Synthesis and Aldose Reductase Inhibitory Activities of Benzyl 2-Oxazolecarbamate Analogues

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Various analogues of benzyl 5-phenyl-2-oxazolecarbamate (1a) were synthesized, and the structure–activity relationship of these analogues as aldose reductase inhibitor was studied. The carbamate group was necessary for the inhibitory activity. The introduction of an alkyl group at the C-4 position of 1a enhanced the inhibitory activity, however, the *N*-carboxymethyl group on the carbamate moiety counteracted to a hydrophobic interaction between the alkyl group at the C-4 position and the enzyme molecule.

Keywords aldose reductase inhibitor; structure–activity relationship; benzyl oxazolecarbamate; oxazolecarboxylic acid derivative; oxazole derivative

The intracellular accumulation of sorbitol in insulin-insensitive tissues is the common basis of the pathological mechanisms resulting in diabetic complications such as cataract, neuropathy, retinopathy and nephropathy.[1] Since sorbitol is produced from glucose by aldose reductase through the polyol pathway, it has been suggested that aldose reductase may be implicated in the pathogenesis of diabetic complications. Therefore, the inhibition of aldose reductase is regarded as a pharmacological approach for preventing and treating chronic complications of diabetes. Some aldose reductase inhibitors, for example tolrestat, ponalrestat, sorbinil and epalrestat have been subjected to clinical trials.

We have previously studied the synthesis and the inhibitory activity of oxazole derivatives, and found that the benzylcarbamate group at the C-2 position and the phenyl group at C-5 of the oxazole skeleton were necessary for potent aldose reductase inhibitory activity and the introduction of an alkyl group at the C-4 position increased the inhibitory activity.[2,3]

We are interested in studying the structure–activity relationship of 5-phenyloxazole derivatives as aldose reductase inhibitor. In this paper, we report the synthesis and inhibitory activity of various analogues of benzyl 5-phenyl-2-oxazolecarbamate (**1a**).

