

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.

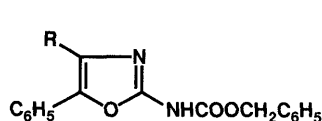
Keywords aldose reductase inhibitor; structure–activity relationship; benzyl oxazolecarbamate; oxazolecarboxylic acid derivative; oxazole derivative

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.

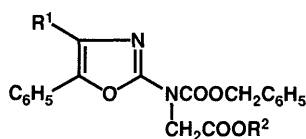
We have previously studied the synthesis and the inhibitory activity of oxazole derivatives, and found that the benzylcarbamate group at the C-2 position and the phenyl group at C-5 of the oxazole skeleton were necessary for potent aldose reductase inhibitory activity and the introduction of an alkyl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

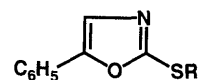
Chemistry The *N*-alkylation of benzyl 5-phenyl-2-



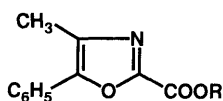
- 1a: R=H
1b: R=CH₃
1c: R=C₂H₅
1d: R=(CH₃)₂CH



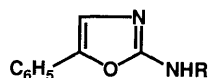
- 2a: R¹=H, R²=C₂H₅
2b: R¹=CH₃, R²=C₂H₅
2c: R¹=C₂H₅, R²=C₂H₅
2d: R¹=(CH₃)₂CH, R²=C₂H₅



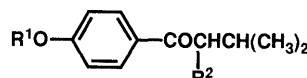
- 4: R=H
5a: R=C₆H₅CH₂
5b: R=C₆H₅CH=CHCH₂



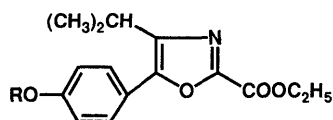
- 6: R=C₂H₅
7a: R=C₆H₅CH₂
7b: R=C₆H₅CH₂CH₂



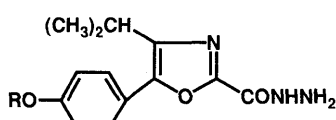
- 8: R=H
9: R=C₆H₅CH₂OCS



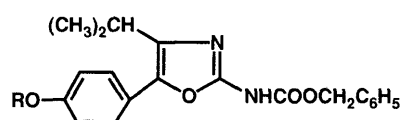
- 11: R¹=H, R²=H
12: R¹=C₆H₅CH₂, R²=H
13: R¹=C₆H₅CH₂, R²=Br
14: R¹=H, R²=NH₂·HCl
15: R¹=C₂H₅OCOCO, R²=C₂H₅OCOCO



