

Studies on Antidiabetic Agents. IX.¹⁾ A New Aldose Reductase Inhibitor, AD-5467, and Related 1,4-Benzoxazine and 1,4-Benzothiazine Derivatives: Synthesis and Biological Activity²⁾

Hiroyuki TAWADA,^a Yasuo SUGIYAMA,^b Hitoshi IKEDA,^b Yujiro YAMAMOTO^c and Kanji MEGURO^{*,a}

Chemistry Research Laboratories^a and Biology Research Laboratories,^b Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan and Senju Pharmaceutical Co., Ltd.,^c 1-1, Sakuragaoka, Oshika, Itami 664, Japan. Received August 28, 1989

N-Acetic acid derivatives (I) of 2-substituted 1,4-benzoxazines and benzothiazines were designed and synthesized for evaluation as new aldose reductase inhibitors. In general, 3-thioxo derivatives were more potent inhibitors of aldose reductase from human placenta *in vitro* than the corresponding 3-oxo derivatives. While many compounds (I) were not very effective in inhibiting sorbitol accumulation in the rat sciatic nerve *in vivo*, the 3-thioxo compounds bearing an isopropyl group at the 2-position showed highly potent activity in the *in vivo* assay. Compound 46 (AD-5467) was selected from this series as a candidate for further development.

Keywords aldose reductase; aldose reductase inhibitor; sorbitol accumulation; thiolactam *N*-acetic acid; 1,4-benzoxazine-4-acetic acid; 1,4-benzothiazine-4-acetic acid

A variety of aldose reductase inhibitors (ARI) have been reported as potential new drugs for the treatment of diabetic complications such as cataract, retinopathy, neuropathy and nephropathy.^{3,4)} Recent potent ARIs can be classified, as shown in Fig. 1, into two main chemical types: type 1, azolidinedione derivatives (e.g., sorbinil, M-79175, CT-112) and type 2, acetic acid derivatives (e.g., tolrestat, epalrestat,⁵⁾ ponalrestat). We have previously reported on some type 1 ARIs, 5-phenyl-2,4-thiazolidinedione derivatives,⁶⁾ including CT-112 which is currently undergoing clinical testing for topical treatment of diabetic keratitis.^{7,8)} In this paper, we report a novel type 2 ARI, AD-5467, and related derivatives (Ia,b)⁹⁾ which are shown in Chart 1.

The general concept behind the molecular design of Ia,b is the appropriate spatial alignment of a benzene ring, a carboxylate anion and another hydrophobic function (*i.e.*, alkyl, phenyl, benzyl, *etc.*), as seen in one of the most potent ARIs, ponalrestat. A carbonyl or a thiocarbonyl group was also included in the molecule, because the presence of this function at a suitable distance from the benzene ring seemed important for ARI activity, as proposed by Kador *et al.*^{4,10)}

Chemistry

The key intermediates, 1,4-benzothiazin-3(4*H*)-ones (IVa) and 1,4-benzoxazin-3(4*H*)-ones (IVb) were prepared using methods A—G shown in Charts 2—4. Reaction of 2-aminothiophenols (II) with 2-haloacetic acid derivatives (III) gave IVa (method A). When both R² and R³ were methyl groups, IVa was obtained in more satisfactory yield by *S*-alkylation of II with III followed by acid cyclization (method B). When the synthesis of the starting aminothiophenols (II) was not easy, IVa was prepared by reacting a halonitrobenzene (VI) with a mercaptoacetic acid derivative (VII) followed by reductive cyclization (method C).

The process shown in method D was newly developed for

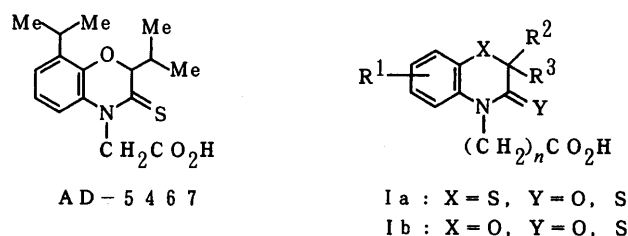


Chart 1

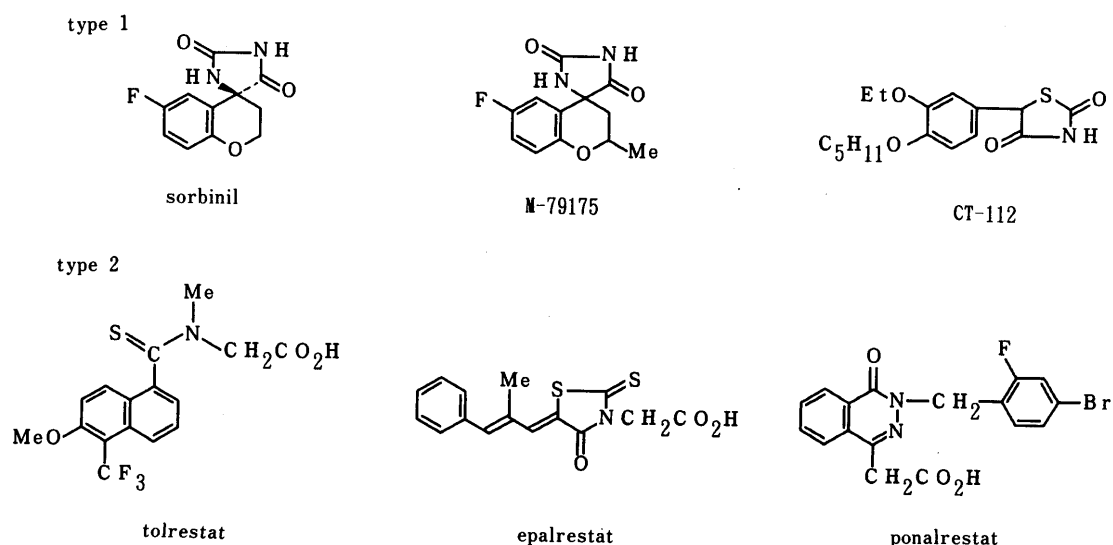


Fig. 1. Known Aldose Reductase Inhibitors

the synthesis of IVa possessing a substituted benzyl moiety at the 2-position of the 1,4-benzothiazine ring. The 2-position of IX was selectively benzylated to afford X when IX was treated with benzyl halide in the presence of potassium carbonate and sodium iodide. Hydrolysis followed by decarboxylation of X gave IVa in good yield.

Compound 55 which has a spirop propane ring was synthesized by method E (Chart 3). After protection of the

hydroxy group, 51 was N-alkylated with methyl bromoacetate to give 52 in good yield. Compound 52 was then converted to the O-mesylate (54), which was cyclized with sodium hydride in tetrahydrofuran to give 55.

The 1,4-benzoxazine derivatives (IVb) were synthesized by acylation of 2-aminophenols (XI) with acid chlorides (XII) followed by cyclization (method F) or by alkylation of 2-nitrophenol (XIV) with III followed by catalytic hydrogenation (method G) as shown in Chart 4.

Alkylation of IVa, b with methyl bromoacetate or methyl acrylate yielded XVI which was then thionated with phosphorus pentasulfide to give XVII. Compounds XVI and XVII were hydrolyzed to give the corresponding Ia, b (Chart 5).

Pharmacological Methods

Inhibition of Aldose Reductase *in Vitro* Aldose reductase (AR) was partially purified from human placenta or from rat lens using ammonium sulfate and the activity was determined using D,L-glyceraldehyde as a substrate according to the method of Hayman and Kinoshita.¹¹ Specific activities of human placental AR and rat lens AR were 27.7 and 10.9 nmol nicotineamide adenine dinucleotide phosphate (NADPH) oxidized/min/mg protein at 30 °C, respectively. Since the K_m values of human placental AR and of rat lens AR for D,L-glyceraldehyde were 0.157 and 0.297 mM, the activity was determined using 1 mM D,L-glyceraldehyde for the human preparation and 2 mM for the rat preparation. The concentration required to reduce the enzyme activity by 50% (IC_{50}) was determined by linear regression after inspection of the plots of the enzyme activities (%) vs. $\log_{10}$ [compound].

