Highly Selective Aldose Reductase Inhibitors. 3. Structural Diversity of 3-(Arylmethyl)-2,4,5-trioxoimidazolidine-1-acetic Acids

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Accumulation of intracellular sorbitol, the reduced product of glucose, catalyzed by aldose reductase (AR) (EC 1.1.1.21), is thought to be the cause of the development of diabetic complications. Our attention is focused on finding compounds which inhibit AR without significantly inhibiting aldehyde reductase (ALR) (EC 1.1.1.2). The uracil or 2,4-dioxoimidazolidine skeleton having the benzothiazolyl or 4-chloro-3-nitrophenyl group as an aryl part indicated not only extremely high AR inhibitory activity but also AR selectivity. The ratio of IC_{50}(ALR)/IC_{50}(AR) of 3-[(5-chlorobenzothiazol-2-yl)methyl]-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acid (**47d**) was more than 17 500. The uracil skeleton with the benzothiazolyl moiety seemed to be the best combination for selective AR inhibition.

Introduction

The therapeutic potential as well as the discovery and development of aldose reductase inhibitors (ARIs) for the prevention of the secondary complications of diabetes have been extensively reported.[1−5] Although a number of ARIs have so far been synthesized and evaluated for their activities (Chart 1),[2,6−9] only a few aldose reductase (AR) (EC 1.1.1.21) selective inhibitors have been found.[10,11] To avoid the adverse effects of ARI therapy, the AR selectivity is one of the most important aspects as described by many reports.[12−19] Although it is not clear how aldehyde reductase (ALR) (EC 1.1.1.2) works in diabetic patients, ALR would be one of the important enzymes for reduction of many aldehydes, counteraction and excretion of drugs,[17] reduction of 3-deoxyglucosone (3-DG), which is an intermediate for advanced glycation end products (AGEs),[20] and metabolism of methylglyoxal (MG).[21]

Our recent efforts[22,23] have led to the discovery of **1a** (Chart 2), an orally active and highly potent ARI, which is of interest because of its high AR inhibitory activity and selectivity. It is presently being evaluated in a clinical study. A new series of ARIs based on the 2,4,5-trioxoimidazolidine-1-acetic acid framework and also the structure−activity relationships (SAR) of **1** were previously reported.[23] Introduction of the benzothiazolyl or 4-chloro-3-nitrophenyl group as an aryl portion was extremely effective for high AR selectivity. Parallel to the optimization of the aryl portion, the modification of the 2,4,5-trioxoimidazolidine framework to the uracil or 2,4-dioxoimidazolidine core unit was investigated. Kador *et al.*[24,25] have shown that the structural requirements for AR inhibitory activity consist of a nearly planar structure with two hydrophobic (aromatic) regions and a common region which is susceptible to charge-transfer interactions. Therefore, it was necessary to reinvestigate the core unit since the 2,4,5-trioxoimidazolidine framework might play an important role for AR selective inhibitory activity. AR selectivity may be deeply influenced by the relative spatial position of the nucleophilic charge-transfer and carboxylic acid moieties. In this paper, the conversion of the 2,4,5-trioxoimidazolidine framework to the uracil or 2,4-dioxoimidazolidine core unit and the results of the AR and ALR inhibitory activities in various combinations of the aryl moiety and the core unit are described.

Chart 1

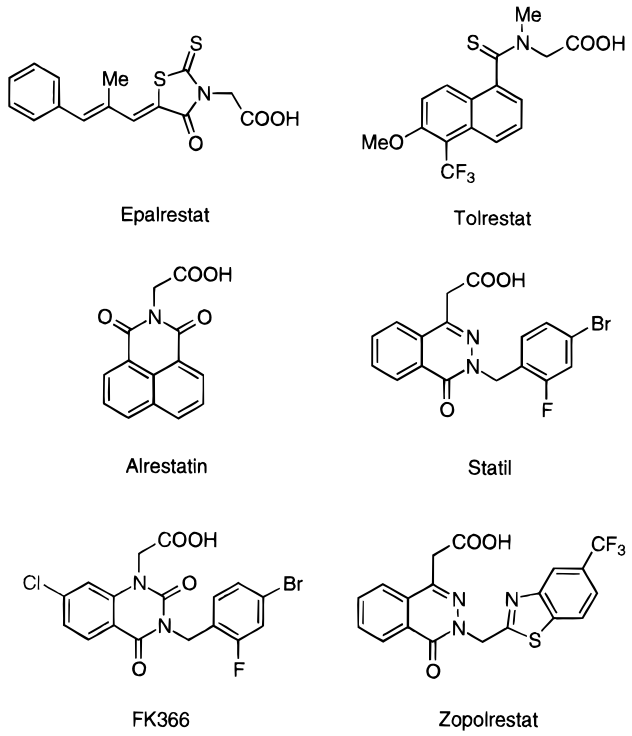
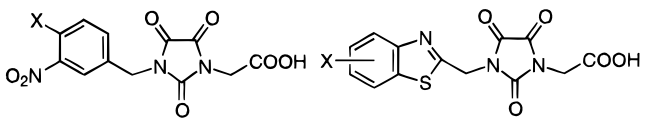


Chart 2



1a : X = H **(NZ-314)**
1b : X = Cl

2a : X = 4-Cl
2b : X = 5-Cl

Chemistry

The 2-methylidene derivative **9** was synthesized in the following procedure. Treatment of 3-nitrobenzyl-

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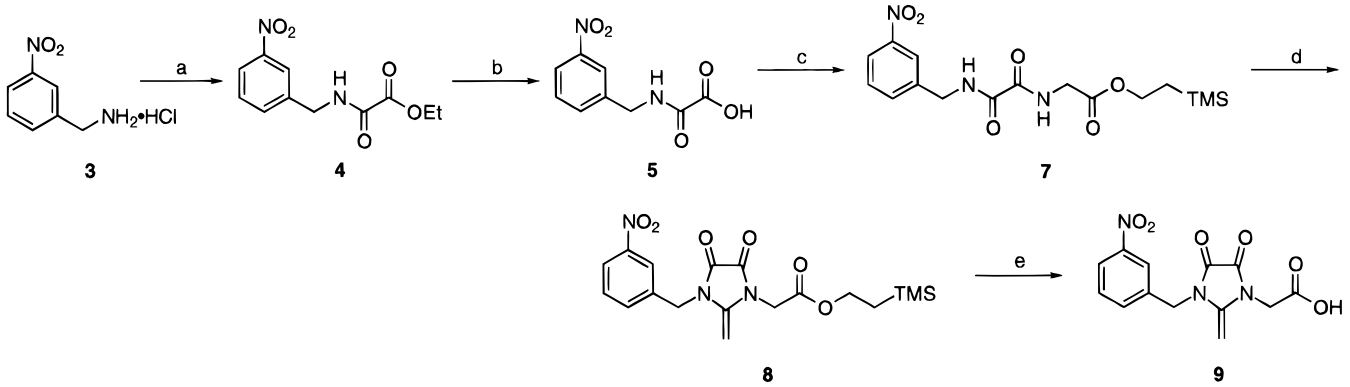
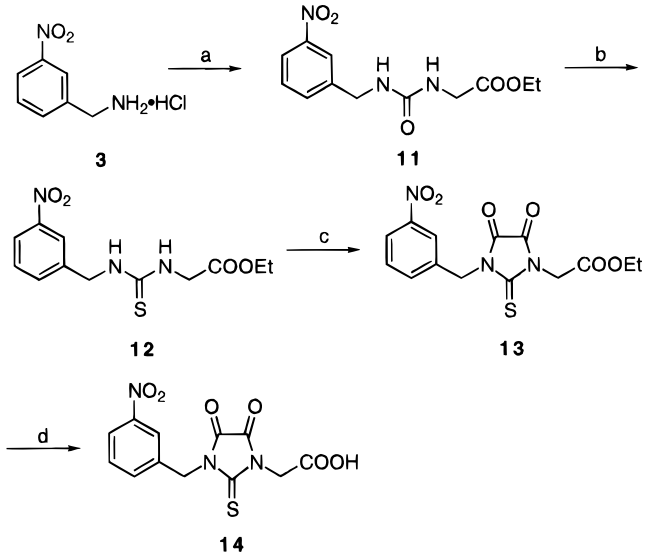
Scheme 1[a]



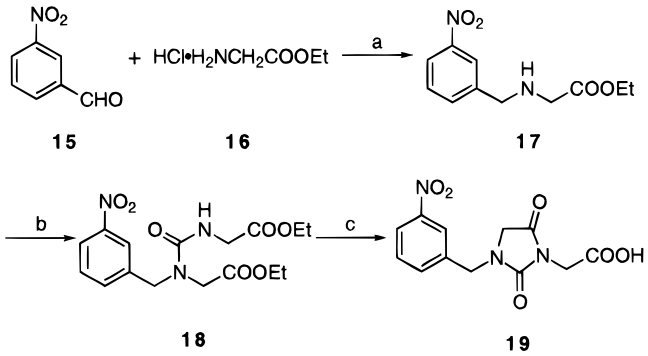
[a] (a) Ethyl oxalyl chloride, Et_3N, CH_2Cl_2, 0 °C; (b) 1 N NaOH, CH_2Cl_2; (c) Gly-OCH_2CH_2TMS (**6**), WSC·HCl, CH_2Cl_2; (d) Ac_2O, AcONa, reflux; (e) $^nBu_4NF$, DMF.

Scheme 2[a]



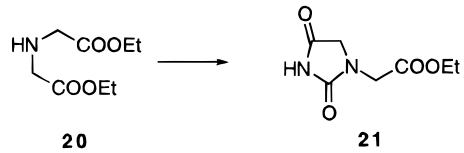
[a] (a) $OCNCH_2COOEt$ (**10**), NaOH, H_2O, EtOH, 0 °C; (b) Lawesson's reagent, dioxane, reflux; (c) oxalyl chloride, CH_2Cl_2, rt; (d) HCl, AcOH, reflux.

Scheme 3[a]



[a] (a) $NaBH_3CN$, MeOH; (b) **10**, Et_2O; (c) HCl, AcOH, reflux.

Scheme 4[a]



[a] KNCO, HCl, H_2O, reflux.

amine hydrochloride (**3**) with ethyl oxalyl chloride in the presence of Et_3N in CH_2Cl_2 gave the oxamate **4**. The oxamate **4** obtained was hydrolyzed and condensed with glycine 2-(trimethylsilyl)ethyl ester (**6**) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSC·HCl) to give the oxamide **7** as white crystals. Introduction of the methylidene moiety[26] was achieved by the treatment of the oxamide **7** with acetic anhydride and sodium acetate at refluxing temperature. Deprotection of the ester **8** with $^nBu_4NF$ gave the desired carboxylic acid **9** as shown in Scheme 1.

The 2-thioxo derivative **14** was synthesized as shown in Scheme 2. Condensation of **3** with ethyl isocyanatoacetate (**10**) in an alkaline solution with vigorous stirring gave the urea **11**. The urea **11** was converted to the thiourea **12** by using Lawesson's reagent[27] in dioxane under reflux. Addition of oxalyl chloride to the solution of the thiourea **12** in CH_2Cl_2 afforded the 4,5-dioxo-2-thioxoimidazolidine-1-acetate derivative **13** which was deprotected under acidic conditions to give the carboxylic acid **14**.

