]ethoxy]benzyl]-2,4-thiazolidinedione (41). NBS (2.75 g, 15 mmol) was added in small portions to a refluxing mixture of 18 (6.0 g, 15 mmol), α,α'-azobis(isobutyronitrile) (0.5 g, 3 mmol), and CCl_4 (150 mL). The mixture was refluxed for 10 min, washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo to leave 5-[4-[2-[5-(bromomethyl)-2-phenyl-4-oxazolyl]ethoxy]benzyl]-2,4-thiazolidinedione as a crude oil (ca. 8.0 g): ^{1}H NMR ($CDCl_3$) δ 3.03 (2 H, t, J = 7 Hz), 2.9–3.2 (1 H, m), 3.48 (1 H, dd, J = 14, 5 Hz), 4.24 (2 H, t, J = 7 Hz), 4.45 (1 H, dd, J = 9, 5 Hz), 4.61 (2 H, s), 6.81 (2 H, d, J = 9 Hz), 7.10 (2 H, d, J = 9 Hz), 7.4 (3 H, m), 8.0 (2 H, m), 8.70 (1 H, br s). The oil was dissolved in dioxane (100 mL)–2 N HCl (100 mL). The mixture was refluxed for 7 h, poured into H_2O, and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave an oil, which was chromatographed on SiO_2 (200 g) with Et_2O–hexane (1:1, v/v) to give the title compound (1.3 g, 21%): mp 98–99 °C (acetone–hexane); ^{1}H NMR ($CDCl_3$) δ 2.36 (1 H, br s), 3.04 (2 H, t, J = 6 Hz), 3.06 (1 H, dd, J = 14, 9 Hz), 3.39 (1 H, dd, J = 14, 9 Hz), 4.6–4.9 (2 H, m), 6.80 (2 H, d, J = 9 Hz), 7.10 (2 H, d, J = 9 Hz), 7.4 (3 H, m), 8.0 (2 H, m), 8.50 (1 H, br s). Anal. ($C_{22}H_{20}N_2O_5S$) C, H, N.

5-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzyl]-2,4-thiazolidinedione (43). A mixture of 5-[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione (31) (0.5 g, 1.2 mmol), Ac_2O (1.0 mL, 10.6 mmol), and DMSO (10 mL) was stirred at room temperature for 1 h and allowed to stand overnight. The mixture was poured into H_2O and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave an oil, which was chromatographed on SiO_2 (40 g) with C_6H_6–acetone (9:1, v/v) to give the title compound (0.41 g, 81%): mp 168–169 °C (AcOEt–hexane); ^{1}H NMR ($CDCl_3$) δ 2.69 (3 H, s), 3.02 (1 H, dd, J = 14, 9 Hz), 3.35 (1 H, dd, J = 14, 4 Hz), 4.82 (1 H, dd, J = 9, 4 Hz), 5.38 (2 H, s), 6.88 (2 H, d, J = 9 Hz), 7.17 (2 H, d, J = 9 Hz), 7.5 (3 H, m), 8.0 (2 H, m). Anal. ($C_{22}H_{18}N_2O_5S$) C, H, N.

(14) Simiti, I.; Chindris, E. Die Delépine-Reaktion bei 2-Aryl-4-chloromethyloxazolen 15. Mitt. Heterozyklische Verbindungen. *Arch. Pharmacol.* 1971, *304*, 425–429.

5-[4-[2-Hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene]-2,4-thiazolidinedione (65). $NaBH_4$ (0.33 g, 8.7 mmol) was added portionwise to a stirred and ice-cooled solution of 5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]-benzylidene]-2,4-thiazolidinedione (**63**) (3.6 g, 8.9 mmol) in DMF–MeOH (1:1, v/v, 80 mL). After stirring at room temperature for 10 min, the reaction mixture was diluted with H_2O and acidified with AcOH to give the title compound (3.56 g, 98%): mp 252–253 °C ($CHCl_3$–MeOH); ^1H NMR (d_6-DMSO) δ 2.43 (3 H, s), 4.27 (2 H, d, J = 7 Hz), 4.85–5.1 (1 H, m), 5.61 (1 H, br s), 7.10 (2 H, d, J = 9 Hz), 7.4–7.65 (5 H, m), 7.73 (1 H, s), 7.85 (2 H, m), 12.47 (1 H, br s). Anal. ($C_{22}H_{18}N_2O_5S$) C, H, N.

