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Novel Benzoxazole 2,4-Thiazolidinediones as Potent Hypoglycemic Agents. Synthesis and Structure–Activity Relationships

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A new series of benzoxazole 2,4-thiazolidinediones was synthesized and evaluated for hypoglycemic activity in genetically obese and diabetic yellow KK mice. 2-Arylmethyl- and 2-(heteroarylmethyl)benzoxazole derivatives showed far more potent activity than known 2,4-thiazolidinedione derivatives such as ciglitazone, troglitazone and pioglitazone. A facile synthesis of benzoxazole 2,4-thiazolidinediones was also established using aminophenol 2,4-thiazolidinedione (11) as a key intermediate. Details of synthesis and structure–activity relationships for this series are described.

Key words hypoglycemic agent; NIDDM; insulin resistance; benzoxazole 2,4-thiazolidinedione; structure–activity relationship

Non-insulin-dependent diabetes mellitus (NIDDM) is characterized by insulin insufficiency and peripheral insulin resistance.[1] The most commonly employed agents for NIDDM patients are sulfonylureas,[2] which act primarily through the stimulation of insulin release. However, sulfonylurea therapy has some problems, such as primary or secondary failure of efficacy, enhancement of obesity, and a high incidence of hypoglycemia.[3]

In 1982, Sohda *et al.* reported a series of 5-(4-alkoxybenzyl)-2,4-thiazolidinediones as antihyperglycemic agents of a new type which reduced insulin resistance in genetically obese and diabetic animal models.[4] The prototypical agent, ciglitazone (Fig. 1), lowered elevated blood glucose, plasma insulin and triglyceride levels in insulin-resistant animals, but showed no hypoglycemic effect in nondiabetic or streptozotocin-induced diabetic rats.[5] Because the improvement of insulin sensitivity and the lack of hypoglycemia are attractive features, numerous reports on additional 2,4-thiazolidinedione derivatives have appeared,[6] and the development of agents of this type is becoming one of the major concerns in the field of antidiabetic drugs. Troglitazone,[6a] pioglitazone[6b] and BRL 49653[6h] (Fig. 1), members of this class of compounds, have been investigated clinically, and improvements in insulin sensitivity and glycemic control were shown in NIDDM subjects.[7]

Although the mechanisms of action of this class of compounds are not fully understood, the existence of a receptor has been suggested. Recently, a member of the nuclear receptor superfamily, peroxisome proliferator-activated receptor γ (PPARγ) was reported as a possible candidate for the target of 2,4-thiazolidinediones.[8] On the other hand, reports on the structure–activity relationships of 2,4-thiazolidinedione derivatives suggested that the structure of the lipophilic tail region (R, Fig. 2) and the conformation of the molecule are important for high potency.[6] As shown in englitazone and a related compound (Fig. 1), conformational restriction of R by the introduction of

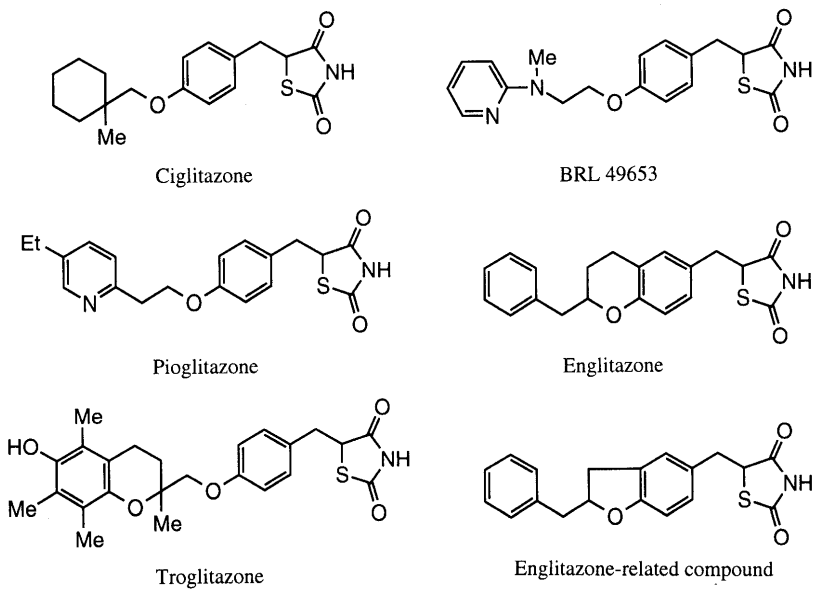

Fig. 1

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a benzopyran or benzofuran ring in the linker part led to an improvement in activity.[6e] Thus, conformationally more restricted 2,4-thiazolidinedione derivatives are expected to show higher activity. We therefore designed benzoxazole derivatives. In this paper, we report the synthesis and structure–activity relationships of benzoxazole 2,4-thiazolidinedione derivatives.

Chemistry

2,4-Thiazolidinediones in this paper were synthesized according to one of the standard methods (Methods A—H) described in Charts 1—6. The method employed for the preparation of each compound is shown in Table 8.

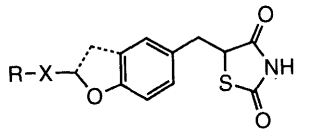
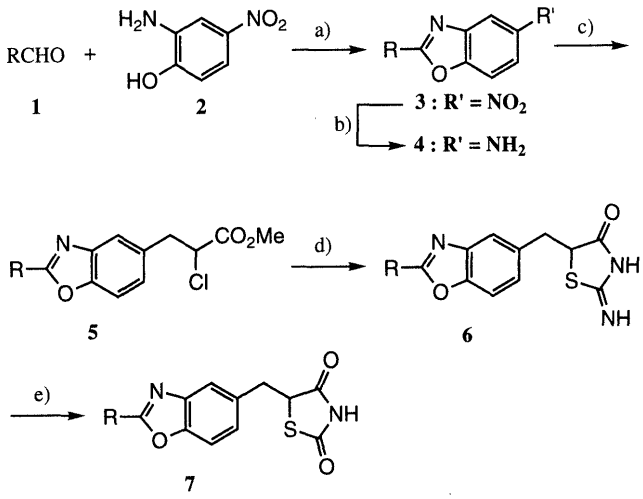


Fig. 2

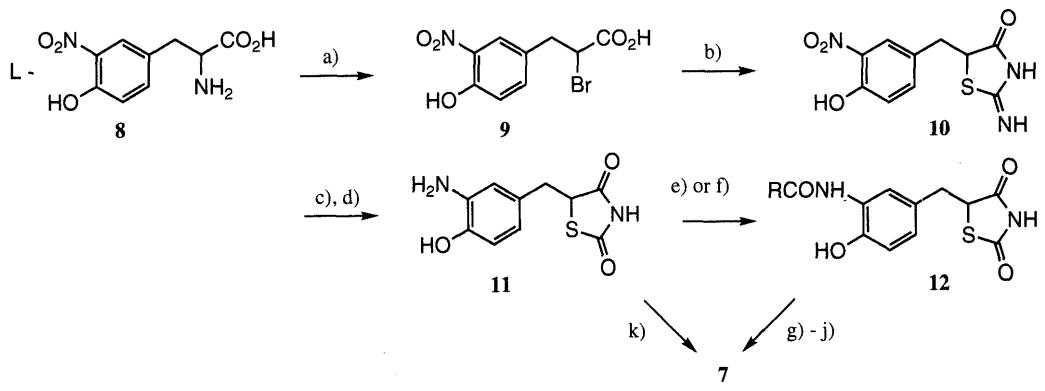


a) EtOH reflux then $Pb(OAc)_4$, benzene ; b) H_2, 10% Pd-C ; c) acetone-H_2O, HCl, $NaNO_2$ then CH_2=$CHCO_2CH_3$, Cu_2O ; d) thiourea, AcONa, $MeOCH_2CH_2OH$; e) *p*-TsOH, $MeOCH_2CH_2OH$-H_2O

Chart 1. Method A

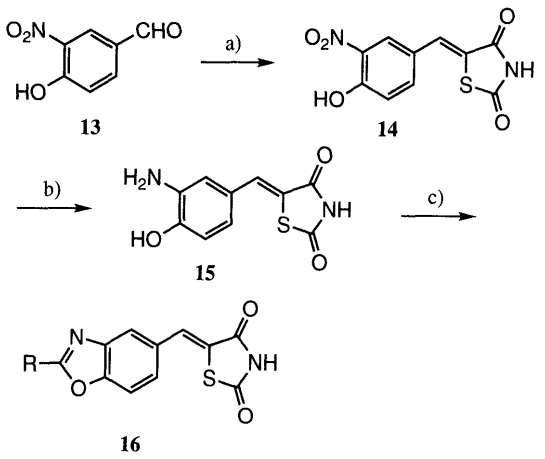
First, 5-(2-substituted-benzoxazol-5-yl)methyl-2,4-thiazolidinediones (**7**) were synthesized from 5-aminobenzoxazole derivatives (**4**) using the method reported for the synthesis of ciglitazone.[4] Meerwein arylation of methyl acrylate with **4** gave 2-chloropropionates (**5**), which were treated with thiourea to afford the iminothiazolidinones (**6**). Acid hydrolysis of **6** provided the desired benzoxazole 2,4-thiazolidinedione derivatives (**7**) (Method A, Chart 1). The requisite 5-aminobenzoxazoles (**4**) were prepared from the corresponding aldehydes (**1**) with 2-amino-4-nitrophenol (**2**). The aldehydes (**1**), on treatment with **2**, afforded the corresponding Schiff bases, which were oxidized with lead tetraacetate ($Pb(OAc)_4$) to give the 5-nitrobenzoxazoles (**3**).[9] Reduction of the nitro group of **3** afforded **4** (Chart 1).

