Synthesis and Biological Evaluation of Alkyl, Alkoxy, Alkylthio, or Amino-Substituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones

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2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones substituted with an alkyl, alkoxy, alkylthio, hydroxy, or amino group on the fused benzene ring of the 1,5-benzothiazepine skeleton were synthesized and their vasodilating, antihypertensive, and platelet aggregation-inhibitory activities were investigated. (−)-*cis*-3-Acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-8-methyl-2-(4-methylphenyl)-1,5-benzothiazepin-4(5*H*)-one ((−)-13e) was selected for further studies as a potent inhibitor of platelet aggregation.

Key words 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one; platelet aggregation; vasodilation; antihypertensive activity; 3-arylglycidic ester; aminothiophenol

Calcium channel blockers are important cardiovascular drugs for the management of angina pectoris and hypertension and may have applications in additional therapeutic areas.[2)] The most studied class of agents is the 1,4-dihydropyridines, and several analogues are currently in clinical use.[3)] The 1,5-benzothiazepin-4(5*H*)-ones are one of three structurally distinct classes of calcium channel blockers that appear to exert their major pharmacological effects by selectively inhibiting the influx of extracellular calcium through the L-type voltage-dependent calcium channels.

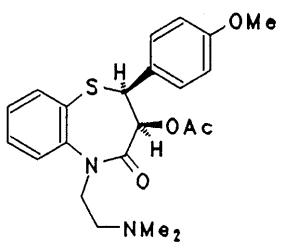
Diltiazem is a typical calcium channel blocker of 1,5-benzothiazepine type and has been clinically used as an effective antianginal and antihypertensive agent in more than 100 countries. In our previous papers,[4,5)] we reported the synthesis of unsubstituted and halogen-substituted derivatives on the fused benzene ring of 1,5-benzothiazepines and discussed their structure–activity relationship (SAR). However, information on the SAR of 1,5-benzothiazepines is limited.

In an attempt to improve the potency and duration of action of diltiazem and to acquire more detailed SAR data on the 1,5-benzothiazepine derivatives, we synthesized novel derivatives substituted with an alkyl, alkoxyl, alkylthio, hydroxy, or amino group on the fused benzene ring of the 1,5-benzothiazepine skeleton and examined their vasodilating, antihypertensive, and platelet aggregation-inhibitory activities.

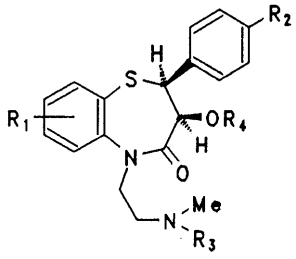
Chemistry

For the synthesis of the desired *cis*-2-aryl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one skeleton bearing an alkyl, alkoxy, or alkylthio substituent on the fused benzene ring as a key intermediate of this study, we initially tried a simple one-step synthesis by the reaction of the *trans*-3-arylglycidic ester (**2**) with 2-aminothiophenols (**1**) having the corresponding substituent (Tables 1, 2). Heating of a mixture of **1** with one equivalent of **2** without solvent at 150—160 °C (Table 1, method A) gave a mixture of the *cis*-lactam (**5**) and the *threo*-amino ester (**3**) in moderate to low yield. In some cases, the *trans*-lactam (**6**) was also isolated in low yield. The reaction may proceed favorably by *cis*-opening of the oxirane ring of **2** with the thiol group of **1** to give the *threo*-amino ester (**3**), with simultaneous thermal cyclization to **5**.[6)]

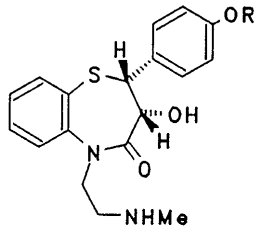
As a more practical approach, the reaction was investigated under milder conditions. When the reaction was carried out at 60—150 °C in toluene or xylene (Table 2, method F), the *threo*-amino ester (**3**) was obtained as a sole product in better yield (40—74%) than that in



diltiazem



R_1=Me, Et, MeO, BzlO, MeS, HO, NH_2, CF_3
R_2=MeO, CF_3O, Me, Et, H
R_3=Me, H, Allyl, Bzl, COOBzl



l-M-2; R=Me
l-M-6; R=H

Chart 1

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method A. In the reaction of 5-methyl-2-aminothiophenol (**1c**) with *trans*-3-(4-methylphenyl)glycidic ester (**2c**), heating at 130 °C gave the best result among the various reaction temperatures. The *p*-methoxy or *p*-trifluoromethyloxy-substituted 3-arylglycidic ester (**2a, b**) was more reactive than the *p*-methyl analogue (**2c**), in accordance with the results of our previous studies.[6] Regarding the substituent on the 2-aminothiophenol, no characteristic influence on the reactivity of the thiol group was observed.

The *threo*-amino ester (**3**) could be easily cyclized to the *cis*-lactam (**5**) directly or *via* the amino carboxylic acid in satisfactory yields without epimerization. Stirring of the amino ester (**3**) with aqueous KOH at room temperature gave the *threo*-amino carboxylic acid (**4**) in good yield (Table 3, method I). Cyclization of **4** by heating in xylene under reflux (Table 1, method B) or by treatment with 1,3-dicyclohexylcarbodiimide (DCC)–1-hydroxybenzotriazole (HOBt) at room temperature (Table 1, method E) afforded the corresponding *cis*-lactam (**5**). Alternatively, direct cyclization of the *threo*-amino ester (**3**) by treatment with NaH in dimethyl sulfoxide (DMSO) (Table 1, method D) at room temperature also gave **5** in quantitative yield.

Reaction of **1c** and **2c** in toluene in the presence of a catalytic amount of $CaCl_2$ (Table 2, method L) gave the *erythro*-amino ester (*erythro*-**3e**) through *trans*-opening of the oxirane ring of **2c** with the thiol group of **1c**.[6] The *erythro*-**3e** was converted into the *trans*-lactam (**6e**) by hydrolysis of the ester group of *erythro*-**3e** followed by thermal cyclization similarly to method B.

The alkyl, alkoxy, or alkylthio-substituted 2-aminothiophenols (**1**) used above as starting materials were synthesized by hydrolysis of the corresponding 2-aminobenzothiazoles (**29**) with about 40% NaOH as shown in Table 4. The 6-substituted 2-aminobenzothiazoles were prepared directly by the reaction of the *para*-substituted anilines with KSCN–Br_2 according to the method reported by Randvere.[7] The 4- or 5-substituted 2-aminobenzothiazoles were synthesized by cyclization with Br_2 of the thioureas (**28**), which were obtained from the corresponding *ortho*- or *meta*-substituted anilines according to the method reported by Tsuda *et al.*[8]

On the other hand, for the synthesis of the amino-substituted lactams (**5aa**, **5bb**), we employed 2,4-dinitrothiophenol, which was readily prepared from 2,4-dinitrochlorobenzene and was more reactive with **2**. Reaction of 2,4-dinitrothiophenol with **2a** was performed at room temperature for 3 d to afford the *threo*-nitro ester (**26**) in 49% yield and then the nitro groups were reduced with $SnCl_2$–HCl in HOAc to give **3bb** (Table 2, method K). Selective protection of the 4-amino group of **3bb** with one equivalent of benzyloxycarbonyl chloride (ZCl) in the presence of $NaHCO_3$ in CH_2Cl_2–dimethylformamide (DMF) gave **3aa**, accompanied with the 2,4-bis[(benzyloxycarbonyl)amino] compound (**27**) as by-product (Table 2, method J). Hydrolysis of the ester group of **3aa** followed by cyclodehydration (method B) gave **5aa** in 47% yield. Finally, removal of the protective group on the amino group of **5aa** to afford **5bb** was performed by means of the following three-step procedure; i) acetylation of the 3-hydroxyl group, ii) removal of the *N*-benzyloxycarbonyl group with HBr–HOAc at room temperature, and then iii) hydrolysis of 3-OAc with 10% NaOH (Table 1, method G).

Stereochemistry of the obtained *cis*- and *trans*-lactams (**5**, **6**) was determined from the values of their vicinal coupling constant between the methine protons at C_2 and C_3 (6.5—8 Hz and 10—11 Hz for *cis*- and *trans*-isomers, respectively).[4]

For the synthesis of the optically active lactams, two methods were applied, that is, optical resolution of the amino carboxylic acid (**4**) with an optically active amine, and chromatographic separation of the diastereomeric isomers of the 3-acylated lactam prepared by acylation of the lactam (**5**) with an optically active carboxylic acid. The optically active isomers of the lactams (**5b, d, e, k**) were prepared by optical resolution of the amino carboxylic acids with methyl (*S*)- or (*R*)-2-(4-hydroxyphenyl)glycinate (Table 3, method H), followed by cyclization. As an alternative route, the lactams (**5e, t, u**) were acylated with (*S*)-*N*-(2-naphthalenesulfonyl)pyrrolidine-2-carbonyl chloride in pyridine, the obtained diastereomeric isomers (**25**) were separated by silica gel column chromatography, and then the acyl group was removed by alkaline hydrolysis (Table 1, method C) to recover the optically active lactams.

N-Alkylation of **5** and **6** with (dialkylamino)alkyl chloride hydrochloride in the presence of K_2CO_3 in acetone–H_2O under reflux (Table 5, method M) or in the presence of KOH in DMSO at room temperature (Table 5, method N) gave the 5-(dialkylamino)alkyl compounds (**7**, **8**, **9**) in good yield. For *N*-alkylation with a less reactive alkylating agent (such as 2-(*N*-benzyloxycarbonyl-*N*-methylamino)ethyl chloride) for preparing **10**, more basic conditions (such as method N) were required.

Acetylation of 3-OH of **7** with Ac_2O at 100 °C (Table 6, method R) afforded **13**. The 3-(*n*-butylamino)carbonyloxy compound (**14**) was obtained by heating of **7** with *n*-butyl isocyanate in benzene under reflux (Table 6, method S). On the other hand, acylation of **7** with acyl halide in pyridine (Table 6, method T) gave **15**, **16**, and **17**. Moreover, benzylation of **7d** with benzyl chloride (Table 6, method X) and methylation of **7e** with Me_2SO_4 (Table 6, method Y) in the presence of NaH as a base gave the 3-alkoxy compounds **23d** and **22e**, respectively.

The 5-[2-(monomethylamino)ethyl] compounds (**18**, **19**, **20**, **21**) were synthesized by the use of three methods. The first procedure was debenzyloxycarbonylation of **10** by stirring with HBr–HOAc at room temperature after protection of the 3-OH with an acyl group (Table 6, method V). As the second procedure, the *N*-benzyl group of **9** was replaced with a benzyloxycarbonyl group by heating with ZCl in toluene under reflux after protection of the 3-OH with an acetyl group and then removal of the *N*-benzyloxycarbonyl group with HBr–HOAc in the same manner as described in method V (Table 6, method W). The third method was *N*-demethylation of the dimethylamino group of **13**. Compound **13** was treated with trichloromethyl chloroformate (TCF) in the presence of Et_3N at room temperature overnight to give **24** as an oil. Heating of **24** in H_2O–MeCN for 40 min (Table 6,

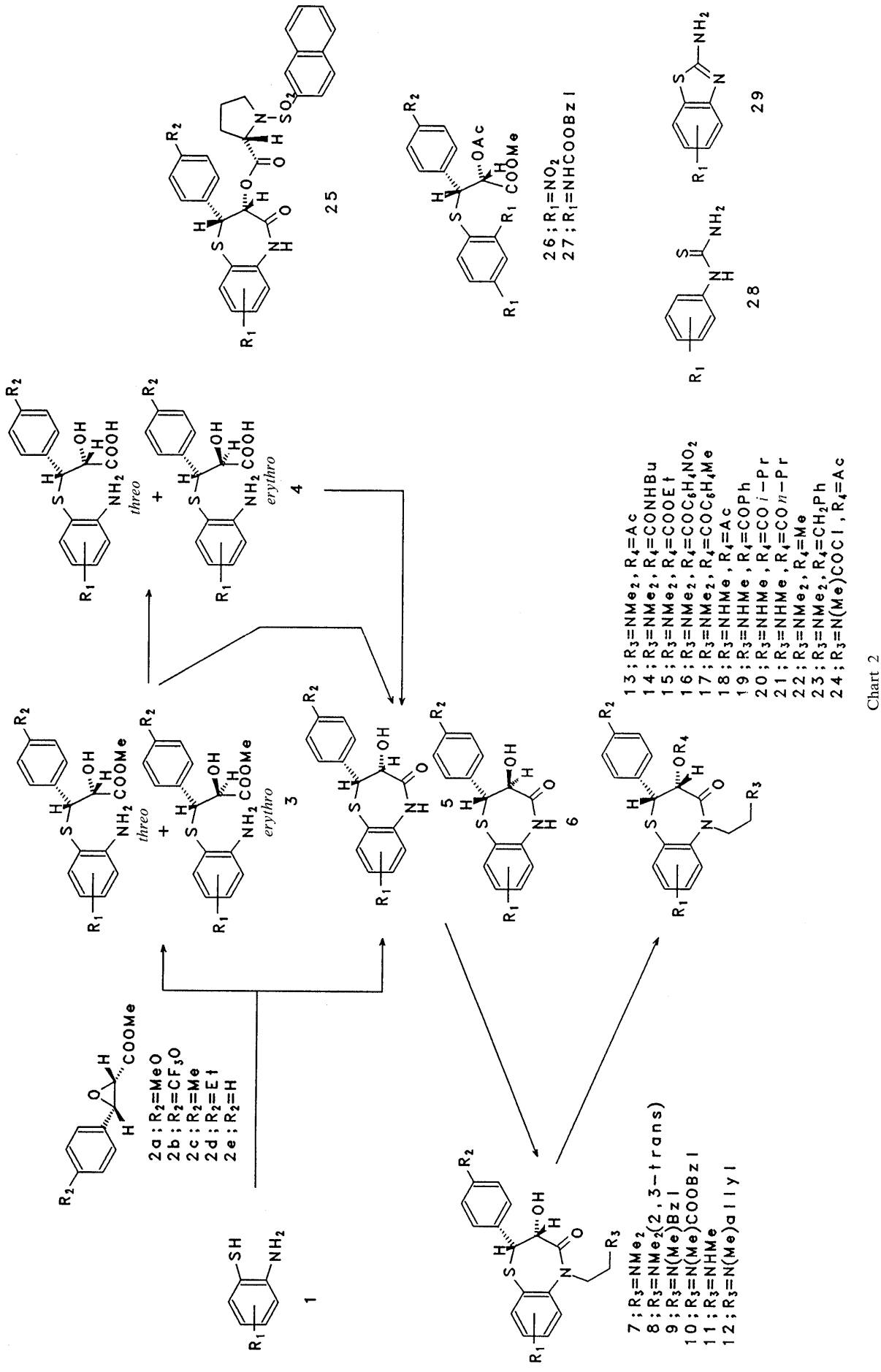

Chart 2

Table 1. Lactams (**5**, **6**)

Compd.	R_1	R_2	mp (°C)	Recrystn. solvent	Method[a]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found)			
								C	H	N	S
5a	6-Me	4-OMe	225—227.5	DMF–EtOH	A	7.3[b]	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.16
								(64.71	5.35	4.54	9.75)
6a	6-Me	4-OMe	231—233	DMF–EtOH	A	3.0	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.16
								(64.66	5.42	4.40	10.22)
5b	7-Me	4-OMe	218—221	DMF	A	27.8	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.16
								(64.52	5.46	4.62	10.05)
(+)-**5b**	7-Me	4-OMe	213—216 (d)[c]	AcOEt	B	89.2	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.16
								(64.81	5.35	4.39	10.06)
(−)-**5b**	7-Me	4-OMe	212—215 (d)[d]	AcOEt	B	86.4	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.16
								(64.78	5.35	4.38	10.15)
5c	7-Me	4-Me	204—205	DMF–EtOH	A	4.5[e]	$C_{17}H_{17}NO_2S$	68.20	5.72	4.68	10.71
								(68.18	5.66	4.64	10.60)
5d	8-Me	4-OMe	224—225.5	DMF–EtOH	A	32.3	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.16
					B	88.0		(64.78	5.35	4.38	10.01)
(+)-**5d**	8-Me	4-OMe	223—226 (d)[f]	AcOEt	B	91.6	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.16
								(64.81	5.39	4.44	10.14)
(−)-**5d**	8-Me	4-OMe	224—226 (d)[g]	AcOEt	B	89.6	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.16
								(64.99	5.37	4.44	10.00)
5e	8-Me	4-Me	182.5—184.5	DMF–EtOH	A	13.2	$C_{17}H_{17}NO_2S$	68.20	5.72	4.68	10.71
					B	92.9		(68.00	5.65	4.67	10.73)
(+)-**5e**	8-Me	4-Me	217.5—219[h]	AcOEt–hexane	C	38.5	$C_{17}H_{17}NO_2S$	68.20	5.72	4.68	10.71
					B	91.6		(68.15	5.61	4.43	10.92)
(−)-**5e**	8-Me	4-Me	216.5—217.5[i]	AcOEt–hexane	C	38.5	$C_{17}H_{17}NO_2S$	68.20	5.72	4.68	10.71
					B	95.7		(68.22	5.73	4.65	10.65)
6e	8-Me	4-Me	207—209 (d)	AcOEt	B	94.0	$C_{17}H_{17}NO_2S$	68.20	5.72	4.68	10.71
								(68.04	5.64	4.81	10.70)
5f	8-Me	4-Et	218.5—220	AcOEt	B	93.7[j]	$C_{18}H_{19}NO_2S$	68.98	6.11	4.47	10.23
								(68.89	6.09	4.36	10.39)
5g	8-Me	4-OCF_3	215—218	Xylene	B	90.0[j]	$C_{17}H_{14}F_3NO_3S$	55.28	3.82	3.79	
								(55.25	3.74	3.77)	
5h	6,7-di-Me	4-OMe	235—238	AcOEt	A	11.6[k]	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.56	5.82	4.19)	
6h	6,7-di-Me	4-OMe	270—271	DMF	A	1.5	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.48	5.82	4.21)	
5i	6,8-di-Me	4-OMe	208—210	AcOEt	A	36.6[l]	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.68	5.79	4.21)	
6i	6,8-di-Me	4-OMe	161—163	AcOEt	A	3.3	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.80	5.79	4.23)	
5j	7,9-di-Me	4-OMe	246—249	AcOEt	A	56.0[m]	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.61	5.76	4.20)	
6j	7,9-di-Me	4-OMe	227—230	AcOEt	A	5.3	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.58	5.72	4.24)	
5k	7,8-di-Me	4-OMe	221—224 (d)	$CHCl_3$–DMF	B	92.0	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
					A	33.9[n]		(65.37	5.72	4.35)	
(+)-**5k**	7,8-di-Me	4-OMe	232—234[o]	AcOEt	B	88.6	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.41	5.72	4.19)	
(−)-**5k**	7,8-di-Me	4-OMe	225—227[p]	AcOET	B	80.2	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.41	5.69	4.23)	
6k	7,8-di-Me	4-OMe	235—237 (d)	AcOEt	A	1.3	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	
								(65.37	5.75	4.17)	
5l	7,8-di-Me	4-Me	230—233	AcOEt	B	87.0	$C_{18}H_{19}NO_2S$	68.98	6.11	4.47	10.23
								(69.25	6.17	4.57	10.39)
5m	7,8-di-Me	4-Et	226.5—228	AcOEt	B	78.0[j]	$C_{19}H_{21}NO_2S$	69.69	6.46	4.28	9.79
								(70.03	6.57	4.29	9.89)
5n	8-Et	4-OMe	230—232.5	Xylene–iso-Pr_2O	B	96.1	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25	9.73
								(65.88	5.76	4.24	9.76)
5o	8-Et	4-Me	210—212	Xylene–iso-Pr_2O	B	95.0	$C_{18}H_{19}NO_2S$	68.98	6.11	4.47	10.23
								(69.12	6.09	4.46	10.30)
5p	8-Et	H	200—201.5	Xylene–iso-Pr_2O	B	93.8	$C_{17}H_{17}NO_2S$	68.20	5.72	4.68	10.71
								(68.26	5.67	4.62	10.81)
5q	7-CF_3	4-OMe	205—207	AcOEt	E	94.1	$C_{17}H_{14}F_3NO_3S$	55.28	3.82	3.79	15.43[x]
								(55.09	3.78	3.80	15.27[x])
5r	6-OMe	4-OMe	208—210	$CHCl_3$–hexane	A	8.9	$C_{17}H_{17}NO_4S \cdot 1/2H_2O$	60.05	5.34	4.12	
								(60.32	5.03	4.12)	
5s	7-OMe	4-OMe	220—222	AcOEt–hexane	A	23.1[q]	$C_{17}H_{17}NO_4S$	61.61	5.17	4.23	
								(61.73	5.18	4.22)	