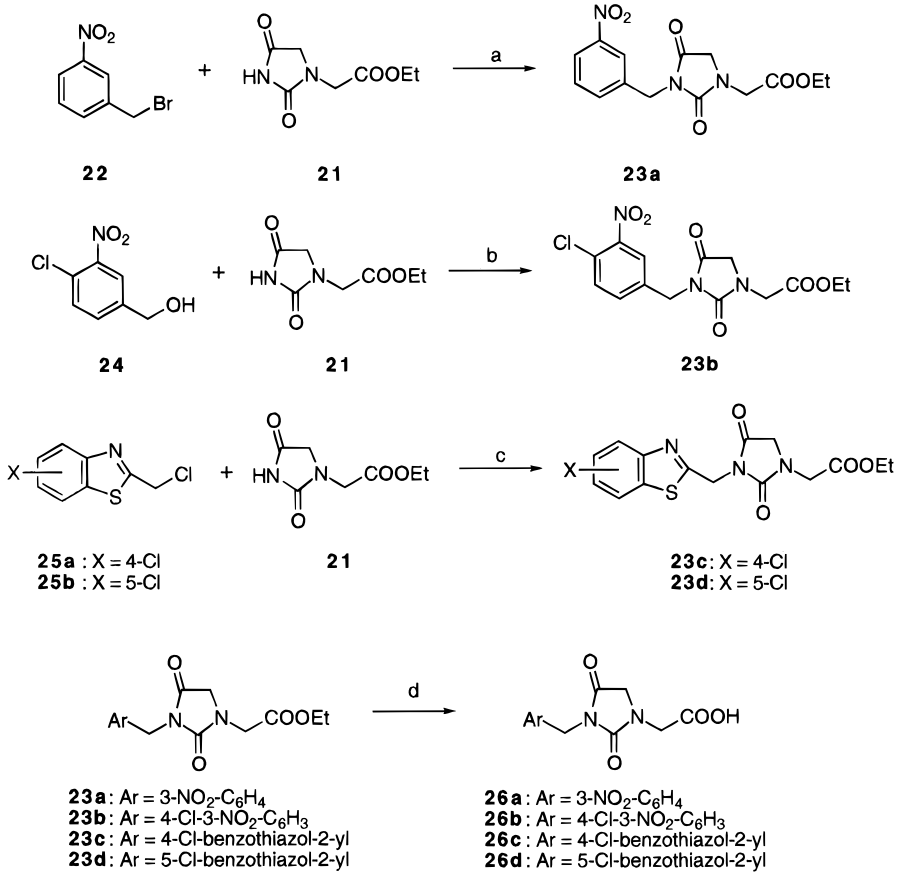
The hydantoin derivatives **19** and **26a**−**d** were prepared in moderate to good yields as shown in Schemes 3−5. *N*-(3-Nitrobenzyl)glycine ethyl ester (**17**) was prepared by reductive alkylation of 3-nitrobenzaldehyde (**15**) with ethyl glycinate (**16**) in the presence of $NaBH_3CN$ in MeOH. The ester **17** was condensed with **10** to give the trialkylated urea **18** whose ester groups were hydrolyzed with AcOH and HCl to give the desired carboxylic acid **19** (Scheme 3).

Ethyl 2,4-dioxoimidazolidine-1-acetate (**21**), the common intermediate for the preparation of **23a**−**d**, was obtained by refluxing a mixture of diethyl iminodiacetate (**20**) and KNCO under acidic conditions as shown in Scheme 4. The hydantoin **21** was alkylated with the benzyl bromide **22** in the presence of NaH, the alcohol **24** by the Mitsunobu reaction,[28] or 2-(chloromethyl)-benzothiazoles **25a,b** in the presence of NaBr and NaH to give **23a**−**d**. Acidic deprotection (AcOH and HCl) afforded the carboxylic acids **26a**−**d** as shown in Scheme 5.

The 5-methylidene derivative **30** was prepared in the following procedure (Scheme 6). *N*-(3-Nitrobenzyl)-serine methyl ester (**28**) was prepared by reductive alkylation of **15** with serine methyl ester (**27**). Treatment of the ester **28** with **10** gave the urea **29**. Base-catalyzed cyclization of **29** gave the carboxylic acid **30** in a quite low yield.

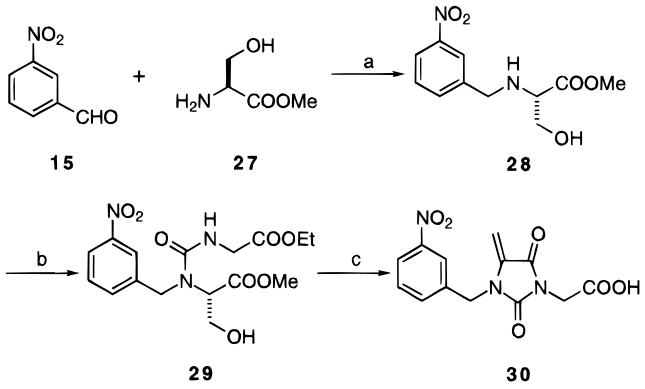
The hydroxyhydantoin derivatives **36** and **40** were synthesized in the procedures as shown in Schemes 7

Scheme 5[a]



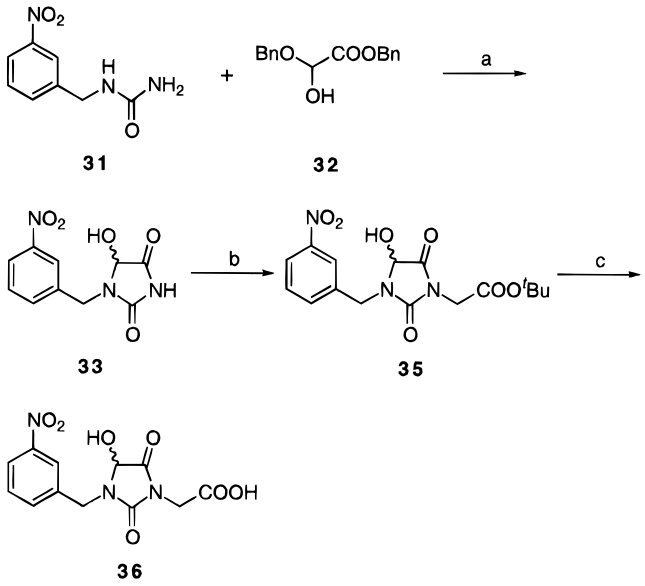
[a] (a) NaH, DMF, −10 °C−rt; (b) DEAD, PPh_3, THF, 0 °C−rt; (c) NaBr, DMF, then NaH, DMF, −10 °C−rt; (d) HCl, AcOH, reflux.

Scheme 6[a]



[a] (a) $NaBH_3CN$, MeOH, 0 °C; (b) **10**, Et_2O, rt; (c) KOH, H_2O, EtOH, 0 °C−rt.

Scheme 7[a]



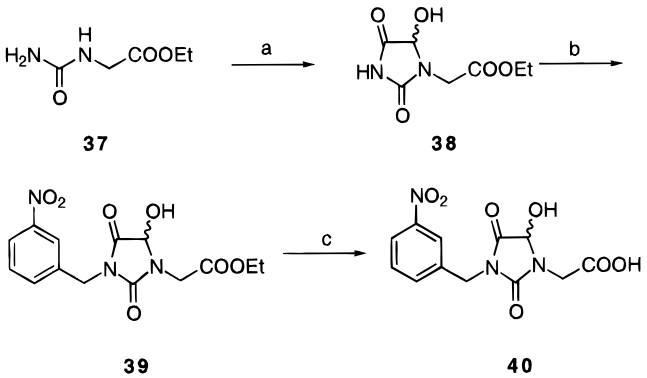
[a] (a) 80% AcOH, 80 °C; (b) $BrCH_2COO^tBu$ (**34**), $KHCO_3$, acetone; (c) 4 N HCl/dioxane.

and 8, respectively. Condensation of (3-nitrobenzyl)-urea (**31**) with **32** in 80% AcOH gave the 5-hydroxy-2,4-dioxoimidazolidine derivative **33**. Introduction of the acetic acid unit to **33** was performed by condensation with *tert*-butyl bromoacetate (**34**) in the presence of $KHCO_3$. Acid-catalyzed hydrolysis of the ester **35** with 4 N HCl/dioxane gave the carboxylic acid **36**. Ethyl 5-hydroxy-2,4-dioxoimidazolidine-1-acetate (**38**), which was prepared from ethyl ureidoacetate (**37**) and **32**, was alkylated with 3-nitrobenzyl bromide (**22**) to give **39**. Hydrolysis of the ester group with AcOH and HCl gave the carboxylic acid **40**.

Conversion of the parabanic acid skeleton to the 6-membered cyclic systems was attempted (Schemes 9−11). Compound **3** was treated with **10** to give the urea **41**. Treatment of the urea **41** with malonyl chloride in CH_2Cl_2 gave the barbituric acid derivative **42**, which was saponified to give the acid **43** as shown in Scheme 9.

Syntheses of the uracil compounds **47a−d** and **51** were carried out as shown in Schemes 10 and 11. The second alkylation of **44**[29] was performed by treatment with **22** and 4-chloro-3-nitrobenzyl mesylate (**46**) in DMF to give the dialkylated uracils **45a,b**, respectively.

Scheme 8[a]



[a] (a) **32**, 80% AcOH, 80 °C; (b) **22**, $KHCO_3$, acetone; (c) HCl, AcOH, reflux.

The (benzothiazol-2-yl)methyl moiety was introduced into the uracil **44** by condensation with the appropriate 2-(chloromethyl)benzothiazole **25a,b** in the presence of NaH or K_2CO_3 as shown in Scheme 10. Hydrolysis of the esters **45a**−**d** gave the desired carboxylic acids **47a**−**d**.

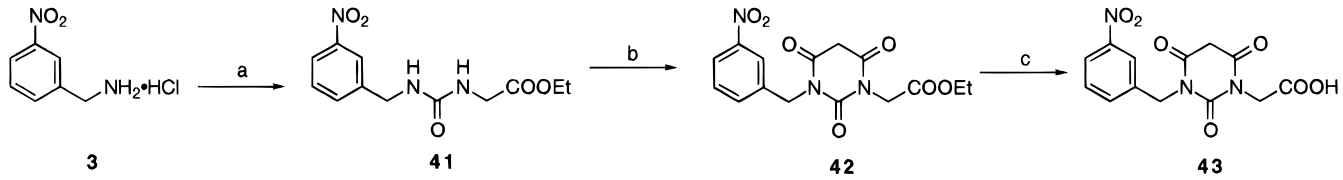
For the preparation of the other uracil-type compound **51**, uracil (**48**) was first alkylated with **22** *via* the TMS enol ether. Thus, **48** was silylated with TMSCl and hexamethyldisilazane (HMDS) at refluxing temperature and alkylated with **22** in the presence of $^nBu_4NI$ to give **49** as shown in Scheme 11. The uracil obtained was alkylated again with ethyl bromoacetate and hydrolyzed to give the carboxylic acid **51**.

Results and Discussion

Inhibitory activities of the target compounds **9**, **14**, **19**, **26a**−**d**, **30**, **36**, **40**, **43**, **47a**−**d**, and **51** against rat lens AR[30] and rat kidney ALR[31] were evaluated in a spectrometric assay with DL-glyceraldehyde as the substrate and NADPH as the cofactor. *In vitro* AR inhibitory activities are expressed as the percentage of inhibitions of the test compounds at 5.0×10^{-7}, 1.0×10^{-7}, 5.0×10^{-8}, 2.0×10^{-8}, 1.0×10^{-8}, and 5.0×10^{-9} M concentrations. ALR inhibitory activity was also measured for the compounds which showed strong AR inhibitory activity.