Inhibition of Sorbitol Accumulation *in Vivo* Six-week old, male Sprague-Dawley rats ($n=5$) were rendered diabetic by an intravenous injection of streptozocin (70 mg/kg, Calbiochem, San Diego, U.S.A.) and were then given a test compound (50 or 30 mg/kg) as a suspension in 5% gum arabic solution orally twice a day for two days. The rats were maintained on a laboratory chow (CE-2, Clea Japan, Tokyo) and water *ad libitum*. Eighteen hours after final administration of the compound, the rats were killed and the sciatic nerves were removed. Sorbitol was extracted from the sciatic nerve by the method of Peterson *et al.*¹² and measured enzymatically by the method of Clements *et*

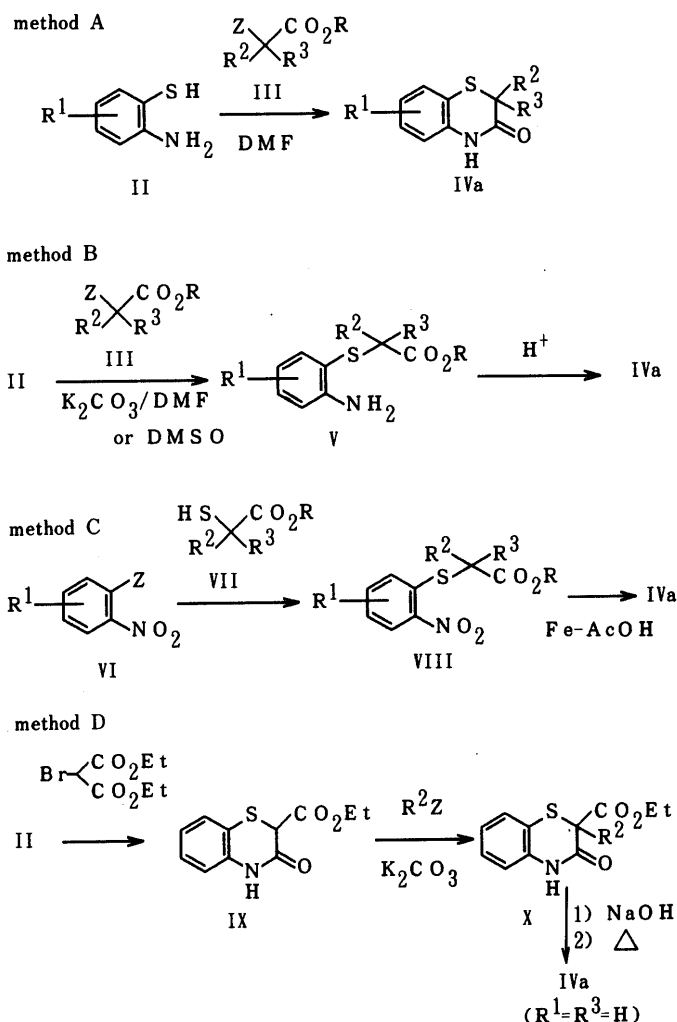


Chart 2

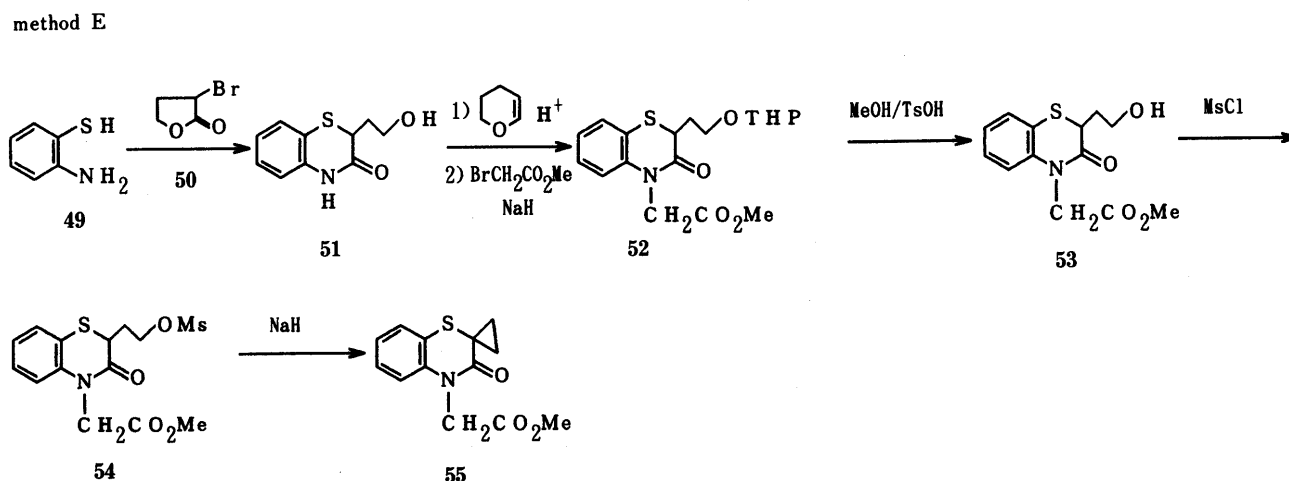
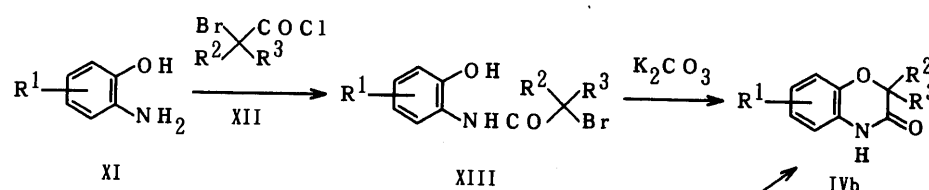


Chart 3

method F



method G

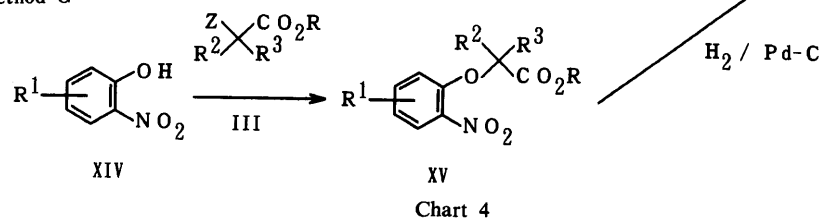


Chart 4

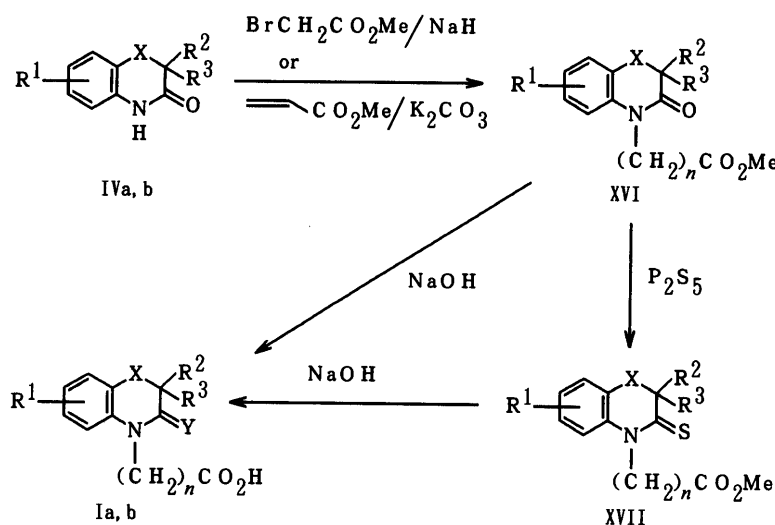


Chart 5

*al.*¹³⁾ The sorbitol contents were compared with that obtained for the control group given vehicle only, and are shown in Table I as percentages.

