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 Activity[2]

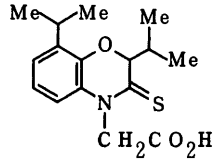
Hiroyuki TAWADA,[a] Yasuo SUGIYAMA,[b] Hitoshi IKEDA,[b] Yujiro YAMAMOTO[c] and Kanji MEGURO*,[a]

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*

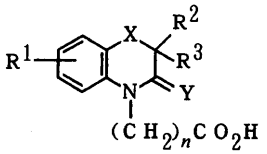
***N*-Acetic acid derivatives (I) of 2-substituted 1,4-benzoxazines and benzothiazines were designed and synthesized for evaluation as new aldose reductase inhibitors. In general, 3-thioxo derivatives were more potent inhibitors of aldose reductase from human placenta *in vitro* than the corresponding 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.



AD-5467



Ia : X=S, Y=O, S
Ib : X=O, Y=O, S

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 R^2 and R^3 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

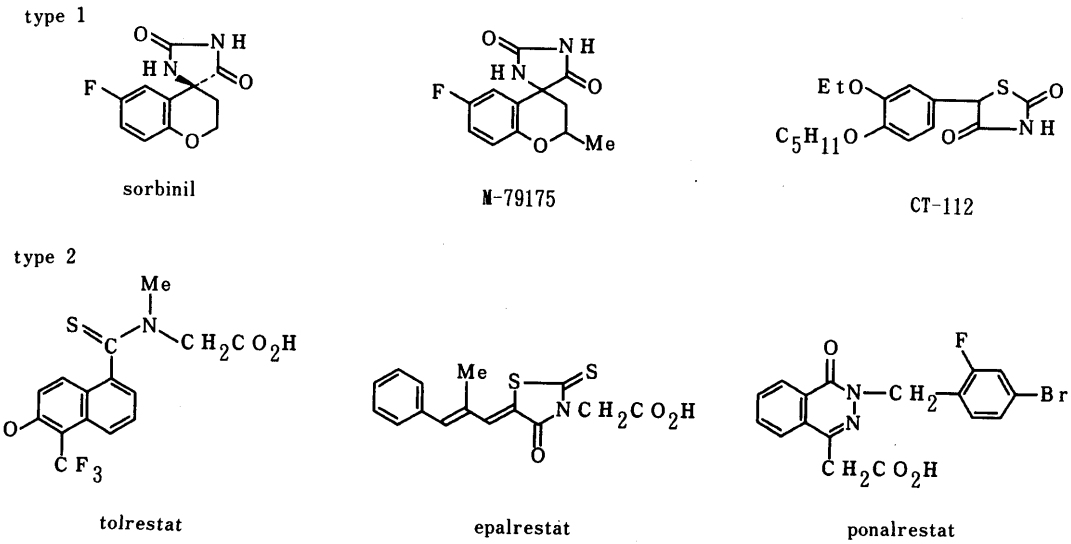


Fig. 1. Known Aldose Reductase Inhibitors

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 spiropropane 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).