Table 1. (continued)

Compd.	R_1	R_2	mp (°C)	Recrystn. solvent	Method[a]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found)			
								C	H	N	S
6s	7-OMe	4-OMe	189—190	AcOEt–hexane	A	3.9	$C_{17}H_{17}NO_4S$	60.70	5.64	3.73	
								(60.53	5.45	3.92)	
5t	8-OMe	4-OMe	214—206	AcOEt	E	74.6	$C_{17}H_{17}NO_4S$	61.61	5.17	4.23	
					A	36.1[r]		(61.83	5.18	4.29)	
(+)-**5t**	8-OMe	4-OMe	187—190[s]	AcOEt	C	74.9 × 45.9	$C_{17}H_{17}NO_4S$	61.61	5.17	4.23	9.68
								(61.62	5.17	3.92	9.53)
(−)-**5t**	8-OMe	4-OMe	187—189[t]	AcOEt	C	75.7 × 49.4	$C_{17}H_{17}NO_4S$	61.61	5.17	4.23	9.68
								(61.36	5.07	4.25	9.84)
6t	8-OMe	4-OMe	150—152	AcOEt–hexane	A	7.1	$C_{17}H_{17}NO_4S$	61.61	5.17	4.23	
								(61.73	5.17	4.56)	
5u	8-OMe	4-Me	202—206	EtOH	B	73.6	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	
					D	90.3		(64.78	5.51	4.47)	
					A	12.9					
(+)-**5u**	8-OMe	4-Me	183—186[u]	AcOEt	C	85.4 × 39.8	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.17
								(64.50	5.70	4.31	9.90)
(−)-**5u**	8-OMe	4-Me	182.5—185[v]	AcOEt	C	82.2 × 41.9	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	10.17
								(64.62	5.69	4.50	10.00)
5v	7,8-di-OMe	4-OMe	240—241.5	DMF–EtOH	A	12.9	$C_{18}H_{19}NO_5S$	59.82	5.30	3.88	8.87
								(60.00	5.39	4.18	8.89)
5w	8-OBzl	4-OMe	172—174	DMF–EtOH	A	17.2	$C_{23}H_{21}NO_4S$	67.79	5.20	3.44	7.87
								(67.87	5.15	3.45	7.78)
5x	8-OBxl	4-Me	164—165	EtOH	A	6.9	$C_{23}H_{21}NO_3S$	70.56	5.41	3.58	8.19
								(70.52	5.34	3.60	8.07)
5y	7-SMe	4-OMe	211—214	DMF–EtOH	D	97.5	$C_{17}H_{17}NO_3S_2$	58.77	4.93	4.03	18.45
								(58.81	4.97	4.15	18.31)
5z	8-SMe	4-OMe	183—184	DMF–EtOH	D	100	$C_{17}H_{17}NO_3S_2$	58.77	4.93	4.03	18.45
					F	2.4[w]		(58.77	4.87	4.05	18.58)
5aa	7-CbzNH	4-OMe	225—228	EtOH	B	47.0[j]	$C_{24}H_{22}N_2O_5S \cdot 1/4H_2O$	63.35	4.95	6.16	
								(63.24	5.25	6.09)	
5bb	7-NH_2	4-OMe	225—228 (d)	EtOH	G	50.6 × 73.4	$C_{16}H_{16}N_2O_3S$	60.74	5.10	8.86	10.14
								(60.18	5.10	8.76	10.07)

a) Method A: Fusion of the aminothiophenol (**1**) with an equivalent of the *trans*-3-arylglycidic ester (**2**) at 160 °C without solvent. Method B: Cyclization of the amino carboxylic acid (**4**) in boiling xylene. Method C: optical resolution of the *cis*-lactam (**5**) *via* 3-[*N*-(β-naphthalenesulfonyl)pyrrolidine-2-carbonyloxy] derivatives (**25**). Method D: Cyclization of the amino ester (**3**) with NaH in DMSO. Method E: Cyclization of the amino carboxylic acid (**4**) with DCC–HOBt. Method F: Reaction of the aminothiophenol (**1**) with one equivalent of the *trans*-3-arylglycidic ester (**2**) in toluene at 90 °C. Method G: Prepared from **5aa** by acetylation, decarbobenzyloxylation with HBr–HOAc, and hydrolysis with aqueous NaOH. *b*) The *trans*-lactam (**6a**) and the *threo*-amino ester (**3a**) were obtained in 3.0 and 9.1% yields, respectively. *c*) $[\alpha]_D^{20}$ +123° (*c*=0.246, DMF). *d*) $[\alpha]_D^{20}$ −124° (*c*=0.358, DMF). *e*) In addition to **5c**, a mixture of the *cis*- and *trans*-lactams (**5c**, **6c**) was obtained in 14.6% yield, but not separated. *f*) $[\alpha]_D^{20}$ +123.8° (*c*=0.707, DMF). *g*) $[\alpha]_D^{20}$ −123.7° (*c*=0.414, DMF). *h*) $[\alpha]_D^{20}$ +122.8° (*c*=1.00, MeOH). *i*) $[\alpha]_D^{20}$ −126.3° (*c*=1.00, MeOH). *j*) The yield was calculated based on the corresponding **3**; i) hydrolysis of the ester, ii) cyclization by method B. *k*) The *threo*-amino ester (**3h**) and the *trans*-lactam (**6h**) were obtained in 26.3 and 1.5% yields, respectively. *l*) The *threo*-amino ester (**3i**) and the *trans*-lactam (**6i**) were obtained in 15.5 and 3.3% yields, respectively. *m*) The *trans*-lactam (**6j**) and the *threo*-amino ester (**3j**) were obtained in 5.3 and 0.4% yields, respectively. *n*) The *trans*-lactam (**6k**) was obtained in 1.3% yield. *o*) $[\alpha]_D^{20}$ +131.4° (*c*=0.778, DMF). *p*) $[\alpha]_D^{20}$ −131.2° (*c*=0.660, DMF). *q*) The *trans*-lactam (**6s**) was obtained in 3.9% yield. *r*) The *trans*-lactam (**6t**) was obtained in 7.1% yield. *s*) $[\alpha]_D^{20}$ +99.0° (*c*=0.386, DMF). *t*) $[\alpha]_D^{20}$ −98.7° (*c*=0.290, DMF). *u*) $[\alpha]_D^{20}$ +42.3° (*c*=0.447, $CHCl_3$). *v*) $[\alpha]_D^{20}$ −42.2° (*c*=0.455, $CHCl_3$). *w*) The *cis*-lactam (**5z**) was obtained as a minor product in the preparation of the *threo*-amino ester (**3z**). *x*) Percentage of fluorine.

method U) afforded the 3-acetoxy compound (**18**), while heating in 10% HCl–MeCN for 2 h (Table 6, method O) gave the deacetylated compound (**11**) in good yield. Compound **18** was hydrolyzed to **11** (Table 5, method Q).

N-Allylation of **11t** with allyl bromide (Table 5, method P) gave **12t**.

Finally, the hydroxy-substituted compounds (**13dd**, **13cc**, **15cc**, **16cc**) were obtained by *O*-debenzylation of the corresponding benzyloxy compounds with HBr–HOAc at room temperature (Table 6, method Z).

The absolute stereochemistry of the most interesting compound ((−)-**13e**) as a potent platelet aggregation inhibitor was proved to be (2*R*,3*R*), as shown in Fig. 1, by X-ray crystallographic analysis.

Biological Results and Discussion

The compounds listed in Tables 5 and 6 were tested for effects on vertebral blood flow (VBF) in anesthetized dogs and coronary blood flow (CBF) in isolated guinea pig hearts, antihypertensive effect in spontaneously hypertensive rats (SHR), and inhibitory effect on aggregation of human platelets.

The data for VBF (Table 7) are given in terms of the potency ratio to papaverine after intraarterial administration. The half duration (in seconds) means the duration of one-half of the maximum change in blood flow. The data for CBF (Table 7) are expressed as "−", if the increase in CBF was less than 0.5 ml/min at the dose of 100 μg/heart. An increase by more than 0.5 ml/min at the doses of 100, 30, 10, and 3 μg/heart is expressed as "+", "++", "+++", and "++++", respectively. The data for hypotensive activity (Table 7) are given as the decrease in blood pressure after oral administration of the test compound at the dose of 30 mg/kg.

The data for inhibitory effect on collagen-induced platelet aggregation (Table 8) are expressed in terms of

Table 2. *threo*-Amino Esters (**3**)

Compd.	R_1	R_2	mp (°C)	Recrystn. solvent	Method[a]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found)			
								C	H	N	S
3a	3-Me	4-OMe	98—100	EtOH	A	9.1[b]	$C_{18}H_{21}NO_4S$	62.23	6.09	4.03	9.23
								(62.35	6.08	4.07	9.02)
3b	4-Me	4-OMe	107—108	EtOH–iso-Pr_2O	F[c]	37.7	$C_{18}H_{21}NO_4S$	62.23	6.09	4.03	9.23
								(62.22	6.09	4.04	9.11)
3d	5-Me	4-OMe	111—113	EtOH–iso-Pr_2O	F[d]	58.5	$C_{18}H_{21}NO_4S$	62.23	6.09	4.03	9.23
								(62.34	6.09	4.05	9.18)
3e	5-Me	4-Me	115.5—117.5	iso-Pr_2O	F[e]	64.6[f]	$C_{18}H_{21}NO_3S$	65.23	6.39	4.23	9.67
								(65.50	6.40	4.21	9.76)
3f	5-Me	4-Et	115.5—117	AcOEt–hexane	F[e]	40.0	$C_{19}H_{23}NO_3S$	66.06	6.71	4.06	9.28
								(65.97	6.75	4.09	9.37)
3g	5-Me	4-OCF_3	127—128	iso-Pr_2O–hexane	F[g]	68.1	$C_{18}H_{18}F_3NO_4S$	53.86	4.52	3.49	7.99
								(53.82	4.77	3.25	8.20)
3h	3,4-di-Me	4-OMe	109.5—111.5	iso-PrOH	A	26.3[h]	$C_{19}H_{23}NO_4S$	63.13	6.41	3.88	8.87
								(63.21	6.39	3.81	8.63)
3i	3,5-di-Me	4-OMe	109—113	iso-Pr_2O	A	15.5[i]	$C_{19}H_{23}NO_4S$	63.13	6.41	3.88	8.87
								(63.30	6.38	3.79	8.69)
3j	4,6-di-Me	4-OMe	130—133	iso-PrOH	A	0.4[j]	$C_{19}H_{23}NO_4S$	63.13	6.41	3.88	8.87
								(63.01	6.35	3.82	8.91)
3k	4,5-di-Me	4-OMe	111—114	AcOEt–hexane	F[d]	73.7	$C_{19}H_{23}NO_4S$	63.13	6.41	3.88	8.87
								(62.87	6.36	3.90	9.18)
3l	4,5-di-Me	4-Me	120—123	AcOEt–hexane	F[k]	51.0	$C_{19}H_{23}NO_3S$	66.06	6.71	4.05	9.28
								(66.17	6.79	4.06	9.13)
3m	4,5-di-Me	4-Et	116—117	iso-Pr_2O–hexane	F[e]	40.0	$C_{20}H_{25}NO_3S$	66.82	7.01	3.90	8.92
								(67.03	7.12	3.95	9.00)
3n	5-Et	4-OMe	107—109	Xylene–hexane	F[k]	71.0	$C_{19}H_{23}NO_4S$	63.14	6.41	3.88	8.87
								(63.26	6.36	3.83	8.83)
3o	5-Et	4-Me	111—113	Xylene–hexane	F[k]	67.2	$C_{19}H_{23}NO_3S$	66.06	6.71	4.05	9.28
								(66.17	6.69	4.00	9.34)
3p	5-Et	H	91—93	Xylene–hexane	F[k]	56.9	$C_{19}H_{23}NO_3S$	66.06	6.71	4.05	9.28
								(66.21	6.71	3.97	9.27)
3q	4-CF_3	4-OMe[l]	131—133	Et_2O–hexane	A[m]	45.3	$C_{18}H_{18}F_3NO_4S$	53.86	4.52	3.49	14.20[p]
								(54.44	4.23	3.59	14.72[p])
3t	5-OMe	4-OMe	99.5—102.5	iso-PrOH	F[n]	56.9	$C_{18}H_{21}NO_5S$	59.49	5.82	3.85	8.82
								(59.59	5.79	3.86	8.94)
3u	5-OMe	4-Me	119.5—121	Xylene–hexane	F[k]	69.0	$C_{18}H_{21}NO_4S$	62.27	6.09	4.03	9.23
								(61.99	6.35	4.00	9.50)
3y	4-SMe	4-OMe	130—133	EtOH	F[o]	55.0	$C_{18}H_{21}NO_4S_2$	56.97	5.58	3.69	16.90
								(57.19	5.60	3.69	16.86)
3z	5-SMe	4-OMe	116—117	EtOH	F[o]	57.3	$C_{18}H_{21}NO_4S_2$	56.97	5.58	3.69	16.90
								(56.77	5.51	3.70	17.01)
3aa	4-CbzNH	4-OMe	Oil	—	J	73.7	$C_{25}H_{26}N_2O_6S$		—		
3bb	4-NH_2	4-OMe	112—114	EtOH–iso-Pr_2O	K	91.4	$C_{17}H_{20}N_2O_4S$	58.60	5.79	8.04	
								(58.78	5.94	8.16)	
erythro-**3e**	5-Me	4-Me	Oil	—	L	27.3	$C_{18}H_{21}NO_3S$		—		

a) Method A: See footnote *a*) in Table 1. Method F: Heating of the aminothiophenol (**1**) with one equivalent of the *trans*-3-arylglycidic ester (**2**) in xylene or toluene. Method J: Reaction of **3bb** with ZCl. The *N*,*N*′-bis(benzyloxycarbonyl) isomer (**27**) was also obtained in 11.6% yield; mp 109—113 °C (Et_2O–iso-Pr_2O), *Anal.* Calcd for $C_{33}H_{32}N_2O_8S$: C, 64.27; H, 5.23; N, 4.54; S, 5.20. Found: C, 64.41; H, 5.34; N, 4.53; S, 5.31. IR (Nujol) ν; 3460, 3340, 1720 cm^{-1}. Method K: Reduction of the corresponding dinitro ester (**26**) with $SnCl_2$–HCl. See experimental section. Method L: Reaction of the aminothiophenol (**1**) with one equivalent of the *trans*-3-arylglycidic ester (**2**) in toluene in the presence of $CaCl_2$ at 50 °C. *b*) See footnote *b*) in Table 1. *c*) Reacted at 60—70 °C. *d*) Reacted at 100 °C. *e*) Reacted at 130 °C. *f*) When the reaction was carried out at 140 °C or 100 °C, 51.0 and 23.8% yields of *threo*-**3e** were obtained, respectively. *g*) Reacted at 150 °C. *h*) See footnote *k*) in Table 1. *i*) See footnote *l*) in Table 1. *j*) See footnote *m*) in Table 1. *k*) Reacted at 120 °C. *l*) Ethyl ester. *m*) See footnote *a*) in Table 1; Reacted at 140—150 °C. *n*) Reacted at 70—75 °C. *o*) Reacted at 90 °C. *p*) Percentage of fluorine.