Results and Discussion

As can be seen from Table I, thiolactam *N*-acetic acid derivatives (Ia, b; Y=S) showed more potent biological activity than the corresponding lactam derivatives (Ia, b; Y=O) irrespective of the basic skeleton (thiazine or oxazine) or the substituents. On the other hand, the *N*-propionic acid derivative (21) was only a weak ARI despite its thiolactam structure. Therefore, synthetic efforts were directed mainly toward thiolactam *N*-acetic acid compounds to clarify the structure-activity relationships.

The 1,4-benzothiazine derivatives possessing benzyl moieties at the 2-position (*e.g.*, 8–12) showed potent ARI activities *in vitro* but were mostly inactive in the *in vivo* test. The *in vitro* activity of compounds with phenyl or alkyl groups at the 2-position of the 1,4-benzothiazine skeleton (*e.g.*, 13–18, 20) was comparable to that of compounds 8–12. However, these compounds tended to have only moderate (but significant) *in vivo* activity, suggesting that the pharmacokinetics of the latter molecules, including intestinal absorption, distribution to the target tissue or possibly rate of metabolism, were greatly improved. In particular, the activity of compounds bearing a branched

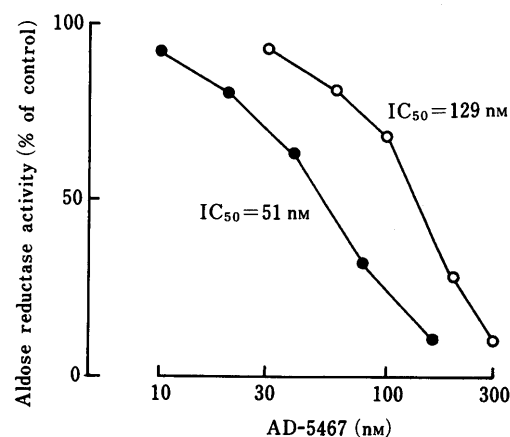
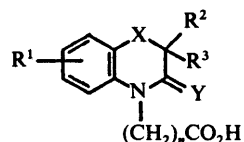


Fig. 2. Inhibition by AD-5467 of Aldose Reductase from Human Placenta (●) and Rat Lens (○)

substituent such as isopropyl (17) or geminal dimethyl (20) at the 2-position seemed remarkable in the *in vivo* test. Compounds with cyclopentyl (19) or spiroalkyls (22, 23), however, did not show significant *in vivo* activity. The effect of the substituents of the benzene ring on the activity was also examined in the *gem*-dimethyl series (24–30). The 8-chloro compound (26) seemed to be the best among them, but a marked improvement over the activity of 20 was not

TABLE I. Physical and Biological Properties of 1,4-Benzothiazines (Ia) and 1,4-Benzoxazines (Ib)



Compd. No.	R ¹	R ²	R ³	n	X	Y	Formula ^{a)}	Recrystn. solvent ^{b)}	mp (°C)	Yield (%)	In vitro IC ₅₀ ^{c)} (nM)	Sorbitol accum. ^{d)} % of control	
												50 mg/kg	30 mg/kg
1	H	C ₆ H ₅ CH ₂	H	1	S	O	C ₁₇ H ₁₅ NO ₃	ET	124–125	75	110	85	NT
2	H	4-Cl-C ₆ H ₄ CH ₂	H	1	S	O	C ₁₇ H ₁₄ ClNO ₃ S	E	172–173	89	>1000	NT	NT
3	H	3,4-(MeO) ₂ C ₆ H ₃ CH ₂	H	1	S	O	C ₁₉ H ₁₉ NO ₃ S	E	182–183	76	>1000	NT	NT
4 ^{i,j)}	H	C ₆ H ₅	H	1	S	O	C ₁₆ H ₁₂ NNaO ₃ S	E	252–254	68	>1000	NT	NT
5	H	Me	Me	1	S	O	C ₁₂ H ₁₃ NO ₃ S	IE-H	115–116	75	>1000	NT	NT
6	H	iso-Pr	H	1	O	O	C ₁₃ H ₁₅ NO ₄	E	144–145	92	>1000	NT	NT
7	8-iso-Pr	iso-Pr	H	1	O	O	C ₁₆ H ₂₁ NO ₄	E	132–133	88	>1000	NT	NT
8	H	C ₆ H ₅ CH ₂	H	1	S	S	C ₁₇ H ₁₅ NO ₂ S ₂	IE	156–157	64	36	79 ^{e)}	NT
9	H	2-Cl-C ₆ H ₄ CH ₂	H	1	S	S	C ₁₇ H ₁₄ ClNO ₂ S ₂	E	189–190	65	600	NT	NT
10	H	3-Cl-C ₆ H ₄ CH ₂	H	1	S	S	C ₁₇ H ₁₄ ClNO ₂ S ₂	IE	144–145	74	240	95	NT
11	H	4-Cl-C ₆ H ₄ CH ₂	H	1	S	S	C ₁₇ H ₁₄ ClNO ₂ S ₂	IE	183–184	56	360	87	NT
12	H	4-CF ₃ -C ₆ H ₄ CH ₂	H	1	S	S	C ₁₈ H ₁₄ F ₃ NO ₂ S ₂	IE-H	138–140	75	600	77	NT
13 ^{j)}	H	C ₆ H ₅	H	1	S	S	C ₁₆ H ₁₃ NO ₂ S ₂	ET-IE	174–176	63	200	58 ^{f)}	NT
14 ^{j)}	H	Me	H	1	S	S	C ₁₁ H ₁₁ NO ₂ S ₂	IE-H	124–125	71	60	71 ^{f)}	NT
15	H	Et	H	1	S	S	C ₁₂ H ₁₃ NO ₂ S ₂	IE	147–148	90	140	83	NT
16	H	n-Pr	H	1	S	S	C ₁₃ H ₁₅ NO ₂ S ₂	IE	147–148	75	380	76 ^{e)}	NT
17	H	iso-Pr	H	1	S	S	C ₁₃ H ₁₅ NO ₂ S ₂	IE	175–176	97	480	46 ^{e)}	NT
18	H	n-Bu	H	1	S	S	C ₁₄ H ₁₇ NO ₂ S ₂	IE-H	112–113	75	230	81 ^{e)}	NT
19	H	cyclo-pentyl	H	1	S	S	C ₁₅ H ₁₇ NO ₂ S ₂	E	180–181	86	680	95	NT
20 ^{j)}	H	Me	Me	1	S	S	C ₁₂ H ₁₃ NO ₂ S ₂	IE	177–178	52	200	52 ^{e)}	NT
21	H	Me	Me	2	S	S	C ₁₃ H ₁₅ NO ₂ S ₂	E	147–148	51	>1000	NT	NT
22	H	-(CH ₂) ₂ -	1	S	S	S	C ₁₂ H ₁₁ NO ₂ S ₂	IE-H	152–153	86	220	106	NT
23	H	-(CH ₂) ₄ -	1	S	S	S	C ₁₅ H ₁₇ NO ₂ S ₂	IE	174–175	38	140	109	NT
24	5-Cl	Me	Me	1	S	S	C ₁₂ H ₁₂ ClNO ₂ S ₂	IE-H	151–152	22	>1000	114	NT
25	6-Cl	Me	Me	1	S	S	C ₁₂ H ₁₂ ClNO ₂ S ₂	IE	171–172	72	180	73 ^{e)}	NT
26	8-Cl	Me	Me	1	S	S	C ₁₂ H ₁₂ ClNO ₂ S ₂	IE-H	147–148	47	66	41 ^{f)}	NT
27	6-F	Me	Me	1	S	S	C ₁₂ H ₁₂ FNO ₂ S ₂	IE	181–182	69	120	58 ^{f)}	NT
28	6-MeO	Me	Me	1	S	S	C ₁₃ H ₁₅ NO ₃ S ₂	IA-W	151–152	52	>1000	85	NT
29	7-MeO	Me	Me	1	S	S	C ₁₃ H ₁₅ NO ₃ S ₂	E-W	182–183	47	120	53 ^{f)}	NT
30	7-Me	Me	Me	1	S	S	C ₁₃ H ₁₅ NO ₂ S ₂	E-W	185–186	49	86	118	NT
31	H	Me	Me	1	O	S	C ₁₂ H ₁₃ NO ₃ S	IE-H	140–142	65	380	90	NT
32	H	iso-Pr	H	1	O	S	C ₁₃ H ₁₅ NO ₃ S	IE-H	96–97	75	30	18 ^{h)}	51 ^{e)}
33 ^{k)}	H	sec-Bu	H	1	O	S	C ₁₄ H ₁₇ NO ₃ S	IE-H	70–72	45	420	57 ^{e)}	94
34	H	C ₆ H ₅	H	1	O	S	C ₁₆ H ₁₃ NO ₃ S	IE	150–151	78	42	56 ^{f)}	NT
35	H	4-MeO-C ₆ H ₄	H	1	O	S	C ₁₇ H ₁₅ NO ₄ S	IE	140–141	38	27	NT	47 ^{f)}
36	6-F	iso-Pr	H	1	O	S	C ₁₃ H ₁₄ FNO ₃ S	IE-H	132–133	60	46	12 ^{h)}	33 ^{e)}
37	7-F	iso-Pr	H	1	O	S	C ₁₃ H ₁₄ FNO ₃ S	IE-H	113–114	62	45	NT	62 ^{e)}
38	8-F	iso-Pr	H	1	O	S	C ₁₃ H ₁₄ FNO ₃ S	IE-H	125–127	71	44	14 ^{h)}	45 ^{e)}
39	8-Cl	iso-Pr	H	1	O	S	C ₁₃ H ₁₄ ClNO ₃ S	IE-H	144–145	70	42	23 ^{e)}	70
40	7-MeO	iso-Pr	H	1	O	S	C ₁₄ H ₁₇ NO ₄ S	IE-H	128–129	68	52	NT	27 ^{h)}
41	8-MeO	iso-Pr	H	1	O	S	C ₁₄ H ₁₇ NO ₄ S	IE	159–160	70	68	11 ^{h)}	29 ^{h)}
42	8-EtO	iso-Pr	H	1	O	S	C ₁₅ H ₁₉ NO ₄ S	IE-H	138–139	72	36	NT	58 ^{f)}
43	7-Me	iso-Pr	H	1	O	S	C ₁₄ H ₁₇ NO ₃ S	IE-H	146–147	72	44	55 ^{e)}	78
44	8-Me	iso-Pr	H	1	O	S	C ₁₄ H ₁₇ NO ₃ S	IE-H	148–149	72	42	16 ^{h)}	29 ^{h)}
45	8-Et	iso-Pr	H	1	O	S	C ₁₅ H ₁₉ NO ₃ S	IE-H	117–118	73	36	NT	35 ^{h)}
46	8-iso-Pr	iso-Pr	H	1	O	S	C ₁₆ H ₂₁ NO ₃ S	IE-H	158–159	72	51	NT	35 ^{h)}
47	8-tert-Bu	iso-Pr	H	1	O	S	C ₁₇ H ₂₃ NO ₃ S	IE	195–196	69	230	NT	15 ^{h)}
48	8-cyclo-hexyl	iso-Pr	H	1	O	S	C ₁₉ H ₂₅ NO ₃ S	IE-H	157–158	70	48	NT	25 ^{h)}