- 16: R=C₂H₅OCOCO
17a: R=H
17b: R=CH₃OCH₂



- 18a: R=H
18b: R=CH₃OCH₂



- 10a: R=H
10b: R=CH₃OCH₂

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 titanate⁴) 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 paper.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. Ethoxalylolation 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.	<i>R</i> ¹	mp (bp/mmHg) (°C)	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm ⁻¹)	¹ H-NMR (δ in CDCl ₃) (<i>J</i> = Hz)	Formula	Analysis (%)		
						Calcd	Found	
						C	H	N
2a	H	52—53 (130/2)	1730	1.25 (3H, t, 7.2, OCH ₂ CH ₃) 4.22 (2H, q, 7.2, OCH ₂ CH ₃) 4.65 (2H, s, CH ₂ CO) 5.33 (2H, s, CH ₂ C ₆ H ₅) 7.16 (1H, s, C ₄ -H)	C ₂₁ H ₂₀ N ₂ O 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 ₂ CH ₃) 2.36 (3H, s, C ₄ -CH ₃) 4.22 (2H, q, 7.1, OCH ₂ CH ₃) 4.64 (2H, s, CH ₂ CO) 5.32 (2H, s, CH ₂ C ₆ H ₅)	C ₂₂ H ₂₂ N ₂ O ₅	67.01 (66.99)	5.58 5.62	7.10 7.10)
2c	C ₂ H ₅	(220/2)	1725	1.26 (3H, t, 7.6, C ₄ -CH ₂ CH ₃) 1.28 (3H, t, 7.3, OCH ₂ CH ₃) 2.71 (2H, q, 7.6, C ₄ -CH ₂ CH ₃) 4.21 (2H, q, 7.3, OCH ₂ CH ₃) 4.65 (2H, s, CH ₂ CO) 5.32 (2H, s, CH ₂ C ₆ H ₅)	C ₂₃ H ₂₄ N ₂ O ₅	67.63 (67.44)	5.92 5.94	6.86 6.61)
2d	(CH ₃) ₂ CH	(180/2)	1730	1.25 (3H, t, 7.2, OCH ₂ CH ₃) 1.26 (6H, d, 6.5, CH ₃ × 2) 3.18 (1H, hep, 6.5, CH(CH ₃) ₂) 4.22 (2H, q, 7.2, OCH ₂ CH ₃) 4.65 (2H, s, CH ₂ CO) 5.31 (2H, s, CH ₂ C ₆ H ₅)	C ₂₄ H ₂₆ N ₂ O 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.	<i>R</i> ¹	mp (°C)	Yield (%) ^{a)}	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm ⁻¹)	¹ H-NMR (δ in CDCl ₃) (<i>J</i> = Hz)	Formula	Analysis (%)		
							Calcd	Found	
							C	H	N
3a	H	157—158	52	3360 1735	4.68 (2H, s, CH ₂ CO) 5.34 (2H, s, CH ₂ C ₆ H ₅) 7.20 (1H, s, C ₄ -H)	C ₁₉ H ₁₆ N ₂ O 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 ₂ CO) 5.32 (2H, s, CH ₂ C ₆ H ₅) 7.64 (1H, br, OH)	C ₂₀ H ₁₈ N ₂ O ₅	65.60 (65.56)	4.95 4.95	7.68 7.65)
3c	C ₂ H ₅	110—112	55	3360 1725	1.26 (3H, t, 7.6, CH ₂ CH ₃) 2.73 (2H, q, 7.6, CH ₂ CH ₃) 4.66 (2H, s, CH ₂ CO) 5.32 (2H, s, CH ₂ C ₆ H ₅) 8.44 (1H, br, OH)	C ₂₁ H ₂₀ N ₂ O ₅	66.30 (66.00)	5.30 5.28	7.37 7.35)
3d	(CH ₃) ₂ CH	110—111	64	3360 1725	1.27 (6H, d, 6.8, CH ₃ × 2) 3.18 (1H, hep, 6.8, CH(CH ₃) ₂) 4.68 (2H, s, CH ₂ CO) 5.31 (2H, s, CH ₂ C ₆ H ₅) 9.18 (1H, br, OH)	C ₂₂ H ₂₂ N ₂ O 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 IC₅₀ 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 (¹H-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 CHCl₃. The extract was washed with water, dried (Na₂SO₄), 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 CHCl₃, washed with water, dried (Na₂SO₄), and concentrated. The resulting solid was recrystallized with CHCl₃–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 K₂CO₃ (1.1 mmol) in Me₂CO (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 CHCl₃. The extract was washed with water, dried (Na₂SO₄), and concentrated. The resulting solid was recrystallized to give the corresponding sulfide (**5a**, **b**).

2-Benzylthio- (5a**):** Yield 73%, colorless needles (from CHCl₃–hexane), mp 85–86 °C. IR ν_{max}^{CHCl₃} cm⁻¹: 1490, 1180. ¹H-NMR (CDCl₃) δ: 4.45 (2H, s, CH₂). Anal. Calcd for C₁₆H₁₃NOS: 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 ν_{max}^{CHCl₃} cm⁻¹: 1490, 1180. ¹H-NMR (CDCl₃) δ: 4.03 (2H, dd, *J* = 8.4, 7.2 Hz, CH₂CH), 6.37 (1H, ddd, *J* = 15.7, 8.4, 7.2 Hz, CH₂CH=CH), 6.67 (1H, d, *J* = 15.7 Hz, CH₂CH=CH). Anal. Calcd for C₁₈H₁₅NOS: 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 CHCl₃. The extract was washed with water, 10% NaHCO₃ and water, dried (Na₂SO₄) 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 ν_{max}^{CHCl₃} cm⁻¹: 1730 (C=O). ¹H-NMR (CDCl₃) δ: 2.50 (3H, s, CH₃), 5.45 (2H, s, CH₂). Anal. Calcd for C₁₈H₁₅NO₃: 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 ν_{max}^{CHCl₃} cm⁻¹: 1730 (C=O). ¹H-NMR (CDCl₃) δ: 2.52 (3H, s, CH₃), 3.14 (2H, t, *J* = 7.5 Hz, OCH₂CH₂), 4.62 (2H, t, *J* = 7.5 Hz, OCH₂CH₂). Anal. Calcd for C₁₉H₁₇NO₃: 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)]sulfide⁸ (0.71 g, 2.12 mmol) in CHCl₃ (18 ml) was stirred at room temperature for 76 h. The reaction mixture was washed with 1 N HCl and water, dried (Na₂SO₄) and concentrated. The resulting solid was recrystallized from CHCl₃ to give **9** (0.83 g, 63%) as pale yellow needles, mp 147–148 °C. IR ν_{max}^{CHCl₃} cm⁻¹: 1221 (C=S). ¹H-NMR (CDCl₃) δ: 5.64 (2H, s, CH₂), 9.18 (1H, br, NH). Anal. Calcd for C₁₇H₁₄N₂O₂S: 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), K₂CO₃ (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 ν_{max}^{CHCl₃} cm⁻¹: 1670 (C=O). ¹H-NMR (CDCl₃) δ: 0.99 (6H, d, *J* = 6.8 Hz, CH₃ × 2), 2.28 (1H, hept, *J* = 6.8 Hz, CH), 2.78 (2H, d, *J* = 6.8 Hz, CH₂CH), 5.14 (2H, s, CH₂C₆H₅). Anal. Calcd for C₁₈H₂₀O₂: C, 80.56; H, 7.51. Found: C, 80.30; H, 7.57.

