Highly Selective Aldose Reductase Inhibitors. II. Optimization of the Aryl Part of 3-(Arylmethyl)-2,4,5-trioxoimidazolidine-1-acetic Acids

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Accumulation of intracellular sorbitol, the product of glucose reduction catalyzed by aldose reductase (AR) [EC 1.1.1.21], is thought to be the main culprit in the development of diabetic complications. A series of 3-arylalkyl-2,4,5-trioxoimidazolidine-1-acetic acids was prepared and tested for inhibitory activities towards AR and aldehyde reductase (ALR) [EC 1.1.1.2]. These derivatives showed strong inhibitory activity against AR without markedly inhibiting ALR. In particular, the compounds with 3-nitrophenyl, 4-chloro-3-nitrophenyl, and chloro-substituted benzothiazolyl groups as the aryl part showed powerful AR-inhibitory activity. The chloro-substituted benzothiazolyl compound showed an AR selectivity of more than 5000 fold.

Key words diabetic complication; aldose reductase inhibitor; aldose reductase; aldehyde reductase; selectivity; 2,4,5-trioxoimidazolidine-1-acetic acid

Recently, much attention has been paid to aldose reductase inhibitors (ARI) owing to their therapeutic potential for the amelioration of diabetic complications.[1-4] In the course of our studies on 3-(arylalkyl)-2,4,5-trioxoimidazolidine-1-acetic acids, we found that some of the derivatives showed strong inhibitory activity against aldose reductase (AR) [EC 1.1.1.21] without markedly inhibiting aldehyde reductase (ALR) [EC 1.1.1.2].[5] Though it is not clear how ALR works in diabetic patients, ALR may be important in the reduction of many aldehydes and may have functions such as counteraction, excretion of drugs, synthesis of ascorbic acid, and metabolism of 4-hydroxybutyric acid.[6] AR is present in mesangium cells or renal medulla in human kidney, where over 100 fold greater expression of ALR can be observed.[7] This means that ARI in the kidney would be consumed by ALR before it can react with AR unless they have high selectivity for AR.[4] To apply ARI for the treatment of diabetes complications clinically, long-term administration would be required.[8] Thus, great case is needed to avoid adverse effects. Therefore, highly selective inhibition of AR seems to be a critical feature. Here, we describe a number of 3-(arylalkyl)-2,4,5-trioxoimidazolidine-1-acetic acids and their inhibitory activities against rat lens AR and rat kidney ALR. In particular, the compounds with 3-nitrophenyl (**1a**), 4-chloro-3-nitrophenyl (**1l**), and chloro-substituted benzothiazolyl groups (**4g** and **4h**) as the aryl part showed powerful AR-inhibitory activity. The chloro-substituted benzothiazolyl group **4h** has an AR selectivity of more than 5000 fold.

Chemistry

All of the parabanic acid derivatives **1**—**4** described in this paper were synthesized in two steps. Thus, most of the esters **7** and **8** were obtained by alkylation of **5**[5] and **6** with arylmethyl bromides (method A, Chart 1) or by the Mitsunobu reaction of **5** and **6** with arylmethyl alcohols (method B, Chart 1). In the case of the 2-(chloromethyl)benzothiazoles (**23c**—**i**, Chart 5) and 3,5-dinitrobenzyl chloride, they were converted to the corresponding bromides or iodides by treatment with NaBr or NaI in *N*,*N*-dimethylformamide (DMF) and condensed with **5** (method C, Chart 1).

The ethyl esters **7** could be hydrolyzed with concentrated HCl and AcOH according to the reported method[5] (method D, Chart 2). On the other hand, when substituents on the aryl rings were susceptible to acid, benzyl esters **8** were adopted instead of the ethyl ester and the benzyl group was removed by hydrogenation with 10% palladium on charcoal under a hydrogen atmosphere (method E, Chart 2). Ethyl and benzyl 2,4,5-trioxoimidazolidine-1-acetates (**5** and **6**) were prepared by the treatment of the ureidoacetates **12** and **13** with oxalyl chloride, respectively (Chart 3).

Substituted arylmethyl halides or alcohols which were not commercially available were prepared as follows. Benzyl bromides **15**, naphthylmethyl bromides **17** and

5 R = Et
6 R = Bn

7 Ar = phenyl, R = Et
8 Ar = phenyl, R = Bn
9 Ar = naphthyl, R = Et
10 Ar = pyridyl, R = Et
11 Ar = benzothiazolyl, R = Et

Method A: $ArCH_2Br$, NaH, DMF.
Method B: $ArCH_2OH$, diethyl azodicarboxylate (DEAD), PPh_3, THF.
Method C: $ArCH_2Cl$, NaBr or NaI, NaH, DMF.

Chart 1

Method D: conc. HCl, AcOH, reflux.
Method E: 10%-Pd/C, H_2, EtOAc.

Chart 2

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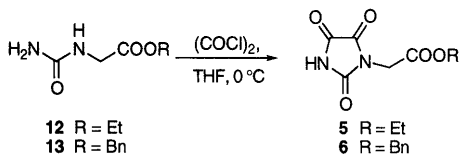
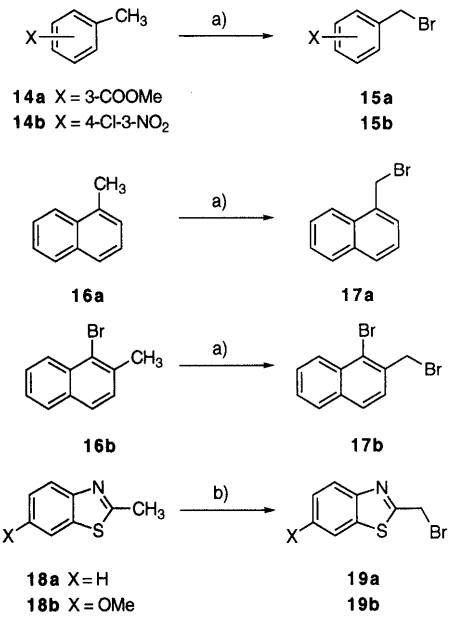
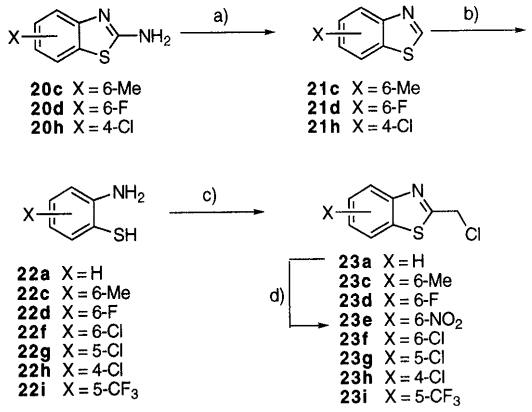


Chart 3



a) Br_2, HBr, CCl_4, reflux, b) NBS, $(BzO)_2$, CCl_4, reflux.

Chart 4



a) $NaNO_2$, H_3PO_4, then H_3PO_2, b) $H_2NNH_2 \cdot H_2O$, EtOH, c) $ClCH_2C(OEt)_3$, EtOH, d) HNO_3, H_2SO_4.

Chart 5

benzothiazolylmethyl bromides **19** were prepared by bromination of the corresponding toluenes **14**, methylnaphthalenes **16**, and 2-methylbenzothiazoles **18** with bromine or *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide ($(BzO)_2$)[9] in CCl_4, as shown in Chart 4. Each of the brominated intermediates thus obtained was used in the next step after purification by column chromatography on silica gel and/or recrystallization.