General Procedure for 4-[2-(4-Azolyl)ethoxy]anilines (1). 4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]aniline. A stirred and ice-cooled solution of 2-(5-methyl-2-phenyl-4-oxazolyl)ethanol (57.0 g, 0.28 mol) and 4-fluoronitrobenzene (39.6 g, 0.28 mol) in DMF (500 mL) was treated with NaH (60% in oil, 14.0 g, 0.35 mol). The reaction mixture was stirred at room temperature for 1 h and poured into H_2O to give 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]nitrobenzene (74.7 g, 82%): mp 97–98 °C (MeOH); ^1H NMR ($CDCl_3$) δ 2.37 (3 H, s), 2.98 (2 H, t, J = 6 Hz), 4.32 (2 H, t, J = 6 Hz), 6.92 (2 H, d, J = 9 Hz), 7.4 (3 H, m), 7.9 (2 H, m), 8.18 (2 H, d, J = 9 Hz). Anal. ($C_{18}H_{16}N_2O_4$) C, H, N.

A mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-nitrobenzene (74.0 g, 0.23 mol), 10% Pd–C (2.5 g), and MeOH (500 mL) was hydrogenated at ambient temperature and atmospheric pressure. The insoluble catalyst was removed by filtration and the filtrate was concentrated in vacuo to give the title compound (65.5 g, 98%): mp 93–94 °C (AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 2.33 (3 H, s), 2.90 (2 H, t, J = 6 Hz), 3.0 (2 H, br), 4.14 (2 H, t, J = 6 Hz), 6.56 (2 H, d, J = 9 Hz), 6.74 (2 H, d, J = 9 Hz), 7.4 (3 H, m), 7.9 (2 H, m). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

General Procedure for 4-[2-Hydroxy-2-(4-oxazolyl)ethoxy]anilines (2). 4-[2-Hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]aniline. A solution of Br_2 (23.2 g, 0.15 mol) in $CHCl_3$ (25 mL) was added dropwise to a stirred solution of 4-acetyl-5-methyl-2-phenyloxazole[15] (26.5 g, 0.13 mol) in $CHCl_3$ (300 mL) at 50 °C. The mixture was stirred at 55 °C for 30 min and poured into saturated aqueous $NaHCO_3$ (500 mL). The $CHCl_3$ layer was separated, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 4-(bromoacetyl)-5-methyl-2-phenyloxazole (33.9 g, 92%): mp 88–89 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 2.70 (3 H, s), 4.56 (2 H, s), 7.4–7.6 (3 H, m), 8.0 (2 H, m). Anal. ($C_{12}H_{10}NO_2Br$) C, H, N.

A mixture of 4-(bromoacetyl)-5-methyl-2-phenyloxazole (33.8 g, 0.12 mol), 4-acetamidophenol (17.3 g, 0.12 mol), K_2CO_3 (27.6 g, 0.2 mol), and methyl ethyl ketone (400 mL) was stirred under reflux for 3 h and concentrated in vacuo. The residue was diluted with H_2O (300 mL) and Et_2O (300 mL)–hexane (100 mL) was added to the mixture. The whole was stirred at room temperature for 10 min, and the crystals were collected by filtration to give 4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]acetanilide (23.5 g, 58%): mp 175–176 °C (EtOH); ^1H NMR (d_6-DMSO) δ 2.11 (3 H, s), 2.70 (3 H, s), 4.34 (2 H, s), 6.92 (2 H, d, J = 9 Hz), 7.30 (2 H, d, J = 9 Hz), 7.45 (3 H, m), 8.1 (2 H, m). Anal. ($C_{20}H_{18}N_2O_4$) C, H, N.