a) All compounds were analyzed for C, H and N and the results were within $\pm 0.4\%$ of the theoretical values. b) E, EtOH; ET, ether; H, hexane; IA, 2-propanol; IE, isopropyl ether; W, H₂O. c) IC₅₀ value for human placental AR. d) Sorbitol accumulation in rat sciatic nerve. NT: not tested. Student's *t*-test: e) $p < 0.05$, f) $p < 0.02$, g) $p < 0.01$, h) $p < 0.001$. i) Na salt. j) See ref. 9. k) Diastomeric mixture (about 1:1).

observed.

On the basis of the above structure-activity studies of the 1,4-benzothiazine series, their isosteric 1,4-benzoxazine-4-acetic acid derivatives (31–48) were then synthesized. Compounds with an isopropyl group at the 2-position (e.g., 32, 36–48) generally had prominent *in vivo* activity. Among the substituents on the benzene ring of the 1,4-

benzoxazine skeleton, those at the 8-position such as 8-fluoro (38), 8-methoxy (41) and 8-alkyl groups (44–48) appear to be particularly effective in improving the biological activity *in vivo*, while a 7-methoxy substituent as in 40 seems to be equally effective.

Based on detailed pharmacological¹⁴⁾ and toxicological¹⁵⁾ evaluations as well as the above-mentioned observa-

tions, 3,4-dihydro-2,8-diisopropyl-3-thioxo-2*H*-1,4-benzoxazine-4-acetic acid (**46**, AD-5467) was selected as a candidate for further development. It is noteworthy that AD-5467 is about 2.5-times more inhibitory against human AR than rat AR (Fig. 2), while the activities of known ARIs are generally greater (2.6–22.3 times)¹⁶⁾ with rat lens rather than human placental enzyme.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 spectrometer in Nujol. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 spectrometer in CDCl₃ unless otherwise noted. Chemical shifts are given in ppm with tetramethylsilane as the internal standard, and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad.

Synthesis of 2*H*-1,4-Benzothiazin-3(4*H*)-one (IVa) Typical examples are given to illustrate the general procedure for methods A–D.

2-Benzyl-2*H*-1,4-benzothiazin-3(4*H*)-one Method A: Methyl 2-bromo-3-phenylpropionate (22.5 g) was added dropwise to a stirred solution of 2-aminothiophenol (12.5 g) in dimethylformamide (DMF) (100 ml). The mixture was heated at 90–95 °C for 15 min and poured into ice-water. The precipitated crystals were collected by filtration and washed with H₂O to give the title compound (16.2 g, 63%). Recrystallization from EtOH gave colorless needles, mp 160–161 °C. IR cm⁻¹: 3210, 1665. NMR δ: 2.80 (1H, dd, *J*=9, 14 Hz), 3.31 (1H, dd, *J*=6, 14 Hz), 3.65 (1H, dd, *J*=6, 9 Hz), 6.82–7.53 (9H, m), 9.28 (1H, br). *Anal.* Calcd for C₁₅H₁₃NOS: C, 70.56; H, 5.22; N, 5.44. Found: C, 70.69; H, 5.14; N, 5.44.

7-Methoxy-2,2-dimethyl-2*H*-1,4-benzothiazin-3(4*H*)-one Method B: K₂CO₃ (1.78 g) was added to a stirred solution of 2-amino-5-methoxythiophenol (2.0 g) and ethyl 2-bromo-2-methylpropionate (1.9 g) in dimethylsulfoxide (DMSO) (20 ml) under an N₂ atmosphere. The mixture was stirred at room temperature for 1 h, diluted with H₂O and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give ethyl 2-(2-amino-5-methoxyphenylthio)-2-methylpropionate as an oil. The oil was dissolved in DMF (20 ml), and concentrated HCl (0.13 ml) was added. The mixture was heated at 80 °C for 1.5 h and diluted with H₂O to give the title compound as crystals (1.78 g, 62.0%). Recrystallization from EtOH gave colorless prisms, mp 149–150 °C. IR cm⁻¹: 3175, 1660. NMR (DMSO-*d*₆) δ: 1.33 (6H, s), 3.70 (3H, s), 6.67–6.97 (3H, m), 10.33 (1H, br). *Anal.* Calcd for C₁₁H₁₃NO₂S: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.17; H, 5.93; N, 6.27.