The substituted (2-chloromethyl)benzothiazoles **23c—i** (except for **23e**) were prepared by condensation of the 2-aminothiophenols **22** with orthoethyl chloroacetate in EtOH under reflux, according to the reported procedure (Chart 5).[9,10] The 2-aminothiophenols **22** were prepared from 2-aminobenzothiazoles **20** by using the reported procedure.[9,11] The 6-nitrobenzothiazole **23e** was obtained by nitration of the benzothiazole **23a**.

Results and Discussion

The test compounds were evaluated for *in vitro* inhibitory activity against rat lens AR[12] and rat kidney ALR[13] in a spectrometric assay with DL-glyceraldehyde as the substrate and NADPH as the cofactor. *In vitro* activity against AR was expressed as % inhibition at 1.0×10^{-7} M concentration of the test compounds. *In vitro* activity against ALR was expressed as % inhibition at 1.0×10^{-4} M concentration of the test compounds.

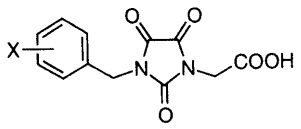
Substituted Benzyl Derivatives In agreement with the previous study,[5] all substituted benzyl derivatives showed moderate to strong AR-inhibitory activity and weak ALR-inhibitory activity. Though the introduction of electron-withdrawing groups on the aryl unit seems to increase the inhibitory activity against AR, a strongly electron-withdrawing group such as the 3,5-dinitro group caused loss of AR-inhibitory activity (Table 1, compound **1m**). The 4-chloro-3-nitrobenzyl group was the optimum substituent in *in vitro* (Table 1, compound **1l**). Hydrophobicity and steric effects of the substituent seemed to have no significant relationship with AR- and ALR-inhibitory activities.

Substituted Pyridyl and Naphthyl Derivatives Introduction of the 1-naphthyl group as the aryl moiety resulted in moderate inhibitory activity against AR, whereas the 2-naphthyl compound showed strong inhibitory activity (Table 2). The electronic factor appeared to be similar benzyl and naphthyl derivatives. Thus, introduction of an electron-withdrawing group onto the naphthyl ring enhanced AR-inhibitory activity compared with the non-substituted compound (Table 2, **2a** *vs.* **2b**). The compounds with pyridine unit as the aryl part showed no AR-inhibitory activity at 1×10^{-7} M concentration (Table 2, compounds **3**).

Substituted Benzothiazolyl Derivatives A number of ARIs having the benzothiazole unit have been reported.[9,14,15] Therefore, the benzothiazole unit was introduced as the aryl part (Table 3). Though the benzothiazole derivatives seemed to have relatively strong ALR-inhibitory activity compared with the other parabanic acid derivatives, the degree of ALR inhibition is still weak compared with other ARIs. As discussed above, introduction of electron-withdrawing groups resulted in enhancement of AR activity. The chlorine atom was found to be optimum in benzothiazole derivatives.

In order to avoid adverse effects of ARI therapy, AR selectivity is one of the most important indices.[4,16-18] We examined the AR selectivity of the parabanic acid derivatives with strong AR-inhibitory activity. As shown in Table 4, all the parabanic acid derivatives showed weak inhibition of ALR. In particular, the ratio of IC_{50}(ALR)/IC_{50}(AR) of **1l** was more than 6250. There are many reports to show that ARIs which have so far been found also inhibit the closely related enzyme ALR.[8,16,17] Since

Table 1. Physical and Biological Data for 3-Benzyl-2,4,5-trioxoimidazolidine-1-acetic Acids (**1**)

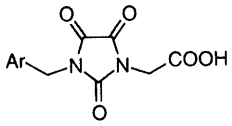


1

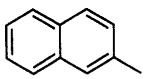
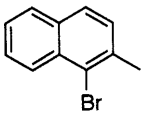
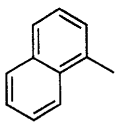
No.	X	mp (°C)	Formula[a]	% inhibition for AR at 1×10^{-7} (M)	% inhibition for ALR at 1×10^{-4} (M)
1a	3-NO_2	192—194	$C_{12}H_{10}N_3O_7$	57.9	37.3
1b	2-CF_3	217—219	$C_{13}H_9F_3N_2O_5$	8.0	25.4
1c	3-CF_3	190—192.5	$C_{13}H_9F_3N_2O_5$	12.3	38.8
1d	4-CF_3	190—192	$C_{13}H_9F_3N_2O_5$	6.6	27.1
1e	3-CN	181—181.5	$C_{13}H_9N_3O_5$	8.3	25.0
1f	4-CN	175—176	$C_{13}H_9N_3O_5$	0.8	12.7
1g	3-COOH	244.5—245	$C_{13}H_{10}N_2O_7$	8.9	77.2
1h	3-COOMe	89—90	$C_{14}H_{12}N_2O_7$	6.5	46.5
1i	3-F	208.5—209	$C_{12}H_9FN_2O_5$	10.6	62.6
1j	2-Br	221—223	$C_{12}H_9BrN_2O_5$	16.3	55.8
1k	3-Br	202—202.5	$C_{12}H_9BrN_2O_5$	17.0	48.8
1l	3-NO_2-4-Cl	234.5—236	$C_{12}H_8ClN_3O_7$	66.3	39.5
1m	3,5-$(NO_2)_2$	182.5—183	$C_{12}H_8N_4O_9$	8.4	67.7

a) Elemental analyses were within ±0.4% of the calculated values.

Table 2. Physical and Biological Data for 3-Arylmethyl-2,4,5-trioxoimidazolidine-1-acetic Acids (**2** and **3**)



2, 3

No.	Ar	mp (°C)	Formula[a]	% inhibition for AR at 1×10^{-7} (M)	% inhibition for ALR at 1×10^{-4} (M)
2a		192.5—194	$C_{16}H_{12}N_2O_5$	42.4	59.0
2b		205—210	$C_{16}H_{11}BrN_2O_5$	60.2	47.0
2c		225—228	$C_{16}H_{12}N_2O_5$	22.5	57.4
3a		251—253	$C_{11}H_9N_3O_5$	4.7	24.4
3b		251—252	$C_{11}H_9N_3O_5$	4.1	67.5
3c		251—253	$C_{11}H_9N_3O_5$	0.0	0.0

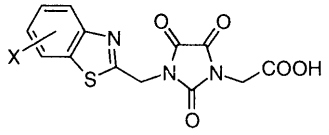
a) Elemental analyses were within ±0.4% of the calculated values.

the primary sequences of AR and ALR are quite similar,[19] this lack of specific inhibition is not surprising. Presumably the inhibitor binding sites of the two enzymes are structurally similar.[19] The parabanic acid-type ARI inhibitors are the first to distinguish the binding sites of these enzymes.

Conclusion

Since the aryl moiety of ARI plays an important role, we synthesized and screened a number of ARI having the

Table 3. Physical and Biological Data for 3-[(Benzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acids (**4**)



4

No.	X	mp (°C)	Formula[a]	% inhibition for AR at 1×10^{-7} (M)	% inhibition for ALR at 1×10^{-4} (M)
4a	H	264—265	$C_{13}H_9N_3O_5S$	42.0	30.0
4b	6-OMe	270—271	$C_{14}H_{11}N_3O_6S\cdot0.1H_2O$	16.4	66.6
4c	6-Me	277—278	$C_{14}H_{11}N_3O_5S$	32.8	73.1
4d	6-F	261—262	$C_{13}H_8FN_3O_5S$	62.9	59.7
4e	6-NO_2	130—131	$C_{13}H_8N_4O_7S$	48.3	57.2
4f	6-Cl	265—266	$C_{13}H_8ClN_3O_5S$	57.7	77.8
4g	5-Cl	244.5—245	$C_{13}H_8ClN_3O_5S$	70.7	55.3
4h	4-Cl	238—240	$C_{13}H_8ClN_3O_5S$	83.1	62.2
4i	5-CF_3	211—212	$C_{14}H_8F_3N_3O_5S\cdot0.1H_2O$	58.2	24.7

a) Elemental analyses were within ±0.4% of the calculated values.