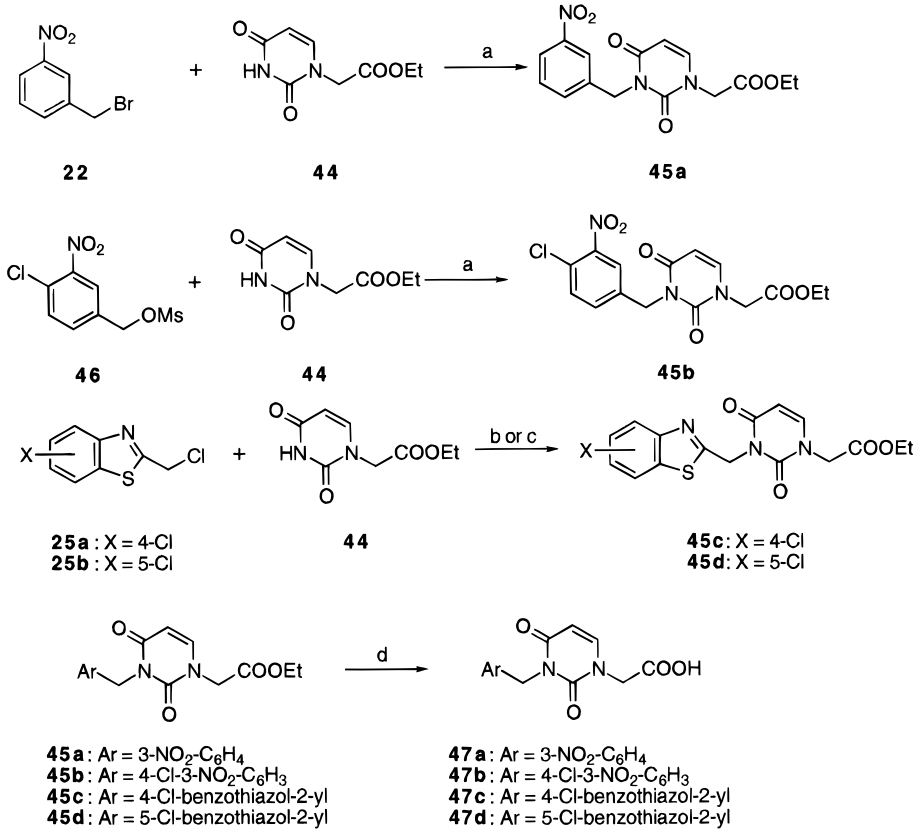
The parabanic acid **1a**, 4,5-dioxo-2-thioxoimidazolidine **14**, 4-methylidene-2,5-dioxoimidazolidine **30**, and uracil **47a** compounds showed strong AR inhibitory activities with IC_{50} values of less than 1×10^{-7} M (Tables 1 and 2). Among them, **1a** and **47a** showed extremely weak inhibition for ALR. In addition, though

Scheme 9[a]



[a] (a) **10**, NaOH, EtOH, H_2O, 0 °C; (b) malonyl chloride, CH_2Cl_2, ambient temperature; (c) concentrated HCl, AcOH, reflux.

Scheme 10[a]



[a] (a) NaH, DMF, −10 °C−rt; (b) K_2CO_3, NaBr, DMF; (c) NaBr, DMF, then NaH, DMF, −10 °C−rt; (d) HCl, AcOH, reflux.

Table 1. Biological Data for 3-Nitrobenzyl-Substituted ARIs

compd	IC_{50} (M) AR[a,b]	IC_{50} (M) ALR[c,d]	IC_{50}(ALR)/ IC_{50}(AR)
1a	6.2×10^{-8}	$>1 \times 10^{-4}$ (37.3%)	>1613
9	(17.7%)	$>1 \times 10^{-4}$ (12.4%)	
14	2.5×10^{-8}	2.8×10^{-5}	1120
19	(4.6%)	$>1 \times 10^{-4}$ (0.0%)	
26a	(38.2%)	$>1 \times 10^{-4}$ (3.8%)	
30	3.2×10^{-8}	5.8×10^{-5}	1813
36	(5.0%)	$>1 \times 10^{-4}$ (19.0%)	
40	(44.0%)	$>1 \times 10^{-4}$ (11.0%)	
epalrestat	2.1×10^{-8}	1.5×10^{-6}	71

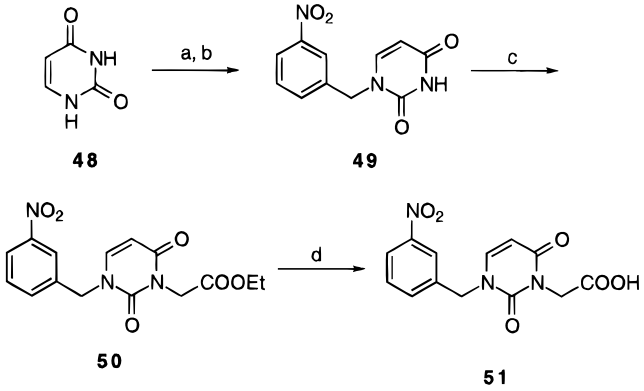
[a] IC_{50} value for rat lens AR. [b] Parentheses indicated percent inhibition of AR at 1×10^{-7} M. [c] IC_{50} value for rat kidney ALR. [d] Parentheses indicate percent inhibition of ALR at 1×10^{-4} M.

Table 2. Biological Data for ARIs with 6-Membered Heterocyclic Core Units

compd	IC_{50} (M) AR[a,b]	IC_{50} (M) ALR[c,d]	IC_{50}(ALR)/ IC_{50}(AR)
43	(1.5%)	$>1 \times 10^{-4}$ (33.5%)	
47a	3.4×10^{-8}	$>1 \times 10^{-4}$ (17.4%)	>2941
51	(27.8%)	$>1 \times 10^{-4}$ (11.8%)	

[a] IC_{50} value for rat lens AR. [b] Parentheses indicate percent inhibition of AR at 1×10^{-7} M. [c] IC_{50} value for rat kidney ALR. [d] Parentheses indicate percent inhibition of ALR at 1×10^{-4} M.

Scheme 11[a]



[a] (a) TMSCl, HMDS, reflux; (b) **22**, $^nBu_4NI$, CH_2Cl_2, rt; (c) NaH, DMF, below 0 °C, then $BrCH_2COOEt$, 0 °C; (d) AcOH, concentrated HCl, reflux.

the 2,4-dioxoimidazolidine **26a** showed moderate AR inhibitory activity, it inhibited ALR only 3.8% at 1×10^{-4} M concentration.

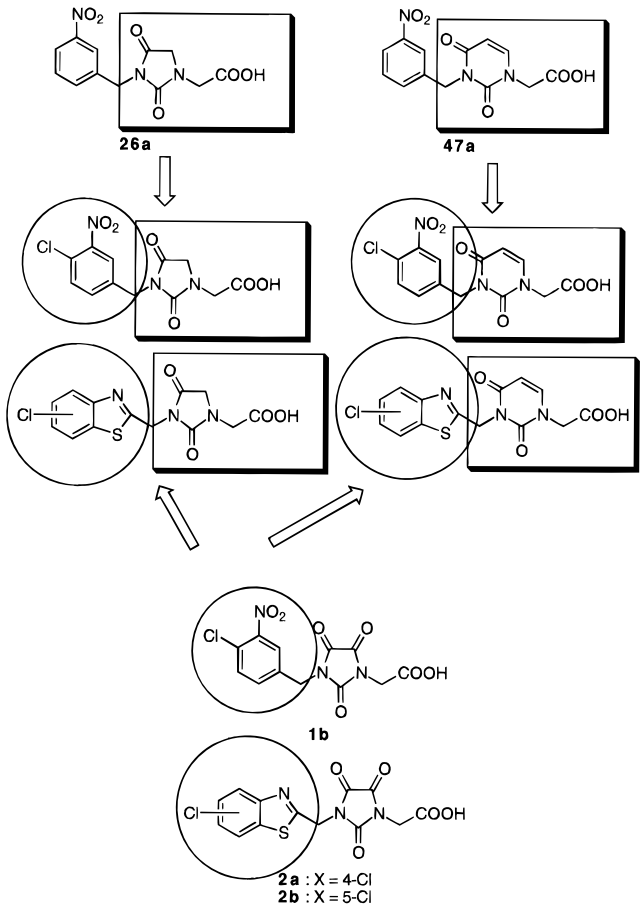
It was anticipated that the introduction of arylmethyl moieties of ARIs, which showed high AR inhibitory activity in the 2,4,5-trioxoimidazolidine-1-acetic acid derivatives, into the 2,4-dioxoimidazolidine-1-acetic acid or the 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acid core unit would produce high AR inhibitory activity without ALR inhibition. In other words, modification of the aryl portion would enhance inhibitory activity against AR without influencing ALR activity. Therefore, the substituted benzothiazolyl or 4-chloro-3-nitrophenyl group was adopted as an aromatic substitution as shown in Chart 3. As expected, introduction of the benzothiazolyl or 4-chloro-3-nitrophenyl group into the 2,4-dioxoimidazolidine-1-acetic acid or the 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acid core unit resulted in high AR inhibitory activity. Results as shown in Table 3. Unfortunately, the 2,4-dioxoimidazolidine-1-acetic acid derivatives **26b**−**d** showed lower enzyme selectivity, though the 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acid derivatives **47b**−**d** had a tendency to show higher enzyme selectivity. From the results of AR and ALR inhibitory activities of **47c,d**, it could be deduced that introduction of the benzothiazolyl group as an aryl moiety onto the 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acid core unit seemed to be the best combination for selective AR inhibition. The IC_{50}(ALR)/IC_{50}(AR) value of 5-chlorobenzothiazole derivative **47d** was more than 17 500. The compound **47d** inhibits AR almost completely without notable inhibition of ALR.

Table 3. AR and ALR Inhibitory Activities of **1**, **2**, **26a**−**d**, and **47a**−**d**

compd	IC_{50} (M) AR[a,b]	IC_{50} (M) ALR[c,d]	IC_{50}(ALR)/ IC_{50}(AR)
1a	6.2×10^{-8}	$>1 \times 10^{-4}$ (37.3%)	>1613
1b	1.6×10^{-8}	$>1 \times 10^{-4}$ (39.5%)	>6250
2a	1.2×10^{-8}	7.2×10^{-5}	6000
2b	1.5×10^{-8}	5.8×10^{-5}	3867
26a	(38.2%)	$>1 \times 10^{-4}$ (3.8%)	
26b	2.4×10^{-8}	$>1 \times 10^{-4}$ (1.6%)	>4167
26c	6.2×10^{-8}	$>1 \times 10^{-4}$ (37.0%)	>1613
26d	(47.5%)		
47a	3.4×10^{-8}	$>1 \times 10^{-4}$ (17.4%)	>2941
47b	2.5×10^{-8}	$>1 \times 10^{-4}$ (26.5%)	>4000
47c	1.1×10^{-8}	$>1 \times 10^{-4}$ (39.3%)	>9091
47d	5.7×10^{-9}	$>1 \times 10^{-4}$ (32.0%)	>17544

[a] IC_{50} value for rat lens AR. [b] Parentheses indicate percent inhibition of AR at 1×10^{-7} M. [c] IC_{50} value for rat kidney ALR. [d] Parentheses indicate percent inhibition of ALR at 1×10^{-4} M.