Chemistry The *N*-alkylation of benzyl 5-phenyl-2-

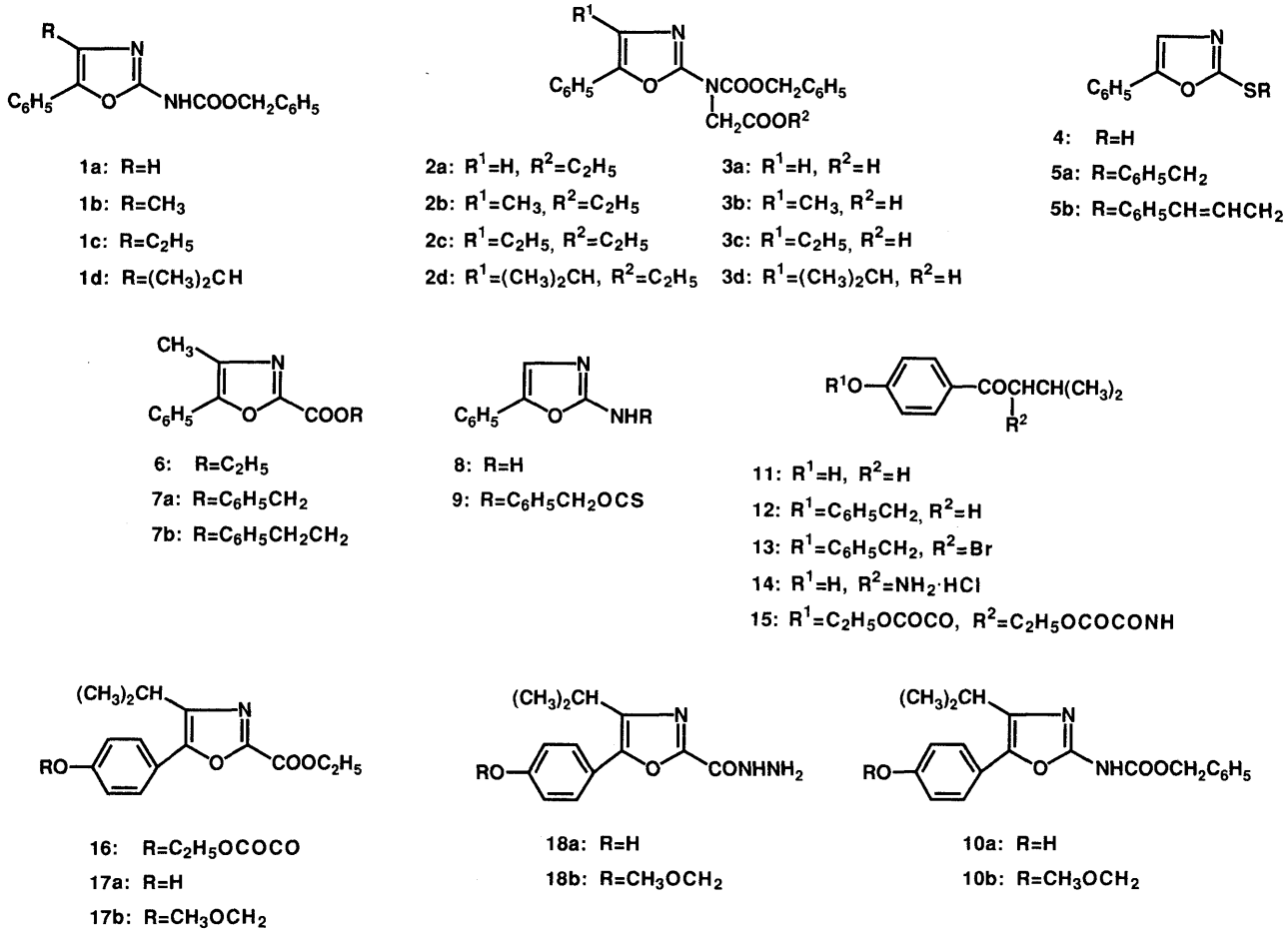

Chart 1

oxazole-carbamates (**1a—d**) with sodium hydride and ethyl bromoacetate provided the *N*-ethoxycarbonylmethyl derivatives (**2a—d**). Hydrolysis of **2a—d** with 1 N NaOH yielded benzyl *N*-carboxymethyl-2-oxazolecarbamates (**3a—d**). The *S*-alkylation of 2-mercapto-5-phenyloxazole (**4**) with potassium carbonate and benzyl chloride or cinnamyl chloride afforded the corresponding aralkylthioxazoles (**5a, b**). Heating of ethyl 4-methyl-5-phenyl-2-oxazolecarboxylate (**6**) with benzyl alcohol or phenethyl alcohol in the presence of tetraethyl titanate[4] afforded the corresponding aralkyl esters (**7a, b**). Stirring of 2-amino-5-phenyloxazole (**8**) with bis[benzyloxy(thiocarbonyl)]sulfide in chloroform afforded benzyl 5-phenyl-2-oxazolethiocarbamate (**9**). Benzyl 5-(*p*-hydroxyphenyl)-4-isopropyl-2-oxazolecarbamate hydrate (**10a**) was prepared by the general method reported in the previous peper.[5] Refluxing of 1-(*p*-hydroxyphenyl)-3-methyl-1-butanone (**11**), benzyl chloride and potassium carbonate in ethanol gave the benzyloxy derivative (**12**). Bromination of **12** in methanol gave the 2-bromo substituent (**13**), which was converted to the 2-amino substituent (**14**) by the Gabriel method. Ethoxalylation of **14** with ethyl chloroglyoxylate followed by dehydration of the *N,O*-bisethoxalyl substituent (**15**) with phosphorus oxychloride gave the 2-oxazolecarboxylic acid derivative (**16**). Hydro-

TABLE I. Physical and Spectral Data for Benzyl *N*-Ethoxycarbonylmethyl-4-R^1-5-phenyl-2-oxazolecarbamates (**2a—d**)