A stirred and ice-cooled mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]acetanilide (23.3 g, 67 mmol) and MeOH (250 mL) was treated with $NaBH_4$ (2.5 g, 67 mmol) for 30 min, and then AcOH (8 mL) was added. The mixture was poured into H_2O and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]acetanilide (23.0 g, 98%): mp 166–167 °C (AcOEt); ^1H NMR (d_6-DMSO) δ 1.99 (3 H, s), 2.43 (3 H, s), 4.15 (2 H, d, J = 6 Hz), 4.91 (1 H, t, J = 6 Hz), 5.5 (1 H, br), 6.82 (2 H, d, J = 9 Hz), 7.5 (5 H, m), 7.9 (2 H, m), 9.7 (1 H, br s). Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

A mixture of 4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]acetanilide (22.7 g, 64 mmol), 4 N KOH (300 mL), and EtOH (300 mL) was refluxed for 24 h and poured into H_2O. The precipitated crystals were collected by filtration and recrystallized from EtOH to give the title compound as colorless prisms (18.7 g, 96%): mp 166–167 °C; ^1H NMR (d_6-DMSO) δ 2.42 (3 H, s), 4.05 (2 H, d, J = 6 Hz), 4.56 (2 H, br s), 4.87 (1 H, q, J = 6 Hz), 5.45 (1 H, d, J = 6 Hz), 6.83 (2 H, d, J = 9 Hz), 7.03 (2 H, d, J = 9 Hz), 7.5 (3 H, m), 7.9 (2 H, m). Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

4-Acetyl-2,5-dimethyloxazole. Concentrated H_2SO_4 (8.8 mL, 0.32 mol) was added dropwise to a stirred mixture of 3-(acetylamino)-2,4-pentanedione (50 g, 0.32 mol) in Ac_2O (250 mL). The mixture was stirred at room temperature for 1 h and at 60 °C for 1 h, concentrated in vacuo, poured into H_2O, and extracted with AcOEt. The AcOEt extract was dried ($MgSO_4$) and concentrated in vacuo to give the title compound (28.8 g, 65%): mp 40–41 °C (hexane); ^1H NMR ($CDCl_3$) δ 2.42 (3 H, s), 2.48 (3 H, s), 2.58 (3 H, s). Anal. ($C_7H_9NO_2$) C, H, N.

General Procedure for 4-[2-(2-Oxazolyl)ethoxy]anilines (3). 4-[2-(4-Methyl-5-phenyl-2-oxazolyl)ethoxy]aniline. A mixture of 3-(4-nitrophenoxy)propionic acid[16] (13.1 g, 62 mmol), $SOCl_2$ (12.8 g, 108 mmol), DMF (0.3 g, 4 mmol), and toluene (100 mL) was stirred at 90 °C for 1 h and concentrated in vacuo. The residual oil was dissolved in AcOEt (30 mL). The solution was added dropwise to a stirred mixture of α-aminopropiophenone hydrochloride (11.5 g, 62 mmol), Na_2CO_3 (10.6 g, 100 mmol), and H_2O (100 mL) at room temperature. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo to give α-[[3-(4-nitrophenoxy)propionyl]amino]propiophenone (16.0 g, 76%): mp 134–135 °C (AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 1.43 (3 H, d, J = 7 Hz), 2.74 (2 H, t, J = 6 Hz), 4.38 (2 H, t, J = 6 Hz), 5.58 (1 H, t, J = 7 Hz), 6.99 (2 H, d, J = 9 Hz), 7.4–7.6 (5 H, m), 8.0 (2 H, m), 8.23 (2 H, d, J = 9 Hz). Anal. ($C_{18}H_{18}N_2O_5$) C, H, N.

A mixture of α-[[3-(4-nitrophenoxy)propionyl]amino]propiophenone (15.5 g, 45 mmol), $POCl_3$ (20.8 g, 136 mmol), and toluene (150 mL) was stirred under reflux for 1 h. The mixture was poured into ice–H_2O, neutralized with aqueous $NaHCO_3$, and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave an oil, which was chromatographed on SiO_2 (150 g) with AcOEt–hexane (1:4, v/v) to give 4-[2-(4-methyl-5-phenyl-2-oxazolyl)ethoxy]nitrobenzene (13.0 g, 89%): mp 117–118 °C (AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 2.37 (3 H, s), 3.29 (2 H, t, J = 6 Hz), 4.48 (2 H, t, J = 6 Hz), 6.97 (2 H, d, J = 9 Hz), 7.2–7.7 (5 H, m), 8.18 (2 H, d, J = 9 Hz). Anal. ($C_{18}H_{16}N_2O_4$) C, H, N.