Method A was rather long and inconvenient to prepare various benzoxazole 2,4-thiazolidinediones for structure–activity relationship studies. In addition, especially when R is alkyl or aralkyl, acid hydrolysis of the iminothiazolidinones proceeded only in poor yield owing to cleavage of the benzoxazole ring. We therefore developed more efficient synthetic routes using an easily obtainable aminophenol 2,4-thiazolidinedione (**11**) as a key intermediate (Chart 2; Methods B—F). The key intermediate **11** was synthesized from 3-nitro-L-tyrosine (**8**) in four steps by the procedure shown in Chart 2. Nitro-tyrosine (**8**) was converted by deamination reaction with $NaNO_2$ and KBr to the α-bromoester (**9**), which, upon treatment with thiourea, gave the iminothiazolidinone (**10**). Acid hydrolysis of **10** followed by catalytic hydrogenation of the nitro group gave **11** in a good overall yield. In the course of reaction, complete racemization occurred, and **11** showed no optical rotation. Reaction of **11** with acid chlorides or carboxylic acid gave the amides (**12**), which were converted to the benzoxazole 2,4-thiazolidinedione derivatives (**7**) by employing one of the following dehydration conditions: trimethylsilyl polyphosphate (PPSE)[10] (Method B), thermocyclization[11] (Method C), catalytic *para*-toluenesulfonic acid (*p*-TsOH)[12] in xylene (Method D) or in *N*,*N*-diethylaniline ($PhNEt_2$) (Method E). When there was a basic moiety (pyridine, piperidine, *etc.*) in the R group, the yields of **7** were low if PPSE was used for



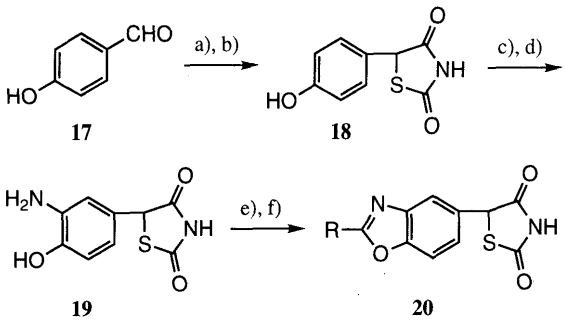
a) $NaNO_2$, KBr, 3N-H_2SO_4 ; b) thiourea, AcONa, $MeOCH_2CH_2OH$; c) c. HCl, $MeOCH_2CH_2OH$; d) H_2, 10 % Pd-C, MeOH-THF ; e) RCOCl, $PhNMe_2$, THF-DMF ; f) RCOOH, DCC, THF-DMF ; g) PPSE in 1,2-dichlorobenzene or 1,2-dichloroethane (Method B) ; h) 230 °C (Method C) ; i) *p*-TsOH in xylene (Method D) ; j) *p*-TsOH in $PhNEt_2$ (Method E) ; k) RCOOH, PPSE in 1,2-dichlorobenzene or 1,2-dichloroethane (Method F)

Chart 2. Method B—F



a) 2,4-thiazolidinedione, piperidine ; b) NaH_2PO_2, 10% Pd-C ;
c) RCOOH, PPSE in 1,2-dichlorobenzene or
1,2-dichloroethane (Method F)

Chart 3

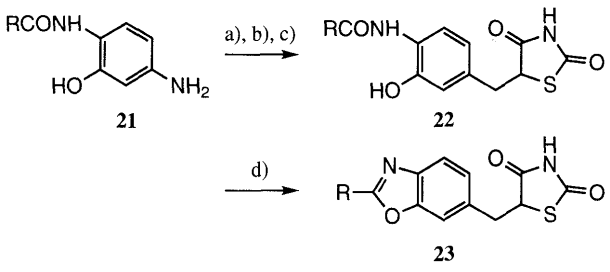


a) NaCN, AcOH ; b) thiourea ; c) 50% HNO_3 ; d) Sn, c. HCl ;
e) RCOCl, $PhNMe_2$, THF-DMF ;
f) PPSE in 1,2-dichlorobenzene (Method B)

Chart 4

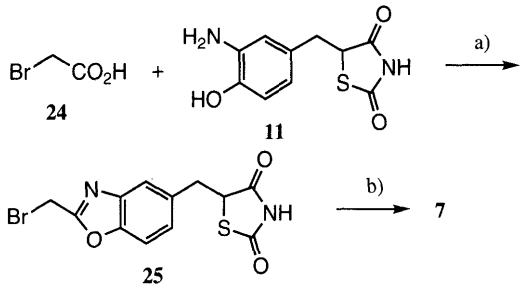
the dehydration (Method B). In such cases, Method E proved to be suitable and gave much higher yields. Other 2-arylmethylbenzoxazole derivatives (**7**) were prepared by one-step benzoxazole ring formation from the carboxylic acid and **11** using PPSE in 1,2-dichlorobenzene or 1,2-dichloroethane (Method F).[10] In this direct method F, however, small amounts of *N*,*O*-diacylated aminophenol 2,4-thiazolidinediones were formed as by-products.

Benzylidene-type 2,4-thiazolidinediones (**16**) were also synthesized by Method F (Chart 3). Knoevenagel condensation of 4-hydroxy-3-nitrobenzaldehyde (**13**) with 2,4-thiazolidinedione in the presence of piperidine[6c] and reduction of the nitro group afforded 5-(3-amino-4-hydroxybenzylidene)-2,4-thiazolidinedione (**15**). 5-(5-Benzoxazolyl)-2,4-thiazolidinedione derivatives (**20**) having no methylene group between the benzoxazole ring and 2,4-thiazolidinedione moiety were prepared by Method B (Chart 4). 4-Hydroxybenzaldehyde (**17**) was converted to 2,4-thiazolidinedione (**19**) *via* thiazolidinedione ring construction[13] followed by successive nitration and reduction. 5-(Benzoxazol-6-ylmethyl)-2,4-thiazolidinediones (**23**) were obtained in a four-step reaction sequence (Chart 5, Method G). Several compounds were synthesized by introducing corresponding nucleophiles into a bromo-



a) acetone-H_2O, HCl, $NaNO_2$ then $CH_2{=}CHCO_2CH_3$, Cu_2O ;
b) thiourea, AcONa, $MeOCH_2CH_2OH$;
c) *p*-TsOH, $MeOCH_2CH_2OH$-H_2O ;
d) PPSE in 1,2-dichlorobenzene

Chart 5. Method G



a) PPSE in 1,2-dichlorobenzene ; b) Nucleophile

Chart 6. Method H

methylbenzoxazole derivative (**25**), which was prepared from 2-bromoacetic acid (**24**) and **11** with PPSE (Chart 6, Method H). Some derivatives were also prepared by functional group transformation from the corresponding parent compounds synthesized by Method D or F (Method Ex).

Biological Methods

The hypoglycemic activity of the compounds prepared was tested using genetically obese and diabetic yellow KK ($KK\text{-}A^y$) mice[14] (Tokyo Experimental Animals, 12—24 weeks old, male, blood glucose level >350 mg/dl). The mice were divided into experimental groups of four to five mice, matched for body weight and blood glucose level. The test compounds were given as dietary admixtures in powdered laboratory chow (CE-2, Clea Japan Inc., Tokyo, Japan) for 4 d. Blood was sampled from the tip of the tail in the conscious animal, and deproteinized with $Ba(OH)_2$ and $ZnSO_4$ solutions. After centrifugation, the supernatant was used for the determination of glucose, which was measured enzymatically with glucose oxidase and peroxidase[15] using a commercial kit "New Blood Sugar Test" (Boehringer Mannheim, Germany). The reductions in blood glucose level were calculated as percentage changes from the control value. Hypoglycemic activity is shown as the dose required to reduce blood glucose level by 25% (ED_{25}), which was determined by nonlinear least-squares analysis using a four-parameter logistic model. The doses of test compounds (mg/kg/d) were calculated from food intake and body weight. Ciglitazone, pioglitazone, troglitazone and an englitazone-related compound (Fig. 1), used as reference compounds, were prepared

according to the literature.[4,6a,6b,6e]

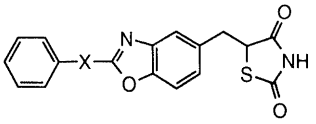
Results and Discussion

Reports on structure–activity relationships of 2,4-thiazolidinediones suggest that the distance between the acidic thiazolidinedione and the lipophilic tail moiety markedly affects the hypoglycemic activity.[6] So, we investigated the structure–activity relationships of the linker part first by altering the length or by modification of the linker chain. Table 1 shows the hypoglycemic activity of these new compounds and reference compounds. The results obtained with the reference compounds are comparable to those reported in the literature.[6b,6e,16] Only the 2-benzylbenzoxazole derivative (**7b**) showed excellent hypoglycemic activity, being more potent than all of the reference compounds. Decrease (**7a**) or increase (**7c**) of the length, modification of the chain by cycloalkyl (**7d**) or phenyl (**7e**, **7f**) branching, and the introduction of an oxo group (**7g**), a double bond (**7h**), or a triple bond (**7i**) all gave poorly active or inactive compounds. These findings led us to synthesize a series of analogues of **7b** and to study the structure–activity relationships of the other parts of the molecule.