Table 4. Ratio of AR IC_{50} and ALR IC_{50} of Compounds **1**, **2**, and **4**

No.	AR IC_{50} (M)[a]	ALR IC_{50} (M)[b]	ALR (IC_{50})/ AR (IC_{50})
1a	6.2×10^{-8}	$>1.0\times10^{-4}$	>1613
1l	1.6×10^{-8}	$>1.0\times10^{-4}$	>6250
2b	5.8×10^{-8}	$>1.0\times10^{-4}$	>1724
4d	7.0×10^{-8}	4.0×10^{-5}	600
4g	1.5×10^{-8}	5.8×10^{-5}	3867
4h	1.2×10^{-8}	7.2×10^{-5}	6000
Epalrestat	2.1×10^{-8}	1.5×10^{-6}	71
EBPC[c]	1.1×10^{-7}	3.2×10^{-5}	291

a) IC_{50} value for rat lens AR. *b*) IC_{50} value for rat kidney ALR. *c*) Ethyl 1-benzyl-3-hydroxy-2(5*H*)-oxopyrrole-4-carboxylate.[20]

parabanic acid core unit. We discovered that this is an effective core unit for AR-selective and strong inhibitory activity. On the other hand, 3-nitrophenyl (**1a**), 4-chloro-3-nitrophenyl (**1l**), and benzothiazolyl groups (**4g** and **4h**) were suitable as the aryl part. In particular, **1a** and **1l** have sufficiently strong *in vitro* activity against AR and extremely weak ALR inhibition. Compound **1a** has been selected for clinical trials.

Experimental

Melting points (mp) were measured on a Yamato MP-21 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined in chloroform-*d* or dimethylsulfoxide-d_6 on a Bruker AM-400 (400 MHz) or a Bruker ARX-500 (500 MHz) spectrometer. Chemical shifts are reported in δ value from internal tetramethylsilane. Infrared (IR) spectra were recorded with a Hitachi 260-30 or a Horiba FT-200 spectrophotometer. Mass spectra (MS) were taken on a Hitachi M-80B mass spectrometer. Elemental analyses (C, H, N) were carried out on a Perkin-Elmer 240C or a Yanaco CHN Corder MT-5 elemental analyzer. Thin-layer chromatographic (TLC) analyses and chromatographic separations were performed with Silica gel 60 F_{254} plates (Merck Art 5715) and Silica gel 60 (Merck Art 7734, 70—230 mesh), respectively.

Preparation of Arylmethyl Bromides 2-Bromomethylbenzothiazole (**19a**): A solution of 2-methylbenzothiazole (**18a**, 10.0 ml, 78.6 mmol) and NBS (17.7 g, 99.4 mmol) in CCl_4 (500 ml) was refluxed in the presence of a catalytic amount of benzoyl peroxide (1.00 g) for 30 h. The mixture was cooled to room temperature, and filtered through a Celite pad to remove the precipitate. The filtrate was dried over Na_2SO_4, and concentrated, then the residue was by column chromatography on silica gel to afford the bromide **19a** (5.4 g, 30%). ^{1}H-NMR ($CDCl_3$) δ: 4.81 (s, 2H, CH_2), 7.42 (dd, J=8.0, 7.5 Hz, 1H, Ar-H), 7.50 (dd, J=8.0, 7.5 Hz, 1H, Ar-H), 7.88 (d, J=8.0 Hz, 1H, Ar-H), 8.02 (d, J=8.0 Hz, 1H, Ar-H).

Preparation of Arylmethyl Chlorides 6-Methylbenzothiazole (**21c**): 2-Amino-6-methylbenzothiazole (**20c**, 10.9 g, 66.2 mmol) was dissolved in warm 85% H_3PO_4 (200 ml). The resulting homogeneous solution was cooled to −10—−5 °C and a solution of $NaNO_2$ (23.0 g, 0.33 mol) in H_2O (130 ml) was slowly added below the surface with stirring while the temperature was maintained below −4 °C. Then cold (0 °C) 50% H_3PO_2 (75 ml) was added dropwise with stirring and the whole was allowed to warm to room temperature. After gas evolution had ceased, the solution was diluted with ice-cold water, neutralized with Na_2CO_3, and extracted several times with $CHCl_3$. The combined extracts were dried over Na_2SO_4, and concentrated. The crude solid was purified by column chromatography on silica gel (EtOAc : hexane = 20 : 1) to give **21c** (2.98 g, 30%). ^{1}H-NMR ($CDCl_3$) δ: 2.51 (s, 3H, CH_3), 7.33 (dd, J=8.3, 1.1 Hz, 1H, Ar-H), 7.75 (d, J=1.1 Hz, 1H, Ar-H), 8.01 (d, J=8.3 Hz, 1H, Ar-H), 8.90 (s, 1H, Ar-H). IR (KBr) cm^{-1}: 1693, 1547, 1473, 1441, 1342, 903, 833.

2-Chloromethyl-6-methylbenzothiazole (**23c**): A mixture of $H_2NNH_2\cdot H_2O$ (15 ml) and 6-methylbenzothiazole (**21c**, 4.52 g, 30.3 mmol) was stirred at ambient temperature for 24 h. It was then concentrated and H_2O was gradually added. The pH of the solution was adjusted to about 2 by addition of concentrated HCl. The precipitated yellow solid was collected by filtration and dried *in vacuo*. The crude aminothiophenol **22c** was used in the subsequent step without further purification.

A solution of **22c** and orthoethyl chloroacetate (5.0 ml, 26.2 mmol) in EtOH (35 ml) was stirred at 60 °C (bath temperature) for 2 h, then poured into H_2O and the mixture extracted 3 times with ether. The ethereal extracts were washed with 2 N HCl, H_2O, saturated $NaHCO_3$, and brine. The extract was dried over Na_2SO_4, then concentrated and the residue was purified by column chromatography on silica gel (EtOAc : hexane = 10 : 1) to give 2-chloromethyl-6-methylbenzothiazole (**23c**) (2.23 g, 37%), mp 84—85 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.49 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 7.31 (d, J=8.2 Hz, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 7.89 (d, J=8.2 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 3007, 1514, 1425, 1310, 1136, 806, 735, 625.

2-Chloromethyl-6-nitrobenzothiazole (**23e**): A mixture of 2-(chloromethyl)benzothiazole (**23a**, 14.3 g, 7.80 mmol) and concentrated H_2SO_4 (40 ml) was treated dropwise with HNO_3 (70%, 40 ml) at 0 °C. The mixture stirred for 4 h, then poured into ice-H_2O and the whole was extracted several times with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated. The residual solid was purified by column chromatography on silica gel (AcOEt : hexane = 10 : 1) to give the nitro compound **23e** (10.7 g, 60%), mp 87—88 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 5.32 (s, 2H, CH_2), 8.22 (d, J=9.0 Hz, 1H, Ar-H), 8.38 (dd, J=9.0, 2.2 Hz, 1H, Ar-H), 9.22 (d, J=2.2 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1508

(NO_2), 1344 (NO_2).