A mixture of 4-[2-(4-methyl-5-phenyl-2-oxazolyl)ethoxy]-nitrobenzene (12.5 g, 39 mmol), Pd–C (5%, 3.0 g), and MeOH (150 mL) was hydrogenated at room temperature and atmospheric pressure. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give the title compound (11.0 g, 97%): mp 106–107 °C (EtOH); ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s), 3.22 (2 H, t, J = 6 Hz), 3.30 (2 H, br s), 4.33 (2 H, t, J = 6 Hz), 6.62 (2 H, d, J = 9 Hz), 6.82 (2 H, d, J = 9 Hz), 7.2–7.7 (5 H, m). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

General Procedure for 4-[2-(4-Azolyl)ethoxy]benzaldehydes (55, Y = CH_2, n = 1). 4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde. A mixture of 2-(5-methyl-2-phenyl-4-oxazolyl)ethanol (57.0 g, 0.28 mol), 4-fluorobenzonitrile (40.8 g, 0.34 mol), and THF (600 mL) was treated with NaH (60% in oil, 13.5 g, 0.34 mol) with ice-cooling for 1 h and at room temperature for 12 h. The reaction mixture was poured into ice–H_2O and acidified with AcOH to give 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzonitrile (77.3 g, 91%): mp 119–120 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 2.36 (3 H, s), 2.98 (2 H, t, J = 6.5 Hz), 4.29 (2 H, t, J = 6.5 Hz), 6.92 (2 H, d, J = 9 Hz), 7.3–7.65 (5 H, m), 7.85–8.05 (2 H, m). Anal. ($C_{19}H_{18}N_2O_2$) C, H, N.

A mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-benzonitrile (76.5 g, 0.25 mol), Ra–Ni alloy (~50%, 25.0 g), and aqueous HCOOH (70%, 600 mL) was stirred at 100 °C for 3 h.

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After cooling, the insoluble solid was removed by filtration and the filtrate was concentrated in vacuo. The residue was diluted with H_2O, made alkaline with aqueous KOH, and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the title compound (50.6 g, 65%): mp 82–84 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 2.37 (3 H, s), 2.99 (2 H, t, J = 6.5 Hz), 4.33 (2 H, t, J = 6.5 Hz), 6.97 (2 H, d, J = 9 Hz), 7.3–7.55 (3 H, m), 7.79 (2 H, d, J = 9 Hz), 7.85–8.1 (2 H, m), 9.85 (1 H, s). Anal. ($C_{19}H_{17}NO_3$) C, H, N.

4-(2-Phenyl-4-thiazolylmethoxy)benzaldehyde. A mixture of 4-(chloromethyl)-2-phenylthiazole (2.1 g, 10 mmol), 4-hydroxybenzaldehyde (1.22 g, 10 mmol), K_2CO_3 (2.76 g, 20 mmol), and DMF (30 mL) was stirred at 120 °C for 1 h. The reaction mixture was poured into H_2O to give the title compound (2.8 g, 95%): mp 88–90 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 5.32 (2 H, s), 7.10 (2 H, d, J = 9 Hz), 7.28 (1 H, s), 7.82 (2 H, d, J = 9 Hz), 7.0–8.1 (5 H, m), 9.87 (1 H, s). Anal. ($C_{17}H_{13}NO_2S$) C, H, N.

General Procedure for 2-(4-Azolyl)ethanols. 2-(5-Methyl-2-phenyl-4-oxazolyl)ethanol. Et_3N (61.7 g, 0.61 mol) was added dropwise to a stirred and ice–salt cooled mixture of L-aspartic acid β-methyl ester hydrochloride (31.2 g, 0.17 mol), benzoyl chloride (23.9 g, 0.17 mol), and CH_2Cl_2 (700 mL). The mixture was stirred at the same temperature for further 1 h and poured into 1 N HCl (1 L). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give *N*-benzoyl-L-aspartic acid β-methyl ester (34.8 g, 82%): mp 153–154 °C (EtOH).