8-Chloro-2,2-dimethyl-2*H*-1,4-benzothiazin-3(4*H*)-one Method C: i) A mixture of 2,3-dichloronitrobenzene (5.76 g), 2-mercapto-2-methylpropionic acid (3.60 g), K₂CO₃ (9.93 g) and DMF (100 ml) was heated at 100 °C for 3 h under an N₂ atmosphere. The mixture was diluted with H₂O, washed with AcOEt, acidified with concentrated HCl and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give an oil. The oil was crystallized from isopropyl ether to give 2-(2-chloro-6-nitrophenylthio)-2-methylpropionic acid (4.10 g, 50%). Recrystallization from MeOH gave yellow prisms, mp 155–156 °C. IR cm⁻¹: 1690. NMR δ: 1.50 (6H, s), 7.25 (1H, br), 7.40–7.73 (3H, m). *Anal.* Calcd for C₁₀H₁₀ClNO₄S: C, 43.56; H, 3.66; N, 5.08. Found: C, 43.55; H, 3.70; N, 5.00.

ii) Fe powder (3.96 g) was added portionwise to a stirred mixture of the crystals (3.85 g) obtained in i), AcOH (30 ml) and H₂O (10 ml). The mixture was stirred at room temperature for 40 min. The precipitate was filtered off and washed with DMF. The filtrate and washings were combined and diluted with H₂O to give the title compound as crystals (2.95 g, 93%). Recrystallization from EtOH gave colorless needles (2.22 g, 70%), mp 207–208 °C. IR cm⁻¹: 3180, 1690. NMR (DMSO-*d*₆) δ: 1.38 (6H, s), 6.90–7.29 (3H, m). *Anal.* Calcd for C₁₀H₁₀ClNOS: C, 52.75; H, 4.43; N, 6.15. Found: C, 52.84; H, 4.46; N, 5.97.

2-(3,4-Dimethoxybenzyl)-2*H*-1,4-benzothiazin-3(4*H*)-one Method D: i) Diethyl bromomalonate (23.9 g) was added dropwise to a stirred solution of 2-aminothiophenol (12.5 g) in DMF (150 ml). The mixture was heated at 80 °C for 20 min and diluted with H₂O to give ethyl 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-2-carboxylate as crystals (21.0 g, 89%). Recrystallization from EtOH gave colorless prisms, mp 144–145 °C. IR cm⁻¹: 3200, 1730, 1670. NMR δ: 1.13 (3H, t, *J*=7 Hz), 4.12 (2H, q, *J*=7 Hz), 4.22 (1H, s), 6.88–7.38 (4H, m), 9.45 (1H, br). *Anal.* Calcd for C₁₁H₁₁NO₃S: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.66; H, 4.77; N, 5.90.

ii) A mixture of the crystals (4.74 g) obtained in i), 3,4-dimethoxybenzyl chloride (4.44 g), K₂CO₃ (3.32 g) and NaI (3.00 g) in 2-butanone (60 ml) was refluxed for 2 h with stirring. After dilution with H₂O, the mixture was extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated to give an oil which was crystallized from Et₂O to give ethyl 2-(3,4-dimethoxybenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-2-carboxylate (6.45 g, 83%). Recrystallization from EtOH gave colorless prisms, mp 149–150 °C. IR cm⁻¹: 3200, 3120, 1710, 1670. NMR δ: 0.98 (3H, t, *J*=7.5 Hz), 3.42 (1H, d, *J*=15 Hz), 3.63 (1H, d, *J*=15 Hz), 3.82 (6H, s), 4.05 (2H, q, *J*=7.5 Hz), 6.68–7.33 (7H, m), 8.83 (1H, br). *Anal.* Calcd for C₂₀H₂₁NO₅S: C, 62.00; H, 5.46; N, 3.62. Found: C, 61.75; H, 5.16; N, 3.53.

iii) A mixture of the crystals (6.45 g) obtained in ii), 2*N* NaOH (21 ml) and EtOH (21 ml) was refluxed for 20 min. The mixture was diluted with H₂O, acidified with 6*N* HCl and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give an oil, which was dissolved in pyridine (40 ml). The mixture was refluxed for 15 min with stirring and the solvent was evaporated off. The residue was diluted with H₂O to give the title compound as crystals (5.07 g, 93%). Recrystallization from MeOH gave colorless needles, mp 178–179 °C. IR cm⁻¹: 3180, 1670. NMR (DMSO-*d*₆) δ: 2.58 (1H, dd, *J*=9, 14 Hz), 3.12 (1H, dd, *J*=6, 14 Hz), 3.70 (6H, s), 3.73 (1H, dd, *J*=6, 9 Hz), 6.58–7.33 (7H, m). *Anal.* Calcd for C₁₇H₁₇NO₃S: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.73; H, 5.49; N, 4.41.

Methyl 3,4-Dihydro-3-oxo-2*H*-1,4-benzothiazine-2-spiro-1'-cyclopropane-4-acetate (55) Method E: i) α-Bromo-γ-butyrolactone (**50**, 33.0 g), was added dropwise to a stirred, ice-cooled mixture of 2-aminothiophenol (**49**, 25.0 g), K₂CO₃ (27.6 g) and EtOH (250 ml). The mixture was stirred for 2 h with cooling, adjusted to pH 1 with concentrated HCl and refluxed for 20 min. After removal of the solvent, the residue was diluted with H₂O and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give 2-(2-hydroxyethyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (**51**) as crystals (36.0 g, 86%). Recrystallization from AcOEt gave colorless prisms, mp 115–116 °C. IR cm⁻¹: 3480, 3400, 3100, 1660. NMR δ: 1.32–2.13 (2H, m), 3.45–3.63 (3H, m), 4.12 (1H, br), 6.85–7.35 (4H, m). *Anal.* Calcd for C₁₀H₁₁NO₂S: C, 57.40; H, 5.30; N, 6.69. Found: C, 57.04; H, 5.15; N, 6.69.

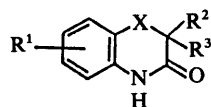
ii) *p*-Toluenesulfonic acid (0.95 g) was added to a stirred, ice-cooled solution of **51** (20.9 g) and 2,3-dihydropyran (9.24 g) in CH₂Cl₂ (200 ml). The mixture was stirred for 2 h with cooling, washed successively with aqueous NaHCO₃ solution and H₂O, dried (MgSO₄) and concentrated *in vacuo* to give 2-[2-(2-tetrahydropyranyloxy)ethyl]-2*H*-1,4-benzothiazin-3(4*H*)-one as crystals (27.5 g, 94%), mp 80–84 °C.

NaH (60% in oil, 1.2 g) was added to a solution of the crystals (8.79 g) obtained above in DMF (90 ml). The mixture was stirred for 15 min at room temperature, then a solution of methyl bromoacetate (3.0 ml) in DMF (6.0 ml) was added dropwise with ice-cooling. The reaction mixture was stirred for 1 h with cooling, diluted with H₂O and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give methyl 3,4-dihydro-3-oxo-2-[2-(2-tetrahydropyranyloxy)ethyl]-2*H*-1,4-benzothiazine-4-acetate (**52**) as an oil.

iii) The oil obtained in ii) was dissolved in MeOH (90 ml), and *p*-toluenesulfonic acid (0.28 g) was added. The mixture was heated at 70 °C for 15 min. After cooling, the mixture was diluted with H₂O and extracted with AcOEt. The extract was washed with aqueous NaHCO₃ solution and H₂O, dried (MgSO₄) and concentrated *in vacuo* to give an oil, which was chromatographed on silica gel (170 g) using benzene–acetone (9:1, v/v) as the eluent. The eluate was concentrated *in vacuo* to give methyl 3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2*H*-1,4-benzothiazine-4-acetate (**53**) as an oil (7.9 g, 94%). NMR δ: 1.70 (2H, m), 2.32 (1H, t, *J*=6 Hz), 3.62–3.85 (3H, m), 3.78 (3H, s), 4.45 (1H, d, *J*=18 Hz), 4.85 (1H, d, *J*=18 Hz), 6.78–7.38 (4H, m).