Compd. No.	R^1	mp (bp/mmHg) (°C)	IR $\nu_{max}^{CHCl_3}$ (cm^{-1})	^{1}H-NMR (δ in $CDCl_3$) (J=Hz)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
2a	H	52—53 (130/2)	1730	1.25 (3H, t, 7.2, $OCH_2C\underline{H}_3$) 4.22 (2H, q, 7.2, $OC\underline{H}_2CH_3$) 4.65 (2H, s, CH_2CO) 5.33 (2H, s, $C\underline{H}_2C_6H_5$) 7.16 (1H, s, C_4-H)	$C_{21}H_{20}N_2O_5$	66.47 (66.30	5.31 5.30	7.26 7.37)
2b	CH_3	(180/2)	1725	1.25 (3H, t, 7.1, $OCH_2C\underline{H}_3$) 2.36 (3H, s, C_4-CH_3) 4.22 (2H, q, 7.1, $OC\underline{H}_2CH_3$) 4.64 (2H, s, CH_2CO) 5.32 (2H, s, $C\underline{H}_2C_6H_5$)	$C_{22}H_{22}N_2O_5$	67.01 (66.99	5.58 5.62	7.10 7.10)
2c	C_2H_5	(220/2)	1725	1.26 (3H, t, 7.6, C_4-$CH_2C\underline{H}_3$) 1.28 (3H, t, 7.3, $OCH_2C\underline{H}_3$) 2.71 (2H, q, 7.6, C_4-$C\underline{H}_2CH_3$) 4.21 (2H, q, 7.3, $OC\underline{H}_2CH_3$) 4.65 (2H, s, CH_2CO) 5.32 (2H, s, $C\underline{H}_2C_6H_5$)	$C_{23}H_{24}N_2O_5$	67.63 (67.44	5.92 5.94	6.86 6.61)
2d	$(CH_3)_2CH$	(180/2)	1730	1.25 (3H, t, 7.2, $OCH_2C\underline{H}_3$) 1.26 (6H, d, 6.5, $CH_3\times2$) 3.18 (1H, hep, 6.5, $C\underline{H}(CH_3)_2$) 4.22 (2H, q, 7.2, $OC\underline{H}_2CH_3$) 4.65 (2H, s, CH_2CO) 5.31 (2H, s, $C\underline{H}_2C_6H_5$)	$C_{24}H_{26}N_2O_5$	68.25 (68.26	6.16 6.22	6.63 6.62)

TABLE II. Physical and Spectral Data for Benzyl *N*-Carboxymethyl-4-R^1-5-phenyl-2-oxazolecarbamates (**3a—d**)

Compd. No.	R^1	mp (°C)	Yield (%)[a]	IR $\nu_{max}^{CHCl_3}$ (cm^{-1})	^{1}H-NMR (δ in $CDCl_3$) (J=Hz)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
3a	H	157—158	52	3360 1735	4.68 (2H, s, CH_2CO) 5.34 (2H, s, $C\underline{H}_2C_6H_5$) 7.20 (1H, s, C_4-H) 7.26 (1H, br, OH)	$C_{19}H_{16}N_2O_5$	64.89 (64.77	4.53 4.58	7.97 7.95)
3b	CH_3	152—154	68	3340 1725	2.36 (3H, s, CH_3) 4.65 (2H, s, CH_2CO) 5.32 (2H, s, $C\underline{H}_2C_6H_5$) 7.64 (1H, br, OH)	$C_{20}H_{18}N_2O_5$	65.60 (65.56	4.95 4.95	7.68 7.65)
3c	C_2H_5	110—112	55	3360 1725	1.26 (3H, t, 7.6, $CH_2C\underline{H}_3$) 2.73 (2H, q, 7.6, $C\underline{H}_2CH_3$) 4.66 (2H, s, CH_2CO) 5.32 (2H, s, $C\underline{H}_2C_6H_5$) 8.44 (1H, br, OH)	$C_{21}H_{20}N_2O_5$	66.30 (66.00	5.30 5.28	7.37 7.35)
3d	$(CH_3)_2CH$	110—111	64	3360 1725	1.27 (6H, d, 6.8, $CH_3\times2$) 3.18 (1H, hep, 6.8, $C\underline{H}(CH_3)_2$) 4.68 (2H, s, CH_2CO) 5.31 (2H, s, $C\underline{H}_2C_6H_5$) 9.18 (1H, br, OH)	$C_{22}H_{22}N_2O_5$	66.99 (66.97	5.62 5.58	7.10 7.38)

a) Yields were calculated from benzyl 2-oxazolecarbamates (**1**).