1-(*p*-Benzyloxyphenyl)-2-bromo-3-methyl-1-butanone (13**)** Br₂ (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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1670 (C=O). $^1\text{H-NMR}$ (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, $\text{CH}(\text{CH}_3)_2$), 4.91 (1H, d, $J=8.6$ Hz, COCH), 5.16 (2H, s, CH_2). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{BrO}_2$: 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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1710 (C=O). $^1\text{H-NMR}$ (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, $\text{CH}(\text{CH}_3)_2$), 5.12 (2H, s, CH_2), 5.32 (1H, d, $J=8.2$ Hz, COCH). Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{NO}_4$: 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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2980 (NH_2 , OH), 1660 (C=O). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) 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, $\text{CH}(\text{CH}_3)_2$), 4.92 (1H, d, $J=4.4$ Hz, COCH), 8.38 (3H, br, NH_2). Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{ClNO}_2$: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.36; H, 6.97; N, 6.00.

2-Ethoxalylamino-1-(*p*-ethoxalylloxyphenyl)-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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3380 (NH), 1730, 1700, 1680 (C=O). $^1\text{H-NMR}$ (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_2CH_3), 1.46 (3H, t, $J=7.2$ Hz, CH_2CH_3), 2.30 (1H, m, $\text{CH}(\text{CH}_3)_2$), 4.39 (2H, q, $J=7.2$ Hz, CH_2CH_3), 4.48 (2H, q, $J=7.2$ Hz, CH_2CH_3), 5.54 (1H, dd, $J=9.6, 4.8$ Hz, CHNH), 7.87 (1H, d, $J=9.6$ Hz, NH).

Ethyl 5-(*p*-Ethoxalylloxyphenyl)-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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1725 (C=O). $^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (6H, d, $J=7.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.46 (3H, t, $J=7.0$ Hz, CH_2CH_3), 1.47 (3H, t, $J=7.0$ Hz, CH_2CH_3), 3.28 (1H, hep, $J=6.8$ Hz, CH), 4.48 (2H, q, $J=7.0$ Hz, CH_2CH_3), 4.52 (2H, q, $J=7.0$ Hz, CH_2CH_3). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_7$: 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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3334, 3234 (OH, NH, C=O). $^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (6H, d, $J=6.6$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.40 (3H, t, $J=7.1$ Hz, CH_2CH_3), 3.25 (1H, hep, $J=6.6$ Hz, CH), 4.48 (2H, q, $J=7.1$ Hz, CH_2CH_3), 4.88 (1H, br, OH). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_4$: 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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3334, 3234 (OH, NH, NH_2), 1685 (C=O). $^1\text{H-NMR}$ ($\text{CMSO}-d_6$) δ : 1.24 (6H, d, $J=6.8$ Hz, $\text{CH}(\text{CH}_3)_2$), 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 $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_3$: 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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3412 (NH), 3350 (OH), 1729 (C=O). $^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J=6.7$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.12 (1H, hep, $J=6.7$ Hz, CH), 5.24 (2H, s, CH_2), 11.00 (1H, br, OH). Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: 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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1731. $^1\text{H-NMR}$ (CDCl_3) δ : 1.31 (6H, d, $J=6.9$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.40 (3H, t, $J=7.0$ Hz, CH_2CH_3), 3.20 (1H, hep, $J=6.9$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.46 (3H, s, OCH_3), 4.46 (2H, q, $J=7.0$ Hz, CH_2CH_3), 5.19 (2H, s, OCH_2O). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$: 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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3436, 3355, 3314 (NH_2 , NH), 1693 (C=O). $^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (6H, d, $J=6.8$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.18 (1H, hep, $J=6.8$ Hz, $\text{CH}(\text{CH}_3)_2$), 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 $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_4$: 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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3420 (NH), 1729 (C=O). $^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, d, $J=6.8$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.12 (1H, hep, $J=6.8$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.47 (3H, s, OCH_3), 5.18 (2H, s, OCH_2O), 5.21 (2H, s, $\text{CH}_2\text{C}_6\text{H}_5$). MS m/z : 396 (M^+). High-resolution MS m/z : Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$: 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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