IC_{50}, the estimated concentration of the test compound which was required to cause 50% inhibition of collagen-induced platelet aggregation of human platelet-rich plasma (PRP) *in vitro*.

Effect on VBF As regards substitution with a methyl, methoxy, methylthio, amino, or hydroxy group on the fused benzene ring, a methyl, methoxy, or methylthio substituent at position of 7 and/or 8 increased the activity on VBF. Compounds (+)-**13b** and (+)-**13e** show stronger activity than diltiazem; the activity of the (+)-7-methyl derivative ((+)-**13b**) is about three times that of diltiazem. In spite of being racemic mixtures, **13u** and **13d** are also more active than diltiazem. The durations of action of (+)-**13e**, **13d**, and **13u** are significantly longer than that of diltiazem. Moreover, the activities of (+)-**13k**, **13h**, **13s**, **13v**, **13y**, **13z**, **7a**, **7d**, **7i**, **7u**, and **7z** are comparable to that of diltiazem. On the other hand, introduction of a methyl or methoxy group at C_6 (**13a**, **13r**, **14a**, **14r**, **15a**, **15r**) resulted in a decrease of the activity. Substitution with a polar group such as hydroxyl, amino, or acetamino (**13bb**, **13cc**, **13dd**, **13ee**, **16cc**) on the fused benzene ring caused a significant decrease of the activity. 7-CF_3 sub-

Table 3. *threo*-Amino Carboxylic Acids (**4**)

Compd.	R_1	R_2	mp (°C)	Recrystn. solvent	Method[a]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found)			
								C	H	N	S
4b	4-Me	4-OMe	168—170	MeOH	I	90.6	$C_{17}H_{19}NO_4S$	61.24	5.74	4.20	9.62
								(61.21	5.72	4.17	9.52)
(+)-**4b**	4-Me	4-OMe	168—170[b]	EtOH	H	36.0×73.3	$C_{17}H_{19}NO_4S$	61.24	5.74	4.20	9.62
								(61.25	5.66	4.22	9.68)
(−)-**4b**	4-Me	4-OMe	170—173[c]	EtOH	H	37.2×67.2	$C_{17}H_{19}NO_4S$	61.24	5.74	4.20	9.62
								(61.36	5.68	4.16	9.58)
4d	5-Me	4-OMe	193—195	MeOH	I	98.3	$C_{17}H_{19}NO_4S$	61.24	5.74	4.20	9.62
								(61.08	5.71	4.15	9.47)
(+)-**4d**	5-Me	4-OMe	158—160[d]	EtOH	H	33.5	$C_{17}H_{19}NO_4S$	61.24	5.74	4.20	9.62
								(61.33	5.74	4.13	9.49)
(−)-**4d**	5-Me	4-OMe	157—160[e]	EtOH	H	30.0	$C_{17}H_{19}NO_4S$	61.24	5.74	4.20	9.62
								(61.55	5.77	4.10	9.56)
4e	5-Me	4-Me	178.5—179.5	EtOH	I	95.0	$C_{17}H_{19}NO_3S$	64.33	6.03	4.41	10.10
								(64.39	6.35	4.26	10.00)
(+)-**4e**	5-Me	4-Me	164—166 (d)[f]	EtOH	H	42.8	$C_{17}H_{19}NO_3S$	64.33	6.03	4.41	10.10
								(64.55	6.21	4.65	9.79)
(−)-**4e**	5-Me	4-Me	163—165 (d)[g]	EtOH	H	56.6	$C_{17}H_{19}NO_3S$	64.33	6.03	4.41	10.10
								(64.43	5.94	4.45	10.31)
erythro-**4e**	5-Me	4-Me	185—186 (d)	EtOH	I	78.2	$C_{17}H_{19}NO_3S$	64.33	6.03	4.41	10.10
								(64.32	5.94	4.45	10.22)
4k	4,5-di-Me	4-OMe	165.5—166.5	EtOH	I	88.5	$C_{18}H_{21}NO_4S$	62.23	6.09	4.03	9.23
								(62.16	6.03	4.00	9.48)
(+)-**4k**	4,5-di-Me	4-OMe	167—169 (d)[h]	EtOH	H	18.8	$C_{18}H_{21}NO_4S$	62.23	6.09	4.03	9.23
								(62.27	5.91	4.06	9.13)
(−)-**4k**	4,5-di-Me	4-OMe	164—167 (d)[i]	EtOH	H	10.6	$C_{18}H_{21}NO_4S$	62.23	6.09	4.03	9.23
								(62.18	5.98	4.05	9.12)
4l	4,5-di-Me	4-Me	170—171.5	EtOH–$CHCl_3$	I	74.0	$C_{18}H_{21}NO_3S$	65.23	6.39	4.23	9.67
								(65.39	6.47	4.25	9.72)
4n	5-Et	4-OMe	174—175 (d)	MeOH–iso-Pr_2O	I	93.1	$C_{18}H_{21}NO_4S$	62.23	6.09	4.03	9.23
								(62.15	6.00	3.98	9.28)
4o	5-Et	4-Me	175—176 (d)	MeOH–iso-Pr_2O	I	95.0	$C_{18}H_{21}NO_3S$	65.23	6.39	4.23	9.67
								(65.28	6.29	4.20	9.78)
4p	5-Et	H	177—178 (d)	MeOH–iso-Pr_2O	I	95.2	$C_{17}H_{19}NO_3S$	64.33	6.03	4.41	10.10
								(64.59	6.08	4.40	10.22)
4q	4-CF_3	4-OMe	183—185	MeOH	I	94.3	$C_{17}H_{16}F_3NO_4S$	52.71	4.16	3.62	8.28
								(52.65	4.09	3.57	8.17)
4t	5-OMe	4-OMe	221—233 (d)	EtOH	I	98.1	$C_{17}H_{19}NO_5S$	58.44	5.48	4.01	9.18
								(58.38	5.39	3.97	8.96)
4u	5-OMe	4-Me	213.5—215 (d)	EtOH–iso-Pr_2O	I	98.9	$C_{17}H_{19}NO_4S$		—		

a) Method H: Optical resolution of the *threo*-amino carboxylic acid. Method I: Hydrolysis of the *threo*-amino ester. *b*) $[\alpha]_D^{20}$ +363° (*c*=0.342, MeOH). *c*) $[\alpha]_D^{20}$ −360° (*c*=0.352, MeOH). *d*) $[\alpha]_D^{20}$ +296° (*c*=0.290, MeOH). *e*) $[\alpha]_D^{20}$ −295° (*c*=0.331, MeOH). *f*) $[\alpha]_D^{20}$ +341° (*c*=0.300, DMF). *g*) $[\alpha]_D^{20}$ −354° (*c*=0.370, DMF). *h*) $[\alpha]_D^{20}$ +361° (*c*=0.556, 1 N NaOH). *i*) $[\alpha]_D^{20}$ −360° (*c*=0.512, 1 N NaOH).

Table 4. Arylthioureas (**28**), 2-Aminobenzothiazoles (**29**), and 2-Aminothiophenols (**1**)

	28			**29**			**1**	
	R_1	mp (°C)	Yield (%)	R_1	mp (°C)	Yield (%)	R_1[a]	Yield (%)
a	2-Me	155—158[b]	25	4-Me	218—220[b,c]	77[d]	3-Me	83
b	3-Me	117—120[b]	36	5-Me	166—168[e,f,g]	52[d]	4-Me	70
c				6-Me	138—140[e,h]	72[i]	5-Me	90
d	2,3-diMe	187—191[b]	87	4,5-diMe	>280[c,j]	55[d]	3,4-diMe	82
e	2,4-diMe	159—161[b]	50	4,6-diMe	>280[c,j]	84[d]	3,5-diMe	74
f	3,4-diMe	172—174[k]	67	5,6-diMe	183—185[e,k]	74[d]	4,5-diMe	96
g	3,5-diMe	157—168[b]	31	5,7-diMe	260—265[c,j]	94[d]	4,6-diMe	87
h				6-Et	110—113[e,h]	73[i]	5-Et	73
i	2-OMe	147—150	63	4-OMe	149—151[e,k]	69[d]	3-OMe	83
j	3-OMe	151—153	58	5-OMe	148—150[e]	78[d]	4-OMe	85
k				6-OMe	164—167[e,l]	84[i]	5-OMe	74[m]
l	3,4-di-OMe	211—217	31	5,6-di-OMe	228—231[e,h,n]	76[d] 91[i]	4,5-di-OMe	94
m				6-OBzl	160—162[e,o]	75[i]	5-OBzl	58
n	3-SMe	107—109[h]	53	5-SMe	257—261[c,f]	72[d]	4-SMe	76
o				6-SMe	145—149[e,f]	66[i]	5-SMe	79

a) Most of the 2-aminothiophenols were obtained as an oil. *b*) Recrystallized from EtOH. *c*) HBr salt. *d*) Synthesized by cyclization of the thiourea (**28**), see reference 8. *e*) Free base. *f*) Recrystallized from aqueous EtOH. *g*) HBr salt: mp 279—283 °C (H_2O). *h*) Recrystallized from $CHCl_3$. *i*) Synthesized by the reaction of the anilines with KSCN–Br_2, see reference 7. *j*) Recrystallized from MeOH. *k*) Recrystallized from AcOEt. *l*) Recrystallized from iso-PrOH. *m*) mp 79—86 °C. *n*) HBr salt: mp 256—259 °C (MeOH). *o*) Recrystallized from C_6H_6.

Table 5. 5-(2-Aminoethyl)lactams (**7**—**12**)

Compd.	R_1	R_2	mp (°C)	Recrystn. solvent	Method[a]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found)				
								C	H	N	S	Cl
7a	6-Me	4-OMe	112—115 (HCl)	$EtOH–Et_2O$	M	77.7	$C_{21}H_{27}N_2O_3S\cdot HCl\cdot 1/4H_2O$	57.78 (57.73	6.58 6.48	6.42 6.39	7.34 7.14	8.12 8.01)
7b	7-Me	4-OMe	125—129[b]	AcOEt	M	89.9	$C_{21}H_{26}N_2O_3S$	65.26 (65.33	6.78 6.75	7.25 7.25	8.29 8.29)	
(+)-**7b**	7-Me	4-OMe	93—95[c]	AcOEt	M	92.6	$C_{21}H_{26}N_2O_3S$	65.26 (65.68	6.78 6.80	7.25 7.21	8.29 8.23)	
(−)-**7b**	7-Me	4-OMe	94—95[d]	AcOEt	M	91.8	$C_{21}H_{26}N_2O_3S$	65.26 (65.39	6.78 6.79	7.25 7.25	8.29 8.19)	
7d	8-Me	4-OMe	157—158[e]	AcOEt	N	90.7	$C_{21}H_{26}N_2O_3S$	65.26 (65.48	6.78 6.81	7.25 7.35	8.29 8.19)	
(+)-**7d**	8-Me	4-OMe	120—123[f]	AcOEt	M	95.7	$C_{21}H_{26}N_2O_3S$	65.26 (65.34	6.78 6.70	7.25 7.26	8.29 8.20)	
(−)-**7d**	8-Me	4-OMe	120—123[g]	AcOEt	M	96.0	$C_{21}H_{26}N_2O_3S$	65.26 (65.34	6.78 6.76	7.25 7.29	8.29 8.19)	
7e	8-Me	4-Me	229—232 (HCl)[h]	EtOH	M	97.5	$C_{21}H_{26}N_2O_3S\cdot HCl$	61.97 (61.90	6.69 6.73	6.88 7.02	7.88 7.86	8.71 8.69)
(+)-**7e**	8-Me	4-Me	164.5—165.5[i]	AcOEt–hexane	M	87.6	$C_{21}H_{26}N_2O_2S$	68.07 (68.22	7.07 7.35	7.56 7.41	8.65 8.57)	
(−)-**7e**	8-Me	4-Me	204—206 (d) (HCl)[j]	EtOH	M	94.8	$C_{21}H_{26}N_2O_2S\cdot HCl\cdot H_2O$	59.35 (59.07	6.88 6.81	6.59 6.52	7.55 7.27	8.34 8.16)
8e	8-Me	4-Me	147—149	EtOH	M	87.0	$C_{21}H_{26}N_2O_2S$	68.07 (67.96	7.07 7.09	7.56 7.52	8.65 8.68)	
7g	8-Me	4-OCF_3	145—147	EtOH	M	91.3	$C_{21}H_{23}F_3N_2O_3S$	57.26 (57.47	5.26 5.16	6.36 6.46	7.28 7.20	12.94 12.84)
7h	6,7-di-Me	4-OMe	117—119 (d) (HCl)	$EtOH–Et_2O$	M	80.0	$C_{22}H_{28}N_2O_3S\cdot HCl\cdot H_2O$	58.07 (58.13	6.87 6.70	6.16 5.99	7.05 7.02	7.79 7.46)
7i	6,8-di-Me	4-OMe	144—148 (d) (HCl)	EtOH	M	81.6	$C_{22}H_{28}N_2O_3S\cdot HCl\cdot H_2O$	58.07 (57.70	6.87 6.55	6.16 6.19	7.05 7.00	7.79 7.60)
7j	7,9-di-Me	4-OMe	224—225 (d) (HCl)	EtOH	M	86.5	$C_{22}H_{28}N_2O_3S\cdot HCl$	60.47 (60.46	6.69 6.64	6.41 6.38	7.34 7.02	8.11 7.65)
7k	7,8-di-Me	4-OMe	248—250 (d) (HCl)	$EtOH–Et_2O$	N	64.0	$C_{22}H_{28}N_2O_3S\cdot HCl$	60.47 (60.18	6.69 6.80	6.41 6.30	7.34 7.11	8.11 8.49)
(+)-**7k**	7,8-di-Me	4-OMe	117—118[k]	AcOEt–hexane	M	90.7	$C_{22}H_{28}N_2O_3S$	65.98 (66.01	7.05 7.03	7.00 7.01	8.01 7.95)	
(−)-**7k**	7,8-di-Me	4-OMe	117—119[l]	AcOEt–hexane	M	84.0	$C_{22}H_{28}N_2O_3S$	65.98 (66.10	7.05 7.02	7.00 7.01	8.01 7.89)	
7l	7,8-di-Me	4-Me	248—250 (d) (HCl)	EtOH	M	93.9	$C_{22}H_{28}N_2O_2S\cdot HCl$	62.77 (62.71	6.94 7.06	6.65 6.84	7.62 7.67	8.42 8.40)
7m	7,8-di-Me	4-Et	154—155	AcOEt–hexane	M	87.2	$C_{23}H_{30}N_2O_2S$	69.31 (69.53	7.59 7.55	7.03 7.06	8.04 7.93)	
7n	8-Et	4-OMe	141.5—143.5	EtOH	M	93.1	$C_{22}H_{28}N_2O_3S$	65.98 (66.17	7.05 7.07	6.99 6.96	8.01 8.06)	
7o	8-Et	4-Me	141—143	EtOH	M	89.9	$C_{22}H_{28}N_2O_2S$	68.72 (68.76	7.34 7.24	7.29 7.27	8.34 8.16)	
7p	8-Et	H	141—143	EtOH	M	91.0	$C_{21}H_{26}N_2O_2S$	68.07 (68.13	7.07 7.05	7.56 7.66	8.65 8.85)	
7q	7-CF_3	4-OMe	207—209 (d) (oxalate)	MeOH	M	71.8	$C_{21}H_{23}F_3N_2O_3S\cdot C_2H_2O_4$	52.07 (51.85	4.75 4.78	5.28 5.25		10.74[z] 10.51[z])
7r	6-OMe	4-OMe	199—202 (d) (HCl)	$EtOH–Et_2O$	M	91.9	$C_{21}H_{26}N_2O_4S\cdot HCl$	57.45 (56.89	6.20 6.35	6.38 6.25)		
7s	7-OMe	4-OMe	212—214 (HCl)	$EtOH–CHCl_3–Et_2O$	N	82.0	$C_{21}H_{26}N_2O_4S\cdot HCl$	57.45 (57.52	6.20 6.34	6.38 5.36)		
8s	7-OMe	4-OMe	123—125	AcOEt	N	94.4	$C_{21}H_{26}N_2O_4S$	62.66 (62.79	6.51 6.54	6.96 6.98)		
7t	8-OMe	4-OMe	130—132 (HCl)	$EtOH–CHCl_3–Et_2O$	M	89.0	$C_{21}H_{26}N_2O_4S\cdot HCl\cdot EtOH$	56.95 (56.64	6.85 6.83	5.79 5.94		7.31 7.73)
(+)-**7t**	8-OMe	4-OMe	139—141[m]	AcOEt	M	96.4	$C_{21}H_{26}N_2O_4S$	62.66 (62.78	6.51 6.47	6.96 6.93)		
(−)-**7t**	8-OMe	4-OMe	139—141[n]	AcOEt	M	93.1	$C_{21}H_{26}N_2O_4S$	62.66 (62.62	6.51 6.47	6.96 6.93)		
8t	8-OMe	4-OMe	135—137	AcOEt	N	81.9	$C_{21}H_{26}N_2O_4S$	62.66 (62.76	6.51 6.59	6.96 7.02)		
7u	8-OMe	4-Me	153—155 (HCl)[o]	$EtOH–Et_2O$	M	79.0	$C_{21}H_{26}N_2O_3S\cdot HCl\cdot 1/2H_2O$	58.38 (58.75	6.53 6.84	6.49 6.32		8.21 8.32)
(+)-**7u**	8-OMe	4-Me	Oil	—	M	62.9	$C_{21}H_{26}N_2O_3S$		—			

Table 5. (continued)