iv) Methyl chloride (2.0 ml) was added dropwise to a stirred and ice-cooled solution of the oil (**53**, 5.6 g) obtained in iii) and Et₃N (3.7 ml) in CH₂Cl₂ (60 ml). The mixture was stirred for 1 h with cooling, washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give methyl 3,4-dihydro-2-(2-mesyloxyethyl)-3-oxo-2*H*-1,4-benzothiazine-4-acetate (**54**) as an oil (7.1 g, 99%). The oil (6.8 g) was dissolved in DMF (50 ml), and NaH (60% in oil, 0.9 g) was added. The mixture was stirred at room temperature for 30 min and at 70 °C for 15 min, diluted with H₂O and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give an oil, which was chromatographed on silica gel (80 g) using hexane–AcOEt (9:1, v/v) as the eluent. The eluate was concentrated *in vacuo* to give **55** as crystals (2.46 g, 49%). Recrystallization from EtOH gave colorless needles, mp 93–94 °C. NMR δ: 0.95–1.09

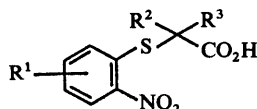
TABLE II. 1,4-Benzothiazin-3-ones (IVa) and 1,4-Benzoxazin-3-ones (IVb)



R ¹	R ²	R ³	X	Method ^{a)}	mp (°C)	Formula ^{b)}	Yield (%)
H	C ₆ H ₅ CH ₂	H	S	A	160—161	C ₁₅ H ₁₃ NOS	63
H	2-Cl-C ₆ H ₄ CH ₂	H	S	A	189—190	C ₁₅ H ₁₂ CINOS	50
H	3-Cl-C ₆ H ₄ CH ₂	H	S	D	145—146	C ₁₅ H ₁₂ CINOS	87
H	4-Cl-C ₆ H ₄ CH ₂	H	S	D	183—184	C ₁₅ H ₁₂ CINOS	89
H	4-CF ₃ -C ₆ H ₄ CH ₂	H	S	A	168—169	C ₁₆ H ₁₂ F ₃ NOS	61
H	3,4-(MeO) ₂ -C ₆ H ₃ CH ₂	H	S	D	178—179	C ₁₇ H ₁₇ NO ₃ S	97
H	C ₆ H ₅	H	S	A	205—206	C ₁₄ H ₁₁ NOS	60
H	Me	H	S	A	129—130	C ₉ H ₉ NOS	72
H	Et	H	S	A	103—104	C ₁₀ H ₁₁ NOS	57
H	<i>n</i> -Pr	H	S	A	85—86	C ₁₁ H ₁₃ NOS	52
H	<i>iso</i> -Pr	H	S	B	152—153	C ₁₁ H ₁₃ NOS	92
H	<i>n</i> -Bu	H	S	A	100—101	C ₁₂ H ₁₅ NOS	49
H	cyclo-pentyl	H	S	A	163—164	C ₁₃ H ₁₅ NOS	69
H	Me	Me	S	B	157—158	C ₁₀ H ₁₁ NOS	90
H	-(CH ₂) ₅ -	Me	S	C	227—228	C ₁₃ H ₁₅ NOS	91
5-Cl	Me	Me	S	A	84—85	C ₁₀ H ₁₀ CINOS	60
6-Cl	Me	Me	S	C	199—200	C ₁₀ H ₁₀ CINOS	86
8-Cl	Me	Me	S	C	207—208	C ₁₀ H ₁₀ CINOS	93
6-F	Me	Me	S	C	178—179	C ₁₀ H ₁₀ FNOS	88
6-MeO	Me	Me	S	C	153—154	C ₁₁ H ₁₃ NO ₂ S	78
7-MeO	Me	Me	S	B	149—150	C ₁₁ H ₁₃ NO ₂ S	62
7-Me	Me	Me	S	B	191—192	C ₁₁ H ₁₃ NOS	92
H	Me	Me	O	F	165—166	C ₁₀ H ₁₁ NO ₂	42
H	<i>iso</i> -Pr	H	O	F, G	118—119	C ₁₁ H ₁₃ NO ₂	94, 92
H	<i>sec</i> -Bu	H	O	F	94—95	C ₁₂ H ₁₅ NO ₂	75
H	C ₆ H ₅	H	O	F	169—170	C ₁₄ H ₁₁ NO ₂	99 ^{c)}
H	4-MeO-C ₆ H ₄	H	O	F	150—151	C ₁₅ H ₁₃ NO ₃	76
6-F	<i>iso</i> -Pr	H	O	F	138—139	C ₁₁ H ₁₂ FNO ₂	94
7-F	<i>iso</i> -Pr	H	O	F	178—179	C ₁₁ H ₁₂ FNO ₂	96
8-F	<i>iso</i> -Pr	H	O	F	146—147	C ₁₁ H ₁₂ FNO ₂	91
8-Cl	<i>iso</i> -Pr	H	O	F	132—133	C ₁₁ H ₁₂ ClNO ₂	85
7-MeO	<i>iso</i> -Pr	H	O	F	126—127	C ₁₂ H ₁₅ NO ₃	87
8-MeO	<i>iso</i> -Pr	H	O	F	149—150	C ₁₂ H ₁₅ NO ₃	56 ^{c)}
8-EtO	<i>iso</i> -Pr	H	O	F	129—130	C ₁₃ H ₁₇ NO ₃	81
7-Me	<i>iso</i> -Pr	H	O	F	129—130	C ₁₂ H ₁₅ NO ₂	95
8-Me	<i>iso</i> -Pr	H	O	F	109—110	C ₁₂ H ₁₅ NO ₂	92
8-Et	<i>iso</i> -Pr	H	O	F	93—94	C ₁₃ H ₁₇ NO ₂	94
8- <i>iso</i> -Pr	<i>iso</i> -Pr	H	O	F	129—130	C ₁₄ H ₁₉ NO ₂	95
8- <i>tert</i> -Bu	<i>iso</i> -Pr	H	O	F	170—171	C ₁₅ H ₂₁ NO ₂	95
8-cyclo-hexyl	<i>iso</i> -Pr	H	O	F	164—165	C ₁₇ H ₂₃ NO ₂	82 ^{c)}

a) See Experimental. b) See footnote a, Table I. c) Yield from the corresponding aminophenol XI.

TABLE III. 2-(2-Nitrophenylthio)propionic Acids (VIII)



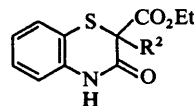
R ¹	R ²	R ³	mp (°C)	Formula ^{a)}	Yield (%)
4-Cl	Me	Me	132—133	C ₁₀ H ₁₀ ClNO ₄ S	69
6-Cl	Me	Me	155—156	C ₁₀ H ₁₀ ClNO ₄ S	50
4-F	Me	Me	105—106	C ₁₀ H ₁₀ FNO ₄ S	73
4-MeO	Me	Me	130—131	C ₁₁ H ₁₃ NO ₅ S	46
H	-(CH ₂) ₅ -		174—175	C ₁₃ H ₁₅ NO ₄ S	77

a) See footnote a, Table I.

(2H, m), 1.51—1.65 (2H, m), 3.80 (3H, s), 4.63 (2H, m), 6.78—7.37 (4H, m). *Anal.* Calcd for C₁₃H₁₇NO₃S: C, 59.30; H, 4.89; N, 5.32. Found: C, 59.57; H, 5.07; N, 5.34.

Synthesis of 2H-1,4-Benzoxazin-3(4H)-one (IVb) Typical examples are given to illustrate the general procedures for methods F and G.

TABLE IV. 2-Benzyl-1,4-benzothiazine-2-carboxylates (X)



R ²	mp (°C)	Formula ^{a)}	Yield (%)
3-Cl-C ₆ H ₄ CH ₂	117—118	C ₁₈ H ₁₆ ClNO ₃ S	74
4-Cl-C ₆ H ₄ CH ₂	132—133	C ₁₈ H ₁₆ ClNO ₃ S	80
3,4-(MeO) ₂ C ₆ H ₃ CH ₂	149—150	C ₂₀ H ₂₁ NO ₃ S	84

a) See footnote a, Table I.