Preparation of Benzyl 2,4,5-Trioxoimidazolidine-1-acetate (6) Benzyl Ureidoacetate (**13**): A solution of glycine benzyl ester *p*-TsOH salt (80.0 g, 0.24 mol) and urea (72.0 g, 1.20 mol) in H_2O (100 ml) was refluxed with AcOH (2 ml) and concentrated HCl (2 ml) for 5 h. The reaction mixture was crystallized by allowing it to stand at ambient temperature. Recrystallization from EtOH gave the urea **13** as white crystals (32.0 g, 64%). ^{1}H-NMR (DMSO-d_6) δ: 4.80 (d, J=7.0 Hz, 2H, NCH_2CO_2), 5.11 (s, 2H, OCH_2), 5.64 (s, 2H, NH_2), 6.37 (t, J=7.0 Hz, 1H, NH), 7.38—7.56 (m, 5H, Ar-H). IR (KBr) cm^{-1}: 3440 (NH_2), 3350 (NH_2), 1735 (C=O), 1645 (C=O).

Benzyl 2,4,5-Trioxoimidazolidine-1-acetate (**6**): A solution of oxalyl chloride (19.0 ml, 218 mmol) in tetrahydrofuran (THF) (200 ml) was added dropwise to a solution of the urea **10** (38.5 g, 185 mmol) in THF (100 ml) at 0 °C. After vigorous stirring for 4 h, the reaction mixture was treated with $BaCO_3$ (90.0 g, 456 mmol) at ambient temperature. After removal of the insoluble material by filtration, the filtrate was concentrated and the residue was recrystallized from EtOAc–hexane to give the parabanic acid derivative **6** (38.4 g, 79%), mp 179—179.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.43 (s, 2H, NCH_2CO_2), 5.19 (s, 2H, OCH_2), 7.27—7.45 (m, 5H, Ar-H), 12.40 (br s, 1H, NH). IR (KBr) cm^{-1}: 3250 (NH), 1750 (C=O), 1725 (C=O).

General Procedure for the Synthesis of Ethyl 3-Arylmethyl-2,4,5-trioxoimidazolidine-1-acetates (7—11) Method A. Ethyl 3-(3-nitrobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7a**): A solution of the parabanic acid **5**[5] (10.0 g, 50 mmol) in DMF (50 ml) was added to a suspension of NaH (60 wt% in oil, 2.00 g, 50 mmol) in DMF (50 ml) while the temperature was maintained below 0 °C over a period of 30 min. The mixture was stirred for 1 h, then a solution of 3-nitrobenzyl bromide (10.8 g, 50 mmol) in DMF (50 ml) was slowly added at 0 °C. The whole was stirred for a further 2 h at 0 °C and poured into ice-H_2O containing concentrated HCl (1 ml) to give a solid, which was collected by filtration and washed well with H_2O and hexane. Recrystallization from EtOH gave the desired compound **5** (12.5 g, 75%) as white crystals, mp 124.5—125.5 °C. ^{1}H-NMR δ: 1.21 (t, J=7.2 Hz, 3H, CH_3), 4.17 (q, J=7.2 Hz, 2H, OCH_2), 4.41 (s, 2H, NCH_2CO_2), 4.91 (s, 2H, CH_2Ar), 7.64—8.26 (m, 4H, Ar-H). IR (KBr) cm^{-1}: 1740 (C=O), 1720 (C=O), 1525 (NO_2), 1350 (NO_2).

Method B. Ethyl 3-(3-Pyridylmethyl)-2,4,5-trioxoimidazolidine-1-acetate (**10b**): A solution of diethyl azodicarboxylate (DEAD) (6.0 ml, 38.1 mmol) in THF (20 ml) was added dropwise to a solution of 3-pyridinemethanol (2.7 ml, 27.8 mmol), the parabanic acid **5** (5.00 g, 25.0 mmol), and PPh_3 (10.00 g, 38.1 mmol) in THF (40 ml) with vigorous stirring at 0 °C. The mixture was stirred for 4.5 h, then poured into H_2O and the whole was extracted several times with EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel to give a solid, which was recrystallized from EtOH–H_2O to give the desired compound **10b** (4.22 g, 58%), mp 112—113 °C. ^{1}H-NMR δ: 1.20 (t, J=7.0 Hz, 3H, CH_3), 4.16 (q, J=7.0 Hz, 2H, OCH_2), 4.39 (s, 2H, NCH_2CO_2), 4.79 (s, 2H, CH_2Ar), 7.38 (dd, J=8.0, 4.5 Hz, 1H, Ar-H), 7.75 (ddd, J=8.0, 2.0, 1.5 Hz, 1H, Ar-H), 8.51 (dd, J=4.5, 1.5 Hz, 1H, Ar-H), 8.57 (d, J=2.0 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1730 (C=O).

Method C. Ethyl 3-[(5-Trifluoromethylbenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**11i**): A solution of the parabanic acid **5** (3.53 g, 17.6 mmol) in DMF (50 ml) was added dropwise to a suspension of NaH (60 wt% in oil, 0.89 g, 22.3 mmol) in DMF (10 ml) over a period of 30 min while the temperature was maintained below 0 °C. The mixture was stirred at the same temperature for an additional 1 h. A solution of 2-bromomethyl-5-trifluoromethylbenzothiazole, prepared by the treatment of the corresponding chloro compound **23i** (3.78 g, 17.5 mmol) with NaBr (2.26 g, 22.0 mmol) in DMF (40 ml), was then added dropwise to the reaction mixture at 0 °C. After having been stirred for 2 h, the mixture was poured into ice-cooled 2 N HCl with vigorous stirring. The precipitate was collected by filtration and washed well with H_2O and hexane. The solid was recrystallized from EtOH (120 ml) to give the ester **11i** (2.23 g, 30%), mp 150—151 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (t, J=7.1 Hz, 3H, CH_3), 4.19 (q, J=7.1 Hz, 2H, OCH_2), 4.49 (s, 2H, NCH_2CO_2), 5.33 (s, 2H, CH_2Ar), 7.80 (d, J=8.4 Hz, 1H, Ar-H), 8.35 (s, 1H, Ar-H), 8.40 (d, J=8.4 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1742 (C=O).

Compounds **7**—**11** were obtained as described above.

Ethyl 3-(2-Trifluoromethylbenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7b**): (Method A, 54%), mp 173.5—174.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (t, J=7.0 Hz, 3H, CH_3), 4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.44 (s, 2H, NCH_2CO_2), 4.89 (s, 2H, CH_2Ar), 7.54 (dd, J=8.0, 7.0 Hz, 1H, Ar-H), 7.59 (d, J=8.0 Hz, 1H, Ar-H), 7.66 (dd, J=8.0, 7.0 Hz, 1H, Ar-H), 7.78 (d, J=8.0 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1735 (C=O). MS m/z: 358 (M^+).

Ethyl 3-(3-Trifluoromethylbenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7c**): (Method A, 73%), mp 109.5—110.5 °C. ^{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), 4.41 (s, 2H, NCH_2CO_2), 4.86 (s, 2H, CH_2Ar), 7.60 (dd, J=7.5, 7.5 Hz, 1H, Ar-H), 7.64—7.71 (m, 2H, Ar-H), 7.74 (s, 1H, Ar-H). IR (KBr) cm^{-1}: 1730 (C=O). MS m/z: 358 (M^+).

Ethyl 3-(4-Trifluoromethylbenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7d**): (Method A, 62%), mp 138—139.5 °C. ^{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), 4.41 (s, 2H, NCH_2CO_2), 4.85 (s, 2H, CH_2Ar), 7.59 (d, J=8.0 Hz, 2H, Ar-H), 7.74 (d, J=8.0 Hz, 2H, Ar-H). IR (KBr) cm^{-1}: 1750 (C=O), 1725 (C=O). MS m/z: 358 (M^+).