Compd.	R_1	R_2	mp (°C)	Recrystn. solvent	Method[a]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found)				
								C	H	N	S	Cl
7v	7,8-di-OMe	4-OMe	192—194 (d) (oxalate)[p]	MeOH	M	75.6	$C_{22}H_{28}N_2O_5S \cdot C_2H_2O_4$	53.32 (53.02)	5.97 5.57	5.18 4.97	5.93 5.51)	
7w	8-OBzl	4-OMe	138—140 (d) (HCl)	EtOH–Et_2O	M	83.5	$C_{27}H_{30}N_2O_4S \cdot HCl \cdot H_2O$	60.83 (60.57)	6.28 5.98	5.25 5.22	6.01 6.03	6.65 6.60)
7x	8-OBzl	4-Me	118—120	AcOEt–Pr_2O	M	91.0	$C_{27}H_{30}N_2O_3S \cdot 1/2H_2O$	68.76 (68.54)	6.63 6.65	5.94 5.95	6.80 6.74)	
7y	7-SMe	4-OMe	239—240 (d) (HCl)	EtOH	M	70.1	$C_{21}H_{26}N_2O_3S_2 \cdot HCl$	55.43 (55.56)	5.98 6.02	6.16 6.17	14.09 13.92	7.79 7.80)
7z	8-SMe	4-OMe	243—247 (d) (HCl)	EtOH	M	85.5	$C_{21}H_{26}N_2O_3S_2 \cdot HCl$	55.43 (55.41)	5.98 5.98	6.16 6.23	14.09 13.96	7.79 7.60)
7bb	7-NH_2	4-OMe	233—237 (HBr)	DMF–EtOH	N Q	36.8 68.6	$C_{20}H_{25}N_3O_3S \cdot 2HBr \cdot 1/2H_2O$	43.02 (42.90)	5.05 5.43	7.53 7.53	5.64 5.91)	
7cc	8-OH	4-OMe	248.5—251.5 (HCl)	EtOH	Q	73.6	$C_{20}H_{24}N_2O_4S \cdot HCl$	56.53 (56.58)	5.93 5.92	6.59 6.59	7.54 7.52	8.34 8.44)
7dd	8-OH	4-Me	261—265 (HCl)[q]	EtOH	Q	52.6	$C_{20}H_{24}N_2O_3S \cdot HCl \cdot 1/4H_2O$	58.10 (58.19)	6.22 6.20	6.78 6.76	7.76 7.68	8.58 8.74)
9d	8-Me	4-OMe	Oil	—	M	94.5	$C_{27}H_{30}N_2O_3S$		—			
(+)-**9d**	8-Me	4-OMe	175—177 ($HClO_4$)[r]	MeOH	M	92.2	$C_{27}H_{30}N_2O_3S \cdot HClO_4$	57.60 (57.78)	5.55 5.55	4.97 4.98	5.70 5.67)	
(−)-**9d**	8-Me	4-OMe	178—181 ($HClO_4$)[s]	MeOH	M	95.9	$C_{27}H_{30}N_2O_3S \cdot HClO_4$	57.60 (57.56)	5.55 5.53	4.97 4.96	5.70 5.66)	
10c	7-Me	4-Me	Oil	—	N	91.8	$C_{20}H_{24}N_2O_2S$		—			
11c	7-Me	4-Me	137—140 (HBr)	EtOH–Et_2O	Q	78.4	$C_{20}H_{24}N_2O_2S \cdot HBr \cdot 1/2H_2O$	53.81 (53.45)	5.87 5.71	6.27 6.23	7.17 7.48	17.90 18.07)
10d	8-Me	4-OMe	Oil	—	N	91.8	$C_{20}H_{24}N_2O_3S$		—			
11d	8-Me	4-OMe	230—232 (d) (HCl)	EtOH	Q	50.5[t]	$C_{20}H_{24}N_2O_3S \cdot HCl$	58.74 (58.69)	6.16 6.18	6.85 6.81	7.84 7.82	8.67 8.76)
(+)-**11d**	8-Me	4-OMe	130—133 (HBr)[u]	EtOH	Q	96.5	$C_{20}H_{24}N_2O_3S \cdot HBr$	52.98 (52.57)	5.56 5.57	6.18 6.14	7.07 7.13)	
(−)-**11d**	8-Me	4-OMe	131—135 (HBr)[v]	EtOH	Q	97.9	$C_{20}H_{24}N_2O_3S \cdot HBr$	52.98 (52.47)	5.56 5.50	6.18 6.11	7.07 7.13)	
10e	8-Me	4-Me	Oil	—	N	86.7	$C_{28}H_{30}N_2O_5S$		—			
(+)-**10e**	8-Me	4-Me	Oil	—	N	54.7	$C_{28}H_{30}N_2O_5S$		—			
(−)-**10e**	8-Me	4-Me	Oil	—	N	64.3	$C_{28}H_{30}N_2O_5S$		—			
11e	8-Me	4-Me	238—243 (d) (HCl)	EtOH	Q	65.0	$C_{20}H_{24}N_2O_2S \cdot HCl$	61.13 (60.98)	6.41 6.39	7.13 7.11	8.16 8.13	9.02 9.01)
(+)-**11e**	8-Me	4-Me	145—147 (HCl)[w]	iso-PrOH	Q	45.9[x]	$C_{20}H_{24}N_2O_2S \cdot HCl \cdot 1/2H_2O$	59.76 (59.92)	6.39 6.31	6.97 6.89	8.00 7.97	8.82 8.54)
(−)-**11e**	8-Me	4-Me	142—145 (HCl)[y]	iso-PrOH	Q O	53.1[x] 86.4	$C_{20}H_{24}N_2O_2S \cdot HCl \cdot 1/2H_2O$	59.76 (59.66)	6.39 6.43	6.97 6.54	8.00 8.05	8.82 8.69)
10r	6-OMe	4-OMe	Oil	—	N	80.8	$C_{28}H_{30}N_2O_6S$		—			
11t	8-OMe	4-OMe	211—216 (d) (HCl)	MeOH	O	81.0	$C_{20}H_{24}N_2O_4S$	56.52 (56.48)	5.93 5.95	6.59 6.54	8.34 8.43)	
12t	8-OMe	4-OMe	145—148 (HCl)	EtOH–Et_2O	P	69.9	$C_{23}H_{28}N_2O_4S \cdot HCl \cdot 1/2H_2O$	58.28 (58.32)	6.38 6.17	5.91 5.94	6.76 6.86	7.48 7.54)
10u	8-OMe	4-Me	Oil	—	N	50.1	$C_{28}H_{30}N_2O_5S$		—			
11u	8-OMe	4-Me	228—231 (HCl)	EtOH	Q	71.1	$C_{20}H_{24}N_2O_3S \cdot HCl$	58.74 (58.61)	6.16 6.20	6.85 6.77	7.84 7.84	8.67 8.74)
10w	8-OBzl	4-Me	Oil	—	N	65.2	$C_{34}H_{34}N_2O_6S$		—			

a) Method M: *N*-Alkylation of the lactams (**5** or **6**) with the halide in the presence of K_2CO_3 in boiling acetone. Method N: *N*-Alkylation of the lactams (**5** or **6**) with the halide in the presence of KOH in DMSO. Method O: i) TCF–Et_3N, ii) 10% HCl–MeCN. Method P: *N*-Allylation of **11t**. Method Q: Hydrolysis of the 3-acetoxy compound (**13** or **18**). *b*) HCl salt: mp 235.5—236 °C (dec.) (EtOH). 65.4% yield by Method N. *c*) $[\alpha]_D^{20}$ +160° (*c*=0.430, MeOH). *d*) $[\alpha]_D^{20}$ −161° (*c*=0.325, MeOH). *e*) HCl salt: mp 232—234 °C (EtOH–Et_2O). *f*) $[\alpha]_D^{20}$ +156° (*c*=0.465, MeOH). *g*) $[\alpha]_D^{20}$ −153° (*c*=0.400, MeOH). *h*) Free base: mp 142—143 °C (AcOEt). *i*) $[\alpha]_D^{20}$ +141° (*c*=0.474, $CHCl_3$). *j*) Free base: mp 165—166 °C (AcOEt–hexane), $[\alpha]_D^{20}$ −142° (*c*=0.320, $CHCl_3$). *k*) $[\alpha]_D^{20}$ +150° (*c*=0.680, MeOH). *l*) $[\alpha]_D^{20}$ −146° (*c*=0.792, MeOH). *m*) $[\alpha]_D^{20}$ +130° (*c*=0.465, MeOH); HCl salt: mp 231—233 °C (EtOH). *n*) $[\alpha]_D^{20}$ −128° (*c*=0.385, MeOH). *o*) Free base: mp 127—130 °C (AcOEt). *p*) Free base: mp 154.5—156 °C (MeOH). *q*) Free base: mp 215—218 °C (EtOH). *r*) $[\alpha]_D^{20}$ +85.8° (*c*=0.169, MeOH). *s*) $[\alpha]_D^{20}$ −85.0° (*c*=0.339, MeOH). *t*) 82.0% yield by Method O. *u*) $[\alpha]_D^{20}$ +86.5° (*c*=0.387, MeOH). *v*) $[\alpha]_D^{20}$ −86.3° (*c*=0.284, MeOH). *w*) $[\alpha]_D^{20}$ +103.8° (*c*=0.285, MeOH). *x*) The yield was calculated based on **10**, i) Ac_2O, ii) HBr–HOAc, iii) hydrolysis. *y*) $[\alpha]_D^{20}$ −96.8° (*c*=0.308, MeOH). *z*) Percentage of fluorine.

stitution (**13q**, **16q**) also resulted in a decrease of the potency and very short duration of action.

The 3-acetylated compounds (**13**) are more potent than the corresponding 3-OH compounds (**7**), except for **13a**, **13i**, **13t**, and **13cc**. Moreover, the duration of action of the 3-OAc compounds (**13**) is usually longer than that of **7**. Therefore, when comparing the total increase of VBF, which is calculated by multiplying the potency ratio by the half-duration, the 3-OAc compounds (**13**) are more potent than the corresponding 3-OH derivatives (**7**). The compounds acylated with groups other than the acetyl group, for example, the *n*-butylcarbamoyl (**14**),

Table 6. 3-Acyloxy-5-(2-aminoethyl)lactams (**13**—**23**)

Compd.	R_1	R_2	R_4	mp (°C)	Recrystn. solvent[a]	Method[b]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found)				
									C	H	N	S	Cl
13a	6-Me	4-OMe	Ac	208—210 (HCl)	A	R	67.6	$C_{23}H_{28}N_2O_4S\cdot HCl$	59.41 (59.35	6.29 6.29	6.02 5.96	6.89 7.07	7.62 7.48)
14a	6-Me	4-OMe	CONHBu	233—237 (d) (HCl)	B	S	60.9	$C_{26}H_{35}N_3O_4S\cdot HCl$	59.81 (60.11	6.95 7.03	8.05 8.05	6.14 6.15	6.79 6.79)
15a	6-Me	4-OMe	CO_2Et	141—145 (d) (HCl)	A	T	53.5	$C_{24}H_{30}N_2O_5S\cdot HCl\cdot H_2O$	56.18 (55.78	6.48 6.35	5.46 5.35	6.25 5.93	6.91 7.03)
16a	6-Me	4-OMe	$COC_6H_4NO_2$	201—202 (d) (1/2 oxalate)	C	T	48.3	$C_{28}H_{29}N_3O_6S\cdot 1/2C_2H_2O_4\cdot 3/2H_2O$	57.32 (57.40	5.47 5.42	6.92 6.24	5.28 5.63)	
13b	7-Me	4-OMe	Ac	157.5—159.5 (HCl)	A	R	80.1	$C_{23}H_{28}N_2O_4S\cdot HCl$	59.41 (59.16	6.29 6.41	6.02 5.90	6.89 6.56	7.62 7.34)
(+)-**13b**	7-Me	4-OMe	Ac	157—160 (HBr)[c]	B	R	96.4	$C_{23}H_{28}N_2O_4S\cdot HBr\cdot 1/4H_2O$	53.75 (53.63	5.79 5.78	5.45 5.34	6.24 6.18)	
(−)-**13b**	7-Me	4-OMe	Ac	157—160 (HBr)[d]	B	R	94.9	$C_{23}H_{28}N_2O_4S\cdot HBr\cdot 1/4H_2O$	53.75 (53.67	5.79 5.79	5.45 5.33	6.24 6.18)	
14b	7-Me	4-OMe	CONHBu	224—227 (d) (HCl)	B	S	67.5	$C_{26}H_{35}N_3O_4S\cdot HCl$	59.81 (59.86	6.95 7.00	8.05 7.99	6.14 5.76	6.79 7.14)
15b	7-Me	4-OMe	CO_2Et	160—161 (d)	B	T	74.1	$C_{24}H_{30}N_2O_5S\cdot HCl$	58.23 (58.19	6.31 6.52	5.66 5.53	7.16 6.44)	
16b	7-Me	4-OMe	$COC_6H_4NO_2$	210—211 (d) (oxalate)	C	T	63.5	$C_{28}H_{29}N_3O_6S\cdot C_2H_2O_4$	57.59 (57.91	4.99 5.07	6.72 6.44	5.12 5.27)	
17b	7-Me	4-OMe	COC_6H_4Me	180—181	C	T	80.3	$C_{29}H_{32}N_2O_4S$	69.02 (69.14	6.39 6.43	5.55 5.70	6.35 6.19)	
18c	7-Me	4-Me	Ac	200.5—203 (d) (oxalate)	C	V	78.2	$C_{22}H_{26}N_2O_3S\cdot C_2H_2O_4$	59.00 (59.05	5.78 5.78	5.73 5.76	6.56 6.54)	
13d	8-Me	4-OMe	Ac	183.5—185 (HCl)[e]	A	R	78.6	$C_{23}H_{28}N_2O_4S\cdot HCl\cdot EtOH$	58.75 (58.88	6.90 6.84	5.48 5.73	6.27 6.40	6.94 7.28)
(+)-**13d**	8-Me	4-OMe	Ac	151—152 (HBr)[f]	B	R	95.8	$C_{23}H_{28}N_2O_4S\cdot HBr$	54.22 (54.44	5.72 6.05	5.50 5.23	6.30 6.65)	
(−)-**13d**	8-Me	4-OMe	Ac	151—153 (HBr)[g]	B	R	93.7	$C_{23}H_{28}N_2O_4S\cdot HBr$	54.22 (54.84	5.72 6.13	5.50 5.23	6.30 5.80)	
14d	8-Me	4-OMe	CONHBu	202.5—204 (HBr)	A	S	74.8	$C_{26}H_{35}N_3O_4S\cdot HBr$	55.12 (54.94	6.41 6.61	7.42 7.39	5.66 5.57	14.10 13.71)
15d	8-Me	4-OMe	CO_2Et	176—177.5 (HCl)	B	T	34.3	$C_{24}H_{30}N_2O_5S\cdot HCl$	58.23 (57.87	6.31 6.35	5.66 5.75	6.48 6.50	7.16 7.30)
16d	8-Me	4-OMe	$COC_6H_4NO_2$	155—160 (HCl)	B	T	93.3	$C_{28}H_{29}N_3O_6S\cdot HCl\cdot 1/2H_2O\cdot 1/2EtOH$	57.66 (57.76	5.67 5.39	6.96 7.10	5.31 5.43	5.87 6.14)
17d	8-Me	4-OMe	COC_6H_4Me	209—211 (1/2 oxalate)	A	T	91.9	$C_{29}H_{32}N_2O_4S\cdot 1/2C_2H_2O_4\cdot H_2O$	63.53 (63.36	6.04 5.85	4.93 4.90	5.65 5.42)	
18d	8-Me	4-OMe	Ac	154—156 (HCl)	B V	U	76.0 50.5	$C_{22}H_{26}N_2O_4S\cdot HCl\cdot 1/2H_2O\cdot 1/2EtOH$	56.50 (56.76	6.42 6.15	5.79 5.64	6.63 6.65	7.33 7.02)
(+)-**18d**	8-Me	4-OMe	Ac	166—168[h] (oxalate)	A	W	80.0	$C_{22}H_{26}N_2O_4S\cdot C_2H_2O_4$	57.13 (56.94	5.59 5.54	5.53 5.52	6.36 6.58)	
(−)-**18d**	8-Me	4-OMe	Ac	166—168[i] (oxalate)	A	W	87.7	$C_{22}H_{26}N_2O_4S\cdot C_2H_2O_4$	57.13 (57.10	5.59 5.55	5.53 5.57	6.36 6.42)	
23d	8-Me	4-OMe	$CH_2C_6H_5$	238—241 ($HClO_4$)	A	X	63.3	$C_{28}H_{33}N_2O_3S\cdot HClO_4$	58.28 (58.38	5.76 5.80	4.85 4.88	5.56 5.69	6.14 5.93)
13e	8-Me	4-Me	Ac	184—186 (HCl)[j]	D	R	85.5	$C_{23}H_{28}N_2O_3S\cdot HCl$	61.52 (61.40	6.51 6.57	6.24 6.19	7.14 7.33	7.90 7.59)
(+)-**13e**	8-Me	4-Me	Ac	179.5—181[k] (oxalate)	B	R	88.0	$C_{23}H_{28}N_2O_3S\cdot C_2H_2O_4\cdot 1/4H_2O$	59.24 (59.22	6.06 6.22	5.52 5.50	6.32 6.29)	
(−)-**13e**	8-Me	4-Me	Ac	178—180[l] (oxalate)	B	R	95.0	$C_{23}H_{28}N_2O_3S\cdot C_2H_2O_4\cdot 1/4H_2O$	59.24 (59.18	6.06 6.22	5.52 5.36	6.32 6.31)	
trans-**13e**	8-Me	4-Me	Ac	147—150 (fumarate)	A	R	79.3	$C_{23}H_{28}N_2O_3S\cdot C_4H_4O_4$	61.34 (61.33	6.10 6.07	5.30 5.31	6.07 6.07)	
14e	8-Me	4-Me	CONHBu	155—158 (HCl)	D	S	66.9	$C_{26}H_{35}N_3O_3S\cdot HCl$	61.70 (61.46	7.17 7.21	8.30 8.21	6.33 6.29	7.00 6.96)
15e	8-Me	4-Me	CO_2Et	173—175 (d) (HCl)	D	T	70.8	$C_{24}H_{30}N_2O_4S\cdot HCl$	60.18 (59.98	6.52 6.54	5.85 5.79	6.69 6.75	7.40 7.18)
16e	8-Me	4-Me	$COC_6H_4NO_2$	215—216 (d) (oxalate)	C	T	67.9	$C_{28}H_{29}N_3O_5S\cdot C_2H_2O_4$	59.10 (59.13	5.13 5.25	6.89 6.97	5.26 5.30)	
17e	8-Me	4-Me	COC_6H_4Me	203—204 (d) (oxalate)	C	T	97.0	$C_{29}H_{32}N_2O_3S\cdot C_2H_2O_4$	64.34 (64.28	5.92 5.90	4.84 5.03	5.54 5.59)	