A mixture of *N*-benzoyl-L-aspartic acid β-methyl ester (25.1 g, 0.1 mol), Ac_2O (95 mL, 1.0 mol), Et_3N (95 mL, 0.68 mol), and DMAP (1.2 g, 10 mmol) was stirred at room temperature for 1 h and at 90 °C for 1 h and poured into H_2O (1 L). The mixture was extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give methyl 3-(benzoylamino)-4-oxovalerate as an oil (15.6 g, 63%): ^1H NMR ($CDCl_3$) δ 2.27 (3 H, s), 2.85 (1 H, dd, J = 20, 5 Hz), 3.08 (1 H, dd, J = 20, 5 Hz), 3.67 (3 H, s), 4.93 (1 H, dt, J = 8, 5 Hz), 7.5 (3 H, m), 7.8 (2 H, m).

A mixture of methyl 3-(benzoylamino)-4-oxovalerate (15.0 g, 60 mmol), $POCl_3$ (27.7 g, 180 mmol), and toluene (250 mL) was stirred under reflux for 2 h and concentrated in vacuo. The residue was diluted with H_2O, neutralized with K_2CO_3, and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give methyl 2-(5-methyl-2-phenyl-4-oxazolyl)acetate as a crude oil (12.6 g, 91%): ^1H NMR ($CDCl_3$) δ 2.31 (3 H, s), 3.49 (2 H, s), 3.68 (3 H, s), 7.3 (3 H, m), 7.9 (2 H, m).

A solution of methyl 2-(5-methyl-2-phenyl-4-oxazolyl)acetate (crude oil, 12.2 g, 53 mmol) in Et_2O (50 mL) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (2.0 g, 53 mmol) in Et_2O (200 mL). The mixture was stirred at ambient temperature for 30 min, and H_2O (11 mL) was added dropwise with ice-cooling. The insoluble solid was removed by filtration and the filtrate was concentrated in vacuo to give the title compound (9.8 g, 91%): mp 73–74 °C (AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 2.30 (3 H, s), 2.70 (2 H, t, J = 6 Hz), 3.20 (1 H, br s), 3.90 (2 H, t, J = 6 Hz), 7.4 (3 H, m), 7.9 (2 H, m). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

Ethyl 2-(2-Phenyl-4-oxazolyl)acetate. A mixture of ethyl 4-chloroacetoacetate (49.4 g, 0.3 mol) and benzamide (60.6 g, 0.5 mol) was heated at 120 °C for 2 h and diluted with saturated aqueous $NaHCO_3$. The mixture was extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave an oil, which was chromatographed on SiO_2 (700 g) with Et_2O–hexane (1:9, v/v) to give the title compound as an oil (26.4 g, 38%): ^1H NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 7 Hz), 3.68 (3 H, s), 4.15 (2 H, q, J = 7 Hz), 7.4 (3 H, m), 7.67 (1 H, s), 8.0 (2 H, m).

Ethyl 2-(2-Cyclohexyl-4-thiazolyl)acetate. A mixture of ethyl 4-chloroacetoacetate (5.74 g, 35 mmol), cyclohexanethiocarboxamide (5.0 g, 35 mmol), and EtOH (50 mL) was refluxed for 1 h, poured into H_2O, and extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave an oil, which was chromatographed on SiO_2 (50 g) with AcOEt–hexane (1:4, v/v) to give the title compound as an oil (6.3 g, 71%): ^1H NMR ($CDCl_3$) δ 1.28 (3 H, t, J = 7 Hz), 1.2–2.3 (10, H, m), 2.97 (1 H, m), 3.77 (2 H, s), 4.17 (2 H, q, J = 7 Hz), 7.0 (1 H, s).