Substitution on the benzene ring in the lipophilic side chain also had a striking effect, and the results are summarized in Table 2. Various substituents at the 4-position of the benzene ring, such as fluoro (**7j**), chloro (**7m**), methoxy (**7t**), ethoxy (**7u**), phenyl (**7y**), nitro (**7z**), and trifluoromethyl (**7aj**) improved the activity. In particular, **7m**, **7z**, and **7aj** were more than 10 times more potent than **7b**. Compounds with other substituents (hydroxyl, alkyl, alkylamino, cyclic imino, *etc.*) exhibited activities either less than or comparable to that of **7b**. Although substituents at the 2 or 3-position were less effective than those at the 4-position (**7k**, **7l** < **7m**, **7r**, **7s** < **7t**), the 3,4-dichloro analogue (**7n**) showed very potent activity. The most potent compounds in this class (**7m**, **7n**, **7aj**) exhibited activity approximately 100 times greater than that of pioglitazone.

Three compounds related to **7m** were prepared to investigate the effect of variation in the 2,4-thiazolidinedione moiety (Table 3). The benzylidene-type compound showed slightly lower potency than the saturated one (**16a** < **7m**).

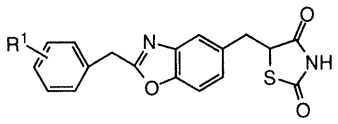
Table 1. Effect of Variation of the Linker Part (X) on Hypoglycemic Activity



Compd.	X	ED_{25} (mg/kg/d)[a]
7a	—	> 50
7b	CH_2	2.1
7c	$(CH_2)_2$	33
7d	CH(c-hex)	11
7e	CH(Ph)	> 50
7f	$CH(Ph)CH_2$	> 50
7g	CO	> 50
7h	(*E*)-CH=CH	> 50
7i	C≡C	> 50
Ciglitazone		47
Pioglitazone		10
Troglitazone		180
Englitazone-related compound[b]		7.5

a) Dose (mg/kg/d) required to reduce blood glucose level by 25% in yellow KK mice. *b*) See Fig. 1.

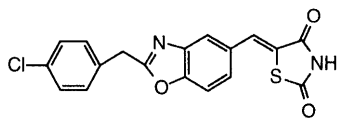
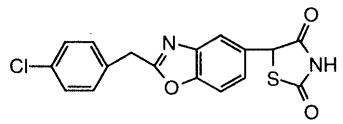
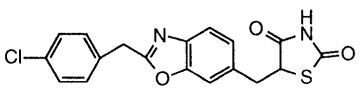
Table 2. Hypoglycemic Activity of 5-(2-Benzylbenzoxazolyl)methyl-2,4-thiazolidinediones



Compd.	R^1	ED_{25} (mg/kg/d)[a]
7j	4-F	0.9
7k	2-Cl	1.1
7l	3-Cl	3.3
7m	4-Cl	0.08
7n	$3,4\text{-}Cl_2$	0.1
7o	4-Me	3.9
7p	4-*tert*-Bu	14
7q	4-OH	6.7
7r	2-OMe	4.4
7s	3-OMe	3.9
7t	4-OMe	0.9
7u	4-OEt	1.0
7v	4-OBu	11
7w	4-OPh	3.1
7x	$3,4\text{-}(OMe)_2$	1.5
7y	4-Ph	0.3
7z	$4\text{-}NO_2$	0.2
7aa	$4\text{-}NH_2$	3.2
7ab	$3\text{-}NMe_2$	1.9
7ac	$4\text{-}NMe_2$	2.9
7ad	$4\text{-}NEt_2$	13
7ae	4-(1-Pyrrolidyl)	7.6
7af	3-(1-Piperidyl)	5.0
7ag	4-(1-Piperidyl)	14
7ah	4-(1-Morpholyl)	5.4
7ai	4-NHAc	9.2
7aj	$4\text{-}CF_3$	0.1
7ak	4-COOMe	31
7al	4-SMe	2.2
7am	4-SOMe	2.8
7an	$4\text{-}SO_2Me$	2.1

a) See footnote a in Table 1.

Table 3. Effect of the Substitution Pattern of the 2,4-Thiazolidinedione Moiety on Hypoglycemic Activity

Compd.	Structure	ED_{25} (mg/kg/d)[a]
16a		0.2
20a		31
23		1.4

a) See footnote a in Table 1.

Removal of the methylene group between the 2,4-thiazolidinedione moiety and the benzoxazole ring resulted in a compound with poor hypoglycemic activity (**20a**≪**7m**). In addition, when the 2,4-dioxothiazolidinylmethyl moiety was shifted from the 5-position to the 6-position on the benzoxazole ring, the potency was clearly decreased (**23**< **7m**).

Our next step was to replace the benzene ring of **7b** with other types of aromatic ring.

Table 4 shows the activity of naphthalenylmethylbenzoxazole derivatives. The hypoglycemic activity of the 2-(2-naphthalenylmethyl)benzoxazole derivative (**7ap**) was superior to that of **7b**, but the 2-(1-naphthalenylmethyl)-benzoxazole analogue (**7ao**) was less potent. Since substitution on the naphthalene ring and the modification of the linker part did not improve the activity, **7ap** was the most potent compound in this series.

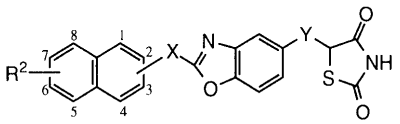
The 2-(4-oxazolylmethyl)- and 2-(4-thiazolylmethyl)-benzoxazole derivatives synthesized are listed in Table 5. Most compounds of this series exhibited activity either higher than or comparable to that of **7b**. In particular, incorporation of 2-phenyloxazole (**7ba**, **7bb**) or 2-phenylthiazole (**7bc**) was most effective for eliciting potent activity. As was the case in **16a** (Table 3), the potency of the benzylidene-type analogues (**16b**, **16c**) was slightly low compared to that of the corresponding saturated compounds. These structure–activity relationships are similar to those of 5-[4-(azolylalkoxy)benzyl]-2,4-thiazolidinediones described in the literature.[6g]

Results for derivatives that have other heteroaromatic rings are summarized in Table 6. The activities of these compounds, including the pioglitazone analogue **7bj**, seem to be lower than those of the 4-oxazolyl and 4-thiazolyl analogues, though most of these compounds (especially 2-phenylbenzoxazol-5-yl derivative **7bo**) retained relatively high levels of activity.

Finally, derivatives having other groups at the 2-position of the benzoxazole ring are listed in Table 7. The 4-chlorophenoxymethyl derivative **7bp** appeared to have potent activity, while the other analogues (**7bq**—**7bu**) did not exhibit noticeable activity.

In summary, potent hypoglycemic activity was attained in a series of 2-arylmethyl- and 2-(heteroarylmethyl)benzoxazolylmethyl-2,4-thiazolidinediones. Among them, compound **7ap** (T-174) was selected for further evaluation

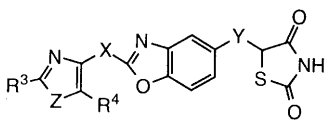
Table 4. Hypoglycemic Activity of Naphthalenylmethylbenzoxazole Derivatives



Compd.	1/2-Naphthalenyl	R^2	X	Y	ED_{25} (mg/kg/d)[a]
7ao	1	H	CH_2	CH_2	5.8
7ap	2	H	CH_2	CH_2	0.4
7aq	2	6-Cl	CH_2	CH_2	1.3
7ar	2	6-Me	CH_2	CH_2	6.2
7as	2	3-Me	CH_2	CH_2	1.2
7at	2	1-NO_2	CH_2	CH_2	3.2
7au	2	6-MeO	CH_2	CH_2	6.3
7av	2	3-MeO	CH_2	CH_2	2.5
7aw	2	6-OH	CH_2	CH_2	39
7ax	2	7-OH	CH_2	CH_2	>50
7ay	1	H	$(CH_2)_2$	CH_2	>50
7az	2	H	$(CH_2)_2$	CH_2	>50
20b	2	H	CH_2	—	>50

a) See footnote a in Table 1.

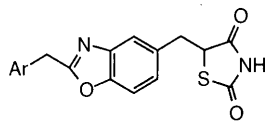
Table 5. Hypoglycemic Activity of Oxazolyl- and Thiazolylmethylbenzoxazole Derivatives



Compd.	Z	R^3	R^4	X	Y	ED_{25} (mg/kg/d)[a]
7ba	O	Ph	H	CH_2	CH_2	0.2
7bb	O	Ph	Me	CH_2	CH_2	0.07
7bc	S	Ph	H	CH_2	CH_2	0.2
7bd	S	c-hex	H	CH_2	CH_2	0.8
7be	S	Me	H	CH_2	CH_2	4.7
7bf	S	MeS	H	CH_2	CH_2	1.0
7ng	S	Ph	H	—	CH_2	7.2
7bh	S	Ph	H	$(CH_2)_2$	CH_2	2.2
16b	O	Ph	Me	CH_2	CH=	0.1
16c	S	Ph	H	CH_2	CH=	0.4

a) See footnote a in Table 1.

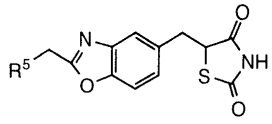
Table 6. Hypoglycemic Activity of Other Heteroarylmethylbenzoxazole Derivatives



Compd.	Ar	ED_{25} (mg/kg/d)[a]
7bi	2-Pyridyl	2.6
7bj	5-Ethyl-2-pyridyl	2.1
7bk	2-Thienyl	16
7bl	2-Benzofuranyl	1.2
7bm	2-Indolyl	2.0
7bn	6-Quinolyl	2.9
7bo	2-Phenylbenzoxazol-5-yl	0.2

a) See footnote a in Table 1.

Table 7. Hypoglycemic Activity of Miscellaneous Benzoxazolylmethyl-2,4-thiazolidinediones



Compd.	R^5	ED_{25} (mg/kg/d)[a]
7bp	4-ClPhO	0.7
7bq	PhS	8.2
7br	1-Pyrrolidyl	36
7bs	1-Piperidyl	8.0
7bt	4-Morpholyl	>50
7bu	*N*-(c-hex)-*N*-Me-amino	21

a) See footnote a in Table 1.