Table 6. (continued)

Compd.	R_1	R_2	R_4	mp (°C)	Recrystn. solvent[a]	Method[b]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found)				
									C	H	N	S	Cl
18e	8-Me	4-Me	Ac	140—142 (d)[m] (oxalate)	A	V	83.4	$C_{22}H_{26}N_2O_3S \cdot$	58.63	5.88	5.60	6.51	
						W	76.1	$C_2H_2O_4$	(59.00	5.78	5.73	6.51)	
(+)-**18e**	8-Me	4-Me	Ac	167—168 (d)[n] (fumarate)	A	U	80.6	$C_{22}H_{26}N_2O_3S \cdot$ $C_4H_4O_4$	60.68 (60.71	5.88 5.86	5.44 5.51	6.23 6.23)	
(−)-**18e**	8-Me	4-Me	Ac	167—169 (d)[o] (fumarate)	A	U	84.6	$C_{22}H_{26}N_2O_3S \cdot$ $C_4H_4O_4$	60.68 (60.55	5.88 5.78	5.44 5.23	6.23 6.12)	
19e	8-Me	4-Me	COPh	212—213 (d) (oxalate)	C	V[p]	76.4	$C_{27}H_{28}N_2O_3S \cdot$ $C_2H_2O_4$	63.26 (62.91	5.49 5.43	5.09 5.07	5.82 5.70)	
20e	8-Me	4-Me	CO-iso-Pr	188.5—190.5 (d) (oxalate)	C	V[p]	79.1	$C_{24}H_{30}N_2O_3S \cdot$ $C_2H_2O_4$	60.45 (60.13	6.24 6.23	5.42 5.43	6.21 6.20)	
21e	8-Me	4-Me	CO-n-Pr	185.5—186 (oxalate)	C	V[p]	80.4	$C_{24}H_{30}N_2O_3S \cdot$ $C_2H_2O_4$	60.45 (59.94	6.24 6.28	5.42 5.56	6.21 6.06)	
22e	8-Me	4-Me	Me	211.5—213.5 (fumarate)	M	Y	29.4	$C_{22}H_{28}N_2O_2S \cdot$ $C_4H_4O_4$	62.38 (62.19	6.44 6.37	5.60 5.62	6.40 6.36)	
13g	8-Me	4-OCF_3	Ac	189—191 (fumarate)	A	R	86.0	$C_{23}H_{25}F_3N_2O_4S \cdot$ $C_4H_4O_4 \cdot 1/3H_2O$	53.64 (53.57	4.95 4.88	4.63 4.76	5.30 5.36	9.43[z] 9.28[z])
13h	6,7-di-Me	4-OMe	Ac	150—152 (HCl)	B	R	64.0	$C_{24}H_{30}N_2O_4S \cdot$ $HCl \cdot 3/2H_2O$	56.96 (57.23	6.77 6.49	5.54 5.43	6.34 6.22	7.01 6.82)
13i	6,8-di-Me	4-OMe	Ac	218—221 (HCl)	B	R	77.4	$C_{24}H_{30}N_2O_4S \cdot$ $HCl \cdot EtOH$	59.47 (59.23	7.10 6.91	5.34 5.42	6.11 6.19	6.75 6.64)
13j	7,9-di-Me	4-OMe	Ac	240—242 (d) (HCl)	B	R	86.0	$C_{24}H_{30}N_2O_4S \cdot$ HCl	60.17 (59.84	6.52 6.65	5.85 5.68	6.69 6.42	7.40 7.31)
13k	7,8-di-Me	4-OMe	Ac	209—211 (HCl)	F	R	94.3	$C_{24}H_{30}N_2O_4S \cdot$ HCl	60.17 (59.82	6.52 6.54	5.85 5.88	6.69 6.71	7.40 7.48)
(+)-**13k**	7,8-di-Me	4-OMe	Ac	191—192 (d)[q] (oxalate)	G	R	83.6	$C_{24}H_{30}N_2O_4S \cdot$ $C_2H_2O_4 \cdot 1/2H_2O$	57.66 (57.98	6.14 6.05	5.17 5.14)		
(−)-**13k**	7,8-di-Me	4-OMe	Ac	189—191 (d)[r] (oxalate)	G	R	82.4	$C_{24}H_{30}N_2O_4S \cdot$ $C_2H_2O_4 \cdot 1/2H_2O$	57.66 (57.98	6.14 6.05	5.17 5.15)		
14k	7,8-di-Me	4-OMe	CONHBu	168—170 (oxalate)	B	S	96.0	$C_{27}H_{37}N_3O_4S \cdot$ $C_2H_2O_4 \cdot 3/2H_2O$	56.47 (56.61	6.29 6.33	6.81 6.59)		
15k	7,8-di-Me	4-OMe	CO_2Et	109—111 (HCl)	F	T	89.0	$C_{25}H_{32}N_2O_5S \cdot$ $HCl \cdot 3/2H_2O$	56.02 (56.19	6.72 6.37	5.23 5.18		6.61 6.48)
16k	7,8-di-Me	4-OMe	$COC_6H_4NO_2$	191—192 (oxalate)	A	T	56.3	$C_{29}H_{31}N_3O_6S \cdot$ $C_2H_2O_4$	58.20 (58.05	5.20 5.15	6.57 6.52)		
17k	7,8-di-Me	4-OMe	COC_6H_4Me	184—186[s] (oxalate)	B	T	96.2	$C_{30}H_{34}N_2O_4S \cdot$ $C_2H_2O_4 \cdot 1/2H_2O$	62.22 (62.60	6.04 5.90	4.54 4.59)		
13l	7,8-di-Me	4-Me	Ac	203.5—206.5 (HCl)	M	R	92.0	$C_{24}H_{30}N_2O_3S \cdot$ $HCl \cdot 2/3H_2O$	60.68 (60.41	6.86 6.70	5.90 5.91	6.75 6.68	7.46 7.60)
13m	7,8-di-Me	4-Et	Ac	209—210.5 (d) (fumarate)	I	R	74.0	$C_{25}H_{32}N_2O_3S \cdot$ $C_4H_4O_4 \cdot H_2O$	60.61 (60.84	6.67 6.51	4.88 4.64	5.58 5.53)	
13n	8-Et	4-OMe	Ac	193—195 (d) (fumarate)	A	R	92.3	$C_{24}H_{30}N_2O_4S \cdot$ $C_4H_4O_4 \cdot 1/5H_2O \cdot$ $1/2EtOH$	59.51 (59.43	6.44 6.15	4.78 4.71	5.48 5.59)	
13o	8-Et	4-Me	Ac	113—116 (maleate)	A	R	76.1	$C_{24}H_{30}N_2O_3S \cdot$ $C_4H_4O_4 \cdot 1/2EtOH$	61.57 (61.47	6.59 6.32	4.95 5.00	5.67 5.89)	
13p	8-Et	H	Ac	102—105 (fumarate)	A	R	85.3	$C_{23}H_{28}N_2O_3S \cdot$ $C_4H_4O_4 \cdot EtOH$	60.61 (60.51	6.67 6.59	4.87 4.92	5.58 5.84)	
13q	7-CF_3	4-OMe	Ac	191—193 (oxalate)	I	R	76.1	$C_{23}H_{25}F_3N_2O_4S \cdot$ $C_2H_2O_4$	52.44 (52.28	4.75 4.68	4.89 4.87		9.95[z] 9.89[z])
16q	7-CF_3	4-OMe	$COC_6H_4NO_2$	175—180 (oxalate)	A	T	76.7	$C_{28}H_{26}F_3N_3O_6S \cdot$ $C_2H_2O_4$	53.02 (52.58	4.15 4.26	6.18 6.01	4.72 4.70	8.39[z] 8.18[z])
13r	6-OMe	4-OMe	Ac	212—213 (d) (oxalate)	F	R	82.0	$C_{23}H_{28}N_2O_5S \cdot$ $C_2H_2O_4 \cdot 1/2H_2O$	55.24 (55.03	5.75 5.65	5.15 5.12)		
14r	6-OMe	4-OMe	CONHBu	157—161	H	S	77.1	$C_{26}H_{35}N_3O_5S \cdot$ $1/2H_2O$	61.15 (61.43	7.11 6.99	8.23 8.21)		
15r	6-OMe	4-OMe	CO_2Et	190—191 (oxalate)	F	T	71.4	$C_{24}H_{30}N_2O_6S \cdot$ $C_2H_2O_4 \cdot H_2O$	53.59 (53.26	5.88 5.75	4.81 4.78)		
17r	6-OMe	4-OMe	COC_6H_4Me	189—191 (d) (oxalate)	F	T	70.9	$C_{29}H_{32}N_2O_5S \cdot$ $C_2H_2O_4 \cdot 1/2H_2O$	60.08 (60.43	5.69 5.54	4.52 4.58)		
18r	6-OMe	4-OMe	Ac	53—56 (oxalate)	A	V	52.2	$C_{22}H_{26}N_2O_5S \cdot$ $C_2H_2O_4 \cdot 1/2H_2O$	54.43 (54.07	5.52 5.36	5.29 5.36)		
13s	7-OMe	4-OMe	Ac	216—218 (HCl)	B	R	84.5	$C_{23}H_{28}N_2O_5S \cdot$ $HCl \cdot 1/2H_2O$	56.37 (56.59	5.96 6.24	5.72 5.61	7.24 7.40)	
trans-**13s**	7-OMe	4-OMe	Ac	225—227 (HCl)	B	R	76.6	$C_{23}H_{28}N_2O_5S \cdot$ $HCl \cdot 1/2H_2O$	56.37 (56.57	5.96 6.15	5.72 5.71	7.24 7.62)	

Table 6. (continued)

Compd.	R_1	R_2	R_4	mp (°C)	Recrystn. solvent[a]	Method[b]	Yield (%)	Formula	Elementary analysis (%) Calcd (Found) C	H	N	S	Cl
14s	7-OMe	4-OMe	CONHBu	221—222 (d) (HCl)	B	S	72.9	$C_{26}H_{35}N_3O_5S\cdot HCl$	58.03 (57.86	6.56 6.79	7.81 7.84		6.59 6.51)
16s	7-OMe	4-OMe	$COC_6H_4NO_2$	180—181.5 (d) (oxalate)	A	T	100	$C_{28}H_{29}N_3O_7S\cdot C_2H_2O_4$	54.62 (54.89	5.04 4.70	6.37 6.55)		
17s	7-OMe	4-OMe	COC_6H_4Me	193.5—195.5 (oxalate)	A	T	84.4	$C_{29}H_{32}N_2O_5S\cdot C_2H_2O_4\cdot 1/2H_2O$	60.08 (60.14	5.69 5.59	4.52 4.80)		
13t	8-OMe	4-OMe	Ac	192—194 (HCl)	F	R	85.3	$C_{23}H_{25}N_2O_5S\cdot HCl\cdot EtOH$	56.43 (56.80	6.69 6.58	5.32 5.57		6.73 7.22)
(+)-**13t**	8-OMe	4-OMe	Ac	164—166 (HCl)[f]	B	R	80.3	$C_{23}H_{28}N_2O_5S\cdot HCl$	57.43 (57.36	6.08 6.30	5.82 5.61	6.67 6.33	7.37 6.90)
(−)-**13t**	8-OMe	4-OMe	Ac	164—166 (HCl)[w]	B	R	83.6	$C_{23}H_{28}N_2O_5S\cdot HCl$	57.43 (57.41	6.08 6.32	5.82 5.64	6.67 6.32	7.37 7.02)
trans-**13t**	8-OMe	4-OMe	Ac	130—133 (HCl)	B	R	75.8	$C_{23}H_{28}N_2O_5S\cdot HCl\cdot H_2O$	55.35 (55.50	6.26 6.40	5.61 5.56		7.11 6.87)
14t	8-OMe	4-OMe	CONHBu	198—200 (HCl)	B	S	89.7	$C_{26}H_{35}N_3O_5S\cdot HCl$	58.03 (57.97	6.56 6.82	7.81 7.72		6.59 6.60)
15t	8-OMe	4-OMe	CO_2Et	152—154.5 (HCl)	B	T	60.5	$C_{24}H_{30}N_2O_6S\cdot HCl\cdot 1/2H_2O$	55.42 (55.34	6.20 6.16	5.31 5.46	6.82 6.85)	
16t	8-OMe	4-OMe	$COC_6H_4NO_2$	168—171 (HCl)	F	T	83.8	$C_{28}H_{29}N_3O_7S\cdot HCl$	57.18 (56.80	5.14 5.15	7.15 7.07		6.03 5.71)
17t	8-OMe	4-OMe	COC_6H_4Me	120—124 (oxalate)	A	T	45.2	$C_{29}H_{32}N_2O_5S\cdot C_2H_2O_4\cdot 1/2H_2O$	60.08 (60.33	5.69 5.86	4.52 4.55)		
13u	8-OMe	4-Me	Ac	209—211 (oxalate)	F	R	95.0	$C_{23}H_{28}N_2O_4S\cdot C_2H_2O_4$	57.90 (57.83	5.83 5.89	5.40 5.39)		
(+)-**13u**	8-OMe	4-Me	Ac	177.5—180 (d)[v] (fumarate)	B	R	89.9	$C_{23}H_{28}N_2O_4S\cdot C_4H_4O_4$	59.54 (59.49	5.92 5.89	5.14 5.17	5.89 6.00)	
18u	8-OMe	4-Me	Ac	143—147 (oxalate)	A V	U V	82.7 51.8	$C_{22}H_{26}N_2O_4S\cdot C_2H_2O_4\cdot 1/2H_2O$	56.13 (55.98	5.69 5.52	5.46 5.48	6.24 6.20)	
13v	7,8-di-OMe	4-OMe	Ac	241.5—243 (d) (HCl)	A	R	89.4	$C_{24}H_{30}N_2O_6S\cdot HCl$	56.41 (56.15	6.11 6.29	5.48 5.50	6.27 6.09	6.94 6.91)
13w	8-OBzl	4-OMe	Ac	171—174 (HCl)	B	R	75.0	$C_{29}H_{32}N_2O_5S\cdot HCl\cdot iso\text{-}PrOH$	61.53 (61.69	6.83 6.35	4.63 4.77	5.30 5.47	5.86 6.21)
18w	8-OBzl	4-OMe	Ac	175—178 (HCl)	B	V	12.9[w]	$C_{28}H_{30}N_2O_5S\cdot HCl$	61.74 (61.39	5.75 5.78	5.16 5.04	5.90 5.87	6.53 6.78)
13y	7-SMe	4-OMe	Ac	198—200 (HCl)	D	R	76.0	$C_{23}H_{28}N_2O_4S_2\cdot HCl\cdot iso\text{-}PrOH$	56.05 (55.89	6.69 6.58	5.03 5.34	11.51 11.71	6.36 6.31)
13z	8-SMe	4-OMe	Ac	180—183 (HCl)	A	R	95.6	$C_{23}H_{28}N_2O_4S_2\cdot HCl\cdot EtOH$	55.29 (55.17	6.50 6.48	5.16 5.56	11.81 11.91	6.53 6.56)
13bb	7-NH_2	4-OMe	Ac	244—247 (d)	G	M	78.5[x]	$C_{22}H_{27}N_3O_4S\cdot 1/4H_2O$	60.88 (60.82	6.39 6.69	9.68 9.24)		
13cc	8-OH	4-OMe	Ac	208.5—211.5 (HBr)	A	Z	60.7	$C_{22}H_{26}N_2O_5S\cdot HBr$	51.67 (51.40	5.31 5.31	5.48 5.42	6.27 6.32	15.62 15.61)
15cc	8-OH	4-OMe	CO_2Et	215—217 (d) (HBr)	C	Z[y]	37.9	$C_{23}H_{28}N_2O_6S\cdot HBr$	51.02 (50.62	5.40 5.51	5.17 5.08	5.92 5.82	14.76 14.72)
16cc	8-OH	4-OMe	$COC_6H_4NO_2$	174—176 (HBr)	K	Z[y]	76.1	$C_{27}H_{27}N_3O_7S\cdot HBr\cdot DMF$	52.10 (52.01	5.10 5.21	8.10 7.92	4.64 4.49	11.55 11.31)
18cc	8-OH	4-OMe	Ac	242—245 (d) (HCl)	A	V	15.9	$C_{21}H_{24}N_2O_5S\cdot HCl\cdot 1/2H_2O$	54.60 (54.28	5.67 5.84	6.06 5.89	6.94 6.80	7.68 7.70)
13dd	8-OH	4-Me	Ac	171—174 (d) (oxalate)	I	Z[y]	39.8	$C_{22}H_{26}N_2O_4S\cdot 1/2C_2H_2O_4$	60.11 (59.95	5.92 5.86	6.10 6.06	6.98 6.93)	
13ee	7-NHAc	4-OMe	Ac	247—249 (HBr)	I	R	84.1	$C_{24}H_{29}N_3O_5S\cdot HBr$	52.17 (52.18	5.47 5.64	7.61 7.47		14.46 14.54)