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Registry No. 1 (R^1 = H, R^2 = Me, x = S, n = 1), 141399-30-6; 1 (R^1 = Me, R^2 = H, x = S, n = 1), 141399-31-7; 1 (R^1 = Et, R^2 = H, x = S, n = 1), 141399-32-8; 1 (R^1 = *i*-Pr, R^2 = H, x = S, n = 1), 141399-33-9; 1 (R^1 = cyclohexyl, R^2 = H, x = S, n = 1), 141399-34-0; 1 (R^1 = Ph, R^2 = H, x = S, n = 1), 141399-35-1; 1 (R^1 = Me, R^2 = H, x = O, n = 1), 141399-36-2; 1 (R^1 = Pr, R^3 = H, x = O, n = 1), 141399-37-3; 1 (R^1 = Me, R^2 = Me, x = O, n = 1), 141399-38-4; 1 (R^1 = Me, R^2 = Et, x = O, n = 1), 141399-39-5; 1 (R^1 = cyclohexyl, R^2 = H, x = O, n = 1), 141399-40-8; 1 (R^1 = Ph, R^2 = H, x = O, n = 1), 141399-41-9; 1 (R^1 = Ph, R^2 = Me, x = O, n = 1), 103788-87-0; 1 (R^1 = Ph, R^2 = Et, x = O, n = 1), 141399-42-0; 1 (R^1 = Ph, R^2 = Me, x = O, n = 2), 141399-43-1; 1 (R^1 = cyclohexyl, R^2 = Me, x = O, n = 1), 141399-44-2; 1 (R^1 = 2-furaryl, R^2 = Me, x = O, n = 1), 141399-45-3; 1 (R^1 = 2-thienyl, R^2 = Me, x = O, n = 1), 141399-46-4; 1 (R^1 = 4-$MeOC_6H_4$, R^2 = Me, x = O, n = 1), 141399-47-5; 1 (R^1 = 3,4-$(MeO)_2C_6H_4$, R^2 = Me, x = O, n = 1), 141399-48-6; 1 (R^1 = *p*-tolyl, R^2 = Me, x = O, n = 1), 141399-49-7; 1 (R^1 = *m*-$MeSC_6H_4$, R^2 = Me, x = O, n = 1), 103789-38-4; 1 (R^1 = *o*-$ClC36H_4$, R^2 = Me, x = O, n = 1), 103789-15-7; 1 (R^1 = *p*-OHC_6H_4, R^2 = Me, x = O, n = 1), 103789-19-1; **2** (R^1 = Me, R^2 = Me, x = O), 103793-55-1; **2** (R^1 = Ph, R^2 = Me, x = O), 103789-07-7; **2** (R^1 = cyclohexyl, R^2 = Me, x = O), 103789-33-9; **3** (R^1 = *i*-Bu, R^2 = Me, x = O), 107325-07-5; **3** (R^1 = cyclohexyl, R^2 = Me, x = O), 141399-50-0; **3** (R^1 = Ph, R^2 = Me, x = O), 141399-51-1; **3** (R^1 = Ph, R^2 = Et, x = O), 107325-06-4; **3** (R^1 = Me, R^2 = Ph, x = O), 107325-05-3; **4** (R^1 = Ph, R^2 = Me, x = O, n = 1), 103814-35-3; **5** (R^1 = Ph, R^2 = Me, x = O, n = 1), 103788-55-2; **6**, 141399-27-1; **7**, 103787-98-0; **8**, 103788-03-0; **9**, 103788-04-1; **10**, 103788-18-7; **11**, 103788-00-7; **12**, 103787-99-1; **13**, 103788-02-9; **14**, 103788-01-8; **15**, 103788-08-5; **16**, 103788-20-1; **17**, 103926-56-3; **18**, 103787-97-9; **19**, 103788-06-3; **20**, 103788-31-4; **21**, 103788-22-3; **22**, 103788-09-6; **23**, 103788-10-9; **24**, 103788-07-4; **25**, 103788-13-2; **26**, 141399-28-2; **27**, 103788-28-9; **28**, 103788-14-3; **29**, 103788-15-4; **30**, 103788-11-0; **31**, 103788-05-2; **32**, 103788-30-3; **33**, 103787-88-8; **34**, 103787-86-6; **35**, 103787-91-3; **36**, 103787-89-9; **37**, 103787-87-7; **38**, 103787-85-5; **39**, 103787-90-2; **40**, 141399-29-3; **41**, 103788-24-5; **41** bromo derivative, 103788-58-5; **42**, 103788-33-6; **43**, 103788-34-7; **44**, 107324-84-5; **45**, 107324-86-7; **46**, 107325-11-1; **47**, 107324-88-9; **48**, 107324-83-4; **49**, 107342-77-8; **50**, 107324-90-3; **51**, 107324-89-0; **52** (R^1 = Me, R^2 = H, x = S), 39238-07-8; **52** (R^1 = Ph, R^2 = H, x = S), 4771-31-7; **52** (R^1 = 3-py, R^2 = H, x = S), 141399-52-2; **52** (R^1 = Me, R^2 = H, x = O), 141399-53-3; **52** (R^1 = Pr R^2 = H, x = O), 103788-63-2; **52** (R^1 = Ph, R^2 = H, x = O), 30494-97-4; **52** (R^1 = Ph, R^2 = Me, x = O), 103788-61-0; **52** (R^1 = 2-furyl, R^2 = Me, x = O), 141399-54-4; **52** (R^1 = H, R^2 = Ph, x = S), 65385-00-4; **52** (R^1, R^2, x = 2-benzothiazolyl), 37859-43-1; **52** (R^1, R^2, x = 2-benzoxazolyl), 41014-43-1; **53** (R^1 = Me, R^2 = H, x = S, 4 = CH_2, n = 1), 103789-55-5; **53** (R^1 = Ph, R^2 = H, x = S, y = CH_2, n = 1), 103789-56-6; **53** (R^1 = Ph, R^2 = Me, x = O, y = CH_2, n = 1), 103788-59-6; **53** (R^1 = Ph, R^2 = Et, x = O, y = CH_2, n = 1), 103789-57-7; **53** (R^1 = 4-ClC_8H_4, R^2 = Me, x = O, y = CH_2, n = 1), 103789-59-9; **53** (R^1 = 3-$MeSC_6H_4$, R^2 = Me, x = O, y = CH_2, n = 1), 103789-60-2; **53** (R^1 = 1-Me-cyclohexyl, R^2 = Me, x = O, y = CH_2, n = 1), 103789-63-5; **53** (R^1 = 2-thienyl, R^2 = Me, x = O, y = CH_2, n = 1), 103789-62-4; **53** (R^1 = Ph, R^2 = Me, x = O, y = CH_2, n = O), 103789-66-8; **53** (R^1 = Ph, R^2 = Me, x = O, y = CO, n = 1), 103789-69-1; **53** (R^1 = Me, R^2 = Me, x = O, y = CO, n = 1), 103789-70-4; **54**, 103788-36-9; **55**, 103788-38-1; **56**, 103788-35-8; **57**, 103788-40-5; **58**, 103788-42-7; **59**, 103788-43-8; **60**, 103788-48-3; **61**, 103788-45-0; **62**, 103788-50-7; **63**, 103788-51-8; **64**, 103788-46-1; **65**, 103788-47-2; **66**, 103788-52-9; 5-(*p*-hydroxybenzyl)-2,4-thiazolidinedione, 74772-78-4; 2-(5-methyl-2-phenyl-4-oxazolyl)ethanol, 103788-65-4; 1-fluoro-4-nitrobenzene, 350-46-9; 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]nitrobenzene, 103788-72-3; 4-acetyl-5-methyl-2-phenyloxazole, 2940-19-4; 4-(bromoacetyl)-5-methyl-2-phenyloxazole, 103788-62-1; 4-acetamidophenol, 103-90-2; 4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]acetanilide, 103789-05-5; 4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)eth-