Benzyl 3-(3-Cyanobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**8e**): (Method A, 85%), mp 148.5—149 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.50 (s, 2H, NCH_2CO_2), 4.82 (s, 2H, CH_2Ar), 5.20 (s, 2H, OCH_2), 7.33—7.43 (m, 5H, Ar-H), 7.57 (dd, J=7.9, 7.9 Hz, 1H, Ar-H), 7.70 (d, J=7.9 Hz, 1H, Ar-H), 7.78 (d, J=7.9 Hz, 1H, Ar-H), 7.87 (s, 1H, Ar-H). IR (KBr) cm^{-1}: 2235 (CN), 1734 (C=O).

Benzyl 3-(4-Cyanobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**8f**): (Method A, 76%), mp 120.5—121 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.49 (s, 2H, NCH_2CO_2), 4.84 (s, 2H, CH_2Ar), 5.20 (s, 2H, OCH_2), 7.30—7.40 (m, 5H, Ar-H), 7.55 (d, J=8.0 Hz, 2H, Ar-H), 7.82 (d, J=8.0 Hz, 2H, Ar-H). IR (KBr) cm^{-1}: 2190 (CN), 1705 (C=O).

Ethyl 3-(3-Methoxycarbonylbenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7g**): (Method A, 71%), mp 121—122 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (t, J=7.0 Hz, 3H, CCH_3), 3.86 (s, 3H, OCH_3), 4.16 (q, J=7.0 Hz, 2H, OCH_2), 4.39 (s, 2H, NCH_2CO_2), 4.82 (s, 2H, CH_2Ar), 7.52 (dd, J=7.5, 7.5 Hz, 1H, Ar-H), 7.63 (d, J=7.5 Hz, 1H, Ar-H), 7.90 (d, J=7.5 Hz, 1H, Ar-H), 7.95 (s, 1H, Ar-H). IR (KBr) cm^{-1}: 1735 (C=O). MS m/z: 348 (M^+).

Benzyl 3-(3-Methoxycarbonylbenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**8h**): (Method A, 47%), mp 105—107 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.86 (s, 3H, OCH_3), 4.49 (s, 2H, NCH_2CO_2), 4.82 (s, 2H, CH_2Ar), 5.19 (s, 2H, OCH_2), 7.30—7.40 (m, 5H, Ar-H), 7.51 (dd, J=7.5, 7.5 Hz, 1H, Ar-H), 7.62 (d, J=7.5 Hz, 2H, Ar-H), 7.90 (d, J=7.5 Hz, 1H, Ar-H), 7.96 (s, 1H, Ar-H). IR (KBr) cm^{-1}: 1734 (C=O).

Ethyl 3-(3-Fluorobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7i**): (Method A, 84%), mp 145—145.5 °C. ^{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_3), 4.41 (s, 2H, NCH_2CO_2), 4.77 (s, 2H, CH_2Ar), 7.04—7.30 (m, 3H, Ar-H), 7.40 (dd, J=8.0, 8.0 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1735 (C=O).

Ethyl 3-(2-Bromobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7j**): (Method A, 81%), mp 157.5—159.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.0 Hz, 3H, CH_3), 4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.43 (s, 2H, NCH_2CO_2), 4.77 (s, 2H, CH_2Ar), 7.27 (ddd, J=7.3, 7.3, 1.6 Hz, 1H, Ar-H), 7.38 (ddd, J=7.3, 7.3, 1.6 Hz, 1H, Ar-H), 7.43 (dd, J=7.3, 1.6 Hz, 1H, Ar-H), 7.66 (dd, J=7.3, 1.6 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1749 (C=O).

Ethyl 3-(3-Bromobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7k**): (Method A, 76%), mp 202—202.5 °C. ^{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), 4.40 (s, 2H, NCH_2CO_2), 4.75 (s, 2H, CH_2Ar), 7.26—7.41 (m, 2H, Ar-H), 7.50 (d, J=7.5 Hz, 1H, Ar-H), 7.58 (s, 1H, Ar-H). IR (KBr) cm^{-1}: 1730 (C=O).

Ethyl 3-(4-Chloro-3-nitrobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7l**): (Method A, 82%), mp 141—144 °C. ^{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), 4.40 (s, 2H, NCH_2CO_2), 4.86 (s, 2H, CH_2Ar), 7.70 (dd, J=8.0, 1.5 Hz, 1H, Ar-H), 7.78 (d, J=8.0 Hz, 1H, Ar-H), 8.08 (d, J=1.5 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1735 (C=O), 1535 (NO_2). MS m/z: 369 (M^+).

Ethyl 3-(3,5-Dinitrobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7m**): (Method A, 57%), mp 182.5—183 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.0 Hz, 3H, CH_3), 4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.41 (s, 2H, NCH_2CO_2), 5.56 (s, 2H, CH_2Ar), 8.69 (d, J=1.5 Hz, 2H, Ar-H), 8.77 (t, J=1.5 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1730 (C=O), 1535 (NO_2), 1355 (NO_2).

Ethyl 3-(2-Naphthylmethyl)-2,4,5-trioxoimidazolidine-1-acetate (**9a**): (Method A, 96%), mp 149—150 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (t, J=7.0 Hz, 3H, CH_3), 4.16 (q, J=7.0 Hz, 2H, OCH_2), 4.43 (s, 2H, NCH_2CO_2), 4.92 (s, 2H, CH_2Ar), 7.47 (dd, J=8.5, 1.8 Hz, 1H, Ar-H),

7.52 (s, 1H, Ar-H), 7.52 (dd, J=9.5, 1.8 Hz, 1H, Ar-H), 7.86—7.95 (m, 4H, Ar-H). IR (KBr) cm^{-1}: 1734 (C=O).

Ethyl 3-[(1-Bromonaphthalen-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**9b**): (Method A, 32%), mp 184.5—185.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.0 Hz, 3H, CH_3), 4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.44 (s, 2H, NCH_2CO_2), 5.04 (s, 2H, CH_2Ar), 7.56 (d, J=8.5 Hz, 1H, Ar-H), 7.64 (dd, J=7.0, 7.0 Hz, 1H, Ar-H), 7.72 (dd, J=8.5, 7.0 Hz, 1H, Ar-H), 7.95—8.05 (m, 2H, Ar-H), 8.25 (d, J=8.5 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1736 (C=O).

Ethyl 3-(1-Naphthylmethyl)-2,4,5-trioxoimidazolidine-1-acetate (**9c**): (Method A, 64%), mp 172—175 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (t, J=7.0 Hz, 3H, CH_3), 4.15 (q, J=7.0 Hz, 2H, OCH_2), 4.43 (s, 2H, NCH_2CO_2), 5.22 (s, 2H, CH_2Ar), 7.45—7.64 (m, 4H, Ar-H), 7.91 (d, J=8.6 Hz, 1H, Ar-H), 7.98 (d, J=8.6 Hz, 1H, Ar-H), 8.19 (d, J=8.6 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1747 (C=O), 1734 (C=O).

Ethyl 3-(2-Pyridylmethyl)-2,4,5-trioxoimidazolidine-1-acetate (**10a**): (Method B, 74%), mp 122—123 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.0 Hz, 3H, CH_3), 4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.55 (s, 2H, NCH_2CO_2), 4.88 (s, 2H, CH_2Ar), 7.32 (dd, J=7.5, 4.5 Hz, 1H, Ar-H), 7.46 (d, J=7.5 Hz, 1H, Ar-H), 7.81 (dd, J=7.5, 7.5 Hz, 1H, Ar-H), 8.50 (d, J=4.5 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1734 (C=O).