Chart 3



Free-Wilson-type neural network analysis of the 5-membered ring compounds **1a**, **9**, **19**, **26a**, **36** and **40** indicated that the carbonyl groups at C_2 and C_5 were important functional groups for AR inhibitory activity. Recently, X-ray crystallography studies of the human

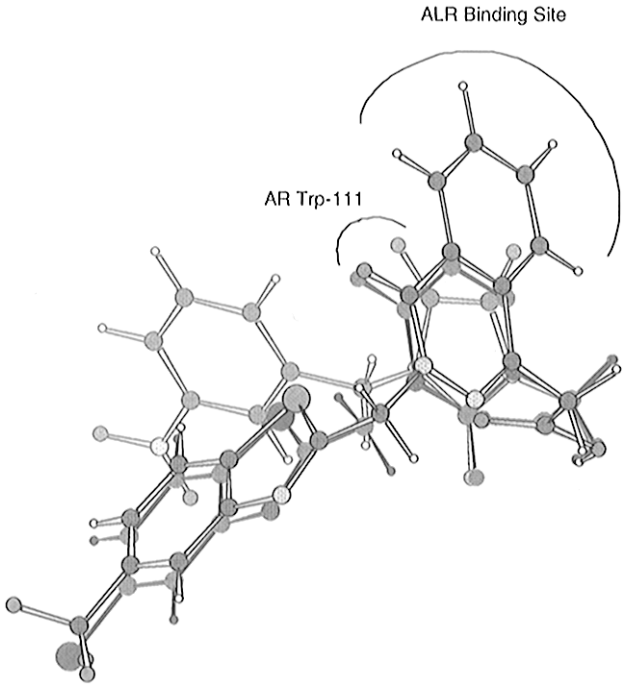


Figure 1. Superimposition of zopolrestat (blue), **1a** (green), and **47d** (red).

AR complex with zopolrestat reported that ^{20}Trp, ^{111}Trp, ^{122}Phe, and ^{300}Leu played important roles in stabilizing the ternary complex.[32] ^{111}Trp and ^{298}Cys were reported to interact with carbonyl and/or imide groups in the core portion. Hence, our interests were focused on conformational differences among our ARIs and other ARIs. **1a** and **47d** were constructed by CAChe (ver. 3.8, CAChe Scientific) using zopolrestat as a template and minimized by molecular mechanics implemented in CAChe. Superimposition of zopolrestat with **1a** and **47d** is diagrammed in Figure 1. The carbonyl oxygens at C_2 of **1a** and **47d** are located so as to interact with ^{298}Cys in the same manner as zopolrestat. The carbonyl oxygen of zopolrestat, the C_4 carbonyl oxygen of **1a**, and the C_5 carbonyl oxygen of **47d** seem to occupy the spatial positions to allow interaction with ^{111}Trp of AR. Petrash *et al*. reported that ^{298}Cys could potentially function as the proton donor.[32] The most significant difference between zopolrestat and **1a** or **47d** seems to be the presence or absence of the benzo group in the core unit. Although accurate molecular modeling has not yet been studied, some of the other ARIs without AR specificity would occupy the same region of the benzo group of zopolrestat. This region may be an important binding site for ALR, and therefore, weak ALR inhibition of **1a** can logically be expected as shown in Figure 1.

Conclusion

A number of modifications of the 2,4,5-trioxoimidazolidine framework to the uracil or hydantoin core unit were investigated. It was found that the conversion of the 2,4,5-trioxoimidazolidine framework to the uracil or 2,4-dioxoimidazolidine core unit was effective for high AR inhibition without ALR inhibition. The steric hindrance of the core unit plays an important role for AR selective inhibitory activity. The results of the AR and ALR inhibitory activities of various combinations of the aryl moiety with the core unit suggested that both the aryl moiety and the core unit were necessary for the AR inhibition and selectivity. The combination of the 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acid core unit and a suitable aryl moiety such as the substituted benzothiazolyl groups showed very high AR inhibitory activity without ALR inhibition. This is especially true for 3-[(5-chlorobenzothiazol-2-yl)methyl]-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acid (**47d**), which showed the IC_{50} value of 5×10^{-9} M with the IC_{50}(ALR)/IC_{50}(AR) value of 17 500. To apply ARI for the treatment of diabetes complications clinically, long-term administration would be required, and therefore, enzyme selectivity is one of the most important indices. Our compounds are ideal as an AR inhibitor at this point because they showed selective inhibition for AR.

Experimental Section

General information is given in the second series of this paper.[23]

Preparation of 3-(3-Nitrobenzyl)-2-methylidene-4,5-dioxoimidazolidine-1-acetic Acid (9). Ethyl *N*-(3-Nitrobenzyl)oxamate (4). A solution of ethyl oxalyl chloride (4.5 mL, 40.3 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a suspension of **3** (7.00 g, 37.0 mmol) and Et_3N (12.0 mL, 86.1 mmol) in CH_2Cl_2 (90 mL) at 0 °C. The mixture was vigorously stirred at the same temperature for 4 h, poured into H_2O, and extracted several times with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. After the residue was passed through a short silica gel column, the eluent was condensed and recrystallized from EtOH to give the oxamate **4** (6.90 g, 74%): mp 82−82.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (t, J = 7.1 Hz, 3H, CH_3), 4.26 (q, J = 7.1 Hz, 2H, OCH_2), 4.47 (d, J = 6.2 Hz, 1H, NCH_2), 7.64 (dd, J = 8.1, 7.6 Hz, 1H, Ar-*H*), 7.76 (d, J = 7.6 Hz, 1H, Ar-*H*), 8.13 (d, J = 8.1 Hz, 1H, Ar-*H*), 8.17 (s, 1H, Ar-*H*), 9.61 (t, J = 6.2 Hz, 1H, CONH); IR (KBr, cm^{-1}) 3284 (NH), 1745 (C=O), 1687 (C=O), 1535 (NO_2), 1350 (NO_2).

***N*-(3-Nitrobenzyl)oxamic Acid (5).** A mixture of the oxamate **4** (8.85 g, 35.1 mmol) and 1 N NaOH (175 mL, 175 mmol) in CH_2Cl_2 (270 mL) was vigorously shaken in a separatory funnel for 15 min. The aqueous layer was filtered off to remove the insoluble material. Acidification of the filtrate gave the white solid, which was filtered and dried under reduced pressure to afford the oxamic acid **5** (6.96 g, 88%): mp 167−168 °C; ^{1}H NMR (DMSO-d_6) δ 4.45 (d, J = 6.2 Hz, 1H, NCH_2), 7.64 (dd, J = 8.2, 7.7 Hz, 1H, Ar-*H*), 7.74 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.13 (d, J = 8.2 Hz, 1H, Ar-*H*), 8.16 (s, 1H, Ar-*H*), 9.16 (t, J = 6.2 Hz, 1H, CONH), 13.50 (br s, 1H, COOH); IR (KBr, cm^{-1}) 3539 (NH), 3373 (OH), 1718 (C=O), 1684 (C=O), 1541, 1520 (NO_2), 1354 (NO_2).

Glycine 2-(Trimethylsilyl)ethyl Ester (6). WSC·HCl (12.91 g, 67.4 mmol) was added to a mixture of Z-Gly-OH (10.07 g, 48.1 mmol), 2-(trimethylsilyl)ethanol (5.80 mL, 47.4 mmol), and DMAP (0.37 g, 0.3 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The mixture was stirred at ambient temperature for 19 h, poured into H_2O, and extracted several times with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was subjected to the next reaction step without further purification.

A mixture of the ester obtained above and 10% Pd/C (0.97 g) in EtOAc (100 mL) was stirred at room temperature under H_2 atmosphere for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residual oil was chromatographed on silica gel (hexane−EtOAc = 1/1) to afford **6** (8.18 g, 97%): mp 175−180 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9H, Si-CH_3), 0.90−1.05 (m, 2H, CH_2-Si), 3.38 (s, 2H, NCH_2-CO_2), 4.15−4.25 (m, 2H, OCH_2); IR (KBr, cm^{-1}) 3290 (NH), 1741 (C=O), 1647 (C=O).

***N*-[[[2-(Trimethylsilyl)ethoxy]carbonyl]methyl]-*N*′-(3-nitrobenzyl)oxamide (7).** A mixture of the oxamic acid **5** (6.96 g, 31.0 mmol), **6** (6.8 g, 39.1 mmol), and DMAP (0.10 g, 0.1 mmol) in CH_2Cl_2 (150 mL) was treated with WSC·HCl (8.62 g, 45.0 mmol) at 0 °C. The mixture was stirred at ambient temperature for 20 h, poured into H_2O, and extracted several

times with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (hexane−EtOAc = 1/1) followed by recrystallization from hexane−EtOAc (50−30 mL) gave the oxamide **7** (4.41 g, 37%): mp 99−100.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.13 (s, 9H, Si-CH_3), 0.80−1.00 (m, 2H, CH_2-Si), 3.84−3.90 (m, 2H, NCH_2CO_2), 4.10−4.20 (m, 2H, OCH_2), 4.56 (d, J = 6.3 Hz, 2H, CH_2Ar), 7.63 (dd, J = 8.1, 7.6 Hz, 1H, Ar-*H*), 7.74 (d, J = 7.6 Hz, 1H, Ar-*H*), 8.13 (d, J = 8.1 Hz, 1H, Ar-*H*), 8.16 (s, 1H, Ar-*H*), 9.08 (t, J = 4.4 Hz, 1H, CONH), 9.56 (t, J = 6.3 Hz, 1H, CONH); IR (KBr, cm^{-1}) 3294 (NH), 1751 (C=O), 1655 (C=O), 1535 (NO_2), 1348 (NO_2).

2-(Trimethylsilyl)ethyl 2-Methylidene-3-(3-nitrobenzyl)-4,5-dioxoimidazolidine-1-acetate (8). A mixture of the oxamide **7** (4.90 g, 12.8 mmol) and AcONa (3.35 g, 40.8 mmol) in Ac_2O (50 mL) was refluxed for 2 days. During the reaction, the color of the mixture changed from colorless to dark brown. The reaction mixture was neutralized with saturated $NaHCO_3$ and extracted three times with EtOAc. The combined extracts were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residual solid was chromatographed on silica gel (hexane−EtOAc = 10/1) and recrystallized from hexane−EtOAc to give **8** (2.19 g, 42%): mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 9H, Si-CH_3), 0.95−1.05 (m, 2H, CH_2-Si), 4.10 (d, J = 5.2 Hz, 1H, CH_2=), 4.17 (d, J = 5.2 Hz, 1H, CH_2=), 4.20−4.30 (m, 2H, OCH_2), 4.43 (s, 2H, NCH_2CO_2), 5.02 (s, 2H, CH_2Ar), 7.57 (dd, J = 8.2, 7.7 Hz, 1H, Ar-*H*), 7.63 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.13 (s, 1H, Ar-*H*), 8.19 (d, J = 8.2 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1753 (C=O), 1741 (C=O), 1728 (C=O), 1527 (NO_2), 1356 (NO_2).

2-Methylidene-3-(3-nitrobenzyl)-4,5-dioxoimidazolidine-1-acetic Acid (9). To a solution of **8** (0.76 g, 1.87 mmol) in THF (20 mL) and hexane (10 mL) was added a solution of ^{n}Bu$_4$NF (1 M solution, 2.0 mL, 2.0 mmol) in THF at room temperature. The mixture was vigorously stirred for 2.5 h. The reaction mixture was acidified with 2 N HCl and extracted three times with EtOAc. The extracts were dried over Na_2SO_4 and concentrated. Recrystallization from EtOH gave the carboxylic acid **9** (0.20 g, 33%): mp 160−160.5 °C; ^{1}H NMR (DMSO-d_6) δ 4.10 (s, 2H, NCH_2CO_2), 4.47 (s, 1H, CH_2=), 4.52 (s, 1H, CH_2=), 4.70 (d, J = 16.2 Hz, 1H, CH_2Ar), 4.80 (d, J = 16.2 Hz, 1H, CH_2Ar), 7.65 (dd, J = 8.4, 8.2 Hz, 1H, Ar-*H*), 7.83 (d, J = 8.2 Hz, 1H, Ar), 8.16 (d, J = 8.4 Hz, 1H, Ar-*H*), 8.24 (s, 1H, Ar-*H*), 12.96 (br s, 1H, COOH); IR (KBr, cm^{-1}) 3020 (OH), 1740 (C=O), 1684 (C=O), 1533 (NO_2), 1348 (NO_2); MS m/z 305 (M^+). Anal. ($C_{13}H_{11}N_3O_6 \cdot 0.9H_2O$) C, H, N.