TABLE III. Aldose Reductase-Inhibitory Activity

Compd.	IC_{50} (μM)	Compd.	IC_{50} (μM)
1a	15	**5a**	213
1b	2.0	**5b**	121
1c	0.68	**6**	82
1d	0.38	**7a**	26
3a	0.56	**7b**	94
3b	0.73	**9**	a)
3c	0.52	**10a**	4.8
3d	0.67	**19**	290
Sorbinil	0.75	Epalrestat	0.02

a) At 10^{-5} M, no inhibition.

lysis of **16** with 1% HCl afforded ethyl 5-(*p*-hydroxyphenyl)-4-isopropyl-2-oxazolecarboxylate (**17a**). Refluxing of **17a** with hydrazine in ethanol followed by the Curtius reaction of the hydrazide derivative (**18a**) afforded **10a** in low yield (23%). On the other hand, stirring of **17a** with chloromethoxymethane and *N*,*N*-diisopropylethylamine in dichloromethane afforded ethyl 4-isopropyl-5-(*p*-methoxymethoxyphenyl)-2-oxazolecarboxylate (**17b**). Compound **17b** was converted to the carbamate derivative (**10b**) *via* the hydrazide derivative (**18b**) by the similar method of **10a**. Deprotection of **10b** with trimethylsilyl bromide or 5% HCl afforded **10a** in good yield (*ca.* 75%).

Inhibitory Activity The inhibitory activities of oxazole derivatives described above were examined using rabbit lens aldose reductase, and the results are shown in Table III. Among the compounds, *N*-carboxymethyl derivatives (**3a—d**) displayed a potency comparable to that of sorbinil, but were less active than epalrestat. Introduction of an alkyl group at the C-4 position of **1a** enhanced the activity in the following order: isopropyl > ethyl > methyl. An increase of activity by that introduction was also observed between benzyl 5-(*p*-hydroxyphenyl)-2-oxazolecarbamate (**19**)[5] and **10a**. By the introduction of the *N*-carboxymethyl group, the activities of **1a** and **1b** were increased and those of **1c** and **1d** were little affected. However, all *N*-carboxymethyl derivatives (**3a—d**) have shown almost the same activities, and had IC_{50} values of *ca.* 6×10^{-7} M. It was suggested that the introduction of the *N*-carboxymethyl group counteracted to a hydrophobic interaction between the alkyl group at the C-4 position and the enzyme molecule. The conversion of the phenyl group into a phenol group at the C-5 position (**1a** → **19**, **1d** → **10a**) decreased the activity more than 10^{-1} times. This finding suggested that the substituent group formed hydrophobic interaction at the C-5 position is preferable to that formed by hydrogen bonding for the appearance of inhibitory activity. The conversion of the carbamate group into a carboxylate group (**1b** → **6**, **7a**, **7b**) also decreased the activity. Introduction of an aralkylthio group at the C-2 position (**1a** → **5a**, **5b**) gave rise to a decrease in the activity. Compound **9** with the thiocarbamate group at the C-2 position virtually did not exhibit the activity. This suggested that the carbamate group (–NHCO–) was essential for the inhibitory activity.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Jasco IRA-1 or IR-700 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Varian Gemini-200 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a Hitachi M-80 mass spectrometer.

Benzyl *N*-Ethoxycarbonylmethyl-5-phenyl-2-oxazolecarbamates (2a—d) NaH (60% dispersed in oil) (0.08 g, 0.2 mmol) was added in portions to a stirred solution of **1a—d**[6] (1 mmol) in anhydrous tetrahydrofuran (THF, 3 ml) over a period of 1 h at 60 °C. To the sodium salt, ethyl bromoacetate (0.68 g, 4 mmol) was added dropwise, and allowed to stir for 3 h at 60 °C. The reaction mixture was poured onto ice water and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and concentrated. The resulting oil was distilled under reduced pressure to give the corresponding ester (**2a—d**). Physical and spectral data are summarized in Table I.

Benzyl *N*-Carboxymethyl-5-phenyl-2-oxazolecarbamates (3a—d) A solution of **2a—d** (1 mmol) and 1 N NaOH (1.5 ml) in EtOH (1 ml) was stirred at 60 °C for 2 h. The reaction mixture was acidified with AcOH, and distilled off *in vacuo*. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and concentrated. The resulting solid was recrystallized with $CHCl_3$–hexane to give the corresponding acid (**3a—d**) as colorless needles. Physical and spectral data are summarized in Table II.