a) A: EtOH, B: EtOH–Et_2O, C: DMF–EtOH, D: iso-PrOH–Et_2O, E: EtOH–iso-Pr_2O, F: $CHCl_3$–EtOH–Et_2O, G: $CHCl_3$–EtOH, H: $CHCl_3$–AcOEt–hexane, I: MeOH, J: AcOEt–hexane, K: DMF–iso-Pr_2O, L: acetone–iso-Pr_2O, M: MeOH–iso-Pr_2O, N: AcOEt. *b*) Method R: Acetylation of **7** and **8** with Ac_2O at 100 °C. Method S: Heating of **7** with *n*-butyl isocyanate in benzene. Method T: Acylation of **7** with acyl chloride–pyridine at room temperature. Method U: i) TCF–NEt_3, ii) H_2O–MeCN. Method V: i) Acetylation of **10**, ii) HBr–HOAc. Method W: i) Acetylation of **9**, ii) ZCl in toluene under reflux, iii) HBr–HOAc. Method X: Benzylation of **7d** with BzlCl–NaH in DMSO at room temperature. Method Y: *O*-Methylation of **7e** with Me_2SO_4–NaH in DMSO–toluene. Method Z: *O*-Debenzylation with HBr–HOAc. *c*) $[\alpha]_D^{20}$ +87.8° (*c*=0.303, MeOH). *d*) $[\alpha]_D^{20}$ −88.7° (*c*=0.549, MeOH). *e*) Oxalate: mp 200—202 °C (A). *f*) $[\alpha]_D^{20}$ +82.5° (*c*=0.308, MeOH). *g*) $[\alpha]_D^{20}$ −82.1° (*c*=0.420, MeOH). *h*) $[\alpha]_D^{20}$ +80.2° (*c*=0.349, MeOH). *i*) $[\alpha]_D^{20}$ −79.4° (*c*=0.355, MeOH). *j*) Oxalate: mp 200—202 °C (F). *k*) $[\alpha]_D^{20}$ +88.2° (*c*=0.288, MeOH), maleate: mp 194—197 °C (B), $[\alpha]_D^{20}$ +83.7° (*c*=0.362, MeOH). *l*) Maleate: mp 199.5—202 °C (B), $[\alpha]_D^{20}$ −82.3° (*c*=0.372, MeOH). *m*) HCl salt: mp 243—245 °C (dec.) (C). *n*) $[\alpha]_D^{20}$ +79.5° (*c*=0.267, MeOH). *o*) $[\alpha]_D^{20}$ −79.3° (*c*=0.242, MeOH). *p*) i) Acylation, ii) HBr–HOAc. *q*) $[\alpha]_D^{20}$ +102° (*c*=0.736, DMF). *r*) $[\alpha]_D^{20}$ −99.5° (*c*=0.790, MeOH). *s*) Free base: mp 167—170 °C. *t*) $[\alpha]_D^{20}$ +79.4° (*c*=0.389, MeOH). *u*) $[\alpha]_D^{20}$ −79.9° (*c*=0.344, MeOH). *v*) $[\alpha]_D^{20}$ +76.5° (*c*=0.388, MeOH). *w*) **18cc** was also obtained in 15.9% yield. *x*) The starting material, *cis*-3-acetoxy-7-amino-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one, was prepared by acetylation of **5aa**, followed by cleavage of the *N*-benzoxycarbonyl group. See Experimental section. *y*) i) Acylation of **7w**, ii) Method Z. *z*) Percentage of fluorine.

Table 7. Effects of the Alkyl-, Alkoxy-, and Alkylthio-Substituted 1,5-Benzothiazepine Derivatives on Vertebral and Coronary Blood Flows and Blood Pressure

Compound	R_1	R_2	Increase in vertebral blood flow in anesthetized dogs (i.a., $n=2$—5)		Increase in coronary blood flow in isolated guinea pig heart[c]	Change in blood pressure (ΔmmHg) in SHR ($p.o.$, $n=3$—6); Period of time after dosing		Dose (mg/kg)
			Potency ratio[a]	Half-duration[b] (s)		1 h	4 h	
7a	6-Me	4-OMe	5.0	43	+	NT		
7b	7-Me	4-OMe	3.7	38	+	NT		
7d	8-Me	4-OMe	5.8	42	++	−78.0	−47.8	100
7e	8-Me	4-Me	2.9	40	+	−49.7	−49.0	100
7h	6,7-di-Me	4-OMe	2.3	56	+	NT		
7i	6,8-di-Me	4-OMe	5.3	59	+++	NT		
7j	7,9-di-Me	4-OMe	2.8	58	++	NT		
7k	7,8-di-Me	4-OMe	2.7	44	++	−50.1	−53.8	100
7q	7-CF_3	4-OMe	0.6	25	+	NT		
7r	6-OMe	4-OMe	2.5	43	++	NT		
7s	7-OMe	4-OMe	1.3	39	+	NT		
7t	8-OMe	4-OMe	2.8	44	+++	−83.8	−64.9	100
8t	8-OMe	4-OMe	0.2	20	−	NT		
7u	8-OMe	4-Me	4.6	41	++	NT		
7v	7,8-di-OMe	4-OMe	2.6	47	++	NT		
7w	8-OBzl	4-OMe	2.4	48	−	NT		
7y	7-SMe	4-OMe	1.5	29	NT	NT		
7z	8-SMe	4-OMe	5.4	43	NT	NT		
7bb	7-NH_2	4-OMe	1.1	60	+	NT		
7cc	8-OH	4-OMe	1.37	83	−	NT		
7dd	8-OH	4-Me	2.2	51	NT	NT		
13a	6-Me	4-OMe	2.1	84	+++	−122.1	−132.3	100
						−77.0	−50.0	30
13b	7-Me	4-OMe	5.4	70	++	−119.8	−110.2	100
						−78.0	−42.0	30
(+)-**13b**	7-Me	4-OMe	11.6	54	++	NT		
(−)-**13b**	7-Me	4-OMe	0.83	32	+	NT		
13d	8-Me	4-OMe	8.0	82	+++	−68.7	−38.7	30
(+)-**13d**	8-Me	4-OMe	NT	—	++++	NT		
(−)-**13d**	8-Me	4-OMe	NT	—	+	NT		
13e	8-Me	4-Me	4.5	81	++	−66.4	−80.8	100
						−46.0	−31.0	30
(+)-**13e**	8-Me	4-Me	8.2 (7.3)[d]	88 (50)[d]	++ (++++)[d]	−42.3	−13.3[e]	30
						−17.0	−2.5[e]	10
(−)-**13e**	8-Me	4-Me	0.7	25	NT (++)[d]	−13.0	−3.0[e]	30
13h	6,7-di-Me	4-OMe	4.4	120	+++	−80.3	−49.3	30
13i	6,8-di-Me	4-OMe	2.8	289	+++	−77.0	−37.7	30
13j	7,9-di-Me	4-OMe	2.8	89	+++	−42.0	−39.3	30
13k	7,8-di-Me	4-OMe	2.7	60	+	−108.4	−120.0	100
						−92.3	−75.0	30
						−61.0	−26.7	10
(+)-**13k**	7,8-di-Me	4-OMe	6.4	120	NT	−76.3	−51.3	30
(−)-**13k**	7,8-di-Me	4-OMe	0.7	51	NT	−27.3	−14.0	30
13l	7,8-di-Me	4-Me	NT	—	+++	NT		
13q	7-CF_3	4-OMe	2.7	31	++	NT		
13r	6-OMe	4-OMe	2.8	120	++	−91.8	−93.8	100
						−75.3	−80.7	30
13s	7-OMe	4-OMe	5.0	56	+	−78.9	−104.7	100
						−63.3	−44.3	30
trans-**13s**	7-OMe	4-OMe	0.2	29	−	NT		
13t	8-OMe	4-OMe	1.4	120	++	−100.1	−94.0	100
						−114.0	−94.0	30
						−13.0	−40.3	10
(+)-**13t**	8-OMe	4-OMe	2.8	171	NT	−78.0	−59.0	30
(−)-**13t**	8-OMe	4-OMe	0.4	31	NT	−13.7	−30.3	30
trans-**13t**	8-OMe	4-OMe	0.2	19	−	NT		
13u	8-OMe	4-Me	8.9	76	++	−109.6	−109.9	100
						−73.3	−39.0	30
13v	7,8-di-OMe	4-OMe	4.4	54	+	−72.7	−27.0	30
13w	8-OBzl	4-OMe	2.4	150	+++	−66.3	−61.0	100
13y	7-SMe	4-OMe	5.2	40	++	NT		
13z	8-SMe	4-OMe	4.8	68	−	NT		

Table 7. (continued)

Compound	R_1	R_2	Increase in vertebral blood flow in anesthetized dogs (i.a., $n=2$—5)		Increase in coronary blood flow in isolated guinea pig heart[c]	Change in blood pressure (ΔmmHg) in SHR (*p.o.*, $n=3$—6); Period of time after dosing		Dose (mg/kg)
			Potency ratio[a]	Half-duration[b] (s)		1 h	4 h	
13bb	7-NH_2	4-OMe	1.3	218	+	NT		
13cc	8-OH	4-OMe	0.7	299	−	NT		
13dd	8-OH	4-Me	1.4	93	NT	NT		
13ee	7-NHAc	4-OMe	<0.05	—	−	NT		
11d	8-Me	4-OMe	1.0	53	+	−30.3	−14.8	30
(−)-**11d**	8-Me	4-OMe	0.22	22	−	NT		
11u	8-OMe	4-Me	0.5	61	−	NT		
14a	6-Me	4-OMe	0.8	71	++	NT		
14b	7-Me	4-OMe	1.6	61	++	NT		
14d	8-Me	4-OMe	0.8	55	+++	NT		
14e	8-Me	4-Me	1.4	68	+	NT		
14k	7,8-di-Me	4-OMe	1.6	68	++	NT		
14r	6-OMe	4-OMe	0.3	66	+++	NT		
14s	7-OMe	4-OMe	0.5	43	+++	NT		
14t	8-OMe	4-OMe	0.7	101	++++	NT		
15a	6-Me	4-OMe	0.8	43	+	−46.9	−27.7	100
15b	7-Me	4-OMe	1.4	38	−	NT		
15d	8-Me	4-OMe	0.86	27	++	NT		
15e	8-Me	4-Me	1.1	36	+	NT		
15k	7,8-di-Me	4-OMe	1.0	38	+	NT		
15r	6-OMe	4-OMe	0.4	42	+	−81.7	−102.7	100
						−58.0	−50.0	30
15t	8-OMe	4-OMe	0.86	52	−	NT		
16a	6-Me	4-OMe	2.0	59	++	−36.7	−39.1	100
16b	7-Me	4-OMe	2.2	63	+++	NT		
16d	8-Me	4-OMe	0.8	76	++	NT		
16e	8-Me	4-Me	1.1	82	++	NT		
16k	7,8-di-Me	4-OMe	1.6	79	+	NT		
16q	7-CF_3	4-OMe	0.3	31	++	NT		
16s	7-OMe	4-OMe	1.1	46	+++	NT		
16t	8-OMe	4-OMe	1.0	79	++	NT		
16cc	8-OH	4-OMe	0.99	83	++	−6.1	−4.8	100
17b	7-Me	4-OMe	2.8	85	+++	−35.3	−42.0	100
17d	8-Me	4-OMe	2.3	152	+++	−38.7	−36.7	30
17e	8-Me	4-Me	2.1	207	++	−55.0	−109.0	100
17k	7,8-di-Me	4-OMe	1.1	141	++	NT		
17r	6-OMe	4-OMe	0.5	225	++	NT		
17s	7-OMe	4-OMe	0.7	73	+++	NT		
17t	8-OMe	4-OMe	2.3	264	++	−27.0	−58.7	100
18d	8-Me	4-OMe	0.81	100	−	−107.3	−97.8	100
						−71.0	−42.3	30
(−)-**18e**	8-Me	4-Me	0.6	28	NT	NT		
18u	8-OMe	4-Me	0.5	120	−	−94.4	−121.5	100
						−34.0	−46.3	30
19e	8-Me	4-Me	NT	—	+	−53.4	−76.2	100
						−37.7	−31.7	30
20e	8-Me	4-Me	NT	—	++	−56.4	−62.4	100
21e	8-Me	4-Me	NT	—	+	NT		
Diltiazem	H	4-OMe	4.3	66	+++	−61.6	−62.3	100

a) Papaverine=1. *b*) Duration of a half of the maximum change in blood flow. *c*) The increase in CBF by more than 0.5 ml/min at the doses of 100, 30, 10, and 3 μg/heart is expressed as +, ++, +++, and ++++, respectively: − denotes an increase of less than 0.5 ml/min at the dose of 100 μg/heart. *d*) Data in parentheses are the results for the fumarate. *e*) At 5 h after dosing. NT: Not tested.

ethoxycarbonyl (**15**), 4-nitrobenzoyl (**16**), and 4-methylbenzoyl (**17**) derivatives, are less active than the corresponding acetyl derivatives (**13**). However, the potency of the 3-(4-methylbenzoyl)oxy derivatives (**17**) is the highest among these derivatives and their duration of action is generally longer than that of diltiazem.

N-Demethylation (**18**, **11**) of the (dimethylamino)alkyl side chain on amide-nitrogen at position 5 resulted in a marked decrease of the activity. Replacement of the methoxy group at the *para*-position on the phenyl ring at the C_2 position with methyl had no clear effect on the activity.

Regarding the absolute stereochemistry (**13b**, **13d**, **13e**, **13k**, **13t**), the dextrorotatory isomers exhibit good activity, while the corresponding levorotatory ones are scarcely active.

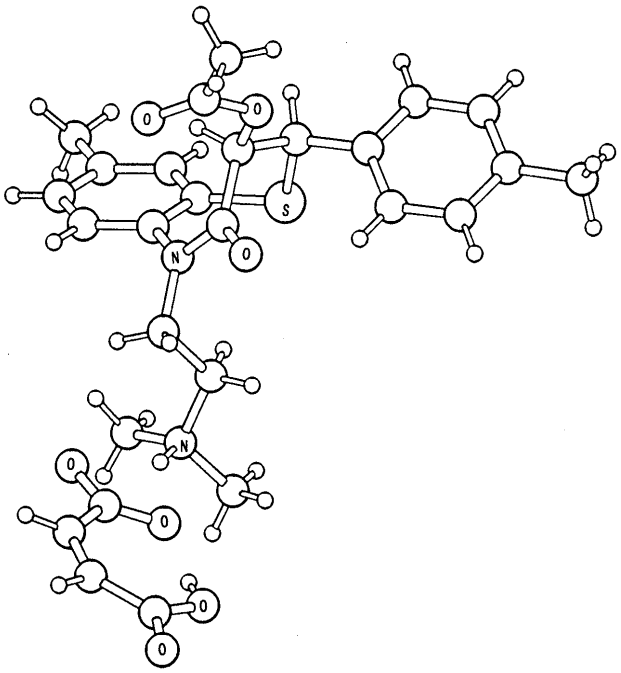

Fig. 1. Perspective Drawing of (−)-**13e**·maleate

Finally, the 2,3-*trans* isomers (*trans*-**13s**, *trans*-**13t**, **8t**) are much less active.

Effect on CBF As shown in Table 7, (+)-**13e** and (+)-**13d**, which showed a good potency on VBF, increased the CBF by more than 0.5 ml/min at the dose of 3 μg/heart in isolated guinea pig heart. Compound **14t** also showed very strong activity. Moreover, the effects of **13a**, **13d**, **13h**, **13i**, **13j**, **13l**, **13w**, **14d**, **14r**, **14s**, **16b**, **16s**, **17b**, **17d**, and **17s** were comparable to that of diltiazem.

No clear relationship between the effects on CBF and VBF was seen. The 3-*n*-butylcarbamoyloxy (**14**) and 3-(4-methylbenzoyl)oxy (**17**) derivatives have relatively high activity, in spite of their low activity on VBF. However, the 3-acetyl derivatives (**13**) are more potent than the 3-OH congener (**7**). The levorotatory isomers, 2,3-*trans* isomers, and the compounds having more polar substituents on the fused benzene ring are less active.

Hypotensive Effect in SHR Hypotensive effects in SHR (*p.o.*) were investigated for the compounds which showed interesting activity on VBF and CBF, and the results are summarized in Table 7.

Compounds **13k** and **13t** exhibited the most promising hypotensive effect, and were active even at the dose of 10 mg/kg in SHR. Moreover, the activities of **13a**, **13b**, **13d**, **13h**, **13i**, **13s**, **13u**, **13v**, **15r**, **18d**, and **18u** were stronger than that of diltiazem. The 3-OH derivative (**7**) is much less active than the 3-OAc derivative (**13**) (see **7d**, **7e**, **7k**, **7t**). *N*-Demethyl compounds (**18d**, **18u**, **19e**, **20e**) have a high potency, in contrast to their lower activity on VBF or CBF.

Inhibitory Effect on Platelet Aggregation in Human PRP In the previous study on diltiazem, some of the metabolites of diltiazem showed a good inhibitory effect on platelet aggregation. In particular, (−)-*N*-demethyldeacetyl diltiazem (l-M-2) and (−)-*N*,*O*-didemethyldeacetyl diltiazem (l-M-6) showed the highest activity *in vitro* among the metabolites of diltiazem and its (−)-enantiomer.[9] With the aim of finding a better compound, we investigated the effects of the compounds newly synthesized in this study.