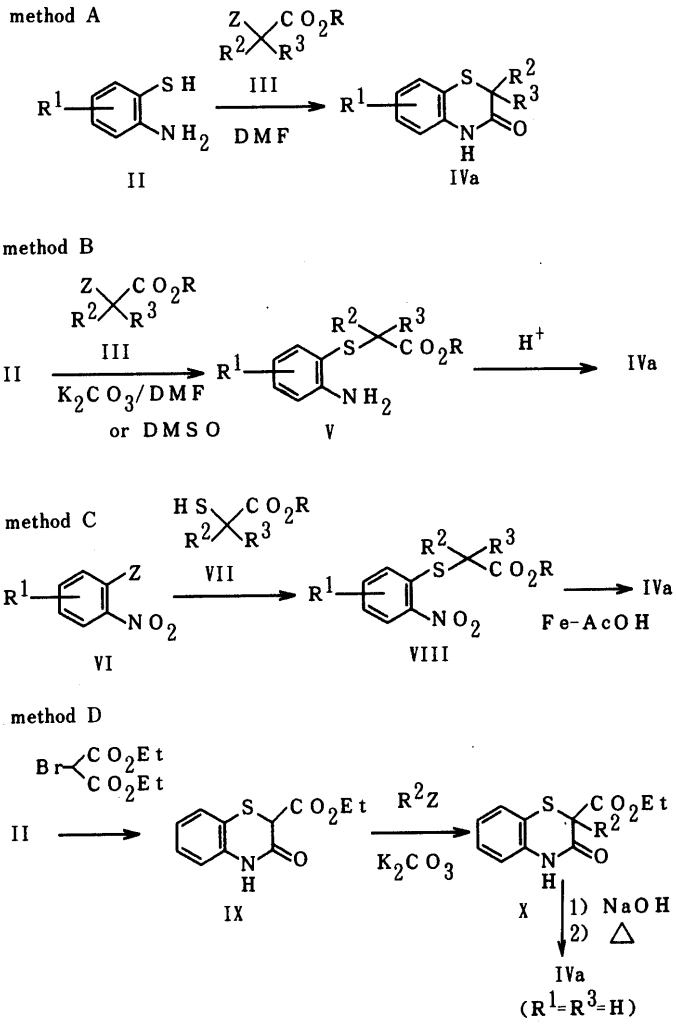


Chart 2

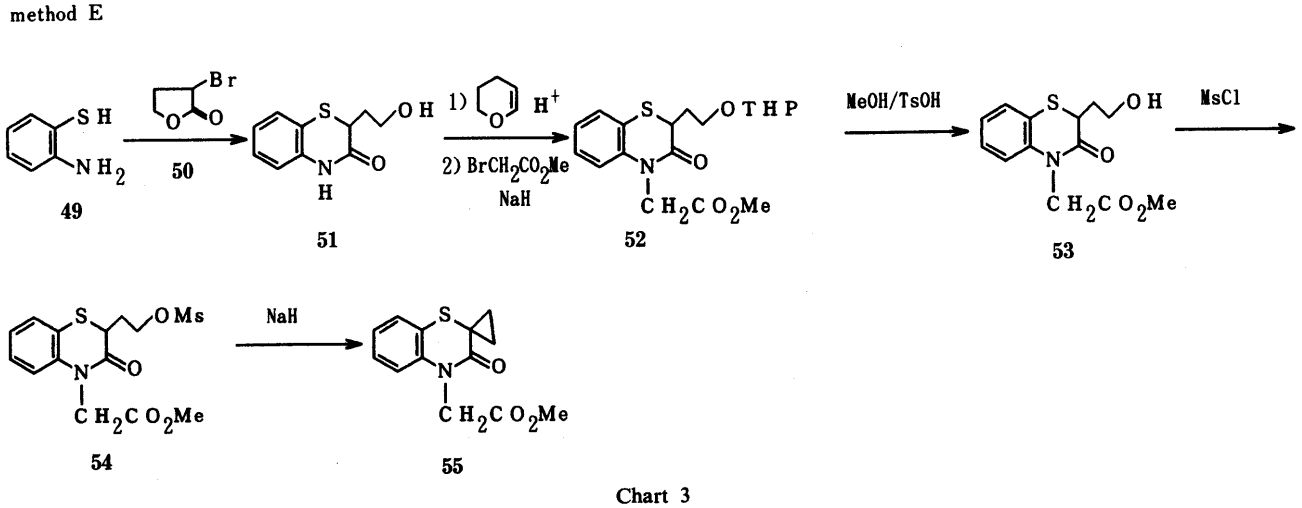


Chart 3

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*

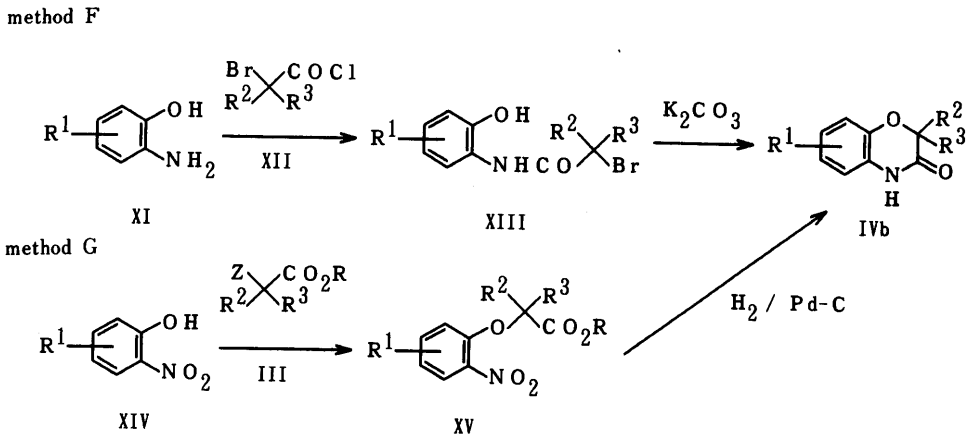


Chart 4

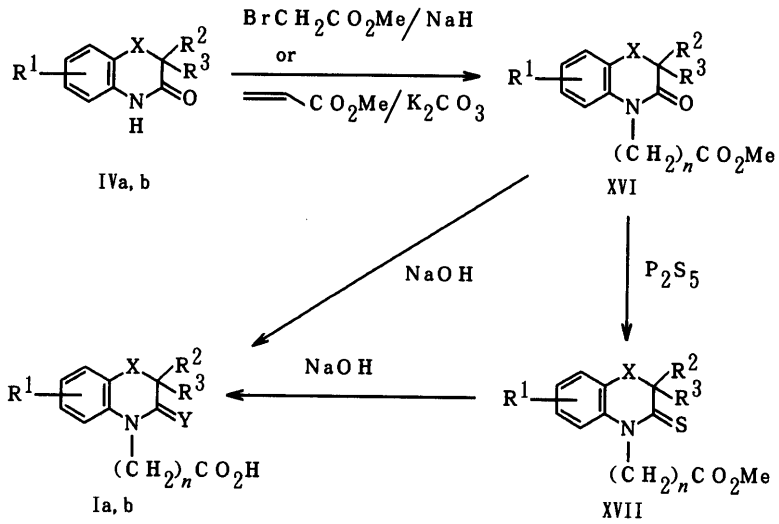


Chart 5

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

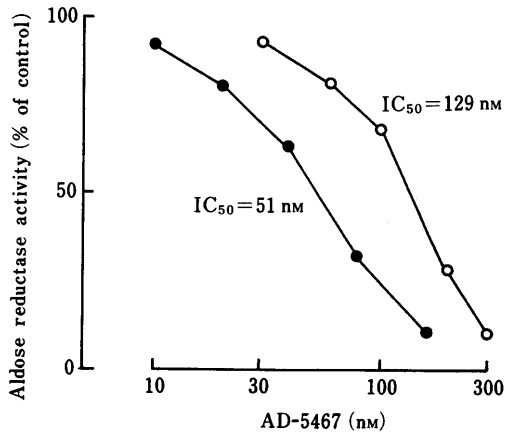
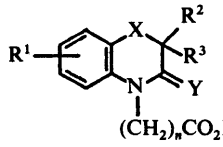


Fig. 2. Inhibition by AD-5467 of Aldose Reductase from Human Placenta (●) and Rat Lens (○)