2-Aralkylthio-5-phenyloxazoles (5a, b) A mixture of **4**[7] (1 mmol), benzyl chloride or cinnamyl chloride (1.4 mmol) and K_2CO_3 (1.1 mmol) in Me_2CO (8 ml) was stirred at room temperature for 36 h. The solvent was distilled off *in vacuo*. The residue was dissolved in water and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and concentrated. The resulting solid was recrystallized to give the corresponding sulfide (**5a, b**).

2-Benzylthio- (**5a**): Yield 73%, colorless needles (from $CHCl_3$–hexane), mp 85—86 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1490, 1180. ^{1}H-NMR ($CDCl_3$) δ: 4.45 (2H, s, CH_2). *Anal.* Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.84; H, 4.86; N, 5.19. MS *m/z*: 267 (M^+).

2-Cinnamylthio- (**5b**): Yield 58%, colorless leaflets (from hexane), mp 45—46 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1490, 1180. ^{1}H-NMR ($CDCl_3$) δ: 4.03 (2H, dd, J=8.4, 7.2 Hz, $C\underline{H}_2CH$), 6.37 (1H, ddd, J=15.7, 8.4, 7.2 Hz, $CH_2C\underline{H}$=CH), 6.67 (1H, d, J=15.7 Hz, CH_2CH=C$\underline{H}$). *Anal.* Calcd for $C_{18}H_{15}NOS$: C, 73.69; H, 5.15; N, 4.78. Found: C, 73.77; H, 5.15; N, 4.73. MS *m/z*: 293 (M^+).

Aralkyl 4-Methyl-5-phenyl-2-oxazolecarboxylates (7a, b) A mixture of **6** (2 mmol), benzyl alcohol or phenethyl alcohol (4 mmol) and tetraethyl titanate (0.03 mmol) was heated with stirring at 100 °C for 15 h. The reaction mixture was quenched with 1 N HCl (1.6 ml), and extracted with $CHCl_3$. The extract was washed with water, 10% $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The resulting solid was recrystallized from hexane to give the corresponding ester (**7a, b**).

Benzyl Ester: Yield 71%, colorless needles, mp 94—95 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s, CH_3), 5.45 (2H, s, CH_2). *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.90; H. 5.17, N, 4.76. MS *m/z*: 293 (M^+).

Phenethyl Ester: Yield 57%, colorless leaflets, mp 79—80 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, CH_3), 3.14 (2H, t, J=7.5 Hz, $OC\underline{H}_2CH_2$), 4.62 (2H, t, J=7.5 Hz, $OCH_2C\underline{H}_2$). *Anal.* Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.57; N, 4.56. Found: C, 74.08; H, 5.58; N, 4.52. MS *m/z*: 307 (M^+).

Benzyl 5-Phenyl-2-oxazolethiocarbamate (9) A solution of **8** (0.68 g, 4.24 mmol) and bis[benzyloxy(thiocarbonyl)]sulfide[8] (0.71 g, 2.12 mmol) in $CHCl_3$ (18 ml) was stirred at room temperature for 76 h. The reaction mixture was washed with 1 N HCl and water, dried (Na_2SO_4) and concentrated. The resulting solid was recrystallized from $CHCl_3$ to give **9** (0.83 g, 63%) as pale yellow needles, mp 147—148 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1221 (C=S). ^{1}H-NMR ($CDCl_3$) δ: 5.64 (2H, s, CH_2), 9.18 (1H, br, NH). *Anal.* Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.02. Found: C, 65.52; H, 4.48; N, 8.90.

1-(*p*-Benzyloxyphenyl)-3-methyl-1-butanone (12) A mixture of **11**[9] (18.9 g, 0.11 mol), benzyl chloride (14.5 g, 0.12 mol), NaI (0.7 g), K_2CO_3 (10.7 g) and EtOH (53 ml) was refluxed for 5 h with stirring. After removal of the solvent, the residue was poured into water. The resulting solid was washed thoroughly with water and recrystallized from EtOH to give **12** (26.4 g, 93%) as colorless leaflets, mp 69—70 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (6H, d, J=6.8 Hz, CH_3 × 2), 2.28 (1H, hep, J=6.8 Hz, CH), 2.78 (2H, d, J=6.8 Hz, $C\underline{H}_2CH$), 5.14 (2H, s, $C\underline{H}_2C_6H_5$). *Anal.* Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.30; H, 7.57.