Preparation of 3-(3-Nitrobenzyl)-4,5-dioxo-2-thioxoimidazolidine-1-acetic Acid (14). *N*-[(Ethoxycarbonyl)methyl]-*N*′-(3-nitrobenzyl)urea (11). Ethyl isocyanatoacetate (**10**; 6.0 mL, 53.5 mmol) was added dropwise to a solution of 3-nitrobenzylamine hydrochloride (**3**; 10.0 g, 53.0 mmol) and NaOH (2.10 g, 52.5 mmol) in H_2O (50 mL) and EtOH (100 mL) with vigorous stirring at 0 °C. After being stirred for 1.5 h, the precipitate was filtered and washed well with H_2O to give a solid, which was recrystallized from EtOH (200 mL) to give the urea **11** (10.70 g, 76%) as white crystals: mp 141.5−142 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, J = 7.0 Hz, 3H, CH_3), 3.78 (d, J = 6.0 Hz, 2H, NCH_2CO_2), 4.08 (q, J = 7.0 Hz, 2H, OCH_2), 4.34 (d, J = 6.1 Hz, 2H, CH_2Ar), 6.45 (t, J = 6.0 Hz, 1H, CONH), 6.87 (t, J = 6.1 Hz, 1H, CONH), 7.61 (dd, J = 7.7, 7.7 Hz, 1H, Ar-*H*), 7.71 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.09 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.10 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3334 (NH), 1722 (C=O), 1597 (NO_2), 1346 (NO_2).

***N*-[(Ethoxycarbonyl)methyl]-*N*′-(3-nitrobenzyl)thiourea (12).** The urea **11** (3.00 g, 11.2 mmol) was treated with Lawesson's reagent (5.00 g, 12.4 mmol) in 1,4-dioxane (30 mL) at refluxing temperature for 1.5 h. During the reaction, the color of the solution changed from colorless to brown. The mixture was poured into H_2O and extracted several times with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexane−EtOAc = 1/1) to afford the thiourea **12** (2.50 g, 79%): ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H, CH_3), 4.20 (q, J = 7.0 Hz, 2H, OCH_2), 4.41 (d, J = 4.9 Hz, 2H, NCH_2CO_2), 4.90 (s, 2H, CH_2Ar), 7.18 (br s, 1H, CONH), 7.52 (dd, J = 7.9, 7.9 Hz, 1H, Ar-*H*), 7.71 (d, J = 7.9 Hz, 1H, Ar-*H*), 8.08 (d, J = 7.9 Hz, 1H, Ar-*H*), 8.16 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3349 (NH), 1739 (C=O), 1533 (NO_2), 1345 (NO_2).

Ethyl 3-(3-Nitrobenzyl)-4,5-dioxo-2-thioxoimidazolidine-1-acetate (13). To a solution of the thiourea **12** (2.50 g, 8.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of oxalyl chloride (1.0 mL, 11.5 mmol) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred for 8 h and concentrated *in vacuo*. The crude product was passed through a short silica gel pad to afford the 2-thioparabanic acid derivative **13**, which was used in the next reaction step without further purification: ^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 7.0 Hz, 3H, CH_3), 4.16 (q, J = 7.0 Hz, 2H, OCH_2), 4.65 (s, 2H, NCH_2CO_2), 5.19 (s, 2H, CH_2Ar), 7.65 (dd, J = 8.0, 8.0 Hz, 1H, Ar-*H*), 7.83 (dd, J = 8.0, 2.4 Hz, 1H, Ar-*H*), 8.15 (dd, J = 8.0, 2.4 Hz, 1H, Ar-*H*), 8.26 (dd, J = 2.4, 2.4 Hz, 1H, Ar-*H*).

3-(3-Nitrobenzyl)-4,5-dioxo-2-thioxoimidazolidine-1-acetic Acid (14). The crude thioparabanic acid derivative **13** was treated with AcOH (4.5 mL) and concentrated HCl (1.5 mL) at refluxing temperature for 1 h. After concentration of the mixture, another portion of AcOH (4.5 mL) and concentrated HCl (1.5 mL) was added to the residue. The resulting mixture was refluxed for an additional 1 h. After concentration, the solid was recrystallized from EtOH−hexane to give the carboxylic acid **14** (0.23 g, 54% yield based on the thiourea **12**): mp 188−188.5 °C; ^{1}H NMR (DMSO-d_6) δ 4.56 (s, 2H, NCH_2CO_2), 5.20 (s, 2H, CH_2Ar), 7.65 (dd, J = 8.0, 7.7 Hz, 1H, Ar-*H*), 7.83 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.16 (d, J = 8.0 Hz, 1H, Ar-*H*), 8.26 (s, 1H, Ar-*H*), 13.38 (br s, 1H, COOH); IR (KBr, cm^{-1}) 3000 (OH), 1784 (C=O), 1722 (C=O), 1531 (NO_2), 1435 (C=S), 1346 (NO_2); MS m/z 323 (M^+). Anal. ($C_{12}H_9N_3O_6S$) C, H, N.

Preparation of 1-(3-Nitrobenzyl)-2,4-dioxoimidazolidine-3-acetic Acid (19). Ethyl [(3-Nitrobenzyl)amino]-acetate (17). A solution of **15** (12.60 g, 83.4 mmol) in MeOH (50 mL) was added to a suspension of **16** (16.20 g, 125 mmol) and $NaBH_3CN$ (8.50 g, 123 mmol) in MeOH (50 mL) at 0 °C. The mixture was stirred at ambient temperature for 24 h. Concentration of the reaction mixture gave a crude solid, which was chromatographed on a silica gel column (hexane−EtOAc = 1/1) to give the ethyl ester **17** (8.70 g, 44%): ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 3H, CH_3), 3.41 (s, 2H, NCH_2CO_2), 3.92 (s, 2H, CH_2Ar), 4.21 (q, J = 7.0 Hz, 2H, OCH_2), 7.50 (dd, J = 8.0, 8.0 Hz, 1H, Ar-*H*), 7.70 (d, J = 8.0 Hz, 1H, Ar-*H*), 8.12 (d, J = 8.0 Hz, 1H, Ar-*H*), 8.23 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3300 (NH), 1738 (C=O), 1527 (NO_2), 1350 (NO_2).

***N*,*N*′-Bis[(ethoxycarbonyl)methyl]-*N*-(3-nitrobenzyl)-urea (18).** To a solution of the ester **17** (5.20 g, 21.8 mmol) in ether (50 mL) was added a solution of **10** (2.6 mL, 23.2 mmol) in ether (50 mL) at room temperature. After being stirred for 15 h, the mixture was concentrated and the residue was directly chromatographed on a silica gel column (hexane−EtOAc = 1/1) to afford the urea **18** (7.93 g, 99%): ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 3H, CH_3), 1.27 (t, J = 7.0 Hz, 3H, CH_3), 3.99 (s, 2H, NCH_2CO_2), 4.04 (s, 2H, NCH_2CO_2), 4.19 (q, J = 7.0 Hz, 4H, OCH_2), 4.68 (s, 2H, CH_2Ar), 5.35 (t, J = 5.0 Hz, 1H, CONH), 7.55 (dd, J = 7.0, 7.0 Hz, 1H, Ar-*H*), 7.70 (d, J = 7.0 Hz, 1H, Ar-*H*), 8.14 (d, J = 7.0 Hz, 1H, Ar-*H*), 8.15 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3353 (NH), 1745 (C=O), 1741 (C=O), 1527 (NO_2), 1350 (NO_2).

1-(3-Nitrobenzyl)-2,4-dioxoimidazolidine-3-acetic Acid (19). A mixture of the urea **18** (6.58 g, 17.9 mmol) in AcOH (21 mL) and concentrated HCl (7 mL) was refluxed for 3 h with vigorous stirring. The mixture was concentrated, and AcOH (21 mL) and concentrated HCl (7 mL) were added. The resulting mixture was refluxed for an additional 2 h. Evaporation of the solvent yielded a crude solid, which was washed with H_2O and recrystallized from EtOH (30 mL) to give the carboxylic acid **19** (3.68 g, 70% yield) as white crystals: mp 168−170 °C; ^{1}H NMR (DMSO-d_6) δ 4.08 (s, 2H, NCH_2CO_2), 4.12 (s, 2H, NCH_2CON), 4.68 (s, 2H, CH_2Ar), 7.67 (dd, J = 8.6, 7.7 Hz, 1H, Ar-*H*), 7.76 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.16 (s, 1H, Ar-*H*), 8.17 (d, J = 8.6 Hz, 1H, Ar-*H*), 13.20 (br s, 1H, COOH); IR (KBr, cm^{-1}) 3100 (OH), 1774 (C=O), 1745 (C=O), 1714 (C=O), 1533 (NO_2), 1359 (NO_2); MS m/z 293 (M^+). Anal. ($C_{12}H_{11}N_3O_6$) C, H, N.

Preparation of 3-(Arylmethyl)-2,4-dioxoimidazolidine-1-acetic Acids (26). Ethyl 2,4-Dioxoimidazolidine-1-acetate (21). To a solution of **20** (50.0 mL, 285 mmol) and KNCO (46.72 g, 576 mmol) in H_2O (500 mL) was added dropwise concentrated HCl (48 mL, 576 mmol) over the period of 1 h with vigorous stirring at room temperature. After being refluxed for 2 h, the mixture was allowed to cool to room temperature and extracted three times with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated. The residual solid was recrystallized from EtOH (100 mL) to give the hydantoin **21** (32.49 g, 61%): mp 92−93.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (t, J = 7.0 Hz, 3H, CH_3), 3.97 (s, 2H, NCH_2CO_2), 4.08 (s, 2H, NCH_2CON), 4.13 (q, J = 7.0 Hz, 2H, OCH_2), 10.96 (br s, 1H, NH); IR (KBr, cm^{-1}) 3188 (NH), 1770 (C=O), 1713 (C=O).

Ethyl 3-(3-Nitrobenzyl)-2,4-dioxoimidazolidine-1-acetate (23a). A solution of the hydantoin **21** (0.82 mg, 4.38 mmol) in DMF (30 mL) was added dropwise to a suspension of NaH (60 wt % in oil, 221 mg, 5.51 mmol) in DMF (20 mL) over a period of 30 min maintaining the temperature below 0 °C. The mixture was stirred at the same temperature for an additional 1 h. A solution of the benzyl bromide **22** (1.30 g, 4.38 mmol) in DMF (30 mL) was added dropwise to the reaction mixture at 0 °C. After stirring for 2 h, the mixture was poured into ice-cooled 2 N HCl with vigorous stirring. The resulting mixture was extracted several times with EtOAc. The combined extracts were washed twice with brine, dried over Na_2SO_4, and concentrated to give a residue, which was chromatographed on a silica gel column (hexane−EtOAc = 3/1) to give the ester **23a** (1.32 g, 94%): ^{1}H NMR (DMSO-d_6) δ 1.19 (t, J = 7.0 Hz, 3H, CH_3), 4.12 (s, 2H, NCH_2CO_2), 4.14 (q, J = 7.0 Hz, 2H, OCH_2), 4.18 (s, 2H, NCH_2CON), 4.74 (s, 2H, CH_2-Ar), 7.66 (dd, J = 9.0, 7.8 Hz, 1H, Ar-*H*), 7.73 (d, J = 7.8 Hz, 1H, Ar-*H*), 8.14 (s, 1H, Ar-*H*), 8.16 (d, J = 9.0 Hz, 1H, Ar-*H*), 10.99 (br s, 1H, CONHCO); IR (neat, cm^{-1}) 1732 (C=O), 1703 (C=O), 1533 (NO_2), 1350 (NO_2).