oxy]acetanilide, 103789-06-6; 3-(acetylamino)-2,4-pentanedione, 5440-23-3; 4-acetyl-2,5-dimethoxazole, 23000-12-6; 3-(4-nitrophenoxy)propionic acid, 10572-16-4; α-aminopropiophenone hydrochloride, 16735-19-6; α-[[3-(4-nitrophenoxy)propionyl]amino]propiophenone, 141399-55-5; 4-[2-(4-methyl-5-phenyl-2-oxazolyl)ethoxy]nitrobenzene, 107325-00-8; 4-fluorobenzonitrile, 1194-02-1; 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzonitrile, 103789-44-2; 4-hydroxybenzaldehyde, 123-08-0; 4-(2-phenyl-4-thiazolylmethoxy)benzaldehyde, 103789-67-9; β-methyl L-aspartate hydrochloride, 16856-13-6; β-methyl N-benzoyl-L-aspartate, 39741-26-9; methyl 3-(benzoxylamino)-4-oxovalerate, 54819-26-0; methyl 2-(5-methyl-2-phenyl-4-oxazolyl)acetate, 103788-64-3; ethyl 4-chloroacetoacetate, 638-07-3; benzamide, 55-21-0; ethyl 2-(2-phenyl-4-oxazolyl)acetate, 84446-03-7; ethyl 2-(2-cyclohexyl-4-thiazolyl)acetate, 24087-96-5; cyclohexanethiocarboxamide, 7390-42-3.