Ethyl 3-(4-Pyridylmethyl)-2,4,5-trioxoimidazolidine-1-acetate (**10c**): (Method B, 58%), mp 92—94 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.0 Hz, 3H, CH_3), 4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.42 (s, 2H, NCH_2CO_2), 4.80 (s, 2H, CH_2Ar), 7.37 (d, J=5.5 Hz, 2H, Ar-H), 8.54 (d, J=5.5 Hz, 2H, Ar-H). IR (KBr) cm^{-1}: 1740 (C=O), 1720 (C=O).

Ethyl 3-(2-Benzothiazolylmethyl)-2,4,5-trioxoimidazolidine-1-acetate (**11a**): (Method A, 52%), mp 151.5—153 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.0 Hz, 3H, CH_3), 4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.47 (s, 2H, NCH_2CO_2), 5.25 (s, 2H, CH_2Ar), 7.46 (ddd, J=7.7, 7.7, 1.2 Hz, 1H, Ar-H), 7.53 (ddd, J=7.7, 7.7, 1.2 Hz, 1H, Ar-H), 7.99 (dd, J=7.7, 1.2 Hz, 1H, Ar-H), 8.11 (dd, J=7.7, 1.2 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1734 (C=O).

Ethyl 3-[(6-Methoxybenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**11b**): (Method A, 55%), mp 150.5—152 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 4.46 (s, 2H, NCH_2CO_2), 5.18 (s, 2H, CH_2Ar), 7.11 (dd, J=9.0, 2.6 Hz, 1H, Ar-H), 7.68 (d, J=2.6 Hz, 1H, Ar-H), 7.86 (d, J=9.0 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1736 (C=O).

Ethyl 3-[(6-Methylbenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**11c**): (Method C, 31%), mp 155—156 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.47 (s, 2H, NCH_2CO_2), 5.21 (s, 2H, CH_2Ar), 7.34 (d, J=8.2 Hz, 1H, Ar-H), 7.86 (d, J=8.2 Hz, 1H, Ar-H), 7.90 (s, 1H, Ar-H). IR (KBr) cm^{-1}: 1738 (C=O).

Ethyl 3-[(6-Fluorobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**11d**): (Method C, 52%), mp 154—155 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 4.46 (s, 2H, NCH_2CO_2), 5.23 (s, 2H, CH_2Ar), 7.39 (ddd, J=9.2, 9.2, 2.5 Hz, 1H, Ar-H), 8.01 (dd, J=9.2, 5.0 Hz, 1H, Ar-H), 8.04 (dd, J=9.2, 2.5 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1734 (C=O).

Ethyl 3-[(6-Nitrobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**11e**): (Method C, 42%), mp 183—184 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.48 (s, 2H, NCH_2CO_2), 5.34 (s, 2H, CH_2Ar), 8.19 (d, J=9.0 Hz, 1H, Ar-H), 8.34 (dd, J=9.0, 2.4 Hz, 1H, Ar-H), 9.22 (d, J=2.4 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1743 (C=O), 1738 (C=O), 1524 (NO_2), 1346 (NO_2).

Ethyl 3-[(6-Chlorobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**11f**): (Method C, 47%), mp 181—182.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 4.47 (s, 2H, NCH_2CO_2), 5.25 (s, 2H, CH_2Ar), 7.56 (dd, J=8.8, 2.2 Hz, 1H, Ar-H), 7.99 (d, J=8.8 Hz, 1H, Ar-H), 8.29 (d, J=2.2 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1734 (C=O).

Ethyl 3-[(5-Chlorobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**11g**): (Method C, 80%), mp 163—163.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.47 (s, 2H, NCH_2CO_2), 5.26 (s, 2H, CH_2Ar), 7.53 (dd, J=8.5, 1.9 Hz, 1H, Ar-H), 8.09 (d, J=1.9 Hz, 1H, Ar-H), 8.17 (d, J=8.5 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1749 (C=O), 1734 (C=O).

Ethyl 3-[(4-Chlorobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetate (**11h**): (Method C, 67%), mp 186.5—187.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.0 Hz, 3H, CH_3), 4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.46 (s, 2H, NCH_2CO_2), 5.28 (s, 2H, CH_2Ar), 7.47 (dd, J=8.0, 8.0 Hz, 1H, Ar-H), 7.64 (d, J=8.0 Hz, 1H, Ar-H), 8.11 (d, J=8.0 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 1735 (C=O), 1729 (C=O).

General Procedure for the Synthesis of 3-Arylmethyl-2,4,5-trioxoimidazolidine-1-acetic Acids (1—4, Chart 2) Method D. 3-(3-Nitrobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1a**): A mixture of ethyl 3-(3-nitrobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (**7a**, 3.70 g, 11.0 mol), AcOH (10 ml), and concentrated HCl (5 ml) was refluxed for 2.5 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was refluxed again with AcOH (10 ml) and concentrated HCl (5 ml) for an additional 2 h. The solid obtained by condensation was dissolved in EtOAc, washed with H_2O, and extracted with 10% aqueous Na_2CO_3. The aqueous layer was washed with EtOAc and acidified with concentrated HCl. The precipitated solid was extracted with EtOAc, washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Concentration followed by crystallization of the residue from Et_2O gave a crude solid, which was recrystallized from hexane–EtOAc to give **1a** as yellow crystals (2.30 g, 68%). ^{1}H-NMR (DMSO-d_6) δ: 4.30 (s, 2H, NCH_2CO_2), 4.91 (s, 2H, CH_2Ar), 7.65—8.25 (m, 4H, Ar-H), 13.42 (br s, 1H, COOH). IR (KBr) cm^{-1}: 1740 (C=O), 1720 (C=O), 1525 (NO_2), 1350 (NO_2). MS m/z: 307 (M^+).

Method E. 3-(3-Cyanobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1e**): A mixture of benzyl 3-(3-cyanobenzyl)-2,4,5-trioxoimidazolidine-1-acetate (1.85 g, 5.48 mmol) and 10% palladium on charcoal (0.23 g) in EtOAc (30 ml) was stirred at ambient temperature for 1.5 h under a hydrogen atmosphere. After removal of the catalyst, the filtrate was concentrated to give a solid, which was recrystallized from EtOH–hexane (30 ml–30 ml) to give **1e** (1.00 g, 64%). ^{1}H-NMR (DMSO-d_6) δ: 4.28 (s, 2H, NCH_2CO_2), 4.82 (s, 2H, CH_2Ar), 7.58 (dd, J=7.3, 7.3 Hz, 1H, Ar-H), 7.71 (d, J=7.3 Hz, 1H, Ar-H), 7.78 (d, J=7.3 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 13.48 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3100 (OH), 2231 (CN), 1738 (C=O), 1714 (C=O). MS m/z: 287 (M^+).

Compounds **1a—m**, **2a—c**, **3a—c**, and **4a—i** were prepared as described above.

3-(2-Trifluoromethylbenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1b**): (Method D, 89%), ^{1}H-NMR (DMSO-d_6) δ: 4.33 (s, 2H, NCH_2CO_2), 4.90 (s, 2H, CH_2Ar), 7.61—7.43 (m, 2H, Ar-H), 7.66 (dd, J=8.5, 7.0 Hz, 1H, Ar-H), 7.78 (d, J=8.5 Hz, 1H, Ar-H), 13.40 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3100 (OH), 1720 (C=O). MS m/z: 330 (M^+).