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	$C_6H_5CH_2$	H	1	S	O	$C_{17}H_{15}NO_3$	ET	124—125	75	110	85	NT
2	H	4-Cl-$C_6H_4CH_2$	H	1	S	O	$C_{17}H_{14}ClNO_3S$	E	172—173	89	>1000	NT	NT
3	H	3,4-$(MeO)_2C_6H_3CH_2$	H	1	S	O	$C_{19}H_{19}NO_5S$	E	182—183	76	>1000	NT	NT
4[i,j]	H	C_6H_5	H	1	S	O	$C_{16}H_{12}NNaO_3S$	E	252—254	68	>1000	NT	NT
5	H	Me	Me	1	S	O	$C_{12}H_{13}NO_3S$	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	$C_6H_5CH_2$	H	1	S	S	$C_{17}H_{15}NO_2S_2$	IE	156—157	64	36	79[e]	NT
9	H	2-Cl-$C_6H_4CH_2$	H	1	S	S	$C_{17}H_{14}ClNO_2S_2$	E	189—190	65	600	NT	NT
10	H	3-Cl-$C_6H_4CH_2$	H	1	S	S	$C_{17}H_{14}ClNO_2S_2$	IE	144—145	74	240	95	NT
11	H	4-Cl-$C_6H_4CH_2$	H	1	S	S	$C_{17}H_{14}ClNO_2S_2$	IE	183—184	56	360	87	NT
12	H	4-CF_3-$C_6H_4CH_2$	H	1	S	S	$C_{18}H_{14}F_3NO_2S_2$	IE–H	138—140	75	600	77	NT
13[j]	H	C_6H_5	H	1	S	S	$C_{16}H_{13}NO_2S_2$	ET–IE	174—176	63	200	58[f]	NT
14[j]	H	Me	H	1	S	S	$C_{11}H_{11}NO_2S_2$	IE–H	124—125	71	60	71[f]	NT
15	H	Et	H	1	S	S	$C_{12}H_{13}NO_2S_2$	IE	147—148	90	140	83	NT
16	H	*n*-Pr	H	1	S	S	$C_{13}H_{15}NO_2S_2$	IE	147—148	75	380	76[e]	NT
17	H	iso-Pr	H	1	S	S	$C_{13}H_{15}NO_2S_2$	IE	175—176	97	480	46[g]	NT
18	H	*n*-Bu	H	1	S	S	$C_{14}H_{17}NO_2S_2$	IE–H	112—113	75	230	81[e]	NT
19	H	cyclo-pentyl	H	1	S	S	$C_{15}H_{17}NO_2S_2$	E	180—181	86	680	95	NT
20[j]	H	Me	Me	1	S	S	$C_{12}H_{13}NO_2S_2$	IE	177—178	52	200	52[e]	NT
21	H	Me	Me	2	S	S	$C_{13}H_{15}NO_2S_2$	E	147—148	51	>1000	NT	NT
22	H	$-(CH_2)_2-$		1	S	S	$C_{12}H_{11}NO_2S_2$	IE–H	152—153	86	220	106	NT
23	H	$-(CH_2)_4-$		1	S	S	$C_{15}H_{17}NO_2S_2$	IE	174—175	38	140	109	NT
24	5-Cl	Me	Me	1	S	S	$C_{12}H_{12}ClNO_2S_2$	IE–H	151—152	22	>1000	114	NT
25	6-Cl	Me	Me	1	S	S	$C_{12}H_{12}ClNO_2S_2$	IE	171—172	72	180	73[e]	NT
26	8-Cl	Me	Me	1	S	S	$C_{12}H_{12}ClNO_2S_2$	IE–H	147—148	47	66	41[f]	NT
27	6-F	Me	Me	1	S	S	$C_{12}H_{12}FNO_2S_2$	IE	181—182	69	120	58[f]	NT
28	6-MeO	Me	Me	1	S	S	$C_{13}H_{15}NO_3S_2$	IA–W	151—152	52	>1000	85	NT
29	7-MeO	Me	Me	1	S	S	$C_{13}H_{15}NO_3S_2$	E–W	182—183	47	120	53[f]	NT
30	7-Me	Me	Me	1	S	S	$C_{13}H_{15}NO_2S_2$	E–W	185—186	49	86	118	NT
31	H	Me	Me	1	O	S	$C_{12}H_{13}NO_3S$	IE–H	140—142	65	380	90	NT
32	H	iso-Pr	H	1	O	S	$C_{13}H_{15}NO_3S$	IE–H	96—97	75	30	18[h]	51[g]
33[k]	H	*sec*-Bu	H	1	O	S	$C_{14}H_{17}NO_3S$	IE–H	70—72	45	420	57[e]	94
34	H	C_6H_5	H	1	O	S	$C_{16}H_{13}NO_3S$	IE	150—151	78	42	56[f]	NT
35	H	4-MeO-C_6H_4	H	1	O	S	$C_{17}H_{15}NO_4S$	IE	140—141	38	27	NT	47[f]
36	6-F	iso-Pr	H	1	O	S	$C_{13}H_{14}FNO_3S$	IE–H	132—133	60	46	12[h]	33[g]
37	7-F	iso-Pr	H	1	O	S	$C_{13}H_{14}FNO_3S$	IE–H	113—114	62	45	NT	62[e]
38	8-F	iso-Pr	H	1	O	S	$C_{13}H_{14}FNO_3S$	IE–H	125—127	71	44	14[h]	45[g]
39	8-Cl	iso-Pr	H	1	O	S	$C_{13}H_{14}ClNO_3S$	IE–H	144—145	70	42	23[g]	70
40	7-MeO	iso-Pr	H	1	O	S	$C_{14}H_{17}NO_4S$	IE–H	128—129	68	52	NT	27[h]
41	8-MeO	iso-Pr	H	1	O	S	$C_{14}H_{17}NO_4S$	IE	159—160	70	68	11[h]	29[h]
42	8-EtO	iso-Pr	H	1	O	S	$C_{15}H_{19}NO_4S$	IE–H	138—139	72	36	NT	58[f]
43	7-Me	iso-Pr	H	1	O	S	$C_{14}H_{17}NO_3S$	IE–H	146—147	72	44	55[e]	78
44	8-Me	iso-Pr	H	1	O	S	$C_{14}H_{17}NO_3S$	IE–H	148—149	72	42	16[h]	29[h]
45	8-Et	iso-Pr	H	1	O	S	$C_{15}H_{19}NO_3S$	IE–H	117—118	73	36	NT	35[h]
46	8-iso-Pr	iso-Pr	H	1	O	S	$C_{16}H_{21}NO_3S$	IE–H	158—159	72	51	NT	35[h]
47	8-*tert*-Bu	iso-Pr	H	1	O	S	$C_{17}H_{23}NO_3S$	IE	195—196	69	230	NT	15[h]
48	8-cyclo-hexyl	iso-Pr	H	1	O	S	$C_{19}H_{25}NO_3S$	IE–H	157—158	70	48	NT	25[h]