Table 8. Inhibitory Effects on Collagen-Induced Platelet Aggregation of Human PRP

Compound	R_1	R_2	IC_{50} (μg/ml)
7a	6-Me	4-OMe	10
7b	7-Me	4-OMe	7
7d	8-Me	4-OMe	36
7e	8-Me	4-Me	2
7k	7,8-di-Me	4-OMe	60
7q	7-CF_3	4-OMe	46
7r	6-OMe	4-OMe	6
7u	8-OMe	4-Me	5
7w	8-OBzl	4-OMe	>100
7bb	7-NH_2	4-OMe	7
7cc	8-OH	4-OMe	4
8t	8-OMe	4-OMe	>100
11c	7-Me	4-Me	16
11d	8-Me	4-OMe	3—10
(+)-**11d**	8-Me	4-OMe	10—30
(−)-**11d**	8-Me	4-OMe	1—3
11e	8-Me	4-Me	0.3
(+)-**11e**	8-Me	4-Me	20
(−)-**11e**	8-Me	4-Me	0.08
11u	8-OMe	4-Me	0.5
13b	7-Me	4-OMe	60
13d	8-Me	4-OMe	17
13k	7,8-di-Me	4-OMe	42
13e	8-Me	4-Me	8
13q	7-CF_3	4-OMe	>100
trans-**13s**	7-OMe	4-OMe	45
13t	8-OMe	4-OMe	10
trans-**13t**	8-OMe	4-OMe	54
13u	8-OMe	4-Me	32
13w	8-OBzl	4-OMe	44
13cc	8-OH	4-OMe	20
13ee	7-NHAc	4-OMe	80
18c	7-Me	4-Me	16
(−)-**18d**	8-Me	4-OMe	15
(+)-**18d**	8-Me	4-OMe	25
18e	8-Me	4-Me	20
18r	6-OMe	4-OMe	20
18u	8-OMe	4-Me	0.5
18w	8-OBzl	4-OMe	30
19e	8-Me	4-Me	>30
Diltiazem	H	4-OMe	25
(−)-*N*-Demethyldeacetyldiltiazem (l-M-2)	H	4-OMe	0.3
Aspirin			18

As with the derivatives of diltiazem, the 5-[2-(monoalkylamino)ethyl] derivatives (**11**, **18**) showed good activity. Regarding the activity of the optically active isomers of **11d**, **11e**, and **18d**, the *levo*-isomers (2*R*,3*R*) were much more effective than the corresponding *dextro*-isomers (2*S*,3*S*). The 5-[2-(dimethylamino)ethyl] derivatives (**7**, **13**) were less active than the monomethylamino isomers (**11**, **18**). The 3-hydroxy derivatives (**7**, **11**) were more active than the corresponding 3-acetoxy derivatives (**13**, **18**) in the *in vitro* test, except for **18d** and **11d**. These results were opposite to the order of their effects on VBF and CBF and their hypotensive effect, as described above.

Compound (−)-**11e** showed the best activity (IC_{50} 0.08 μg/ml) on collagen-induced platelet aggregation of

human PRP among the compounds tested in this study, being about 200 times more active than aspirin. Compounds (±)-**11e**, (±)-**11u**, and (±)-**18u** exhibited comparable activity to l-M-2.

Finally, the 2,3-*trans*-compounds (**8t**, *trans*-**13s**, *trans*-**13t**) were less active than the corresponding 2,3-*cis*-isomers.

(−)-*cis*-3-Acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-8-methyl-2-(4-methylphenyl)-1,5-benzothiazepin-4(5*H*)-one ((−)-**13e**) was selected for further studies as a potent inhibitor of the platelet aggregation, which is easily metabolized to the *N*-monomethyl derivatives ((−)-**18e** and (−)-**11e**). The results of further studies on the metabolism and pharmacology of these compounds have been reported separately.[10)]

Experimental

Melting points were determined with a Buchi 535 apparatus and are uncorrected. Evaporation of solvents was performed under reduced pressure. IR spectra were recorded on an Analect RFX-65 spectrometer. ^{1}H-NMR were measured in the mentioned solvent with a JEOL PMX-60, Hitachi RH-90H, or JEOL FX-200 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (Me_4Si: 0.0) as an internal standard. They were measured by the Analytical Department of the Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd.

Reaction of the Aminothiophenol (1) and the *trans*-3-Arylglycidic Ester (2) without Solvent. Method A A mixture of 2-amino-3-methylthiophenol (**1a**, 6.851 g) and methyl *trans*-3-(4-methoxyphenyl)glycidate (**2a**, 8.22 g) was stirred at 150—160 °C for 15 h. After cooling, the reaction mixture was dissolved in benzene, washed with 18% HCl and then water, dried, and concentrated. Trituration of the residual oil with EtOH gave the mixture of *cis*- and *trans*-lactams as a solid. Fractional recrystallization of the solid and separation of the oil obtained from the mother liquors by flash column chromatography (SiO_2, $CHCl_3$–AcOEt (10 : 1)) gave the *cis*-lactam (**5a**, 1.14 g, 7.3%), mp 225—227.5 °C. IR (Nujol) ν: 3500, 1670 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.30 (3H, s), 3.75 (3H, s), 4.21 (1H, t, J=7 Hz), 4.55 (1H, d, J=7 Hz), 4.96 (1H, d, J=7 Hz), 6.8—7.7 (7H, m) and the *trans*-lactam (**6a**, 0.46 g, 3.0%), mp 231—233 °C. IR (Nujol) ν: 3500, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.30 (3H, s), 3.73 (3H, s), 4.08 (1H, dd, J=7, 10 Hz), 4.33 (1H, d, J=10 Hz), 5.25 (1H, d, J=7 Hz, OH), 6.7—7.5 (7H, m).

The aqueous layers (washings with 10% HCl and water) were combined, made basic with K_2CO_3 and extracted with $CHCl_3$. The extracts were combined, washed with water, dried, and concentrated. The residual oil was purified by column chromatography (SiO_2, eluted with C_6H_6–AcOEt (5 : 1)) to give the *threo*-amino ester (*threo*-**3a**, 1.56 g, 9.1%), mp 98—100 °C. IR (Nujol) ν: 3500, 3450, 3350, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 3.58 (3H, s), 3.80 (3H, s), 4.45 (2H, s), 6.5—7.5 (7H, m).

Cyclization of the Amino Carboxylic Acid (4). Method B A suspension of the *threo*-amino carboxylic acid (*threo*-**4e**, 93.9 g) in xylene (950 ml) was heated under reflux using a Dean–Stark apparatus for 7 h. After cooling, the precipitated needles were collected on a filter and recrystallized from DMF–EtOH to give the *cis*-lactam (**5e**, 82.3 g, 92.9%), mp 182.5—184.5 °C. IR (Nujol) ν: 3475, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.30 (6H, s), 4.27 (1H, dd, J=7, 6 Hz), 4.53 (1H, d, J=6 Hz), 5.01 (1H, d, J=7 Hz), 7.0—7.4 (7H, m).

Optical Resolution of the Lactam (5). Method C i) (*S*)-*N*-(2-Naphthalenesulfonyl)pyrrolidine-2-carbonyl chloride (9.85 g) was added to a solution of the *cis*-lactam (**5e**, 7.0 g) in pyridine (140 ml) at 2—5 °C. After having been stirred at room temperature for 7 h, the reaction mixture was diluted with AcOEt, washed with water, 10% HCl, water, 5% $NaHCO_3$, and water successively, dried, and concentrated. The residual oil was separated by column chromatography (SiO_2, eluted with AcOEt–hexane (1 : 2—1 : 1)) to isolate each diastereomeric isomer (**25a**, **25b**). From the first eluate, **25a** (6.49 g, 47%) as an oil, $[\alpha]_D^{20}$ −49.3° (c=1.00, $CHCl_3$) was obtained and the second eluate afforded **25b** (6.48 g, 47%) as an oil, $[\alpha]_D^{20}$ −41.7° (c=1.00, $CHCl_3$).

ii) Hydrolysis of **25a** (6.49 g) in a mixture of aqueous NaOH (880 mg in 24 ml), THF (48 ml), and MeOH (48 ml) at room temperature for 30 min and work-up in a usual manner gave the (+)-*cis*-lactam ((+)-**5e**, 2.69 g, 82%), mp 217.5—219 °C. $[\alpha]_D^{20}$ +122.8° (c=1.00, MeOH). IR (Nujol) ν: 3320, 3180, 1680, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.29 (6H, s), 4.28 (1H, d, J=7 Hz), 5.02 (1H, d, J=7 Hz), 7.0—7.4 (7H, m).

Similarly, hydrolysis of **25b** gave the (−)-*cis*-lactam ((−)-**5e**) in the same manner in 82% yield, mp 216.5—217.5 °C. $[\alpha]_D^{20}$ −126.3° (c=1.00, MeOH). The IR and ^{1}H-NMR spectra were superimposable on those of (+)-**5e**.

Cyclization of the Amino Ester (3). Method D A solution of the *threo*-amino ester(*threo*-**3u**, 19.26 g) in DMSO (50 ml) was added to a solution of dimethylsulfinyl carbanion (prepared from NaH (63% dispersion in mineral oil, 4.45 g) and DMSO (50 ml)) at 20 °C during a period of 45 min. After having been stirred at room temperature for 30 min, the reaction mixture was poured into ice–water and the precipitated solid was collected on a filter and purified by recrystallization from acetone to give **5u** (15.84 g, 90.3%), mp 202—206 °C. IR (Nujol) ν: 3330, 3190, 1675, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 3.05 (1H, d, J=9.2 Hz), 3.82 (3H, s), 4.48 (1H, dd, J=6.8, 9.2 Hz), 5.07 (1H, d, J=6.8 Hz), 6.6—7.7 (3H, m), 7.09 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.0 Hz).

Cyclization of the Amino Carboxylic Acid (4) Using DCC–HOBt. Method E DCC (5.83 g) was added to a solution of the *threo*-amino carboxylic acid (*threo*-**4q**, 7.84 g) and HOBt (3.10 g) in tetrahydrofuran (THF) (100 ml)–CH_2Cl_2 (200 ml) at 0—3 °C. The mixture was stirred at the same temperature for 8 h and at room temperature overnight, then the precipitated crystals were collected. Fractional recrystallization from AcOEt gave the less soluble dicyclohexylurea (4.21 g) and the more soluble **5q** (7.03 g, 94.1%), mp 205—207 °C. IR (Nujol) ν: 3320, 3160, 1680, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 3.75 (3H, s), 4.37 (1H, d, J=6 Hz), 5.10 (1H, d, J=6 Hz), 6.82 (2H, d, J=8 Hz), 7.2—7.8 (3H, m), 7.48 (2H, d, J=8 Hz).

Reaction of the Aminothiophenol (1) and the *trans*-3-Arylglycidic Ester (2) in Xylene. Method F A solution of **1c** (195 g) and methyl *trans*-3-(4-methylphenyl)glycidate (**2c**, 350 g) in xylene (980 ml) was reacted under an argon atmosphere at 130 °C for 3.5 h. After cooling, the reaction mixture was diluted with hexane (400 ml) and the precipitated crystals were collected on a filter and purified by recrystallization from iso-Pr_2O to give the *threo*-amino ester (*threo*-**3e**, 299.7 g, 64.6%), mp 115.5—117.5 °C. IR (Nujol) ν: 3390, 3300, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.33 (3H, s), 3.54 (3H, s), 4.51 (2H, s), 6.64 (1H, d, J=7.9 Hz), 6.93 (2H, m), 7.11 (2H, d, J=7.9 Hz), 7.31 (2H, d, J=7.9 Hz).

Synthesis of the 7-Amino-Substituted Lactam (5bb). Method G i) A mixture of the 7-benzyloxycarbonylamino compound (**5aa**, 870 mg) and Ac_2O (1 ml) was heated at 100—110 °C for 1.5 h, and then concentrated under reduced pressure. The residual oil was dissolved in Et_2O–$CHCl_3$ (1 : 1), washed with water, dried, and concentrated to give the 3-acetoxy compound (1.0 g) as an oil.

ii) The acetate obtained in i) was dissolved in 25% HBr–HOAc (3.5 ml) at room temperature. After having been stirred for 3 h, the reaction mixture was diluted with Et_2O. The precipitated amorphous solid was washed with Et_2O to remove benzyl bromide and the excess of HBr–HOAc and then dissolved in $CHCl_3$. The solution was washed with aqueous K_2CO_3 and water, dried, and concentrated. The residual oil was triturated with Et_2O and the obtained crystals were recrystallized from MeOH to give *cis*-3-acetoxy-7-amino-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (350 mg, 50.6% from **5aa**), mp 248—250 °C. *Anal.* Calcd. for $C_{18}H_{18}N_2O_4S \cdot H_2O$: C, 57.43; H, 5.35; N, 7.44. Found: C, 57.21; H, 5.51; N, 7.18.

iii) Hydrolysis of the 3-acetoxy-7-amino compound (200 mg) in MeOH (30 ml)–$CHCl_3$ (8 ml)–THF (2 ml) by stirring with 10% NaOH (2 ml) at room temperature for 30 min. The reaction mixture was worked up in a usual manner to give **5bb** (130 mg, 73.4%), mp 225—228 °C. IR (Nujol) ν: 3400—2800, 1675, 1650, 1630, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.75 (3H, s), 4.23 (1H, t, J=7 Hz), 4.47 (1H, d, J=7 Hz), 4.89 (1H, d, J=7 Hz), 5.56 (2H, s), 6.36 (2H, m), 6.86 (2H, d, J=8.8 Hz), 7.20 (1H, d, J=9 Hz), 7.35 (2H, d, J=8.8 Hz).

Optical Resolution of the Amino Carboxylic Acid (4). Method H i) The *threo*-amino carboxylic acid (*threo*-**4e**, 410.4 g) and D-(4-hydroxyphenyl)glycine methyl ester (D-HPGE, 304.6 g) were dissolved in MeOH (2.8 l)–THF (1.4 l) and the mixture was concentrated under reduced pressure below 30 °C. The residual gum was dissolved in EtOH (1.3 l) below 30 °C and then about 300 ml of EtOH was evaporated under reduced pressure. The solution was kept in a refrigerator and

the precipitated crystals were filtered and washed with chilled EtOH. Repeated recrystallization gave the optically pure (−)-*threo*-**4e** D-HPGE salt (210.4 g, 65.3%), $[\alpha]_D^{20}$ −294.7° (c=0.52, MeOH), mp 166—167 °C (dec.).

The (−)-*threo*-**4e** D-HPGE salt (210 g) was suspended in MeOH (1.1 l), then the solution was acidified with 10% HCl (pH 3—4), and diluted with H_2O (1.1 l). The precipitated crystals were collected and recrystallized from EtOH to give (−)-*threo*-**4e** (116.1 g, 56.6% from (±)-*threo*-**4e**), mp 163—165 °C (dec.). $[\alpha]_D^{20}$ −354° (c=0.370, DMF). IR (Nujol) ν: 3300—3000, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.97 (3H, s), 2.23 (3H, s), 4.27 (1H, d, J=5.5 Hz), 4.30 (1H, d, J=5.5 Hz), 6.45—7.2 (7H, m).

The mother liquor of the crystallization of crude (−)-*threo*-**4e** D-HPGE salt and the washings were combined and concentrated. The obtained gum of (+)-rich *threo*-**4e** D-HPGE salt was dissolved in MeOH (900 ml), diluted with water (900 ml). This solution was acidified with 10% HCl (pH 3—4), and further diluted with water (1.3 l). The precipitated crystals of (+)-rich *threo*-**4e** (free base, 321 g) were collected and fractional recrystallization of the crystals from EtOH gave pure (+)-*threo*-**4e** (87.9 g, 42.7%), mp 164—166 °C (dec.). $[\alpha]_D^{20}$ +341° (c=0.300, DMF) after removal of (±)-*threo*-**4e** (41.9 g, 10.2%). The IR and ^{1}H-NMR spectra of (+)-*threo*-**4e** were superimposable on those of (−)-*threo*-**4e**.

Hydrolysis of the Amino Ester (3). Method I Hydrolysis of *threo*-**3e** (464 g) was carried out by stirring with a mixture of KOH (155 g), H_2O (1.25 l), THF (1.75 l), and MeOH (1.75 l) at room temperature for 1.5 h. The reaction mixture was diluted with water and concentrated to remove MeOH and THF. The residual aqueous solution was acidified with 10% HCl (pH 4). The precipitated crystals were collected on a filter and recrystallized from EtOH to give *threo*-**4e** (424 g, 95.0%), mp 178.5—179.5 °C. IR (Nujol) ν: 3290, 2600, 2070, 1620 cm^{-1}.

Selective Benzyloxycarbonylation of the 4-Amino Group of 3bb. Method J A solution of benzyloxycarbonyl chloride (2.941 g) in CH_2Cl_2 (7.3 ml) was added to a mixture of methyl *threo*-3-(2,4-diaminophenyl)-thio-2-hydroxy-3-(4-methoxyphenyl)propionate (*threo*-**3bb**, 6.0 g) and $NaHCO_3$ (3.0 g) in CH_2Cl_2 (65 ml)–DMF (10 ml) at −50—−60 °C over a period of 30 min and the reaction mixture was stirred at the same temperature for 3 h, warmed slowly to −10 °C during a period of 1 h, and then diluted with water (below −5 °C). The organic layer was separated, washed with water, dried, and concentrated. The residual oil was dissolved in $CHCl_3$–Et_2O (1 : 2) and this solution was extracted with concentrated HCl–H_2O (1 : 1). The extracts were combined, made basic with K_2CO_3, and extracted with $CHCl_3$. Washing of the extracts with water and concentration after drying with Na_2SO_4 gave *threo*-**3aa** (6.12 g, 73.7%) as an oil. IR (liquid) ν: 3450, 3350, 1720, 1600 cm^{-1}.

On the other hand, the organic layer which was not extracted with HCl (the neutral part) was washed with water, dried, and concentrated. Trituration of the residual oil with Et_2O gave methyl *threo*-3-[2,4-bis-(benzyloxycarbonylamino)phenyl]thio-2-hydroxy-3-(4-methoxyphenyl)-propionate (**27**, 1.23 g, 11.6%), mp 106—109 °C, after recrystallization from iso-Pr_2O–Et_2O. *Anal.* Calcd for $C_{33}H_{32}N_2O_8S$: C, 64.27; H, 5.23; N, 4.54. Found: C, 64.41; H, 5.34; N, 4.53.