3-(3-Trifluoromethylbenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1c**): (Method D, 89%), ^{1}H-NMR (DMSO-d_6) δ: 4.32 (s, 2H, NCH_2CO_2), 4.87 (s, 2H, CH_2Ar), 7.60 (dd, J=7.5, 7.5 Hz, 1H, Ar-H), 7.64—7.72 (m, 2H, Ar-H), 7.74 (s, 1H, Ar-H), 13.44 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1730 (C=O). MS m/z: 330 (M^+).

3-(4-Trifluoromethylbenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1d**): (Method D, 88%), ^{1}H-NMR (DMSO-d_6) δ: 4.29 (s, 2H, NCH_2CO_2), 4.85 (s, 2H, CH_2Ar), 7.58 (d, J=7.9 Hz, 2H, Ar-H), 7.73 (d, J=7.9 Hz, 2H, Ar-H), 13.45 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1715 (C=O). MS m/z: 330 (M^+).

3-(3-Cyanobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1e**): (Method E, 64%), ^{1}H-NMR (DMSO-d_6) δ: 4.28 (s, 2H, NCH_2CO_2), 4.82 (s, 2H, CH_2Ar), 7.58 (dd, J=7.3, 7.3 Hz, 1H, Ar-H), 7.71 (d, J=7.3 Hz, 1H, Ar-H), 7.78 (d, J=7.3 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 13.48 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3100 (OH), 2231 (CN), 1738 (C=O), 1714 (C=O). MS m/z: 287 (M^+).

3-(4-Cyanobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1f**): (Method E, 90%), ^{1}H-NMR (DMSO-d_6) δ: 4.30 (s, 2H, NCH_2CO_2), 4.85 (s, 2H, CH_2Ar), 7.56 (d, J=7.9 Hz, 2H, Ar-H), 7.84 (d, J=7.9 Hz, 2H, Ar-H), 13.41 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 2250 (CN), 1730 (C=O). MS m/z: 287 (M^+).

3-(3-Carboxybenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1g**): (Method D, 89%), ^{1}H-NMR (DMSO-d_6) δ: 4.29 (s, 2H, NCH_2CO_2), 4.81 (s, 2H, CH_2Ar), 7.50 (dd, J=8.0, 8.0 Hz, 1H, Ar-H), 7.59 (d, J=8.0 Hz, 1H, Ar-H), 7.88 (d, J=8.0 Hz, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 13.14 (br s, 2H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1730 (C=O), 1705 (C=O). MS m/z: 306 (M^+).

3-(3-Methoxycarbonylbenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1h**): (Method E, 33%), ^{1}H-NMR (DMSO-d_6) δ: 3.86 (s, 3H, OCH_3), 4.30 (s, 2H, NCH_2CO_2), 4.82 (s, 2H, CH_2Ar), 7.52 (dd, J=8.0, 8.0 Hz, 1H, Ar-H), 7.63 (d, J=8.0 Hz, 2H, Ar-H), 7.90 (d, J=8.0 Hz, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 13.38 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3100 (OH), 1728 (C=O). MS m/z: 320 (M^+).

3-(3-Fluorobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1i**): (Method D, 75%), ^{1}H-NMR (DMSO-d_6) δ: 4.30 (s, 2H, NCH_2CO_2),

4.77 (s, 2H, CH_2Ar), 7.01—7.30 (m, 3H, Ar-H), 7.40 (dd, J=8.0, 8.0 Hz, 1H, Ar-H), 13.39 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1735 (C=O). MS m/z: 280 (M^+).

3-(2-Bromobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1j**): (Method D, 72%), ^{1}H-NMR (DMSO-d_6) δ: 4.32 (s, 2H, NCH_2CO_2), 4.48 (s, 2H, CH_2Ar), 7.27 (ddd, J=7.7, 7.7, 1.6 Hz, 1H, Ar-H), 7.37 (ddd, J=7.7, 7.7, 1.6 Hz, 1H, Ar-H), 7.42 (dd, J=7.7, 1.6 Hz, 1H, Ar-H), 7.66 (dd, J=7.7, 1.6 Hz, 1H, Ar-H), 13.40 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1734 (C=O), 1716 (C=O). MS m/z: 342 (M^+, ^{81}Br), 340 (M^+, ^{79}Br).

3-(3-Bromobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1k**): (Method D, 77%), ^{1}H-NMR (DMSO-d_6) δ: 4.30 (s, 2H, NCH_2CO_2), 4.76 (s, 2H, CH_2Ar), 7.25—7.43 (m, 2H, Ar-H), 7.50 (d, J=7.5 Hz, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 13.68 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1720 (C=O). MS m/z: 342 (M^+, ^{81}Br), 340 (M^+, ^{79}Br).

3-(4-Chloro-3-nitrobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1l**): (Method D, 66%), ^{1}H-NMR (DMSO-d_6) δ: 4.29 (s, 2H, NCH_2CO_2), 4.86 (s, 2H, CH_2Ar), 7.70 (dd, J=8.0, 1.5, 1H, Ar-H), 7.78 (d, J=8.0 Hz, 1H, Ar-H), 8.06 (d, J=1.5 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 3000 (OH), 1730 (C=O), 1710 (C=O), 1535 (NO_2), 1345 (NO_2). MS m/z: 343 (M^+, ^{37}Cl), 341 (M^+, ^{35}Cl).

3-(3,5-Dinitrobenzyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**1m**): (Method D, 67%), ^{1}H-NMR (DMSO-d_6) δ: 4.31 (s, 2H, NCH_2CO_2), 5.06 (s, 2H, CH_2Ar), 8.69 (d, J=1.5 Hz, 2H, Ar-H), 8.77 (t, J=1.5 Hz, 1H, Ar-H), 13.35 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1725 (C=O), 1535 (NO_2), 1355 (NO_2). MS m/z: 352 (M^+).

3-(2-Naphthylmethyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**2a**): (Method D, 99%), ^{1}H-NMR (DMSO-d_6) δ: 4.42 (s, 2H, NCH_2CO_2), 4.92 (s, 2H, CH_2Ar), 7.47 (dd, J=8.9, 2.0 Hz, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.52 (dd, J=9.4, 2.0 Hz, 1H, Ar-H), 7.86—7.94 (m, 4H, Ar-H), 13.46 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1768 (C=O), 1738 (C=O), 1716 (C=O). MS m/z: 312 (M^+).

3-[(1-Bromonaphthalen-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**2b**): (Method D, 77%), ^{1}H-NMR (DMSO-d_6) δ: 4.33 (s, 2H, NCH_2CO_2), 5.04 (s, 2H, CH_2Ar), 7.55 (d, J=8.9 Hz, 1H, Ar-H), 7.64 (dd, J=8.1, 7.4 Hz, 1H, Ar-H), 7.72 (dd, J=8.1, 7.4 Hz, 1H, Ar-H), 7.98 (d, J=8.1 Hz, 1H, Ar-H), 8.00 (d, J=8.1 Hz, 1H, Ar-H), 8.25 (d, J=8.9, 1H, Ar-H), 13.46 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1738 (C=O), 1720 (C=O). MS m/z: 392 (M^+, ^{81}Br), 390 (M^+, ^{79}Br).

3-(1-Naphthylmethyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**2c**): (Method D, 89%), ^{1}H-NMR (DMSO-d_6) δ: 4.34 (s, 2H, NCH_2CO_2), 5.21 (s, 2H, CH_2Ar), 7.34—7.64 (m, 4H, Ar-H, 7.90 (d, J=7.9 Hz, 1H, Ar-H), 7.98 (d, J=7.9 Hz, 1H, Ar-H), 8.20 (d, J=7.9 Hz, 1H, Ar-H). 13.42 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1738 (C=O), 1722 (C=O). MS m/z: 312 (M^+).