2,8-Diisopropyl-2H-1,4-benzoxazin-3(4H)-one Method F: i) 2-Bromo-3-methylbutyryl chloride (42.0 g) was added dropwise to a stirred mixture of 2-amino-6-isopropylphenol (31.7 g), NaHCO₃ (26.7 g), AcOEt (240 ml) and H₂O (240 ml) with ice-cooling. The mixture was stirred for 30 min with cooling, and the aqueous and organic layers were separated. The aqueous layer was extracted with AcOEt. The organic layers were combined, washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give 2-(2-

TABLE V. 2-Acylaminophenols (XIII)

R ¹	R ²	R ³	mp (°C)	Formula ^{a)}	Yield (%)
H	Me	Me	100—101	C ₁₀ H ₁₂ BrNO ₂	90
H	iso-Pr	H	110—111	C ₁₁ H ₁₄ BrNO ₂	88
H	sec-Bu	H	108—109	C ₁₂ H ₁₆ BrNO ₂	82
H	C ₆ H ₅	H	— ^{b)}	C ₁₄ H ₁₂ BrNO ₂	—
4-F	iso-Pr	H	93—94	C ₁₁ H ₁₃ BrFNO ₂	82
5-F	iso-Pr	H	105—106	C ₁₁ H ₁₃ BrFNO ₂	85
6-F	iso-Pr	H	123—124	C ₁₁ H ₁₃ BrFNO ₂	89
6-Cl	iso-Pr	H	98—99	C ₁₁ H ₁₃ BrClNO ₂	53
5-MeO	iso-Pr	H	143—144	C ₁₂ H ₁₆ BrNO ₃	88
6-MeO	iso-Pr	H	Oil ^{b)}	C ₁₂ H ₁₆ BrNO ₃	—
6-EtO	iso-Pr	H	Oil ^{b)}	C ₁₃ H ₁₈ BrNO ₃	—
5-Me	iso-Pr	H	109—110	C ₁₂ H ₁₅ BrNO ₂	85
6-Me	iso-Pr	H	113—114	C ₁₂ H ₁₅ BrNO ₂	87
6-Et	iso-Pr	H	106—107	C ₁₃ H ₁₈ BrNO ₂	83
6-iso-Pr	iso-Pr	H	90—91	C ₁₄ H ₂₀ BrNO ₂	75
6-tert-Bu	iso-Pr	H	103—104	C ₁₅ H ₂₂ BrNO ₂	77
6-cyclo-hexyl	iso-Pr	H	Oil ^{b)}	C ₁₇ H ₂₄ BrNO ₂	—

a) See footnote a, Table I. b) The compounds were used in the next reaction without purification.

bromo-3-methylbutyl)amino-6-isopropylphenol as crystals, which were recrystallized from isopropyl ether(IPE)–hexane to yield colorless needles (49.2 g, 75%), mp 90—91°C. IR cm⁻¹: 3280, 3150, 3085, 1625. NMR δ: 1.05 (3H, d, *J* = 6 Hz), 1.13 (3H, d, *J* = 6 Hz), 1.23 (6H, d, *J* = 7 Hz), 2.32—2.67 (1H, m), 3.40 (1H, m), 4.50 (1H, d, *J* = 4.5 Hz), 6.77—7.25 (3H, m), 7.87 (1H, s), 8.47 (1H, br). Anal. Calcd for C₁₄H₂₀BrNO₂: C, 53.51; H, 6.42; N, 4.46. Found: C, 53.53; H, 6.48; N, 4.41.

ii) A mixture of 2-(2-bromo-3-methylbutyl)amino-6-isopropyl phenol (47.0 g), K₂CO₃ (27.8 g) and DMF (150 ml) was stirred at room temperature for 1 h. The mixture was diluted with H₂O to give the title compound as crystals (35.1 g, 97%). Recrystallization from 2-propanol–H₂O gave colorless needles, mp 128—129°C. IR cm⁻¹: 3200, 3150, 1675. NMR δ: 1.05 (3H, d, *J* = 6 Hz), 1.15 (3H, d, *J* = 6 Hz), 1.23 (6H, d, *J* = 6 Hz), 2.22—2.58 (1H, m), 3.32 (1H, m), 4.34 (1H, d, *J* = 4.5 Hz), 6.57—6.90 (3H, m), 8.87 (1H, br). Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.03; H, 8.20; N, 6.00.

2-Isopropyl-2H-1,4-benzoxazin-3(4H)-one Method G: i) A mixture of 2-nitrophenol (5.56 g), methyl 2-bromo-3-methylbutyrate (7.8 g), K₂CO₃ (5.52 g) and DMF (80 ml) was heated at 100—110°C for 12 h with stirring. The mixture was allowed to stand overnight, diluted with H₂O, acidified with concentrated HCl and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give an oil which was chromatographed on silica gel (120 g) using hexane–AcOEt (9:1, v/v) as the eluent. The eluate was concentrated *in vacuo* to give methyl 2-(2-nitrophenoxy)-3-methylbutyrate as a yellow oil (3.8 g, 38%). NMR δ: 1.10 (6H, d, *J* = 7 Hz), 2.18—2.62 (1H, m), 3.75 (3H, s), 4.53 (1H, d, *J* = 4.5 Hz), 6.80—7.88 (4H, m).

ii) A solution of methyl 2-(2-nitrophenoxy)-3-methylbutyrate (3.8 g) in MeOH (40 ml) was hydrogenated in the presence of 5% palladium on charcoal (1.2 g) at room temperature under atmospheric pressure. After hydrogenation was complete, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in DMF (40 ml), and concentrated HCl (0.3 ml) was added. The mixture was heated at 80°C for 30 min and diluted with H₂O to give the title compound as crystals (2.63 g, 92%). Recrystallization from EtOH gave colorless plates, mp 118—119°C. IR cm⁻¹: 3180, 3125, 1675. NMR δ: 1.03 (3H, d, *J* = 6 Hz), 1.12 (3H, d, *J* = 6 Hz), 2.13—2.50 (1H, m), 4.34 (1H, d, *J* = 6 Hz), 6.70—6.97 (4H, m), 9.27 (1H, br). Anal. Calcd for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.10; H, 6.91; N, 7.33.

Data for compounds IVa, b and their intermediates VIII, X and XIII are summarized in Tables II, III, IV and V, respectively.

Synthesis of 1,4-Benzothiazine (or Benzoxazine)-4-acetic Acid (Ia, b; n=1) Typical examples are given to illustrate the general procedure.

3,4-Dihydro-2,8-diisopropyl-3-oxo-2H-1,4-benzoxazine-4-acetic Acid (7) i) NaH (60% in oil, 0.63 g) was added to a stirred solution of 2,8-

diisopropyl-2H-1,4-benzoxazin-3(4H)-one (3.5 g) in DMF (45 ml). The mixture was stirred at room temperature for 10 min, and a solution of methyl bromoacetate (1.5 ml) in DMF (3.0 ml) was added dropwise with cooling. The stirring was continued for 30 min with cooling, and the mixture was poured into ice-water and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated to give methyl 3,4-dihydro-2,8-diisopropyl-3-oxo-2H-1,4-benzoxazine-4-acetate as an oil in a quantitative yield.

ii) The oil obtained in i) was dissolved in MeOH (15 ml), and 2N NaOH (15 ml) was added. The mixture was stirred at room temperature for 30 min, diluted with H₂O, washed with Et₂O, acidified with 2N HCl and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated to give the title compound as crystals (3.40 g, 78%). Recrystallization from IPE–hexane gave colorless crystals, mp 132—133°C. NMR δ: 1.03, (3H, d, *J* = 7 Hz), 1.10 (3H, d, *J* = 7 Hz), 1.20 (3H, d, *J* = 6 Hz), 1.23 (3H, d, *J* = 6 Hz), 2.37 (1H, m), 3.35 (1H, m), 4.35 (1H, d, *J* = 6 Hz), 4.53 (1H, d, *J* = 18 Hz), 4.80 (1H, d, *J* = 18 Hz), 6.47—6.67 (1H, m), 6.82—7.10 (2H, m), 7.93 (1H, br s). Anal. Calcd for C₁₆H₂₁NO₄: C, 65.96; H, 4.81; N, 7.27. Found: C, 65.89; H, 7.32; N, 4.66.