a) All compounds were analyzed for C, H and N and the results were within ±0.4% of the theoretical values. *b*) E, EtOH; ET, ether; H, hexane; IA, 2-propanol; IE, isopropyl ether; W, H_2O. *c*) IC_{50} 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*) Diasteromeric 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 pharmacological[14] and toxicological[15] 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 $CDCl_3$ 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 H_2O 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 $C_{15}H_{13}NOS$: 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: K_2CO_3 (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 N_2 atmosphere. The mixture was stirred at room temperature for 1 h, diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 H_2O 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 $C_{11}H_{13}NO_2S$: 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), K_2CO_3 (9.93 g) and DMF (100 ml) was heated at 100 °C for 3 h under an N_2 atmosphere. The mixture was diluted with H_2O, washed with AcOEt, acidified with concentrated HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 $C_{10}H_{10}ClNO_4S$: 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 H_2O (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 H_2O 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 $C_{10}H_{10}ClNOS$: 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 H_2O 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 $C_{11}H_{11}NO_3S$: 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), K_2CO_3 (3.32 g) and NaI (3.00 g) in 2-butanone (60 ml) was refluxed for 2 h with stirring. After dilution with H_2O, the mixture was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give an oil which was crystallized from Et_2O 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 $C_{20}H_{21}NO_5S$: 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 H_2O, acidified with 6 N HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 H_2O 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 $C_{17}H_{17}NO_3S$: 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), K_2CO_3 (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 H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N, 6.69. Found: C, 57.04; H, 5.15; N, 6.69.

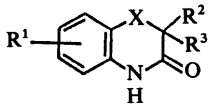
ii) *p*-Toluenesulfonic acid (0.95 g) was added to a stirred, ice-cooled solution of **51** (20.9 g) and 2,3-dihydropyran (9.24 g) in CH_2Cl_2 (200 ml). The mixture was stirred for 2 h with cooling, washed successively with aqueous $NaHCO_3$ solution and H_2O, dried ($MgSO_4$) and concentrated *in vacuo* 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 H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 H_2O and extracted with AcOEt. The extract was washed with aqueous $NaHCO_3$ solution and H_2O, dried ($MgSO_4$) 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) Mesyl 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 Et_3N (3.7 ml) in CH_2Cl_2 (60 ml). The mixture was stirred for 1 h with cooling, washed with H_2O, dried ($MgSO_4$) 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 H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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