3-(2-Pyridylmethyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**3a**): (Method D, 67%), ^{1}H-NMR (DMSO-d_6) δ: 4.33 (s, 2H, NCH_2CO_2), 4.88 (s, 2H, CH_2Ar), 7.32 (dd, J=7.5, 3.5 Hz, 1H, Ar-H), 7.45 (d, J=7.5 Hz, 1H, Ar-H), 7.80 (dd, J=7.5, 7.5 Hz, 1H, Ar-H), 8.50 (d, J=3.5 Hz, 1H, Ar-H), 13.43 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1737 (C=O). MS m/z: 263 (M^+).

3-(3-Pyridylmethyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**3b**): (Method D, 56%), ^{1}H-NMR (DMSO-d_6) δ: 4.29 (s, 2H, NCH_2CO_2), 4.82 (s, 2H, CH_2Ar), 7.49 (dd, J=7.5, 5.0 Hz, 1H, Ar-H), 7.75 (d, J=7.5 Hz, 1H, Ar-H), 8.57 (d, J=5.0 Hz, 1H, Ar-H), 8.63 (s, 1H, Ar), 13.16 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1735 (C=O), 1705 (C=O).

3-(4-Pyridylmethyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**3c**): (Method D, 51%), ^{1}H-NMR (DMSO-d_6) δ: 4.31 (s, 2H, NCH_2CO_2), 4.80 (s, 2H, CH_2Ar), 7.37 (d, J=5.5 Hz, 2H, Ar-H), 8.54 (d, J=5.5 Hz, 2H, Ar-H), 13.30 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1740 (C=O).

3-(2-Benzothiazolylmethyl)-2,4,5-trioxoimidazolidine-1-acetic Acid (**4a**): (Method D, 87%), ^{1}H-NMR (DMSO-d_6) δ: 4.38 (s, 2H, NCH_2CO_2), 5.25 (s, 2H, CH_2Ar), 7.46 (dd, J=7.4, 7.4 Hz, 1H, Ar-H), 7.52 (dd, J=7.4, 7.4 Hz, 1H, Ar-H), 7.99 (d, J=7.4 Hz, 1H, Ar-H), 8.12 (d, J=7.4 Hz, 1H, Ar-H), 13.43 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3100 (OH), 1736 (C=O). MS m/z: 331 (M^+).

3-[(6-Methoxybenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**4b**): (Method D, 77%), ^{1}H-NMR (DMSO-d_6) δ: 3.83 (s, 3H, OCH_3), 4.34 (s, 2H, NCH_2CO_2), 5.18 (s, 2H, CH_2Ar), 7.11 (dd, J=8.9, 2.4 Hz, 1H, Ar-H), 7.67 (d, J=2.4 Hz, 1H, Ar-H), 7.87 (d, J=8.9 Hz, 1H, Ar-H). IR (KBr) cm^{-1}: 3000 (OH), 1734 (C=O). MS m/z: 349 (M^+).

3-[(6-Methylbenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**4c**): (Method D, 83%), ^{1}H-NMR (DMSO-d_6) δ: 2.44 (s, 3H, CH_3), 4.35 (s, 2H, NCH_2CO_2), 5.21 (s, 2H, CH_2Ar), 7.34 (d, J=8.3 Hz, 1H, Ar-H), 7.86 (d, J=8.3 Hz, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 13.47 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1738 (C=O). MS m/z: 333 (M^+).

3-[(6-Fluorobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**4d**): (Method D, 75%), ^{1}H-NMR (DMSO-d_6) δ: 4.34 (s, 2H, NCH_2CO_2), 5.22 (s, 2H, CH_2Ar), 7.34—7.41 (m, 1H, Ar-H), 7.97—8.06 (m, 2H, Ar-H), 13.43 (br s, 1H, COOH). IR (KBr) cm^{-1}: 2900 (OH), 1744 (C=O), 1721 (C=O). MS m/z: 337 (M^+).

3-[(6-Nitrobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**4e**): (Method D, 40%), ^{1}H-NMR (DMSO-d_6) δ: 4.36 (s, 2H, NCH_2CO_2), 5.34 (s, 2H, CH_2Ar), 8.19 (d, J=9.0 Hz, 1H, Ar-H), 8.34 (dd, J=9.0, 2.3 Hz, 1H, Ar-H), 9.21 (d, J=2.3 Hz, 1H, Ar-H), 13.47 (br s, 1H, COOH). IR (KBr) cm^{-1}: 1743 (C=O), 1738 (C=O), 1524 (NO_2), 1346 (NO_2). MS m/z: 364 (M^+).

3-[(6-Chlorobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**4f**): (Method D, 34%), ^{1}H-NMR (DMSO-d_6) δ: 4.36 (s, 2H, NCH_2CO_2), 5.25 (s, 2H, CH_2Ar), 7.56 (d, J=8.7 Hz, 1H, Ar-H), 7.99 (d, J=8.7 Hz, 1H, Ar-H), 8.29 (s, 1H, Ar-H), 13.45 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3000 (OH), 1746 (C=O), 1734 (C=O). MS m/z: 355 (M^+, ^{37}Cl), 353 (M^+, ^{35}Cl).

3-[(5-Chlorobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**4g**): (Method D, 52%), ^{1}H-NMR (DMSO-d_6) δ: 4.36 (s, 2H, NCH_2CO_2), 5.26 (s, 2H, CH_2Ar), 7.52 (dd, J=8.6, 2.0 Hz, 1H, Ar-H), 8.10 (d, J=2.0 Hz, 1H, Ar-H), 8.16 (d, J=8.6 Hz, 1H, Ar-H), 13.45 (br s, 1H, COOH). IR (KBr) cm^{-1}: 3006 (OH), 1782 (C=O), 1741 (C=O). MS m/z: 355 (M^+, ^{37}Cl), 353 (M^+, ^{35}Cl).

3-[(4-Chlorobenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**4h**): (Method D, 99%), ^{1}H-NMR (DMSO-d_6) δ: 4.35 (s, 2H, NCH_2CO_2), 5.27 (s, 2H, CH_2Ar), 7.47 (dd, J=8.0, 8.0 Hz, 1H, Ar-H), 7.63 (d, J=8.0 Hz, 1H, Ar-H), 8.11 (d, J=8.0 Hz, 1H, Ar-H), 13.41 (br s, 1H, COOH). IR (KBr) cm^{-1}: 2900 (OH), 1732 (C=O), 1741 (C=O). MS m/z: 355 (M^+, ^{37}Cl), 353 (M^+, ^{35}Cl).

3-[(5-Trifluoromethylbenzothiazol-2-yl)methyl]-2,4,5-trioxoimidazolidine-1-acetic Acid (**4i**): (Method D, 77%), ^{1}H-NMR (DMSO-d_6) δ: 4.36 (s, 2H, NCH_2CO_2), 5.32 (s, 2H, CH_2Ar), 7.80 (d, J=8.4 Hz, 1H, Ar-H), 8.37 (s, 1H, Ar-H), 8.39 (d, J=8.4 Hz, 1H, Ar-H), 13.47 (br s, 1H, COOH). IR (KBr) cm^{-1}: 2926 (OH), 1741 (C=O). MS m/z: 387 (M^+).

Purification of Enzymes The procedures employed for isolation of rat lens AR and rat kidney ALR were reported in the previous publication.[5]

Enzyme Assay *In vitro* AR and ALR inhibition assays were conducted according to the method reported elsewhere.[5]

References and Notes

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