3-(3-Nitrobenzyl)-2,4-dioxoimidazolidine-1-acetic Acid (26a). The ester **23a** (1.70 g, 5.29 mmol) was treated with AcOH (12 mL) and concentrated HCl (4 mL) at refluxing temperature for 1 h. After condensation, the mixture was treated again with AcOH (12 mL) and concentrated HCl (4 mL) under reflux for an additioal 1 h. The resulting mixture was poured into ice-cooled EtOAc−aqueous NaOH and extracted several times with cold 10% aqueous NaOH. The combined aqueous layer was acidified with concentrated HCl and extracted several times with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated. The residual solid was recrystallized from EtOH (200 mL) to give the carboxylic acid **26a** (0.35 g, 44%): mp 165−166 °C; ^{1}H NMR (DMSO-d_6) δ 4.08 (s, 2H, NCH_2CO_2), 4.10 (s, 2H, NCH_2-CON), 4.73 (s, 2H, CH_2Ar), 7.65 (dd, J = 7.9, 7.4 Hz, 1H, Ar-*H*), 7.74 (d, J = 7.9 Hz, 1H, Ar-*H*), 8.14 (s, 1H, Ar-*H*), 8.16 (d, J = 7.4 Hz, 1H, Ar-*H*), 13.09 (br s, 1H, COOH); IR (KBr, cm^{-1}) 2990 (OH), 1789 (C=O), 1732 (C=O), 1686 (C=O), 1525 (NO_2), 1351 (NO_2); MS *m*/*z* 277 (M^+ − OH). Anal. ($C_{12}H_{11}N_3O_6$) C, H, N.

Ethyl 3-(4-Chloro-3-nitrobenzyl)-2,4-dioxoimidazolidine-1-acetate (23b). A solution of DEAD (5.2 mL, 33.0 mmol) in THF (30 mL) was added to a solution of the alcohol **24** (5.13 g, 27.3 mmol), the ester **21** (4.70 g, 25.2 mmol), and PPh_3 (8.68 g, 33.1 mmol) in THF (30 mL) at 0 °C. The mixture was stirred at ambient temperature for 24 h. The reaction mixture was poured into H_2O and extracted several times with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexane−EtOAc = 3/1) and recrystallized twice from EtOH−H_2O to give the ethyl ester **23b** (7.01 g, 78%): mp 76−77 °C; ^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 7.1 Hz, 3H, CH_3), 4.11 (s, 2H, NCH_2CO_2), 4.14 (q, J = 7.1 Hz, 2H, OCH_2), 4.18 (s, 2H, NCH_2CON), 4.69 (s, 2H, CH_2Ar), 7.60 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.77 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.97 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1770 (C=O), 1732 (C=O), 1713 (C=O), 1527 (NO_2), 1333 (NO_2).

Ethyl 3-[(4-Chlorobenzothiazol-2-yl)methyl]-2,4-dioxoimidazolidine-1-acetate (23c). A solution of the hydantoin **21** (0.78 g, 4.19 mmol) in DMF (30 mL) was added dropwise to a suspension of NaH (60 wt % in oil, 0.25 g, 6.25 mmol) in DMF (10 mL) at −10−0 °C. After stirring at the same temperature for 2 h, a mixture prepared by the treatment of the benzothiazole **25a** (0.78 g, 4.19 mmol) with NaBr (0.79 g, 4.57 mmol) in DMF (40 mL) at room temperature for 30 min was added at 0 °C. The resulting mixture was stirred at ambient temperature for 16 h, poured into ice-cooled 2 N HCl, and extracted three times with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed on silica gel (hexane−EtOAc = 2/1) and recrystallized from EtOH (50 mL) to give the ester **23c** (1.23 g, 73%): mp 133−135 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (t, J = 7.0 Hz, 3H, CH_3), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 4.19 (s, 2H, NCH_2CO_2), 4.22 (s, 2H, NCH_2CON), 5.08 (s, 2H, CH_2Ar), 7.45 (dd, J = 8.2, 7.8 Hz, 1H, Ar-*H*), 7.63 (dd, J = 7.8, 0.8 Hz, 1H, Ar-*H*), 8.08 (dd, J = 8.2, 0.8 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1721 (C=O), 1717 (C=O).

Preparation of 5-Methylidene-1-(3-nitrobenzyl)-2,4-dioxoimidazolidine-3-acetic Acid (30). Methyl 3-Hydroxy-2-[(3-nitrobenzyl)amino]propionate (28). A solution of **15** (12.64 g, 8.36 mmol) in MeOH (50 mL) was added to a suspension of **27** (12.69 g, 8.17 mmol) in MeOH (50 mL) at 0 °C. After stirring for 30 min at 0 °C, a solution of $NaBH_3$-CN (0.78 g, 11.3 mmol) in MeOH (50 mL) was added. The resulting mixture was stirred at ambient temperature for 15 h, poured into saturated $NaHCO_3$, and extracted several times with EtOAc. The combined extracts were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed on a silica gel column (hexane−EtOAc = 1/1) to give **28** (3.46 g, 17%): ^{1}H NMR ($CDCl_3$) δ 2.51 (br s, 1H, OH), 3.44 (dd, J = 6.6, 4.6 Hz, 1H, OCH_2), 3.68 (dd, J = 10.9, 6.2 Hz, 1H, OCH_2), 3.78 (s, 3H, OCH_3), 3.75−7.80 (m, 1H, NCHCO), 3.82 (d, J = 13.6 Hz, 1H, CH_2Ar), 4.04 (d, J = 13.6 Hz, 1H, CH_2Ar), 7.51 (dd, J = 7.9, 7.6 Hz, 1H, Ar-*H*), 7.79 (d, J = 7.6 Hz, 1H, Ar-*H*), 8.14 (d, J = 7.9 Hz, 1H, Ar-*H*), 8.27 (s, 1H, Ar-*H*); IR (neat, cm^{-1}) 3334 (OH), 1738 (C=O), 1527 (NO_2), 1352 (NO_2).

***N′*-[(Ethoxycarbonyl)methyl]-*N*-[2-hydroxy-1-(methoxycarbonyl)ethyl]-*N*-(3-nitrobenzyl)urea (29).** Ethyl isocyanatoacetate (**10**; 1.9 mL, 16.9 mmol) was added to a solution of the ester **28** (3.46 g, 13.6 mmol) in ether (50 mL) at room temperature. Immediately after addition, a white solid precipitated. After stirring vigorously for 7 h, the precipitated solid was filtered and washed with ether. Recrystallization from hexane−EtOAc (60−20 mL) gave the urea **29** (4.15 g, 80%) as white crystals: mp 88.5−90.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.16 (t, J = 7.1 Hz, 3H, CH_3), 3.56 (s, 3H, OCH_3), 3.65−3.75 (m, 2H, NCH_2CO_2), 3.76 (d, J = 5.5 Hz, 2H, OCH_2), 4.05 (q, J = 7.1 Hz, 2H, OCH_2), 4.58 (t, J = 5.5 Hz, 1H, CH), 4.66 (d, J = 18.1 Hz, 1H, CH_2Ar), 4.76 (d, J = 18.1 Hz, 1H, CH_2-Ar), 4.97 (br s, 1H, OH), 7.00 (t, J = 5.5 Hz, 1H, CONH), 7.61 (dd, J = 8.0, 7.6 Hz, 1H, Ar-*H*), 7.83 (d, J = 7.6 Hz, 1H, Ar-*H*), 8.10 (d, J = 8.0 Hz, 1H, Ar-*H*), 8.27 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3388 (OH), 3332 (NH), 1745 (C=O), 1630 (C=O), 1527 (NO_2), 1352 (NO_2).

5-Methylidene-1-(3-nitrobenzyl)-2,4-dioxoimidazolidine-3-acetic Acid (30). To a solution of KOH (0.38 g, 6.54 mmol) in H_2O (70 mL) and EtOH (30 mL) was added a solution of the urea **29** (2.53 g, 6.13 mmol) at 0 °C. The mixture was stirred at ambient temperature for 24 h and washed three times with EtOAc. After acidification with concentrated HCl, the aqueous layer was extracted several times with EtOAc. The extracts were concentrated and purified by chromatography on a silica gel column ($CHCl_3$−MeOH = 3/1) to give the carboxylic acid **30** (0.10 g, 5%): mp 169−171 °C; ^{1}H NMR (DMSO-d_6) δ 4.24 (s, 2H, NCH_2CO_2), 5.01 (s, 2H, CH_2Ar), 5.15 (d, J = 2.6 Hz, 1H, CH_2=), 5.35 (d, J = 2.6 Hz, 1H, CH_2=), 7.66 (dd, J = 8.1, 7.7 Hz, 1H, Ar-*H*), 7.75 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.17 (d, J = 8.1 Hz, 1H, Ar-*H*), 8.20 (s, 1H, Ar-*H*), 13.32 (br s, 1H, COOH); IR (KBr, cm^{-1}) 3000 (OH), 1738 (C=O), 1718 (C=O), 1662 (C=O), 1527 (NO_2), 1354 (NO_2); MS *m*/*z* M^+ was not detected. Anal. ($C_{13}H_{11}N_3O_6$) C, H, N.

Preparation of 5-Hydroxy-1-(3-nitrobenzyl)-2,4-dioxoimidazolidine-3-acetic Acid (36). Benzyl 2-(Benzyloxy)-2-hydroxyacetate (32). A mixture of glyoxylic acid monohydrate (110 g, 1.20 mol), benzyl alcohol (500 mL, 4.80 mol),

and *p*-TsOH·H_2O (100 mg) in toluene was refluxed for 2 h on a Dean−Stark apparatus. After cooling, the mixture was washed twice with H_2O. The organic phase was dried over Na_2SO_4 and concentrated. The residual oil was distilled to give **32** (204.9 g, 63%): bp 95−100 °C/1 mmHg; ^{1}H NMR ($CDCl_3$) δ 3.73 (d, J = 11.4 Hz, 1H, OH), 4.68 (d, J = 11.9 Hz, 1H, CH_2), 4.82 (d, J = 11.9 Hz, 1H, CH_2), 5.04 (d, J = 11.4 Hz, 1H, CH), 5.23 (d, J = 5.1 Hz, 1H, CH_2), 5.25 (d, J = 5.1 Hz, 1H, CH_2), 7.25−7.37 (m, 10H, Ar-*H*).

5-Hydroxy-1-(3-nitrobenzyl)imidazolidine-2,4-dione (33). A solution of the urea **31** (78.0 g, 0.40 mol) and **32** (120.0 g, 0.44 mol) in 80% AcOH (500 mL) was stirred at 80 °C for 2 h. After removal of the solvent, the mixture was coevaporated with toluene. The residue was chromatographed on silica gel ($CHCl_3$−EtOAc = 1/1) followed by recrystallization from hexane−EtOAc (1/1) to give the hydantoin derivative **33** (48.9 g, 62%): mp 155−158 °C; ^{1}H NMR (DMSO-d_6) δ 4.50 (d, J = 16.2 Hz, 1H, CH_2Ar), 4.59 (d, J = 16.2 Hz, 1H, CH_2Ar), 5.07 (d, J = 8.1 Hz, 1H, CH), 7.03 (d, J = 8.1 Hz, 1H, OH), 7.63 (dd, J = 8.3, 7.9 Hz, 1H, Ar-*H*), 7.78 (d, J = 7.9 Hz, 1H, Ar-*H*), 8.12 (dd, J = 8.3, 2.2 Hz, 1H, Ar-*H*), 8.17 (d, J = 2.2 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3373 (OH), 1757 (C=O), 1718 (C=O), 1540 (NO_2), 1346 (NO_2).