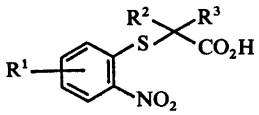
TABLE II. 1,4-Benzothiazin-3-ones (IVa) and 1,4-Benzoxazin-3-ones (IVb)



R^1	R^2	R^3	X	Method[a]	mp (°C)	Formula[b]	Yield (%)
H	$C_6H_5CH_2$	H	S	A	160—161	$C_{15}H_{13}NOS$	63
H	2-Cl-$C_6H_4CH_2$	H	S	A	189—190	$C_{15}H_{12}ClNOS$	50
H	3-Cl-$C_6H_4CH_2$	H	S	D	145—146	$C_{15}H_{12}ClNOS$	87
H	4-Cl-$C_6H_4CH_2$	H	S	D	183—184	$C_{15}H_{12}ClNOS$	89
H	4-CF_3-$C_6H_4CH_2$	H	S	A	168—169	$C_{16}H_{12}F_3NOS$	61
H	3,4-$(MeO)_2$-$C_6H_3CH_2$	H	S	D	178—179	$C_{17}H_{17}NO_3S$	97
H	C_6H_5	H	S	A	205—206	$C_{14}H_{11}NOS$	60
H	Me	H	S	A	129—130	C_9H_9NOS	72
H	Et	H	S	A	103—104	$C_{10}H_{11}NOS$	57
H	*n*-Pr	H	S	A	85—86	$C_{11}H_{13}NOS$	52
H	iso-Pr	H	S	B	152—153	$C_{11}H_{13}NOS$	92
H	*n*-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	$-(CH_2)_5-$		S	C	227—228	$C_{13}H_{15}NOS$	91
5-Cl	Me	Me	S	A	84—85	$C_{10}H_{10}ClNOS$	60
6-Cl	Me	Me	S	C	199—200	$C_{10}H_{10}ClNOS$	86
8-Cl	Me	Me	S	C	207—208	$C_{10}H_{10}ClNOS$	93
6-F	Me	Me	S	C	178—179	$C_{10}H_{10}FNOS$	88
6-MeO	Me	Me	S	C	153—154	$C_{11}H_{13}NO_2S$	78
7-MeO	Me	Me	S	B	149—150	$C_{11}H_{13}NO_2S$	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	iso-Pr	H	O	F, G	118—119	$C_{11}H_{13}NO_2$	94, 92
H	*sec*-Bu	H	O	F	94—95	$C_{12}H_{15}NO_2$	75
H	C_6H_5	H	O	F	169—170	$C_{14}H_{11}NO_2$	99[c]
H	4-MeO-C_6H_4	H	O	F	150—151	$C_{15}H_{13}NO_3$	76
6-F	iso-Pr	H	O	F	138—139	$C_{11}H_{12}FNO_2$	94
7-F	iso-Pr	H	O	F	178—179	$C_{11}H_{12}FNO_2$	96
8-F	iso-Pr	H	O	F	146—147	$C_{11}H_{12}FNO_2$	91
8-Cl	iso-Pr	H	O	F	132—133	$C_{11}H_{12}ClNO_2$	85
7-MeO	iso-Pr	H	O	F	126—127	$C_{12}H_{15}NO_3$	87
8-MeO	iso-Pr	H	O	F	149—150	$C_{12}H_{15}NO_3$	56[c]
8-EtO	iso-Pr	H	O	F	129—130	$C_{13}H_{17}NO_3$	81
7-Me	iso-Pr	H	O	F	129—130	$C_{12}H_{15}NO_2$	95
8-Me	iso-Pr	H	O	F	109—110	$C_{12}H_{15}NO_2$	92
8-Et	iso-Pr	H	O	F	93—94	$C_{13}H_{17}NO_2$	94
8-iso-Pr	iso-Pr	H	O	F	129—130	$C_{14}H_{19}NO_2$	95
8-*tert*-Bu	iso-Pr	H	O	F	170—171	$C_{15}H_{21}NO_2$	95
8-cyclo-hexyl	iso-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.