3,4-Dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic Acid (46, AD-5467) i) Reaction of 2,8-diisopropyl-2H-1,4-benzoxazin-3(4H)-one (35.0 g) with methyl bromoacetate (17.0 ml) as described above gave methyl 3,4-dihydro-2,8-diisopropyl-3-oxo-2H-1,4-benzoxazine-4-acetate as an oil in a quantitative yield.

ii) A mixture of the oil obtained in i), P₂S₅ (66.6 g) and toluene (300 ml) was refluxed for 2 h with stirring. After cooling, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. Hexane (300 ml) was added to the residue, and the insoluble material was filtered off. The filtrate was concentrated to give methyl 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetate as a red yellow oil in a quantitative yield. NMR δ: 0.95—1.30 (12H, m), 2.25—2.62 (1H, m), 3.27—3.58 (1H, m), 3.80 (3H, s), 4.80 (1H, d, *J* = 6 Hz), 4.81 (1H, d, *J* = 17 Hz), 5.60 (1H, d, *J* = 17 Hz), 6.62—7.10 (3H, m).

iii) A 2N NaOH solution (150 ml) was added dropwise to a stirred solution of the oil obtained in ii) in dioxane–MeOH (2:1, v/v, 300 ml) over a period of 30 min. The mixture was stirred for an additional 10 min, diluted with H₂O, washed with Et₂O, acidified with 6N HCl and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give **46** as an oil, which was crystallized from hexane (33.3 g, 72%). Recrystallization from IPE–hexane gave pale yellow prisms (31.3 g, 67%), mp 156—157°C. IR cm⁻¹: 1725. NMR δ: 0.98 (3H, d, *J* = 7 Hz), 1.10 (3H, d, *J* = 7 Hz), 1.18 (3H, d, *J* = 6 Hz), 1.27 (3H, d, *J* = 6 Hz), 2.23—2.60 (1H, m), 3.17—3.63 (1H, m), 4.81 (1H, d, *J* = 6 Hz), 4.90 (1H, d, *J* = 18 Hz), 5.63 (1H, d, *J* = 18 Hz), 6.67—7.10 (3H, m), 8.87 (1H, br). Anal. Calcd for C₁₆H₂₁NO₃S: C, 62.51; H, 6.89; N, 4.56. Found: C, 62.52; H, 6.94; N, 4.60.

3,4-Dihydro-2,2-dimethyl-3-thioxo-2H-1,4-benzothiazine-4-propionic Acid (21) i) A mixture of 2,2-dimethyl-2H-1,4-benzothiazin-3(4H)-one (1.93 g), methyl acrylate (2.25 ml), K₂CO₃ (2.76 g) and DMF (30 ml) was heated at 100°C for 7 h with stirring. After dilution with H₂O, the mixture was extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give an oil, which was chromatographed on silica gel (50 g) using hexane–AcOEt (9:1, v/v) as the eluent. The eluate was concentrated *in vacuo* to give methyl 3,4-dihydro-2,2-dimethyl-3-oxo-2H-1,4-benzothiazine-4-propionate as an oil (2.3 g, 82%). NMR δ: 1.40 (6H, s), 2.66 (2H, t, *J* = 7.5 Hz), 3.65 (3H, s), 4.28 (2H, t, *J* = 7.5 Hz), 6.84—7.03 (4H, m).

ii) A mixture of the oil (1.3 g) obtained in i), P₂S₅ (1.55 g) and toluene (15 ml) was refluxed for 7 h with stirring. After cooling, the precipitate was filtered off, and the filtrate was concentrated *in vacuo* to give an oil, which was chromatographed on silica gel (30 g) using hexane–AcOEt (9:1, v/v) as the eluent. The eluate was concentrated to give methyl 3,4-dihydro-2,2-dimethyl-3-thioxo-2H-1,4-benzothiazine-4-propionate as a yellow oil in a quantitative yield.

iii) The oil obtained in ii) was dissolved in dioxane–MeOH (1:1, v/v 10 ml), and 2N NaOH (5.0 ml) was added dropwise. The mixture was stirred at room temperature for 1 h, diluted with H₂O and acidified with 2N HCl to give **21** as crystals (0.88 g, 67%). Recrystallization from EtOH gave colorless prisms, mp 147—148°C. IR cm⁻¹: 1690. NMR δ: 1.50 (6H, s), 2.94 (2H, t, *J* = 7.5 Hz), 4.87 (2H, t, *J* = 7.5 Hz), 6.98—7.40 (4H, m). Anal. Calcd for C₁₃H₁₅NO₂S₂: C, 55.49; H, 5.37; N, 4.98. Found: C, 55.67; H, 5.36; N, 5.00.

Acknowledgement The authors thank Messrs. E. Ishikawa and T. Sanada and Mrs. Y. Sawai for their technical assistance.

References and Notes

- 1) Part VIII: T. Sohda, Y. Momose, K. Meguro, Y. Kawamatsu, Y. Sugiyama and H. Ikeda, *Arzneim.-Forsch.*, **40**, 37 (1990).
- 2) This work was presented at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1989.
- 3) C. A. Lipinski and N. J. Huston, *Annu. Rep. Med. Chem.*, **19**, 169 (1984).
- 4) P. F. Kador, J. H. Kinoshita and N. E. Sharpless, *J. Med. Chem.*, **28**, 841 (1985).
- 5) Recently the geometry of epalrestat was revised as depicted in Fig. 1: T. Ishida, Y. In, M. Inoue, Y. Ueno and C. Tanaka, *Tetrahedron Lett.*, **30**, 959 (1989).
- 6) T. Sohda, K. Mizuno, E. Imamiya, H. Tawada, K. Meguro, Y. Kawamatsu and Y. Yamamoto, *Chem. Pharm. Bull.*, **30**, 3601 (1982).
- 7) M. Matsuda, T. Awata, Y. Ohashi, M. Inaba, I. Ishimoto, Y. Yamamoto, M. Fukuda and R. Manabe, "Polyol Pathway and Its Role in Diabetic Complications," ed. by N. Sakamoto, J. H. Kinoshita, P. F. Kador and N. Hotta, Elsevier Science Publishers, Amsterdam, 1988, pp. 244—249.
- 8) Y. Ohashi, M. Matsuda, H. Hosotani, Y. Tano, I. Ishimoto, M. Fukuda and R. Manabe, *Am. J. Ophthalmol.*, **105**, 233 (1988).
- 9) While this work was in progress, ARI activity of similar 1,4-benzoxazine- and 1,4-benzothiazine-4-acetic acids with rather simple substituents was reported: J. M. Teulon, Eur. Patent Appl. 162776 (1985) [*Chem. Abstr.*, **104**, 109668r (1986)].
- 10) P. F. Kador and N. E. Sharpless, *Mol. Pharmacol.*, **24**, 521 (1983).
- 11) S. Hayman and J. H. Kinoshita, *J. Biol. Chem.*, **240**, 877 (1965).
- 12) M. J. Peterson, R. Sarges, C. E. Aldinger and D. P. MacDonald, *Metabolism*, **28**, Suppl. 1, 456 (1979).
- 13) R. S. Clements, J. A. D. Morrison and A. I. Winegrad, *Science*, **166**, 1007 (1969).
- 14) A part of the pharmacological data of AD-5467 was presented at the 3rd International Symposium on Treatment of Diabetes Mellitus, Nagoya, July 1988.
- 15) Unpublished data.
- 16) N. Sakamoto and N. Hotta, *Farumashia*, **19**, 43 (1983).