Table 8. Physical Properties of Benzoxazole 2,4-Thiazolidinediones

Compd. No.	Method	Yield (%)	mp (°C)	Recrystn. solvent	Formula[a]
7a	A	33[b]	192—194	THF–AcOEt	$C_{17}H_{12}N_2O_3S$
7b	D	77	158—159	AcOEt–hexane	$C_{18}H_{14}N_2O_3S$
7c	F	62	135—138	AcOEt–hexane	$C_{19}H_{16}N_2O_3S$
7d	B	60	Amorphous		$C_{24}H_{24}N_2O_3S$
7e	B	67	Amorphous		$C_{24}H_{18}N_2O_3S$
7f	B	67	174—178	AcOEt–hexane	$C_{25}H_{26}N_2O_3S$
7g	F	52	188—189	THF–hexane	$C_{18}H_{12}N_2O_4S$
7h	A	20[b]	219—222	AcOEt	$C_{19}H_{14}N_2O_3S$
7i	B	86	180—183	THF–hexane	$C_{19}H_{12}N_2O_3S$
7j	D	82	187—189	THF–EtOH	$C_{18}H_{13}N_2O_3SF$
7k	F	63	173—174	AcOEt–hexane	$C_{18}H_{13}N_2O_3SCl$
7l	F	57	171—172	AcOEt–hexane	$C_{18}H_{13}N_2O_3SCl$
7m	F	68	169—170	CH_3CN	$C_{18}H_{13}N_2O_3SCl$
7n	F	54	156—160	MeOH	$C_{18}H_{12}N_2O_3SCl_2$
7o	F	51	180—183	AcOEt–hexane	$C_{19}H_{16}N_2O_3S$
7p	F	39	159—162	AcOEt–hexane	$C_{22}H_{22}N_2O_3S$
7q	Ex	71	205—206	THF–hexane	$C_{18}H_{14}N_2O_4S$
7r	D	85	81—84	EtOH–Et_2O	$C_{19}H_{16}N_2O_4S$
7s	F	63	137—141	AcOEt–hexane	$C_{19}H_{16}N_2O_4S$
7t	D	65	152—153	THF–EtOH	$C_{19}H_{16}N_2O_4S$
7u	F	67	192—194	AcOEt–hexane	$C_{20}H_{18}N_2O_4S$
7v	D	91	157—158	THF–hexane	$C_{22}H_{22}N_2O_4S$
7w	F	48	122—123	AcOEt–hexane	$C_{24}H_{18}N_2O_4S$
7x	D	93	166—169	AcOEt–hexane	$C_{20}H_{18}N_2O_5S$
7y	F	68	194—197	THF–AcOEt	$C_{24}H_{18}N_2O_3S$
7z	D	78	182—184	MeOH–iso-Pr_2O	$C_{18}H_{13}N_3O_5S$
7aa	Ex	53	187—192	AcOEt	$C_{18}H_{15}N_3O_3S$
7ab	E	66	170—172	EtOH	$C_{20}H_{19}N_3O_3S$
7ac	E	78	217—218	THF–MeOH	$C_{20}H_{19}N_3O_3S$
7ad	C	30	162—163	AcOEt	$C_{22}H_{23}N_3O_3S$
7ae	E	72	240—243	THF–iso-Pr_2O	$C_{22}H_{21}N_3O_3S$
7af	E	85	179—181	EtOH–Et_2O	$C_{23}H_{23}N_3O_3S$
7ag	C	40	205—208	THF–hexane	$C_{23}H_{23}N_3O_3S$
7ah	E	48	216—218	THF–hexane	$C_{22}H_{21}N_3O_4S$
7ai	Ex	83	241—244	THF–hexane	$C_{20}H_{17}N_3O_4S$
7aj	F	63	173—174	THF–EtOH	$C_{19}H_{13}N_2O_3SF_3$
7ak	B	71	153—154	AcOEt–hexane	$C_{20}H_{16}N_2O_5S$
7al	F	65	142—147	MeOH	$C_{19}H_{16}N_2O_3S_2$
7am	Ex	64	Amorphous		$C_{19}H_{16}N_2O_4S_2$
7an	Ex	69	168—169	THF–hexane	$C_{19}H_{16}N_2O_5S_2$
7ao	B	84	150—153	AcOEt–hexane	$C_{22}H_{16}N_2O_3S$
7ap	D	92	212—213	THF–EtOH	$C_{22}H_{16}N_2O_3S$
7aq	D	86	216—217	THF–hexane	$C_{22}H_{15}N_2O_3SCl$
7ar	D	74	225—226	THF–EtOH	$C_{23}H_{18}N_2O_3S$
7as	F	66	201—202	THF–hexane	$C_{23}H_{18}N_2O_3S$
7at	D	62	190—192	MeOH	$C_{22}H_{15}N_3O_5S$
7au	D	81	206—208	THF–hexane	$C_{23}H_{18}N_2O_4S$
7av	D	79	184—189	AcOEt–hexane	$C_{23}H_{18}N_2O_4S$
7aw	Ex	68	229—231	THF–hexane	$C_{22}H_{16}N_2O_4S$
7ax	Ex	41	255—257	THF–iso-Pr_2O	$C_{22}H_{16}N_2O_4S$
7ay	F	32	Amorphous		$C_{23}H_{18}N_2O_3S$
7az	F	47	140—143	MeOH	$C_{23}H_{18}N_2O_3S$
7ba	F	19	171—177	CH_3CN	$C_{21}H_{15}N_3O_4S$
7bb	F	35	174—176	AcOEt–hexane	$C_{22}H_{17}N_3O_4S$
7bc	F	53	83—89	MeOH	$C_{21}H_{15}N_3O_3S_2$
7bd	F	81	Amorphous		$C_{21}H_{21}N_3O_3S_2$
7be	C	33	167—168	AcOEt	$C_{16}H_{13}N_3O_3S_2$
7bf	C	29	174—176	MeOH–CH_3CN	$C_{16}H_{13}N_3O_3S_3$
7bg	B	75	242—245	THF–hexane	$C_{20}H_{13}N_3O_3S_2$
7bh	D	78	116—119	AcOEt–hexane	$C_{22}H_{17}N_3O_3S_2$
7bi	C	37	183—187	AcOEt	$C_{17}H_{13}N_3O_3S$
7bj	C	33	165—167	AcOEt	$C_{19}H_{17}N_3O_3S$
7bk	F	57	139—141	MeOH	$C_{16}H_{12}N_2O_3S_2$
7bl	D	83	161—163	AcOEt–hexane	$C_{20}H_{14}N_2O_4S$
7bm	E	54	160—161	THF–iso-Pr_2O	$C_{20}H_{15}N_3O_3S$
7bn	E	50	252—254	THF–hexane	$C_{21}H_{15}N_3O_3S$
7bo	B	48	Amorphous		$C_{25}H_{17}N_3O_4S$
7bp	B	87	155—156	MeOH	$C_{18}H_{18}N_2O_4SCl$

Table 8. (continued)

Compd. No.	Method	Yield (%)	mp (°C)	Recrystn. solvent	Formula[a]
7bq	H	86	Amorphous		$C_{18}H_{14}N_2O_3S_2$
7br	H	88	153—157	THF–hexane	$C_{16}H_{17}N_3O_3S$
7bs	H	71	112—115	AcOEt–hexane	$C_{17}H_{19}N_3O_3S$
7bt	H	75	170—174	Et_2O	$C_{16}H_{17}N_3O_4S$
7bu	H	81	Amorphous		$C_{19}H_{23}N_3O_3S$
16a	F	33	218—219	AcOEt	$C_{18}H_{11}N_2O_3SCl$
16b	F	26	262—263	THF	$C_{22}H_{15}N_3O_4S$
16c	F	15	221—223	THF–AcOEt	$C_{21}H_{13}N_3O_3S_2$
20a	B	79	262—264	THF–hexane	$C_{16}H_9N_2O_3SCl$
20b	B	91	210—212	THF–hexane	$C_{21}H_{14}N_2O_3S$
23	G	64[c]	220—221	AcOEt	$C_{18}H_{13}N_2O_3SCl$

a) All compounds were analyzed for C, H and N (if necessary, S and halogens also); analytical results obtained for these elements were within ±0.4% of calculated values. *b*) Overall yield from the corresponding benzoxazol-5-ylamine (**4**). *c*) Overall yield from *N*-(4-amino-2-hydroxyphenyl)-4-chlorophenylacetamide (**21**).

based on its high potency and low toxicity in rat 14-day toxicity studies. Compound **7ap** (T-174), however, showed cardiac hypertrophy and anemia in 90-day toxicity studies in rats and dogs.[17] Further studies on the structure–activity relationships and mechanisms of cardiotoxicity and hematotoxicity aimed at finding less toxic compounds,[18] will be presented elsewhere.

Experimental

All melting points are uncorrected. Infrared spectra were taken with a Hitachi IR-215 or an Analect FX-6200 FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded with a Hitachi R-90H, a JEOL JNM-FX-200 or a JEOL JNM-GSX-400 spectrometer. Chemical shifts are given as δ values using tetramethylsilane as an internal standard. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, br = broad. Electron impact (EI) mass spectra were recorded with a Hitachi RMU-6 or a JEOL JMS-HX-100 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B C, H, N analyzer and a Yokokawa IC-100 ion chromatographic analyzer. Organic extracts were dried over Na_2SO_4 or $MgSO_4$. All evaporations were carried out *in vacuo*.

Typical examples are given to illustrate the general procedure.