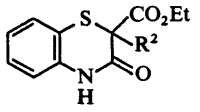
TABLE III. 2-(2-Nitrophenylthio)propionic Acids (VIII)



R^1	R^2	R^3	mp (°C)	Formula[a]	Yield (%)
4-Cl	Me	Me	132—133	$C_{10}H_{10}ClNO_4S$	69
6-Cl	Me	Me	155—156	$C_{10}H_{10}ClNO_4S$	50
4-F	Me	Me	105—106	$C_{10}H_{10}FNO_4S$	73
4-MeO	Me	Me	130—131	$C_{11}H_{13}NO_5S$	46
H	$-(CH_2)_5-$		174—175	$C_{13}H_{15}NO_4S$	77

a) See footnote *a*, Table I.

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



R^2	mp (°C)	Formula[a]	Yield (%)
3-Cl-$C_6H_4CH_2$	117—118	$C_{18}H_{16}ClNO_3S$	74
4-Cl-$C_6H_4CH_2$	132—133	$C_{18}H_{16}ClNO_3S$	80
3,4-$(MeO)_2C_6H_3CH_2$	149—150	$C_{20}H_{21}NO_5S$	84

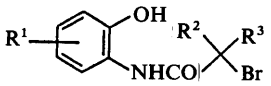
a) See footnote *a*, Table I.

(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 $C_{13}H_{17}NO_3S$: C, 59.30; H, 4.89; N, 5.32. Found: C, 59.57; H, 5.07; N, 5.34.

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

2,8-Diisopropyl-2*H*-1,4-benzoxazin-3(4*H*)-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), $NaHCO_3$ (26.7 g), AcOEt (240 ml) and H_2O (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 H_2O, dried ($MgSO_4$) 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_6H_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-methylbutyryl)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 $C_{14}H_{20}BrNO_2$: 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-methylbutyryl)amino-6-isopropyl phenol (47.0 g), K_2CO_3 (27.8 g) and DMF (150 ml) was stirred at room temperature for 1 h. The mixture was diluted with H_2O to give the title compound as crystals (35.1 g, 97%). Recrystallization from 2-propanol–H_2O 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 $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.03; H, 8.20; N, 6.00.

2-Isopropyl-2*H*-1,4-benzoxazin-3(4*H*)-one Method G: i) A mixture of 2-nitrophenol (5.56 g), methyl 2-bromo-3-methylbutyrate (7.8 g), K_2CO_3 (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 H_2O, acidified with concentrated HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 H_2O 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 $C_{11}H_{13}NO_2$: 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-2*H*-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-2*H*-1,4-benzoxazin-3(4*H*)-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 wth H_2O, dried ($MgSO_4$) and concentrated to give methyl 3,4-dihydro-2,8-diisopropyl-3-oxo-2*H*-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 2 N NaOH (15 ml) was added. The mixture was stirred at room temperature for 30 min, diluted with H_2O, washed with Et_2O, acidified with 2 N HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 $C_{16}H_{21}NO_4$: 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-2*H*-1,4-benzoxazine-4-acetic Acid (46, AD-5467) i) Reaction of 2,8-diisopropyl-2*H*-1,4-benzoxazin-3(4*H*)-one (35.0 g) with methyl bromoacetate (17.0 ml) as described above gave methyl 3,4-dihydro-2,8-diisopropyl-3-oxo-2*H*-1,4-benzoxazine-4-acetate as an oil in a quantitative yield.

ii) A mixture of the oil obtained in i), P_2S_5 (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-2*H*-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 2 N 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 H_2O, washed with Et_2O, acidified with 6 N HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 $C_{16}H_{21}NO_3S$: 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-2*H*-1,4-benzothiazine-4-propionic Acid (21) i) A mixture of 2,2-dimethyl-2*H*-1,4-benzothiazin-3(4*H*)-one (1.93 g), methyl acrylate (2.25 ml), K_2CO_3 (2.76 g) and DMF (30 ml) was heated at 100 °C for 7 h with stirring. After dilution with H_2O, the mixture was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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-2*H*-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), P_2S_5 (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-2*H*-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 2 N NaOH (5.0 ml) was added dropwise. The mixture was stirred at room temperature for 1 h, diluted with H_2O and acidified with 2 N 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 $C_{13}H_{15}NO_2S_2$: C, 55.49; H, 5.37; N, 4.98. Found: C, 55.67; H, 5.36; N, 5.00.

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References and Notes

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