1-(*p*-Benzyloxyphenyl)-2-bromo-3-methyl-1-butanone (13) Br_2 (3.84 g, 24 mmol) was added dropwise to a solution of **12** (5.33 g, 20 mmol) in MeOH (14 ml) with stirring at 50 °C. The stirring was continued for 3 h at 50 °C. After removal of the solvent, the residue was recrystallized from

$CHCl_3$–hexane to give **13** (4.71 g, 68%) as colorless plates, mp 91—93 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=6.6 Hz, CH_3), 1.23 (3H, d, J=6.6 Hz, CH_3), 2.47 (1H, d of hep, J=8.6, 6.6 Hz, C<u>H</u> (CH_3)$_2$), 4.91 (1H, d, J=8.6 Hz, COCH), 5.16 (2H, s, CH_2). *Anal.* Calcd for $C_{18}H_{19}BrO_2$: C, 62.23; H, 5.51. Found: C, 62.39; H, 5.52.

2-Amino-1-(*p*-hydroxyphenyl)-3-methyl-1-butanone Hydrochloride (14) A mixture of **13** (35.0 g, 0.10 mol), potassium phthalimide (20.2 g, 0.11 mol) and dimethylformamide (DMF, 95 ml) was heated at 120 °C for 12 h with stirring. The reaction mixture was poured into water. The precipitate was recrystallized from EtOH to give the phthalimido derivative (34.2 g, 82%) as colorless prisms, mp 133—134 °C. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.6 Hz, CH_3), 1.05 (3H, d, J=6.6 Hz, CH_3), 2.79 (1H, d of hep, J=8.2, 6.6 Hz, C<u>H</u>(CH_3)$_2$), 5.12 (2H, s, CH_2), 5.32 (1H, d, J=8.2 Hz, COCH). *Anal.* Calcd for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.70; H, 5.60; N, 3.36.

A mixture of the above phthalimido derivative (38.7 g), conc. HCl (52 ml) and AcOH (13 ml) was refluxed for 24 h. The reaction mixture was poured into water, and the precipitate was filtered off. The filtrate was evaporated *in vacuo*. The residue was recrystallized from EtOH to give **14** (15.5 g, 72%) as colorless prisms, mp 270 °C. IR ν_{max}^{KBr} cm^{-1}: 2980 (NH_3, OH), 1660 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 0.81 (3H, d, J=7.0 Hz, CH_3), 1.02 (3H, d, J=7.0 Hz, CH_3), 2.21 (1H, m, C<u>H</u>(CH_3)$_2$), 4.92 (1H, d, J=4.4 Hz, COCH), 8.38 (3H, br, NH_3). *Anal.* Calcd for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.36; H, 6.97; N, 6.00.

2-Ethoxalylamino-1-(*p*-ethoxalyloxyphenyl)-3-methyl-1-butanone (15) A mixture of **14** (2.75 g, 12 mmol), ethyl chloroglyoxylate (3.92 g, 29 mmol) and dry benzene (13 ml) was refluxed for 12 h. The reaction mixture was poured into water and extracted with benzene. The extract was washed with water, 10% $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated to give the crude **15** (3.27 g, 69.5%) as oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (NH), 1730, 1700, 1680 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=6.8 Hz, CH_3), 1.06 (3H, d, J=6.8 Hz, CH_3), 1.41 (3H, t, J=7.2 Hz, CH_2C<u>H</u>$_3$), 1.46 (3H, t, J=7.2 Hz, CH_2C<u>H</u>$_3$), 2.30 (1H, m, C<u>H</u>(CH_3)$_2$), 4.39 (2H, q, J=7.2 Hz, C<u>H</u>$_2CH_3$), 4.48 (2H, q, J=7.2 Hz, C<u>H</u>$_2CH_3$), 5.54 (1H, dd, J=9.6, 4.8 Hz, C<u>H</u>NH), 7.87 (1H, d, J=9.6 Hz, NH).