Method A 5-(2-Phenyl-1,3-benzoxazol-5-ylmethyl)-1,3-thiazolidine-2,4-dione (7a) A solution of $NaNO_2$ (1.76 g, 25.5 mmol) in water (5 ml) was added dropwise to a solution of 2-phenyl-1,3-benzoxazol-5-ylamine (4.87 g, 23.2 mmol) in concentrated HCl (6 ml) and acetone (50 ml) under ice-cooling. The mixture was stirred at the same temperature for 10 min. After addition of methyl acrylate (12.1 g, 140 mmol), Cu_2O (150 mg) was added portionwise to the mixture at 40 °C. After nitrogen gas evolution ceased, the mixture was stirred at 35 °C for 20 min, and extracted with AcOEt. The extract was washed with water, dried and concentrated. The residual oil was purified by SiO_2 chromatography ($CHCl_3$) to give methyl 2-chloro-3-(2-phenyl-1,3-benzoxazol-5-yl)propionate as a pale brown oil (5.30 g, 70%). MS *m/z*: 317, 315 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1740, 1550. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (1H, dd, J = 7.7, 14.5 Hz), 3.49 (1H, dd, J = 6.9, 14.5 Hz), 3.74 (3H, s), 4.50 (1H, t, J = 7.5 Hz), 7.15—8.35 (8H, m). A mixture of methyl 2-chloro-3-(2-phenyl-1,3-benzoxazol-5-yl)propionate (5.30 g, 16.2 mmol), thiourea (2.3 g, 30 mmol) and NaOAc (1.5 g, 18 mmol) in ethylene glycol monomethyl ether (35 ml) was heated at 100 °C for 8 h. The solvent was removed by evaporation. Hexane and water were added. The resulting precipitate was collected, washed and dried *in vacuo* to give 2-imino-5-(2-phenyl-1,3-benzoxazol-5-ylmethyl)-1,3-thiazolidin-4-one as colorless crystals (4.35 g, 83%), mp 281—283 °C (decomp.). MS *m/z*: 323 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3240, 1660, 1500. ^{1}H-NMR (DMSO-d_6) δ: 3.0—3.4 (1H, m), 3.56 (1H, dd, J = 4.2, 14.5 Hz), 4.71 (1H, dd, J = 4.2, 8.5 Hz), 7.26—7.79 (6H, m), 8.14—8.28 (2H, m), 8.4—9.2 (2H, br).

A mixture of 2-imino-5-[(2-phenyl-1,3-benzoxazol-5-yl)methyl]-1,3-thiazolidin-4-one (3.18 g, 9.85 mmol) and *p*-TsOH·H_2O (2.05 g, 10.8 mmol) in water (6 ml) and ethylene glycol monomethyl ether (50 ml) was refluxed for 2 h. The solvent was removed by evaporation. The residue was dissolved in water and extracted with AcOEt. The extract was washed with water and saturated aqueous NaCl, dried and concentrated. The residue was purified by SiO_2 chromatography ($CHCl_3$: MeOH = 20 : 1) to give **7a** (1.83 g, 57%) after crystallization from tetrahydrofuran (THF)–AcOEt, mp 192—194 °C. MS *m/z*: 324 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3180, 1745, 1680. ^{1}H-NMR (DMSO-d_6) δ: 3.1—3.4 (1H, m), 3.57 (1H, dd, J = 4.8, 13.3 Hz), 5.06 (1H, dd, J = 5.0, 8.5 Hz), 7.29—7.83 (6H, m), 8.08—8.30 (2H, m), 12.00 (1H, br s).

The starting materials for method A were prepared as follows:

2-Phenyl-1,3-benzoxazol-5-ylamine (4; R = Ph)[19] A mixture of 2-amino-4-nitrophenol (6.16 g, 40 mmol) and benzaldehyde (4.77 g, 45 mmol) in EtOH (250 ml) was refluxed for 1.3 h, then concentrated. After ice-cooling, the resulting precipitate was collected and dried *in vacuo* to give 7.81 g of pale brown solid. A mixture of the crude imine and lead tetraacetate (15.5 g, 35 mmol) in benzene (100 ml) was stirred at room temperature for 30 min and the precipitate was removed by filtration. The filtrate was concentrated and the residue was purified by SiO_2 chromatography ($CHCl_3$). Recrystallization from EtOH gave 5-nitro-2-phenyl-1,3-benzoxazole as yellow crystals (5.08 g, 53% overall), mp 169—172 °C. MS *m/z*: 240 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1610, 1520. ^{1}H-NMR ($CDCl_3$) δ: 7.4—8.4 (7H, m), 8.58 (1H, d, J = 2.1 Hz). A mixture of the nitro compound (8.85 g, 36.9 mmol) and 10% Pd–C (1.5 g) in AcOH (150 ml) was stirred under H_2 (1 atm) at room temperature for 1.5 h. The catalyst was removed by filtration and the filtrate was concentrated. Recrystallization of the residual solid from $CHCl_3$–hexane gave 2-phenyl-1,3-benzoxazol-5-ylamine as light brown needles (7.02 g, 91%), mp 151—153 °C (ref. mp 151—152 °C). MS *m/z*: 210 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3320, 1620. ^{1}H-NMR ($CDCl_3$) δ: 3.73 (2H, br s), 6.78 (1H, dd, J = 2.2, 8.5 Hz), 7.13 (1H, d, J = 2.1 Hz), 7.27—7.54 (4H, m), 8.00—8.29 (2H, m).

Method B 5-[2-(4-Biphenylmethyl)-1,3-benzoxazol-5-ylmethyl)-1,3-thiazolidine-2,4-dione (7y) A solution of PPSE in 1,2-dichlorobenzene was prepared according to the literature.[10a] A mixture of hexamethyldisiloxane (150 ml) and phosphorus pentoxide (60 g) in 1,2-dichlorobenzene (300 ml) was refluxed for 10 min and, after cooling the resulting solution was used as such for Methods B and F.

Under an Ar atmosphere, a mixture of *N*-[5-(2,4-dioxo-1,3-thiazolidin-5-ylmethyl)-2-hydroxyphenyl]-4-biphenylacetamide (4.42 g, 10.2 mmol) and a 1,2-dichlorobenzene solution of PPSE (30 ml) was stirred at 150 °C for 1 h. After cooling, the resulting solution was diluted with AcOEt–THF, washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated. Purification of the crude product by SiO_2 chromatography ($CHCl_3$–MeOH = 20 : 1) and recrystallization from THF-hexane gave **7y** as colorless needles (3.38 g, 80%), mp 196—198 °C. MS *m/z*: 414 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2770, 1745, 1680. ^{1}H-NMR (DMSO-d_6) δ: 3.23 (1H, dd, J = 8.8, 14.1 Hz), 3.52 (1H, dd, J = 4.8, 14.1 Hz), 4.37 (2H, s), 4.97 (1H, dd, J = 4.8, 8.8 Hz), 7.1—7.8 (12H, m), 12.01 (1H, br s).

Method C 5-[2-(2-Pyridylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7bi) *N*-[5-(2,4-Dioxo-1,3-thiazolidin-5-ylmethyl)-2-hydroxyphenyl]-2-pyridylacetamide (850 mg, 2.38 mmol) was heated at 230 °C under reduced pressure for 30 min. After cooling, the crude product was purified by SiO_2 chromatography ($CHCl_3$–MeOH = 10:1). Recrystallization from THF–AcOEt gave **7bi** as pale brown crystals (300 mg, 37%), mp 183—187 °C. MS *m/z*: 339 (M^+). IR ν_{max}^{Nujol} cm^{-1}:

2670, 1760, 1730, 1700, 1595, 1565. ^{1}H-NMR (DMSO-d_6) δ: 3.23 (1H, dd, J=9.0, 14.0 Hz), 3.50 (1H, dd, J=4.8, 14.0 Hz), 4.49 (2H, s), 4.97 (1H, dd, J=4.8, 9.0 Hz), 7.1—7.9 (6H, m), 8.45 (1H, d, J=5.3 Hz), 11.98 (1H, br s).

Method D 5-[2-(2-Naphthalenylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7ap (T-174)) Under an Ar atmosphere, a mixture of *N*-[5-(2,4-dioxo-1,3-thiazolidin-5-ylmethyl)-2-hydroxyphenyl]-2-naphthalenylacetamide (82.3 g, 202 mmol) and *p*-TsOH·H_2O (3.84 g, 20.2 mmol) in xylene (2.5 l) was refluxed using a Dean–Stark apparatus for 3 h. After ice-cooling, the precipitate was collected and washed with MeOH. Recrystallization from THF–EtOH gave **7ap** as colorless needles (72.3 g, 92%), mp 212—213 °C. MS m/z: 388 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2760, 1750, 1685, 1590. ^{1}H-NMR (DMSO-d_6) δ: 3.24 (1H, dd, J=8.8, 14.2 Hz), 3.49 (1H, dd, J=4.4, 14.2 Hz), 4.50 (2H, s), 4.97 (1H, dd, J=4.4, 8.8 Hz), 7.24 (1H, dd, J=1.5, 8.3 Hz), 7.4—7.6 (5H, m), 7.8—7.9 (4H, m), 12.02 (1H, br s).