***tert*-Butyl 5-Hydroxy-1-(3-nitrobenzyl)-2,4-dioxoimidazolidine-3-acetate (35).** A mixture of the hydantoin **33** (12.5 g, 50 mmol), **34** (9.0 mL, 60 mmol), and $KHCO_3$ (10.0 g, 100 mmol) was refluxed for 8 h. After removal of the insoluble material, the filtrate and washings were concentrated. The residue was dissolved in EtOAc, washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residual gum was chromatographed on silica gel (EtOAc) and recrystallized from hexane−EtOAc to give **35** (12.4 g, 68%): mp 117−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H, CH_3), 4.09 (d, J = 17.5 Hz, 1H, CH_2CO_2), 4.12 (d, J = 17.5 Hz, 1H, CH_2CO_2), 4.58 (d, J = 16.2 Hz, 1H, CH_2Ar), 4.68 (d, J = 16.2 Hz, 1H, CH_2Ar), 5.29 (d, J = 6.4 Hz, 1H, CH), 7.36 (d, J = 6.4 Hz, 1H, OH), 7.65 (dd, J = 8.2, 7.8 Hz, 1H, Ar-*H*), 7.79 (d, J = 7.8 Hz, 1H, Ar-*H*), 8.14 (dd, J = 8.2, 1.7 Hz, 1H, Ar-*H*), 8.20 (d, J = 1.7 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3430 (OH), 1732 (C=O), 1705 (C=O), 1531 (NO_2), 1350 (NO_2).

5-Hydroxy-1-(3-nitrobenzyl)-2,4-dioxoimidazolidine-3-acetic Acid (36). A solution of **35** (3.60 g, 10.0 mmol) in 4 N HCl/dioxane (50 mL) was stirred at room temperature for 1 day and concentrated. The residue was crystallized by addition of $CHCl_3$ and rinsed with $CHCl_3$ to give **36** (0.80 g, 26%) as a solid: mp 123−125 °C; ^{1}H NMR (DMSO-d_6) δ 4.09 (d, J = 17.6 Hz, 1H, CH_2CO_2), 4.13 (d, J = 17.6 Hz, 1H, CH_2CO_2), 4.58 (d, J = 16.2 Hz, 1H, CH_2Ar), 4.68 (d, J = 16.2 Hz, 1H, CH_2Ar), 5.20 (s, 1H, CH), 7.36 (br s, 1H, OH), 7.65 (dd, J = 8.1, 7.8 Hz, 1H, Ar-*H*), 7.79 (d, J = 7.8 Hz, 1H, Ar-*H*), 8.14 (d, J = 8.1 Hz, 1H, Ar-*H*), 8.20 (s, 1H, Ar-*H*), 13.13 (br s, 1H, COOH); IR (KBr, cm^{-1}) 1782 (C=O), 1718 (C=O), 1529 (NO_2), 1352 (NO_2); MS *m*/*z* 310 ([M + H]$^+$). Anal. ($C_{12}H_{11}N_3O_7$) C, H, N.

Preparation of 5-Hydroxy-3-(3-nitrobenzyl)-2,4-dioxoimidazolidine-1-acetic Acid (40). Ethyl 5-Hydroxy-2,4-dioxoimidazolidine-1-acetate (38). A solution of **37** (58.5 g, 0.40 mol) and **32** (130.0 g, 0.48 mol) in 80% AcOH (500 mL) was stirred at 80 °C for 2 h. The mixture was concentrated and coevaporated with toluene. The residue was chromatographed on silica gel (EtOAc−CH_2Cl_2) followed by recrystallization from hexane−EtOAc (1/1) to give the hydantoin derivative **38** (37.6 g, 47%): mp 107−108 °C; ^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 7.0 Hz, 3H, CH_3), 3.88 (d, J = 18.0 Hz, 1H, CH_2CO_2), 4.13 (dq, J = 7.0, 1.0 Hz, 2H, OCH_2), 4.14 (d, J = 18.0 Hz, 1H, CH_2CO_2), 5.07 (d, J = 8.4 Hz, 1H, CH), 7.01 (d, J = 8.4 Hz, 1H, OH), 11.04 (s, 1H, NH); IR (KBr, cm^{-1}) 3460 (NH), 3260, 1786 (C=O), 1720 (C=O).

Ethyl 5-Hydroxy-3-(3-nitrobenzyl)-2,4-dioxoimidazolidine-1-acetate (39). A mixture of **38** (20.0 g, 0.10 mol), **22** (26.0 g, 0.12 mol), and $KHCO_3$ (20.0 g, 0.20 mol) in acetone (250 mL) was refluxed for 10 h. After removal of the solvent, the mixture was dissolved in EtOAc and washed with H_2O and brine. The organic phase was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (EtOAc) and crystallized by addition of Et_2O to give the hydantoin derivative **39** (17.2 g, 62%): mp 101−102 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H, CH_3), 4.14 (d, J = 18.0 Hz, 1H, CH_2CO_2), 4.22 (q, J = 7.2 Hz, 2H, OCH_2), 4.27 (d, J = 18.0 Hz, 1H, CH_2CO_2), 4.30 (d, J = 8.0 Hz, 1H, OH), 4.74 (d, J = 15.0 Hz, 1H, CH_2Ar), 4.77 (d, J = 15.0 Hz, 1H, CH_2Ar), 5.35 (d, J = 8.0 Hz, 1H, CH), 7.51 (dd, J = 8.2, 7.9 Hz, 1H, Ar-*H*), 7.70 (d, J = 7.9 Hz, 1H, Ar-*H*), 8.16 (d, J = 8.2 Hz, 1H, Ar-*H*), 8.19 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3413 (OH), 1713 (C=O), 1525 (NO_2), 1352 (NO_2).

5-Hydroxy-3-(3-nitrobenzyl)-2,4-dioxoimidazolidine-1-acetic Acid (40). A mixture of the ester **39** (15.0 g, 45 mmol) in AcOH (45 mL) and concentrated HCl (15 mL) was refluxed for 2 h. The mixture was concentrated, and the residue was allowed to stand at room temperature to give a solid. The solid was filtered, washed well with Et_2O, and recrystallized from EtOH−H_2O (1/1) to give the carboxylic acid **40** (8.10 g, 59%): mp 153−155 °C; ^{1}H NMR (DMSO-d_6) δ 3.90 (d, J = 18.0 Hz, 1H, CH_2CO_2), 4.16 (d, J = 18.0 Hz, 1H, CH_2CO_2), 4.73 (d, J = 15.6 Hz, 1H, CH_2Ar), 4.78 (d, J = 15.6 Hz, 1H, CH_2Ar), 5.24 (s, 1H, CH), 7.20 (br s, 1H, OH), 7.66 (dd, J = 8.0, 7.6 Hz, 1H, Ar-*H*), 7.76 (d, J = 7.6 Hz, 1H, Ar-*H*), 8.14−8.17 (m, 2H, Ar-*H*), 13.00 (br s, 1H, COOH); IR (KBr, cm^{-1}) 3533 (OH), 1776 (C=O), 1713 (C=O), 1527 (NO_2), 1350 (NO_2); MS *m*/*z* 310 ([M + H]$^+$). Anal. ($C_{12}H_{11}N_3O_7$) C, H, N.

Preparation of 3-(3-Nitrobenzyl)-2,4,6-trioxohexahydropyrimidine-1-acetic Acid (43). *N*-[(Ethoxycarbonyl)methyl]-*N*′-(3-nitrobenzyl)urea (41). Ethyl isocyanatoacetate (**10**; 6.0 mL, 53.5 mmol) was added dropwise to a solution of **3** (10.0 g, 53.0 mmol) and NaOH (2.10 g, 52.5 mmol) in H_2O (50 mL) and EtOH (100 mL) with vigorous stirring at 0 °C. After stirring for 1.5 h, the precipitate was filtered, washed well with H_2O, and recrystallized from EtOH (200 mL) to give the urea **41** (10.70 g, 76%) as white crystals: mp 141.5−142 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, J = 7.0 Hz, 3H, CH_3), 3.78 (d, J = 6.0 Hz, 2H, NCH_2CO_2), 4.08 (q, J = 7.0 Hz, 2H, OCH_2), 4.34 (d, J = 6.1 Hz, 2H, CH_2Ar), 6.45 (t, J = 6.0 Hz, 1H, CONH), 6.87 (t, J = 6.1 Hz, 1H, CONH), 7.61 (dd, J = 7.7, 7.7 Hz, 1H, Ar-*H*), 7.71 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.09 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.10 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3334 (NH), 1722 (C=O), 1597 (NO_2), 1346 (NO_2).

Ethyl 3-(3-Nitrobenzyl)-2,4,6-trioxohexahydropyrimidine-1-acetate (42). A solution of malonyl chloride (3.2 mL, 32.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a suspension of the urea **41** (8.60 g, 32.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred at the same temperature for 4.5 h, neutralized with saturated $NaHCO_3$, and extracted three times with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane−EtOAc = 1/1) to give the barbituric acid derivative **42** (6.70 g, 60%): mp 115−116.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, J = 7.1 Hz, 3H, CH_3), 4.00 (br s, 2H, $COCH_2CO$), 4.12 (q, J = 7.1 Hz, 2H, OCH_2), 4.50 (s, 2H, NCH_2CO_2), 5.06 (s, 2H, CH_2Ar), 7.63 (dd, J = 8.0, 7.5 Hz, 1H, Ar-*H*), 7.78 (d, J = 7.5 Hz, 1H, Ar-*H*), 8.14 (d, J = 8.0 Hz, 1H, Ar-*H*), 8.20 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1749 (C=O), 1714 (C=O), 1682 (C=O), 1527 (NO_2), 1352 (NO_2).

3-(3-Nitrobenzyl)-2,4,6-trioxohexahydropyrimidine-1-acetic Acid (43). A mixture of the ester **42** (2.98 g, 8.53 mmol), AcOH (9 mL), and concentrated HCl (3 mL) was refluxed for 2 h. After concentration, the residue was treated again with AcOH (9 mL) and concentrated HCl (3 mL) with refluxing for 1 h. Condensation gave a solid, which was washed well with H_2O and recrystallized from EtOH to give the carboxylic acid **43** (1.90 g, 67%): mp 89−90 °C dec; ^{1}H NMR (DMSO-d_6) δ 4.00 (br s, 2H, $COCH_2CO$), 4.41 (s, 2H, NCH_2CO_2), 5.05 (s, 2H, CH_2Ar), 7.62 (dd, J = 8.0, 7.2 Hz, 1H, Ar-*H*), 7.78 (d, J = 7.2 Hz, 1H, Ar-*H*), 8.13 (d, J = 8.0 Hz, 1H, Ar-*H*), 8.20 (s, 1H, Ar-*H*), 13.06 (br s, 1H, COOH); IR (KBr, cm^{-1}) 2970 (OH), 1716 (C=O), 1531 (NO_2), 1354 (NO_2); MS *m*/*z* 321 (M^+). Anal. ($C_{13}H_{11}N_3O_7$·0.6H_2O) C, H, N.