N-[4-[[(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-6-yl)methyl]amino]benzoyl]-L-glutamic Acid, a Novel A-Ring Analogue of 2-Desamino-5,8-dideazafolic Acid[1]

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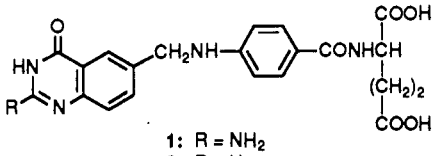
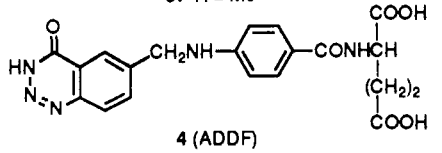
N-[4-[[(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-6-yl)methyl]amino]benzoyl]-L-glutamic acid ("2-aza-2-desamino-5,8-dideazafolic acid", ADDF) was synthesized from 2-amino-5-methylbenzamide via a four-step sequence consisting of diazotization, benzylic bromination, condensation with dimethyl N-(4-aminobenzoyl)-L-glutamate, and ester hydrolysis. ADDF was an inhibitor of recombinant mouse thymidylate synthase; inhibition was competitive with 5,10-methylenetetrahydrofolate as variable substrate (K_i = 2.3 μM). It was a substrate for murine folylpolyglutamate synthetase with kinetic characteristics (K_m = 28 μM) comparable to those of aminopterin, and it inhibited the growth of L1210 cells in culture (IC_{50} = 0.52 μM). The structural modification of the A-ring embodied in ADDF appears to offer a novel, heretofore unexplored approach to the design of TS inhibitors.

The potential therapeutic significance of folic acid analogues targeted against thymidylate synthase (TS) as opposed to dihydrofolate reductase (DHFR) was predicted more than 20 years ago by Borsa and Whitmore.[2] Shortly thereafter, Bird and co-workers[3] reported the potent biological activity of 5,8-dideazafolic acid (1).[4] This led to an extensive program of synthesis of quinazoline analogues substituted at the N^{10} position,[5-7] on the phenyl ring,[8] and in ring B,[9,10] and to selection of N^{10}-propargyl-5,8-dideazafolic acid (CB3717) as a suitable candidate for biochemical[11-13] and clinical[14,15] evaluation. While CB3717 had many desirable pharmacological properties, such as the ability to enter cells by a transport mechanism distinct from that of reduced folates and the classical DHFR inhibitor methotrexate (MTX), its clinical usefulness was hampered by low solubility at physiological pH, which gave rise to hepatic and renal toxicity.[16]



1: R = NH_2
2: R = H
3: R = Me



4 (ADDF)

The toxicity encountered during clinical trials with CB3717 prompted a vigorous search for more soluble congeners, culminating in the discovery of a family of second-generation TS inhibitors that included 2-desamino-5,8-dideazafolic acid (2), 2-desamino-2-methyl-5,8-dideazafolic acid (3), and the corresponding N^{10}-methyl and N^{10}-propargyl analogues.[17-19] Biochemical studies[20-22] revealed that, in general, replacement of the NH_2 group at C^2 by H or Me resulted in weaker binding to purified TS but increased inhibition of the growth of cultured cells.

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(1) Paper 47 in this series. For previous paper, see: Rosowsky, A.; Forsch, R. A.; Reich, V. E.; Freisheim, J. H.; Moran, R. G. Side chain modified 5-deazafolate and 5-deazatetrahydrofolate analogues as mammalian folylpolyglutamate synthetase and glycinamide ribonucleotide formyltransferase inhibitors: synthesis and in vitro biological evaluation. *J. Med. Chem.* **1992**, *35*, 1578–1588.
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