Method E 5-[2-(4-Dimethylaminophenylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7ac) Under an Ar stream, a mixture of *N*-[5-(2,4-dioxo-1,3-thiazolidin-5-ylmethyl)-2-hydroxyphenyl]-4-dimethylaminophenylacetamide (60.0 g, 150 mmol) and *p*-TsOH·H_2O (2.85 g, 15.0 mmol) in *N*,*N*-diethylaniline (350 ml) was gently refluxed for 1.5 h at such a rate that water liberated was continuously removed by azeotropic distillation. After cooling, the precipitate was collected, washed with AcOEt, water and MeOH, and dried *in vacuo*. Recrystallization from THF–MeOH gave **7ac** as pale yellow needles (44.7 g, 78%), mp 217—218 °C. MS m/z: 381 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3130, 2720, 2600, 1745, 1685, 1610, 1570. ^{1}H-NMR (DMSO-d_6) δ: 2.86 (6H, s), 3.23 (1H, dd, J=8.8, 14.2 Hz), 3.49 (1H, dd, J=4.4, 14.2 Hz), 4.16 (2H, s), 4.97 (1H, dd, J=4.4, 8.8 Hz), 6.6—6.7 (2H, m), 7.1—7.3 (3H, m), 7.5—7.6 (2H, m), 12.02 (1H, s).

Method F 5-[2-(4-Phenoxyphenylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7w) Under an Ar atmosphere, a mixture of 4-phenoxyphenylacetic acid (0.69 g, 3.0 mmol) and **11** (0.93 g, 3.9 mmol) in 1,2-dichlorobenzene solution of PPSE (25 ml) was stirred at 150 °C for 1.5 h. After cooling, the mixture was diluted with AcOEt, washed with water and saturated aqueous NaCl, dried and concentrated. Trituration of the crude product with iso-Pr_2O and recrystallization from AcOEt–hexane gave **7w** as colorless needles (0.62 g, 48%), mp 122—123 °C. MS m/z: 430 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3140, 2760, 1745, 1690. ^{1}H-NMR (DMSO-d_6) δ: 3.23 (1H, dd, J=8.7, 14.0 Hz), 3.52 (1H, dd, J=4.8, 14.0 Hz), 4.31 (2H, s), 4.97 (1H, dd, J=4.8, 8.7 Hz), 6.9—7.7 (12H, m), 12.00 (1H, br s).

5-[2-(4-Chlorophenylmethyl)-1,3-benzoxazol-5-ylmethylene]-1,3-thiazolidine-2,4-dione (16a) A mixture of 4-chlorophenylacetic acid (616 mg, 3.61 mmol) and **15** (832 mg, 3.27 mmol) in a 1,2-dichlorobenzene solution of PPSE (15 ml) was stirred at 150—160 °C for 1.5 h. After cooling, water was added and the mixture was extracted with THF–AcOEt. The extract was washed with water, dried and concentrated. Recrystallization of the crude product from AcOEt gave **16a** as colorless needles (394 mg, 33%), mp 218—220 °C. MS m/z: 372, 370 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2750, 1735, 1705, 1605, 1590. ^{1}H-NMR (DMSO-d_6) δ: 4.39 (2H, s), 7.42 (4H, s), 7.58 (1H, dd, J=1.5, 8.5 Hz), 7.82 (1H, d, J=8.5 Hz), 7.89 (1H, d, J=1.5 Hz), 7.91 (1H, s), 12.57 (1H, br).

The starting materials for Methods B—F were prepared as follows:

5-(3-Amino-4-hydroxyphenylmethyl)-1,3-thiazolidine-2,4-dione (11) A solution of $NaNO_2$ (4.95 g, 71.7 mmol) in water (10 ml) was added to an ice-cooled solution of 3-nitro-L-tyrosine (**8**) (13.3 g, 46 mmol) and KBr (35 g, 0.29 mol) in aqueous 3 N H_2SO_4 (170 ml) over a period of 30 min. The mixture was stirred for an additional 10 min, and extracted with AcOEt. The extract was washed with water, dried and concentrated to give 2-bromo-3-(4-hydroxy-3-nitrophenyl)propionic acid (**9**) as a brown solid (15.2 g, 89%), mp 92 °C. The crude product was used for the next step without further purification. MS m/z: 291, 289 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1730, 1540. ^{1}H-NMR ($CDCl_3$) δ: 3.34 (2H, t, J=7.7 Hz), 4.41 (1H, t, J=7.7 Hz), 7.12 (1H, d, J=8.6 Hz), 7.45 (1H, dd, J=2.2, 8.6 Hz), 7.99 (1H, d, J=2.2 Hz), 10.40 (2H, br s). A mixture of **9** (15.1 g, 52.1 mmol), thiourea (6.14 g, 80.7 mmol) and NaOAc (5.51 g, 67.2 mmol) in EtOH (150 ml) was refluxed for 3 h. The solvent was removed by evaporation and water was added to the residue. The precipitate was collected, washed with Et_2O and dried *in vacuo* to give 5-(4-hydroxy-3-nitrophenylmethyl)-2-imino-1,3-thiazolidin-4-one (**10**) as pale brown crystals (12.2 g, 88%), mp 228—230 °C. The crude product was used for the next step without further purification. MS m/z: 267 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3270, 1680, 1660, 1580. ^{1}H-NMR (DMSO-d_6) δ: 2.97 (1H, dd, J=8.1, 14.3 Hz), 3.30 (1H, dd, J=4.4, 14.3 Hz), 4.57 (1H, dd, J=4.4, 8.1 Hz), 7.03 (1H, d, J=8.6 Hz), 7.37 (1H, dd, J=2.2, 8.6 Hz), 7.75 (1H, d, J=2.2 Hz), 8.68 (1H, br). A mixture of **10** (12.1 g, 45.3 mmol), ethylene glycol monomethyl ether (125 ml), concentrated HCl (15.6 ml) and water (12.5 ml) was refluxed for 4 h, and concentrated. The residue was diluted with water and extracted with AcOEt. The extract was washed with water, dried and evaporated. Recrystallization of the residual solid from AcOEt–hexane gave 5-(4-hydroxy-3-nitrophenylmethyl)-1,3-thiazolidine-2,4-dione as yellow crystals (10.4 g, 86%), mp 144—146 °C. MS m/z: 268 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3320, 1760, 1710, 1700, 1535. ^{1}H-NMR (DMSO-d_6) δ: 3.14 (1H, dd, J=8.1, 14.3 Hz), 3.37 (1H, dd, J=5.0, 14.3 Hz), 4.90 (1H, dd, J=5.0, 8.1 Hz), 7.06 (1H, d, J=8.6 Hz), 7.43 (1H, dd, J=2.2, 8.6 Hz), 7.79 (1H, d, J=2.2 Hz), 10.85 (1H, br s), 12.00 (1H, br s). *Anal.* Calcd for $C_{10}H_8N_2O_5S$: C, 44.77; H, 3.01; N, 10.44; S, 11.95. Found: C, 44.50; H, 2.75; N, 10.22; S, 11.80. The nitro compound (10.3 g, 38.4 mmol) was dissolved in THF–MeOH (1 : 1, 340 ml) and 10% Pd–C (2.5 g) was added. The mixture was stirred under H_2 (1 atm) for 8 h. The catalyst was removed by filtration and the filtrate was concentrated. Recrystallization of the residual solid from iso-PrOH gave 5-(3-amino-4-hydroxyphenylmethyl)-1,3-thiazolidine-2,4-dione (**11**) as colorless crystals (8.77 g, 96%), mp 220—224 °C. MS m/z: 238 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3330, 3170, 3040, 1740, 1680. ^{1}H-NMR (DMSO-d_6) δ: 2.83 (1H, dd, J=9.5, 14.0 Hz), 3.20 (1H, dd, J=4.5, 14.0 Hz), 4.72 (1H, dd, J=4.5, 9.5 Hz), 6.27 (1H, dd, J=2.0, 8.0 Hz), 6.47 (1H, d, J=2.0 Hz), 6.57 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.57; H, 4.21; N, 11.70; S, 13.68.

***N*-[5-(2,4-Dioxo-1,3-thiazolidin-5-ylmethyl)-2-hydroxyphenyl]-2-naphthalenylacetamide (12; R=2-Naphthalenylmethyl)** Dimethylformamide (DMF) (0.2 ml) was added dropwise to a suspension of 2-naphthalenylacetic acid (42.63 g, 229 mmol) and oxalyl chloride (87.2 g, 687 mmol) in CH_2Cl_2 (840 ml) under ice-cooling. The mixture was stirred at room temperature for 2.5 h, and concentrated to give crude 2-naphthalenylacetyl chloride as a pale yellow solid. A solution of this crude acid chloride in THF (300 ml) was added dropwise to a solution of **11** (60.0 g, 252 mmol) and *N*,*N*-dimethylaniline (87.0 ml, 687 mmol) in THF (800 ml)–DMF (160 ml) over a period of 35 min under ice-cooling. The mixture was stirred at room temperature for 1 h, diluted with AcOEt (1 l), washed with 10% aqueous HCl, water and saturated aqueous NaCl (1 l each), dried, and concentrated. The residual solid was triturated with AcOEt–hexane to afford *N*-[5-(2,4-dioxo-1,3-thiazolidin-5-ylmethyl)-2-hydroxyphenyl]-2-naphthalenylacetamide as colorless crystals (82.8 g, 89%), mp 221—223 °C. MS m/z: 406 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3380, 3160, 3120, 1760, 1730, 1700, 1645. ^{1}H-NMR (DMSO-d_6) δ: 2.96 (1H, dd, J=9.3, 14.2 Hz), 3.25 (1H, dd, J=4.2, 14.2 Hz), 3.92 (2H, s), 4.77 (1H, dd, J=4.2, 9.3 Hz), 6.7—6.8 (2H, m), 7.4—7.5 (3H, m), 7.72 (1H, s), 7.8—7.9 (4H, m), 9.38 (1H, br s), 9.78 (1H, br s), 11.97 (1H, br). *Anal.* Calcd for $C_{22}H_{18}N_2O_4S$: C, 65.01; H, 4.46; N, 6.89; S, 7.89. Found: C, 65.23; H, 4.22; N, 6.71; S, 7.85.