Ethyl 5-(*p*-Ethoxalyloxypheny)-4-isopropyl-2-oxazolecarboxylate (16) A mixture of **15** (3.19 g, 8.1 mmol), $POCl_3$ (3.9 g, 25.4 mmol) and dry benzene (5 ml) was refluxed for 10 h. After removal of the solvent and excess $POCl_3$, the residue was poured onto ice water, and extracted with $CHCl_3$. The extract was washed with water, 10% $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The resulting oil was distilled in reduced pressure to give **16** (2.86 g, 94%) as colorless oil, bp 230 °C (3 mmHg) (bath temperature). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, d, J=7.0 Hz, CH (CH_3)$_2$), 1.46 (3H, t, J=7.0 Hz, CH_2C<u>H</u>$_3$), 1.47 (3H, t, J=7.0 Hz, CH_2C<u>H</u>$_3$), 3.28 (1H, hep, J=6.8 Hz, CH), 4.48 (2H, q, J=7.0 Hz, C<u>H</u>$_2CH_3$), 4.52 (2H, q, J=7.0 Hz, C<u>H</u>$_2CH_3$). *Anal.* Calcd for $C_{19}H_{21}NO_7$: C, 60.79; H, 5.64; N, 3.73. Found: C, 60.81; H, 5.85, N, 3.97.

Ethyl 5-(*p*-Hydroxyphenyl)-4-isopropyl-2-oxazolecarboxylate (17a) A solution of **16** (10.6 g, 28.2 mmol) and 1% HCl (150 ml) in EtOH (100 ml) was refluxed for 10 h. The solvent was evaporated off *in vacuo*, and the residue was recrystallized from EtOH–water to give **17a** (5.90 g, 76%) as colorless needles, mp 232—233 °C. IR ν_{max}^{KBr} cm^{-1}: 3334, 3234 (OH, NH, (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (6H, d, J=6.6 Hz, CH(CH_3)$_2$), 1.40 (3H, t, J=7.1 Hz, CH_2C<u>H</u>$_3$), 3.25 (1H, hep, J=6.6 Hz, CH), 4.48 (2H, q, J=7.1 Hz, C<u>H</u>$_2CH_3$), 4.88 (1H, br, OH). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08. Found: C, 65.56; H, 6.23; N, 4.94.

5-(*p*-Hydroxyphenyl)-4-isopropyl-2-oxazolecarbohydrazide (18a) A mixture of **17a** (3.49 g, 12.7 mmol), hydrazine hydrate (0.76 g, 15.2 mmol) and EtOH (24 ml) was refluxed for 1 h. After removal of the solvent, the resulting solid was recrystallized from EtOH to give **18a** (3.12 g, 95%) as colorless needles, mp 232—233 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3334, 3234 (OH, NH, NH_2), 1685 (C=O). ^{1}H-NMR (CMSO-d_6) δ: 1.24 (6H, d, J=6.8 Hz, CH(CH_3)$_2$), 3.19 (1H, hep, J=6.8 Hz, CH), 4.62 (2H, br, NH_2), 9.90 (1H, s, OH), 10.11 (1H, br, NH). *Anal.* Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.66; H, 5.80; N, 16.01.

Benzyl 5-(*p*-Hydroxyphenyl)-4-isopropyl-2-oxazolecarbamate Hydrate (10a) A solution of $NaNO_2$ (0.54 g, 7.8 mmol) in water (2 ml) was added dropwise to a stirred mixture of **18a** (1.6 g, 6.1 mmol), conc. HCl (0.8 ml), AcOH (6 ml) and benzene (12 ml) at 0—5 °C. The stirring was continued for 1 h. The reaction mixture was diluted with water, extracted with $CHCl_3$. The extract was washed with water, 10% $NaHCO_3$ and water, dried (Na_2SO_4). Both benzyl alcohol (1.26 g, 12 mmol) and toluene (10 ml) were added to the above solution, and the whole was concentrated to *ca.* 10 ml, then refluxed for 1.5 h. After removal of the solvent, the resulting solid was subjected to silica gel column chromatography using $CHCl_3$–EtOAc (5 : 1) and recrystallized from $CHCl_3$–hexane to give **10a** (0.5 g, 23%) as colorless leaflets, mp 146—148 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3412 (NH), 3350 (OH), 1729 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, d, J=6.7 Hz, CH(CH_3)$_2$), 3.12 (1H, hep, J=6.7 Hz, CH), 5.24 (2H, s, CH_2), 11.00 (1H, br, OH). *Anal.* Calcd for $C_{20}H_{20}N_2O_4 \cdot H_2O$: C, 64.85; H, 5.99; N, 7.56. Found; C, 64.84; H, 5.73; N, 7.56. MS *m/z*: 352 (M^+).