Preparation of 3-(Arylmethyl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic Acids (47). Ethyl 1,2,3,4-Tetrahydro-3-(3-nitrobenzyl)-2,4-dioxopyrimidine-1-acetate (45a). A solution of **44** (2.31 g, 11.7 mmol) in DMF (40 mL) was added dropwise to a suspension of NaH (60 wt % in

oil, 0.58 g, 14.5 mmol) in DMF (30 mL) while maintaining the temperature below 0 °C. After stirring for 1.5 h, a solution of **22** (3.42 g, 11.6 mmol) in DMF (70 mL) was added at 0 °C. The mixture was stirred at 0 °C for 2 h, poured into H_2O, and extracted several times with EtOAc. The combined extracts were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (hexane−EtOAc = 1/1) and recrystallized from EtOH to give **45a** (1.86 g, 48%): mp 105−107 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (t, J = 7.1 Hz, 3H, CH_3), 4.14 (q, J = 7.1 Hz, 2H, CH_2), 4.60 (s, 2H, NCH_2CO_2), 5.10 (s, 2H, CH_2Ar), 5.86 (d, J = 7.9 Hz, 1H, COCH=C), 7.63 (dd, J = 7.6, 7.6 Hz, 1H, Ar-*H*), 7.71 (d, J = 7.6 Hz, 1H, Ar-*H*), 7.75 (d, J = 7.9 Hz, 1H, COC=CH), 8.11 (s, 1H, Ar-*H*), 8.13 (d, J = 7.6 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1730 (C=O), 1697 (C=O), 1664 (C=O), 1531 (NO_2), 1350 (NO_2).

Ethyl 3-[(4-Chlorobenzothiazol-2-yl)methyl]-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetate (45c). A solution of the uracil **44** (0.89 g, 4.49 mmol) in DMF (20 mL) was added to a suspension of NaH (60 wt % in oil, 0.29 g, 7.25 mmol) in DMF (10 mL) at −10 °C. After stirring for 30 min, a mixture prepared by the treatment of 4-chloro-2-(chloromethyl)benzothiazole (**25a**) (0.96 g, 4.40 mmol) with NaBr (0.55 g, 5.35 mmol) in DMF (20 mL) at room temperature for 30 min was added dropwise to the reaction mixture at −10 °C. The resulting mixture was stirred for an additional 2.5 h and poured into H_2O. The precipitate was filtered and washed well with H_2O and hexane. The crude solid was chromatographed on silica gel (hexane−EtOAc = 1/1) to give the ester **45c** (0.56 g, 34%): mp 151−152.5 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, J = 7.0 Hz, 3H, CH_3), 4.15 (d, J = 7.0 Hz, 2H, OCH_2), 4.63 (s, 2H, NCH_2CO_2), 5.43 (s, 2H, CH_2Ar), 5.90 (d, J = 8.0 Hz, 1H, CH=), 7.43 (dd, J = 8.0, 8.0 Hz, 1H, Ar-*H*), 7.61 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.80 (d, J = 8.0 Hz, 1H, CH=), 8.04 (d, J = 8.0 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1705 (C=O), 1661 (C=O).

Ethyl 3-[(5-Chlorobenzothiazol-2-yl)methyl]-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetate (45d). A mixture of **44** (1.75 g, 8.83 mmol), **25b** (1.96 g, 8.99 mmol), K_2CO_3 (1.33 g, 9.62 mmol), and NaBr (0.98 g, 9.52 mmol) in DMF (40 mL) was stirred at 80 °C for 4 h. The mixture was poured into ice−H_2O, and the precipitate was filtered and washed well with H_2O and hexane. The crude solid was recrystallized from EtOH (60 mL) to give the ester **45d** (2.01 g, 67%): mp 138−138.5 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.19 (t, J = 7.0 Hz, 3H, CH_3), 4.15 (d, J = 7.0 Hz, 2H, OCH_2), 4.62 (s, 2H, NCH_2CO_2), 5.41 (s, 2H, CH_2Ar), 5.91 (d, J = 7.8 Hz, 1H, CH=), 7.49 (dd, J = 8.6, 2.0 Hz, 1H, Ar-*H*), 7.80 (d, J = 7.8 Hz, 1H, CH=), 8.05 (d, J = 2.0 Hz, 1H, Ar-*H*), 8.11 (d, J = 8.6 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1751 (C=O), 1728 (C=O), 1685 (C=O).

1,2,3,4-Tetrahydro-3-(3-nitrobenzyl)-2,4-dioxopyrimidine-1-acetic Acid (47a). A mixture of **45a** (1.60 g, 4.80 mmol), AcOH (6 mL), and HCl (2 mL) was refluxed for 2 h. After concentration, the residue was refluxed again with AcOH (6 mL) and HCl (2 mL) for 2 h. Condensation of the reaction mixture gave a crude solid, which was washed well with H_2O and recrystallized from EtOH to give the carboxylic acid **47a** (1.39 g, 95%) as white crystals: mp 161−161.5 °C; ^{1}H NMR (DMSO-d_6) δ 4.50 (s, 2H, NCH_2CO_2), 5.10 (s, 2H, CH_2Ar), 5.83 (d, J = 7.9 Hz, 1H, COCH=C), 7.62 (dd, J = 7.9, 7.9 Hz, 1H, Ar-*H*), 7.72 (d, J = 7.9 Hz, 1H, Ar-*H*), 7.73 (d, J = 7.9 Hz, 1H, COC=CH), 8.12 (s, 1H, Ar-*H*), 8.13 (d, J = 7.9 Hz, 1H, Ar-*H*), 13.20 (br s, 1H, COOH); IR (KBr, cm^{-1}) 2980 (OH), 1734 (C=O), 1703 (C=O), 1537 (NO_2), 1350 (NO_2); MS *m*/*z* 305 (M^+). Anal. ($C_{13}H_{11}N_3O_6$) C, H, N.

Preparation of 1,2,3,4-Tetrahydro-1-(3-nitrobenzyl)-2,4-dioxopyrimidine-3-acetic Acid (51). 1-(3-Nitrobenzyl)uracil (49). A suspension of **48** (5.29 g, 47.2 mmol) and TMSCl (12.0 mL, 94.6 mmol) in hexamethyldisilazane (HMDS) (100 mL) was refluxed for 2 h. The clear solution was concentrated under reduced pressure (*ca*. 5 mmHg). To the residue was added a solution of the bromide **22** (14.00 g, 47.3 mmol) and ^{n}Bu$_4$NI (1.11 g, 3.0 mmol) in CH_2Cl_2 (100 mL). The resulting mixture was stirred at room temperature for 4 days and poured into H_2O. The precipitate was filtered, washed well with H_2O and EtOAc, and dried to give the benzyluracil **49** (8.60 g, 74%): mp 255−257 °C dec; ^{1}H NMR (DMSO-d_6) δ 5.08 (s, 2H, CH_2Ar), 5.65 (d, J = 8.0 Hz, 1H, COCH=C), 7.68 (dd, J = 7.7, 7.7 Hz, 1H, Ar-*H*), 7.78 (d, J = 7.7 Hz, 1H, Ar-*H*), 7.86 (d, J = 8.0 Hz, 1H, COC=CH), 8.19 (d, J = 7.7 Hz, 1H, Ar-*H*), 8.20 (s, 1H, Ar-*H*), 11.39 (br s, 1H, NH); IR (KBr, cm^{-1}) 3007 (NH), 1707 (C=O), 1666 (C=O), 1533 (NO_2), 1346 (NO_2).

Ethyl 1,2,3,4-Tetrahydro-1-(3-nitrobenzyl)-2,4-dioxopyrimidine-3-acetate (50). A suspension of **49** (5.91 g, 23.9 mmol) in DMF (100 mL) was added to a suspension of NaH (60 wt % in oil, 1.21 g, 30.3 mmol) in DMF (20 mL) while maintaining the temperature below 0 °C. The mixture was stirred at the same temperature for 3 h. A solution of ethyl bromoacetate (2.7 mL, 24.3 mmol) in DMF (20 mL) was added dropwise to the above mixture. After stirring for 2.5 h, the mixture was poured into H_2O and extracted several times with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexane−EtOAc = 1/1) and recrystallized from EtOH (40 mL) to give the dialkylated uracil **50** (3.15 g, 40%): mp 97−98 °C; ^{1}H NMR (DMSO-d_6) δ 1.16 (t, J = 7.1 Hz, 3H, CH_3), 4.10 (q, J = 7.1 Hz, 2H, CH_2), 4.54 (s, 2H, NCH_2-CO), 5.10 (s, 2H, CH_2Ar), 5.88 (d, J = 7.9 Hz, 1H, COCH=C), 7.68 (dd, J = 8.3, 7.6 Hz, 1H, Ar-*H*), 7.77 (d, J = 7.6 Hz, 1H, Ar-*H*), 8.02 (d, J = 7.9 Hz, 1H, COC=CH), 8.18 (d, J = 8.3 Hz, 1H, Ar-*H*), 8.22 (s, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1757 (C=O), 1716 (C=O), 1670 (C=O), 1533 (NO_2), 1348 (NO_2).

1,2,3,4-Tetrahydro-1-(3-nitrobenzyl)-2,4-dioxopyrimidine-3-acetic Acid (51). A mixture of the ethyl ester **50** (2.29 g, 6.87 mmol), AcOH (9 mL), and HCl (3 mL) was refluxed for 1.5 h. After being concentrated, the mixture was refluxed again with AcOH (9 mL) and HCl (3 mL) for 2 h and condensed. The residual solid was filtered, washed well with H_2O, and recrystallized from EtOH−EtOAc (100−40 mL) to give the carboxylic acid **51** (1.82 g, 87%): mp 200−201.5 °C; ^{1}H NMR (DMSO-d_6) δ 4.46 (s, 2H, NCH_2CO), 5.10 (s, 2H, CH_2-Ar), 5.86 (d, J = 7.9 Hz, 1H, COCH=C), 7.68 (dd, J = 8.1, 7.7 Hz, 1H, Ar), 7.78 (d, J = 7.7 Hz, 1H, Ar), 8.00 (d, J = 7.9 Hz, 1H, COC=CH), 8.18 (d, J = 8.1 Hz, 1H, Ar), 8.22 (s, 1H, Ar), 12.99 (br s, 1H, OH); IR (KBr, cm^{-1}) 2900 (OH), 1741 (C=O), 1705 (C=O), 1524 (NO_2), 1350 (NO_2); MS *m*/*z* 305 (M^+). Anal. ($C_{13}H_{11}N_3O_6$) C, H, N.

Purification of Enzymes. The procedures employed for isolation of rat lens AR and rat kidney ALR are reported in the previous publications.[22,23]

Enzyme Assay. *In vitro* AR and ALR inhibition assays were conducted according to the method reported elsewhere.[22,23]

Neural Network Analysis. Free−Wilson-type neural network analysis of the 5-membered ring compounds **1a**, **9**, **19**, **26a**, **36**, and **40** was carried out with PSDD[33] (Perceptron Simulator for Drug Design) running on a Macintosh Quadra 950 workstation. The inhibitory activity is expressed as five classes based on the percentage of inhibition at 1×10^{-7} M. Active classes 1, 2, 3, 4, and 5 indicate less than 20% inhibition, 20−40% inhibition, 40−60% inhibition, 60−80% inhibition, and more than 80% inhibition, respectively. As the structural descriptor, the Free−Wilson descriptors for three carbonyl groups were used. Classification using ALS-type training patterns were used for calculation.

Molecular Modeling. An active conformation of zopolrestat was obtained from PDB (1MAR).[34] **1a** and **47a** were constructed by CAChe (ver. 3.8, CAChe Scientific) using zopolrestat as a template and minimized by molecular mechanics implemented in CAChe. The carboxylic acid moieties of zopolrestat, **1a**, and **47a** were superimposed.

Supporting Information Available: Melting point, ^{1}H NMR, IR, and MS data for compounds **23d**, **26b**−**d**, **45b**, and **47b**−**d** (3 pages). Ordering information is given on any current masthead page.

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