5-(3-Amino-4-hydroxyphenylmethylene)-1,3-thiazolidine-2,4-dione (15) A mixture of 4-hydroxy-3-nitrobenzaldehyde (**13**) (1.00 g, 5.98 mmol), 1,3-thiazolidine-2,4-dione (702 mg, 5.93 mmol) and piperidine (0.12 ml, 1.2 mmol) in dioxane (10 ml) was refluxed for 10 h. After cooling, the mixture was poured into 1% aqueous HCl, and extracted with AcOEt. The organic layer was washed with water, dried and concentrated. Recrystallization of the residual solid from THF–hexane gave 5-(4-hydroxy-3-nitrophenylmethylene)-1,3-thiazolidine-2,4-dione (**14**) as yellow needles (1.23 g, 77%), mp 255—256 °C (decomp.). MS m/z: 266 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3280, 2760, 1750, 1740, 1710, 1620. ^{1}H-NMR (DMSO-d_6) δ: 7.25 (1H, d, J=9.0 Hz), 7.72 (1H, dd, J=2.2, 9.0 Hz), 7.75 (1H, s), 8.11 (1H, d, J=2.2 Hz). *Anal.* Calcd for $C_{10}H_6N_2O_5S$: C, 45.12; H, 2.27; N, 10.52; S, 12.04. Found: C, 45.16; H, 2.13; N, 10.58; S, 11.89. A catalyst 10% Pd–C (0.10 g) was added to a solution of **14** (1.00 g, 3.76 mmol) and 2.4 M aqueous NaH_2PO_2 (5 ml, 12 mmol) in DMF (20 ml), and the mixture was stirred at room temperature for 1.5 h.[20] The catalyst was removed by filtration and the filtrate was diluted with water. The precipitate was collected and dried to give the monohydrate of **15** as yellow needles (885 mg, 93%), mp 258—259 °C. MS m/z: 236 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3580, 3400, 3340, 1720, 1685, 1625. ^{1}H-NMR (DMSO-d_6) δ: 6.76 (2H, s), 6.83 (1H, s), 7.75 (1H, s). *Anal.* Calcd for $C_{10}H_8N_2O_3S \cdot H_2O$: C, 47.24; H, 3.96; N, 11.02; S, 12.61. Found: C, 47.48; H, 3.80; N, 11.08; S, 12.53.

5-(3-Amino-4-hydroxyphenyl)-1,3-thiazolidine-2,4-dione (19) A solution of NaCN (448 mg, 9.14 mmol) in water (1.5 ml) was added to a solution of 4-hydroxybenzaldehyde (**17**; 1.02 g, 8.31 mmol) and acetic

acid (550 mg, 9.14 mmol) in ethylene glycol monomethyl ether (15 ml) and the mixture was stirred at room temperature for 1.5 h. After addition of thiourea (930 mg, 11.6 mmol) and concentrated HCl (3 ml), the mixture was stirred at 100 °C for 18 h, diluted with water and extracted with AcOEt. The extract was washed with water and saturated aqueous NaCl, dried and concentrated. The residual solid was triturated with iso-Pr_2O and recrystallized from EtOH to afford 5-(4-hydroxyphenyl)-1,3-thiazolidine-2,4-dione (**18**)[13] as colorless needles (705 mg, 41%), mp 236—237 °C. MS *m/z*: 209 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3340, 3205, 3070, 1735, 1670, 1610. ^{1}H-NMR (DMSO-d_6) δ: 5.68 (1H, s), 6.6—6.9 (2H, m), 7.0—7.3 (2H, m), 8.5—13.0 (2H, br). *Anal.* Calcd for $C_9H_7NO_3S$: C, 51.67; H, 3.37; N, 6.69; S, 15.33. Found: C, 51.46; H, 3.27; N, 6.69; S, 15.28. A suspension of **18** (660 mg, 3.15 mmol) in acetic acid (10 ml) was treated with 50% nitric acid (2.4 g, 19 mmol) under ice-cooling. The mixture was stirred at room temperature for 50 min and diluted with water. The precipitate was collected, washed with water, and dried *in vacuo* to afford 5-(4-hydroxy-3-nitrophenyl)-1,3-thiazolidine-2,4-dione as yellow crystals (691 mg, 86%). An analytically pure sample was obtained by recrystallization from EtOH, mp 203—204 °C. MS *m/z*: 254 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3280, 3140, 3060, 1745, 1685, 1630. ^{1}H-NMR (DMSO-d_6) δ: 5.87 (1H, s), 7.16 (1H, d, J=8.7 Hz), 7.61 (1H, dd, J=2.4, 8.7 Hz), 7.99 (1H, d, J=2.2 Hz), 10.0—13.0 (2H, br). *Anal.* Calcd for $C_9H_6N_2O_5S$: C, 42.52; H, 2.38; N, 11.02; S, 12.61. Found: C, 42.35; H, 2.29; N, 10.96; S, 12.50. Concentrated HCl (93 ml) was added dropwise to a suspension of the nitrophenol (24.8 g, 97.5 mmol) and Sn (34.7 g, 0.29 mol) in THF–MeOH (1 : 1, 800 ml) under reflux over a period of 30 min. The mixture was further refluxed for 30 min, diluted with water and neutralized with 10% NaOH under ice-cooling. The precipitate was filtered off through a Celite pad. The aqueous layer was extracted with AcOEt. The combined organic layer was washed with water and saturated aqueous NaCl, dried and concentrated. The residual solid was triturated with iso-PrOH to afford 5-(3-amino-4-hydroxyphenyl)-1,3-thiazolidine-2,4-dione (**19**) as colorless crystals (17.2 g, 79%), mp 210—211 °C. An additional amount of **19** was obtained from the mother liquor (1.2 g, 5%). MS *m/z*: 224 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3365, 3335, 3295, 2675, 1685, 1610. ^{1}H-NMR (DMSO-d_6) δ: 5.51 (1H, s), 6.41 (1H, dd, J=8.0, 2.4 Hz), 6.59 (1H, d, J=2.4 Hz), 6.61 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49; S, 14.30. Found: C, 47.96; H, 3.62; N, 12.28; S, 14.19.

Method G 5-[2-(4-Chlorophenylmethyl)-1,3-benzoxazol-6-ylmethyl]-1,3-thiazolidine-2,4-dione (23) A mixture of 4-chlorophenylacetic acid (51.6 g, 303 mmol) and thionyl chloride (150 ml) was refluxed for 2 h, and the volatile material was removed by evaporation to give the acid chloride as a yellow oil. A mixture of 2-amino-5-nitrophenol (46.6 g, 303 mmol), and *N*,*N*-dimethylaniline (51.4 g, 424 mmol) in THF (600 ml) was added dropwise to a solution of the acid chloride in THF (100 ml) under ice-cooling. The mixture was stirred at room temperature for 1 h, and concentrated. To the residue was added 3% aqueous HCl (300 ml). The precipitate was collected, washed with 10% aqueous HCl, water and Et_2O–hexane, and dried *in vacuo* to give 4-chlorophenyl-*N*-(2-hydroxy-4-nitrophenyl) acetamide as yellow crystals (90.0 g, 97%), mp 220—221 °C. MS *m/z*: 308, 306 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3360, 3340, 2720, 1675, 1660, 1605, 1585. ^{1}H-NMR (DMSO-d_6) δ: 3.88 (2H, s), 7.38 (4H, s), 7.5—7.8 (2H, m), 8.1—8.4 (1H, d, J=9.7 Hz), 9.64 (1H, br s), 11.01 (1H, br s).

A solution of the nitro compound (89.9 g, 293 mmol) and $SnCl_2 \cdot 2H_2O$ (265 g, 1.18 mol) in AcOEt (2 l) was refluxed for 5 h. An additional amount of $SnCl_2 \cdot 2H_2O$ (51 g, 0.23 mol) was added and the mixture was refluxed for a further 3.5 h. After cooling, water (2 l) was added and the pH was adjusted to 8 with 10% NaOH. The organic layer was washed with water (2 × 0.5 l) and saturated aqueous NaCl (0.5 l), dried and concentrated. The crude product was digested with hot $CHCl_3$, collected and dried *in vacuo* to afford *N*-(4-amino-2-hydroxyphenyl)-4-chlorophenylacetamide (**21**; R = 4-chlorobenzyl) as light brown crystals (56.6 g, 70%), mp 155—157 °C. MS *m/z*: 278, 276 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3360, 3300, 3260, 1630, 1610, 1595. ^{1}H-NMR (DMSO-d_6) δ: 3.65 (2H, s), 4.83 (2H, br s), 6.00 (1H, dd, J=2.4, 8.4 Hz), 6.12 (1H, d, J=2.4 Hz), 7.12 (1H, d, J=8.4 Hz), 7.36 (4H, s), 9.24 (2H, br s).

The aniline derivative (**21**) (57.9 g, 209 mmol) was converted to 4-chlorophenyl-*N*-[4-(2,4-dioxo-1,3-thioazolidin-5-ylmethyl)-2-hydroxyphenyl] acetamide (**22**; R = 4-chlorobenzyl) by the same procedure as described under Method A in three steps (18.9 g, 23% overall), mp 174—178 °C. MS *m/z*: 392, 390 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3140, 3030, 1730, 1680, 1650, 1615, 1590. ^{1}H-NMR (DMSO-d_6) δ: 2.99 (1H, dd, J=8.8, 14.1 Hz), 3.29 (1H, dd, J=4.6, 14.1 Hz), 3.74 (2H, s), 4.83 (1H, dd, J=4.6, 8.8 Hz), 6.4—6.7 (2H, m), 7.37 (4H, s), 7.68 (1H, d, J=7.9 Hz), 9.32 (1H, br s), 9.80 (1H, br s), 11.95 (1H, br s).