Ethyl 4-Isopropyl-5-(*p*-methoxymethoxyphenyl)-2-oxazolecarboxylate (17b) A solution of **17a** (0.5 g, 1.8 mmol), *N*,*N*-diisopropylethylamine (0.7 g, 5.4 mmol) and chloromethoxymethane (0.29 g, 3.6 mmol) in CH_2Cl_2 (7 ml) was stirred at room temperature for 4 h. The reaction mixture was washed with 10%AcOH, 10%$NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The resulting oil was subjected to silica gel column chromatography using $CHCl_3$–EtOAc (10 : 1) and distilled in reduced pressure to give **17b** (0.23 g, 77%) as pale yellow solid, bp 170 °C (1 mmHg) (bath temperature), mp 35—37 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1731. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, d, J=6.9 Hz, CH (CH_3)$_2$), 1.40 (3H, t, J=7.0 Hz, CH_2C<u>H</u>$_3$), 3.20 (1H, hep, J=6.9 Hz, C<u>H</u>(CH_3)$_2$), 3.46 (3H, s, OCH_3), 4.46 (2H, q, J=7.0 Hz, C<u>H</u>$_2CH_3$), 5.19 (2H, s, OCH_2O). *Anal.* Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.94; H, 6.67; N, 4.39. MS *m/z*: 319 (M^+).

4-Isopropyl-5-(*p*-methoxymethoxyphenyl)-2-oxazolecarbohydrazide (18b) Compound **17b** (1.49 g, 4.69 mmol) and hydrazine hydrate (0.47 g, 5.63 mmol) were treated as described for **18a** to give **18b** (1.30 g, 92%) as yellow needles, mp 94—96 °C. IR ν_{max}^{KBr} cm^{-1}: 3436, 3355, 3314 (NH_2, NH), 1693 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, *d*, J=6.8 Hz, CH(CH_3)$_2$), 3.18 (1H, hep, J=6.8 Hz, C<u>H</u>(CH_3)$_2$), 3.47 (3H, s, OCH_3), 4.06 (2H, br, NH_2), 5.19 (2H, s, OCH_2O), 8.21 (1H, br, NH). *Anal.* Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.88; H, 6.25; N, 13.51. MS *m/z*: 305 (M^+).

Benzyl 4-Isopropyl-5-(*p*-methoxymethoxyphenyl)-2-oxazolecarbamate (10b) Compound **18b** (0.78 g, 2.6 mmol), $NaNO_2$ (0.2 g, 3.0 mmol) and benzyl alcohol (0.5 ml, 4.4 mmol) were treated as described for **10a** to give **10b** (0.7 g, 58%) as colorless oil, bp 120 °C (1 mmHg) (bath temperature). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 1729 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, d, J=6.8 Hz, CH(CH_3)$_2$), 3.12 (1H, hep, J=6.8 Hz, C<u>H</u>(CH_3)$_2$), 3.47 (3H, s, OCH_3), 5.18 (2H, s, OCH_2O), 5.21 (2H, s, C<u>H</u>$_2C_6H_5$). MS *m/z*: 396 (M^+). High-resolution MS *m/z*: Calcd for $C_{22}H_{24}N_2O_5$: 396.1686; Found: 396.1685.

Synthesis of 10a by Deprotection of 10b Method A: A solution of **10b** (0.29 g, 0.73 mmol) and trimethylsilyl bromide (0.38 ml, 2.93 mmol) in CH_2Cl_2 (5 ml) was stirred for 2 h at −30 °C. The reaction mixture was poured into 10% $NaHCO_3$, extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated. The residue was chromatographed to give **10a** (0.20 g, 77%).

Method B: A solution of **10b** (0.19 g, 0.48 mmol) and 5%HCl (0.4 ml) in AcOH (2 ml) was evaporated off *in vacuo* at 80 °C. The residue afforded **10a** (0.13 g, 76%).

Determination of Aldose Reductase Activity and IC_{50} The determination of rabbit lens aldose reductase activity and the concentration of inhibitor giving 50% inhibition of enzyme activity (IC_{50}) was performed by the method described in the previous paper.[3]

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