Benzoxazole ring formation was performed by the same procedure as described under Method B with a 1,2-dichlorobenzene solution of PPSE, to afford **23** as faintly yellow crystals (11.5 g, 64%), mp 220—221 °C. MS *m/z*: 374, 372 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2730, 1740, 1690, 1605, 1565. ^{1}H-NMR (DMSO-d_6) δ: 3.23 (1H, dd, J=8.8, 14.1 Hz), 3.54 (1H, dd, J=4.8, 14.1 Hz), 4.34 (2H, s), 4.96 (1H, dd, J=4.8, 8.8 Hz), 7.1—7.7 (7H, m), 12.01 (1H, br s).

Method H 5-(2-Bromomethyl-1,3-benzoxazol-5-ylmethyl)-1,3-thiazolidine-2,4-dione (25) A mixture of bromoacetic acid (1.11 g, 7.93 mmol) and **11** (2.47 g, 10.4 mmol) in a 1,2-dichlorobenzene solution of PPSE (25 ml) was stirred at 150 °C for 30 min and worked up as described under Method F. Recrystallization from AcOEt gave **25** as colorless crystals (2.14 g, 79%), mp 138—142 °C. MS *m/z*: 342, 340 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3120, 2780, 1745, 1685. ^{1}H-NMR ($CDCl_3$) δ: 3.29 (1H, dd, J=8.6, 13.9 Hz), 3.49 (1H, dd, J=4.8, 13.9 Hz), 4.89 (2H, s), 4.94 (1H, dd, J=4.8, 8.6 Hz), 7.2—7.8 (3H, m), 12.00 (1H, br s).

5-(2-Phenylthiomethyl-1,3-benzoxazol-5-ylmethyl)-1,3-thiazolidine-2,4-dione (7bq) Under an Ar atmosphere, a mixture of the 2-bromomethylbenzoxazole **25** (6.82 g, 20.0 mmol), thiophenol (2.20 g, 20.0 mmol) and powdered K_2CO_3 (5.52 g, 40.0 mmol) in THF (100 ml) was refluxed for 2 h. After cooling, the mixture was acidified with 10% aqueous HCl and extracted with AcOEt. The extract was washed with saturated aqueous NaCl, dried and concentrated. The crude product was purified by SiO_2 chromatography ($CHCl_3$–MeOH = 50 : 1) to afford **7bq** as a colorless amorphous powder (5.86 g, 79%). MS *m/z*: 370 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3150, 2780, 1755, 1695. ^{1}H-NMR ($CDCl_3$) δ: 3.34 (1H, dd, J=8.8l, 14.2 Hz), 3.56 (1H, dd, J=4.4, 14.2 Hz), 4.30 (2H, s), 4.57 (1H, dd, J=4.4, 8.8 Hz), 7.1—7.7 (8H, m), 8.81 (1H, br s).

5-[2-(Pyrrolidin-1-ylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7br) A mixture of **25** (1.00 g, 2.93 mmol) and pyrrolidine (0.71 g, 10 mmol) in EtOH (10 ml) was stirred at room temperature for 20 min. The mixture was diluted with AcOEt, washed with saturated $(NH_4)_2SO_4$, dried and concentrated. The crude product was purified by SiO_2 chromatography ($CHCl_3$–MeOH = 20 : 1). Recrystallization from Et_2O gave **7br** as colorless crystals (0.85 g, 88%), mp 153—157 °C. MS *m/z*: 331 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 2550, 2360, 1920, 1745, 1700. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (4H, br s), 2.74 (4H, br s), 3.33 (1H, dd, J=7.8, 14.0 Hz), 3.55 (1H, dd, J=4.4, 14.0 Hz), 3.96 (2H, s), 4.57 (1H, dd, J=4.4, 7.8 Hz), 7.19 (1H, dd, J=1.6, 8.5 Hz), 7.36 (1H, dd, J=0.7, 8.5 Hz), 7.60 (1H, d, J=0.9 Hz), 10.41 (1H, br s).

Compounds (**7bs**—**7bu**) were prepared similarly.

Method Ex 5-[2-(4-Aminophenylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7aa) A solution of the nitro compound **7z** (33.5 g, 87.5 mmol) in THF–MeOH (1 : 1, 1.3 l) was stirred in the presence of 10% Pd–C (10 g) under H_2 (1 atm) for 3 h. The catalyst was removed by filtration and the filtrate was concentrated. Purification of the crude product by SiO_2 chromatography ($CHCl_3$–MeOH = 20 : 1) and recrystallization from THF–AcOEt gave **7aa** as pale yellow needles (16.4 g, 53%), mp 187—192 °C. MS *m/z*: 353 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3350, 2740, 1735, 1700. ^{1}H-NMR (DMSO-d_6) δ: 3.22 (1H, dd, J=8.8, 14.1 Hz), 3.51 (1H, dd, J=4.6, 14.1 Hz), 4.09 (2H, s), 4.96 (1H, dd, J=4.6, 8.8 Hz), 6.3—6.7 (2H, m), 6.8—7.7 (5H, m), 5.5—9.0 (3H, br).

5-[2-(4-Acetylaminophenylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7ai) A solution of **7aa** (14.0 g, 39.7 mmol) in pyridine (140 ml) was treated with acetic anhydride (20 ml, 0.21 mol). The mixture was stirred at room temperature for 2 h, and concentrated. The residue was dissolved in THF–AcOEt, washed with 10% aqueous HCl and saturated aqueous NaCl, dried and concentrated. Trituration with $CHCl_3$–hexane and recrystallization of the crude product from THF–hexane gave **7ai** as colorless needles (13.1 g, 83%), mp 241—244 °C. MS *m/z*: 395 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3350, 2730, 1745, 1685, 1665, 1660. ^{1}H-NMR (DMSO-d_6) δ: 2.03 (3H, s), 3.23 (1H, dd, J=8.6, 14.2 Hz), 3.52 (1H, dd, J=4.7, 14.2 Hz), 4.25 (2H, s), 4.96 (1H, dd, J=4.7, 8.6 Hz), 7.0—7.8 (7H, m), 9.89 (1H, br s), 11.69 (1H, br s).

5-[2-(4-Methylsulfinylphenylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7am) A mixture of the sulfide **7al** (1.00 g, 2.69 mmol) and *m*-chloroperbenzoic acid (80%, 580 mg, 2.69 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 10 min. The solvent was removed by evaporation. The residue was dissolved in AcOEt, washed with saturated $NaHSO_3$, saturated aqueous $NaHCO_3$, water and saturated aqueous NaCl, dried and concentrated. Purification of the

crude product by SiO_2 chromatography ($CHCl_3$–MeOH = 20 : 1) and trituration with AcOEt–Et_2O gave **7am** as a colorless amorphous powder (670 mg, 64%). MS *m/z*: 400 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3130, 2770, 1750, 1695, 1565. ^{1}H-NMR (DMSO-d_6) δ: 2.73 (3H, s), 3.28 (1H, dd, J = 8.6, 14.0 Hz), 3.60 (1H, dd, J = 4.4, 14.0 Hz), 4.33 (2H, s), 4.55 (1H, dd, J = 4.4, 8.6 Hz), 7.1—7.7 (7H, m).

5-[2-(4-Methylsulfonylphenylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7an) A mixture of **7al** (1.20 g, 3.22 mmol) and *m*-chloroperbenzoic acid (80%, 2.10 g, 9.68 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 20 min. The mixture was worked up and the crude product was purified as described for **7am**. Recrystallization from THF–hexane gave **7an** as colorless needles (930 mg, 69%), mp 168—169 °C. MS *m/z*: 416 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3230, 2730, 1760, 1730, 1695, 1565. ^{1}H-NMR (DMSO-d_6) δ: 3.20 (3H, s), 3.40 (2H, m), 4.48 (2H, s), 4.95 (1H, dd, J = 4.8, 8.5 Hz), 7.22, (1H, dd, J = 1.5, 8.8 Hz), 7.5—8.0 (6H, m), 11.98 (1H, br s).

5-[2-(6-Hydroxy-2-naphthalenylmethyl)-1,3-benzoxazol-5-ylmethyl]-1,3-thiazolidine-2,4-dione (7aw) Under an Ar atmosphere, a suspension of the methoxy compound **7au** (834 mg, 1.99 mmol) in CH_2Cl_2 (40 ml) was treated with BBr_3 (1.9 ml, 20 mmol) at −78 °C. The mixture was stirred at −78 °C to room temperature for 3 h, and poured into saturated aqueous $NaHCO_3$. The organic solvent was removed by evaporation. The resulting aqueous solution was acidified with 10% aqueous HCl and extracted with AcOEt. The extract was washed with water and saturated aqueous NaCl, dried and concentrated. The residual solid was recrystallized from THF–hexane to afford **7aw** as colorless crystals (547 mg, 68%), mp 229—231 °C. MS *m/z*: 404 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3500, 3120, 2740, 2620, 2420, 1750, 1680. ^{1}H-NMR (DMSO-d_6) δ: 3.23 (1H, dd, J = 9.0, 14.2 Hz), 3.49 (1H, dd, J = 4.4, 14.2 Hz), 4.41 (2H, s), 4.97 (1H, dd, J = 4.4, 9.0 Hz), 6.9—7.4 (4H, m), 7.5—7.8 (5H, m), 9.71 (1H, br s), 12.00 (1H, br s).

Compounds (**7q** and **7ax**) were prepared by the same procedure.

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