Synthesis of the Diamino Ester (3bb). Method K i) A mixture of 2,4-dinitrothiophenol (9.0 g) and **2a** (11.2 g) in CH_3CN (140 ml) was stirred at room temperature for 3 d. The precipitated bis(2,4-dinitrophenyl)disulfide was removed by filtration, then evaporation of the filtrate, trituration of the residual oil with Et_2O, and recrystallization of the obtained crystals from AcOEt–iso-Pr_2O gave methyl *threo*-3-(2,4-dinitrophenyl)thio-2-hydroxy-3-(4-methoxyphenyl)propionate (**26**, 8.98 g, 48.9%), mp 130—131 °C as yellow needles. *Anal.* Calcd for $C_{17}H_{16}N_2O_8S$: C, 50.00; H, 3.95; N, 6.86; S, 7.85. Found: C, 50.11; H, 4.26; N, 6.78; S, 7.78. IR (Nujol) ν: 3480, 1735, 1510, 1340 cm^{-1}.

ii) The dinitro ester (8 g) was reduced by adding it to a mixture of $SnCl_2 \cdot 2H_2O$ (32.2 g), concentrated HCl (23.5 ml), and AcOH (120 ml) at 0—2 °C over a period of 5 min, followed by stirring at room temperature for 3 h and at 45—50 °C for 1 h. The reaction mixture was poured into a mixture of cracked ice (2 kg) and NaOH (112 g) and extracted with $CHCl_3$. The extracts were combined, washed with water, dried, and concentrated. The residual oil was triturated with Et_2O and the obtained crystals were recrystallized from EtOH–iso-Pr_2O to give *threo*-**3bb** (6.24 g, 91.4%), mp 112—114 °C. IR (Nujol) ν: 3460, 3370, 3230, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (3H, s), 3.79 (3H, s), 4.37 (1H, d, J=3.0 Hz), 4.49 (1H, d, J=3.0 Hz), 5.97 (2H, dd, J=2.6, 8.2 Hz), 6.03 (1H, d, J=2.6 Hz), 6.82 (2H, d, J=8.8 Hz), 6.87 (1H, d, J=8.2 Hz), 7.32 (2H, d, J=8.8 Hz).

Reaction of the Aminothiophenol (1) and the 3-Arylglycidic Ester (2) in the Presence of a Catalytic Amount of $CaCl_2$. Method L A mixture of **1c** (5.0 g) and **2c** (6.21 g) in toluene (50 ml) in the presence of $CaCl_2$ (0.5 g) was stirred at 50 °C for 8 h and poured into a mixture of AcOEt–ice–water. The organic layer was separated and extracted with concentrated HCl twice. The extracts were combined, made basic with K_2CO_3, and extracted with AcOEt. These extracts were concentrated after a usual work-up, and the product was purified by column chromatography (SiO_2, eluted with hexane–AcOEt (2 : 1)) to give *erythro*-**3e** (2.93 g, 27.3%) as an oil. IR (liquid) ν: 3460, 3360, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s), 2.31 (3H, s), 3.59 (3H, s), 4.1—4.5 (3H, m), 6.5—7.3 (7H, m).

***N*-Alkylation of the Lactam (5 or 6). a) By Use of K_2CO_3–Acetone. Method M** A mixture of **5e** (80.5 g), 2-(dimethylamino)ethyl chloride hydrochloride (42.6 g), and K_2CO_3 (93 g) in acetone (800 ml)–H_2O (16 ml) was stirred vigorously under reflux overnight. After cooling, inorganic compounds and the solvent were removed. The residual crystalline solid was purified by recrystallization from AcOEt–hexane to give **7e** (97.2 g, 97.5%), mp 142—143 °C, which was converted into the hydrochloride and recrystallized from AcOEt to give **7e**·HCl, mp 229—232 °C. IR (Nujol) ν: 3200, 3100—2200, 1680, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.30 (3H, s), 2.35 (3H, s), 2.78 (6H, s), 4.25 (1H, d, J=7.3 Hz), 4.89 (1H, d, J=7.3 Hz), 7.14 (2H, d, J=8.1 Hz), 7.30 (2H, d, J=8.1 Hz), 7.4—7.6 (3H, m).

b) By Use of KOH–DMSO. Method N A mixture of **5d** (12.0 g) and KOH (4.90 g) in DMSO (180 ml) was stirred at room temperature for 20 min, then 2-(dimethylamino)ethyl chloride hydrochloride (5.48 g) was added. The reaction mixture was stirred at 30—35 °C overnight and poured into ice–water. The precipitated solid was collected on a filter and purified by recrystallization from AcOEt to give **7d** (9.83 g, 66.8%), mp 157—158 °C. IR (Nujol) ν: 3360, 1660, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (6H, s), 2.34 (3H, s), 3.78 (3H, s), 4.32 (1H, d, J=8 Hz), 4.89 (1H, d, J=8 Hz), 6.8—7.5 (7H, m).

When a less reactive alkylating agent, such as 2-(*N*-benzyloxycarbonyl-*N*-methylamino)ethyl chloride, was used, a longer reaction time was required for completion of the reaction.

***N*-Demethylation of 13. a) Method O** i) Trichloromethyl chloroformate (10.0 g) was added to a solution of (−)-**13e** (13.9 g) and Et_3N (2.38 g) in toluene (164 ml) under ice-cooling. After having been stirred at room temperature overnight, the reaction mixture was concentrated under reduced pressure to give an oil. The oil was dissolved in AcOEt, and this solution was washed with 10% HCl, water, 5% $NaHCO_3$, and water successively, dried, and concentrated to give the *N*-chloroformyl compound (**24**, 16.56 g) as an oil.

ii) The *N*-chloroformyl compound (**24**, 8.28 g) was heated in CH_3CN (100 ml)–10% HCl (100 ml) under reflux for 2 h and then concentrated under reduced pressure to remove CH_3CN. The residue was dissolved in water. The solution was made basic with NH_4OH, and extracted. The extracts were combined, washed with water, dried, and concentrated. The obtained oily (−)-**11e** was converted into the HCl salt and purified by recrystallization from iso-PrOH to give (−)-**11e**·HCl (5.73 g, 86.4%), mp 142—145 °C. IR (Nujol) ν: 3440, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.30 (3H, s), 2.35 (3H, s), 2.56 (3H, s), 4.0—4.4 (3H, m), 7.13 (2H, d, J=8.1 Hz), 7.29 (2H, d, J=8.1 Hz), 7.4—7.5 (3H, m).

b) Method U When the *N*-chloroformyl compound (**24**, 8.28 g) was heated in CH_3CN (100 ml)–H_2O (100 ml) for 40 min and worked up in the same manner as above, (−)-**18e** (3-OAc derivative of (−)-**11e**) was obtained. It was converted into the fumarate to give (−)-**18e**·fumarate (7.34 g, 84.6%) after recrystallization from EtOH, mp 167—169 °C (dec.). IR (Nujol) ν: 3150, 2730, 2440, 2360, 1740, 1685 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.82 (3H, s), 2.31 (3H, s), 2.35 (3H, s), 2.47 (3H, s), 5.03 (1H, d, J=7.5 Hz), 5.10 (1H, d, J=7.5 Hz), 7.1—7.6 (7H, m).

***N*-Allylation of 11t. Method P** *N*-Allylation of **11t**·HCl (833 mg) was carried out by stirring with allyl bromide (249 mg) and K_2CO_3 (1.2 g) in DMF (10 ml) at room temperature for 2 d. The reaction mixture was diluted with water, and extracted with $CHCl_3$–AcOEt (1 : 2). After washing of the extract with water, drying, and concentration, conversion of the residual oil into the HCl salt gave **12t**·HCl·1/2H_2O (650 mg, 69.9%) after recrystallization from EtOH–Et_2O–H_2O, mp 145—148 °C. IR (Nujol) ν: 3550, 3400, 3200—2400, 1645, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.75 (3H, br s), 2.9—3.2 (2H, m), 3.76 (3H, s), 3.83 (3H, s), 4.26 (1H, d, J=7.3 Hz), 4.89 (1H, d, J=7.3 Hz), 5.5—5.6 (2H, m), 5.8—6.2 (1H, m), 6.98 (2H, d, J=8.8 Hz), 7.0—7.6 (5H, m).

Hydrolysis of the 3-Acetoxy Compound (18 or 13). Method Q Hydrolysis of the 3-OAc group was carried out by stirring with

aqueous NaOH at room temperature for 0.5—5 h according to the method described in method C-ii).

Acetylation of the 3-Hydroxyl Group of 7 or 8. Method R Acetylation of the 3-OH group was carried out by heating with Ac_2O–AcOH (1 : 1) or Ac_2O and a catalytic amount of pyridine at 100—110 °C for 1.5—4 h and the reaction mixture was worked up in a usual manner.

Synthesis of the 3-Butylaminocarbonyloxy Compound (14). Method S A mixture of **7t** (800 mg), butyl isocyanate (592 mg), and Et_3N (1 drop) in benzene (10 ml) was heated under reflux for 2 d and then concentrated. The residual viscous oil was converted into the HCl salt and purified by recrystallization from EtOH–Et_2O to give **14t**·HCl (900 mg, 89.7%) as colorless needles, mp 198—200 °C. IR (Nujol) *v*: 3300, 2700—2300, 1720, 1680, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.5 (7H, m), 2.9 (2H, m), 2.95 (6H, s), 3.95 (6H, br s), 5.1 (2H, br s), 6.6—7.5 (7H, m).

Synthesis of the 3-(4-Nitrobenzoyl)oxy (16), 3-(4-Methylbenzoyl)oxy (17), and 3-Ethoxycarbonyloxy Compounds (15). Method T A solution of **7s** (1.0 g) in pyridine (10 ml) was treated with 4-nitrobenzoyl chloride (510 mg) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h, poured into ice–water, and extracted with AcOEt. The extracts were combined, washed with 5% $NaHCO_3$ and water, dried, and concentrated, and the product was converted into the oxalate to give **16s**·oxalate (630 mg, 100%) as yellow needles after recrystallization from EtOH, mp 180—181.5 °C (dec.). IR (Nujol) *v*: 1730, 1675, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (6H, s), 3.80 (3H, s), 3.84 (3H, s), 5.07 (1H, d, J=7 Hz), 5.32 (1H, d, J=7 Hz), 6.7—8.17 (11H, m). (free base)

Similarly, **15** and **17** were synthesized by use of ethyl chloroformate and 4-methylbenzoyl chloride as acylating agents, respectively.

Removal of the *N*-Benzyloxycarbonyl Group of 10. Method V i) Acetylation of **10u** (4.69 g) with Ac_2O (28 ml)–pyridine (1 ml) by heating at 100 °C for 2 h gave the 3-OAc compound (5.2 g) as an oil.

ii) A solution of the 3-OAc compound in HOAc (17 ml) was treated with 25% HBr–HOAc (8.5 ml). The reaction mixture was stirred at room temperature for 2 h and diluted with Et_2O. The precipitated HBr salt was washed with Et_2O, converted into the oxalate in a usual manner, and then purified by recrystallization from EtOH to give 18u·oxalate (2.42 g, 51.8%), mp 143—147 °C. IR (Nujol) *v*: 3500, 3200—2200, 1750, 1685 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.94 (3H, s), 2.33 (3H, s), 2.88 (3H, s), 3.85 (3H, s), 5.05 (2H, m), 7.0—7.7 (7H, m).

***N*-Debenzylation of the 5-[2-(*N*-Benzyl-*N*-methylamino)ethyl] Compound (9). Method W** i) (+)-**9d** (4.91 g) was acetylated with Ac_2O (40 ml)–pyridine (20 drops) according to method R.

ii) A solution of benzoxycarbonyl chloride (4.5 g) in benzene (10 ml) was added to a solution of the obtained 3-OAc compound in benzene (70 ml) under reflux over a period of 15 min. After having been heated under reflux for a further 4 h, the reaction mixture was concentrated under reduced pressure to give (+)-*cis*-3-acetoxy-5-[2-(*N*-benzyloxycarbonyl-*N*-methylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-8-methyl-1,5-benzothiazepin-4(5*H*)-one (6.17 g, quantitative yield) as an oil.

iii) The *N*-benzyloxycarbonyl compound obtained in ii) was treated with HBr–HOAc in the same manner as described in Method V to give (+)-**18d**·oxalate (4.04 g, 80.0%), mp 166—168 °C. IR (Nujol) *v*: 3100—2300, 1735, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.83 (3H, s), 2.36 (3H, s), 2.59 (3H, s), 3.78 (3H, s), 5.01 (1H, d, J=7.7 Hz), 5.13 (1H, d, J=7.7 Hz), 6.92 (2H, d, J=8.8 Hz), 7.37 (2H, d, J=8.8 Hz), 7.45 (1H, dd, J=8.2, 1.6 Hz), 7.55 (1H, d, J=8.2 Hz), 7.58 (1H, d, J=1.6 Hz).

Benzylation of the 3-Hydroxyl Group of 7d. Method X NaH (63% dispersion in mineral oil, 96 mg) was added to a solution of **7d** (610 mg) in DMF (10 ml). The reaction mixture was stirred for 1 h, then benzyl chloride (220 mg) was added. The whole was stirred for 1 h and concentrated under reduced pressure to remove DMF. The residue was dissolved in AcOEt, washed with water, dried, and concentrated. The residual oil was converted into the $HClO_4$ salt and recrystallized from acetone–EtOH to give **23d**·perchlorate (540 mg, 63.3%), mp 238—241 °C. IR (Nujol) *v*: 1660, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.35 (3H, s), 2.85 (6H, s), 3.75 (3H, s), 4.16 (1H, d, J=7.5 Hz), 4.31 (2H, s), 5.12 (1H, d, J=7.5 Hz), 6.8—7.7 (12H, m).

Methylation of the 3-Hydroxyl Group of 7e. Method Y NaH (63% dispersion, 320 mg) and **7e** (2.43 g) in toluene (60 ml)–DMSO (6 ml) was stirred at room temperature for 15 min, followed by addition of dimethyl sulfate (930 mg) in toluene (5 ml) at room temperature. The reaction mixture was stirred at 50 °C for 3 h, diluted with AcOEt after cooling, washed with water, dried, and concentrated. The residue was purified by column chromatography (SiO_2, eluted with $CHCl_3$–MeOH (96 : 4)) and converted into the fumarate. After recrystallization from MeOH–iso-Pr_2O, **22e**· fumarate (980 mg, 29.4%), mp 211.5—213.5 °C. IR (Nujol) *v*: 2640, 2520—2440, 1700, 1675, 1615 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.30 (9H, s), 2.34 (3H, s), 3.01 (3H, s), 3.93 (1H, d, J=7.5 Hz), 5.04 (1H, d, J=7.5 Hz), 6.9—7.6 (7H, m), was obtained.

***O*-Debenzylation of 13w. Method Z** *O*-Debenzylation of **13w** (1.5 g) using 25% HBr–HOAc was performed according to the method described in method V-ii) to give **13cc**·HBr (720 mg, 60.7%) after recrystallization from EtOH, mp 208.5—211.5 °C. IR (Nujol) *v*: 3150, 1750, 1680, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.83 (3H, s), 2.83 (6H, s), 3.76 (3H, s), 5.06 (2H, s), 6.8—7.6 (7H, m).

15cc, **16cc**, and **13dd** were synthesized from the corresponding 3-hydroxy compounds (**7w**, **7x**) in the same manner as described above after acylation of the 3-OH group.

2-Amino-5-methylthiophenol (1c) A mixture of 2-amino-6-methylbenzothiazole (**29c**, 247 g), NaOH (1.2 kg), and water (2 l) was heated under reflux under an argon atmosphere for 24 h and poured into ice–water (3 l). The mixture was acidified with concentrated HCl (pH 2—3), neutralized with K_2CO_3 (pH 4—5), and extracted with toluene. The extracts were combined, washed with water, dried, and concentrated to give **1c** (189.5 g, 90.8%).

The other aminothiophenols (**1**) were similarly prepared from the corresponding benzothiazoles (**29**) (Table 4).

2-Amino-4-(trifluoromethyl)thiophenol i) The Zn salt of 2-amino-4-(trifluoromethyl)thiophenol (24.4 g)[11] was dissolved in concentrated HCl (25 ml)–H_2O (48 ml) on a steam bath and cooled. The precipitated crystals of the HCl salt (27.6 g), mp 198—201 °C, were collected on a filter and washed with a small amount of chilled concentrated HCl. The obtained HCl salt was dissolved in water, neutralized with $(NH_4)_2CO_3$, and extracted. The extracts were combined, washed with water, dried, and concentrated to give free 2-amino-4-(trifluoromethyl)thiophenol (17.0 g, 81.2%) as an oil.

Effect on VBF in Anesthetized Dogs Male or female mongrel dogs were anesthetized with sodium pentobarbital (PB, 30—35 mg/kg, i.v.) and artificially ventilated. Throughout the experiment, PB (3—5 mg/kg per h) was continuously infused into the femoral vein to maintain anesthesia. The right vertebral artery was exposed, and the blood flow was measured with an electromagnetic flow meter (MFV-2100 or MF-27; Nihon-Kohden, Tokyo, Japan). Test compounds and diltiazem dissolved in saline were directly administered into the right vertebral artery *via* a cannula into the artery.

From the values of peak response, we obtained the dose-response curve. Increasing effects of the test compounds on VBF were expressed as the potency ratio to that of diltiazem calculated from the dose–response curves.

Effect on CBF in Isolated Guinea Pig Hearts Isolated hearts from Hartley guinea pigs were perfused according to Langendorff's method with modified Locke–Ringer solution containing defibrinated rabbit blood (perfusion pressure, 40 cm H_2O; temperature of perfusate, 29±1 °C). Outflow of perfusate, *i.e.* coronary blood flow, was measured by means of a drop counter method. Test compounds were dissolved in saline and administered into the aortic cannula. If coronary blood flow increased by 0.5 ml/min or more at doses of 3, 10, 30, and 100 μg/heart, we judged the response to be "++++", "+++", "++", and "+", respectively. If CBF increased by less than 0.5 ml/min at 100 μg/heart, we judged the response to be "−".

Hypotensive Action in SHR Male SHR which had been starved overnight were used. Blood pressure was measured by means of a tail-cuff method in the conscious state. Test compounds dissolved in deionized water were administered orally. Hypotensive action was expressed in terms of change of blood pressure from the predosing value at 1 and 4 h after the dosing.

Inhibitory Effect on Collagen-Induced Platelet Aggregation of Human Platelets Nine volumes of human blood were mixed with one volume of an aqueous 3.8% (w/v) trisodium citrate solution, and the mixture was centrifuged to give PRP as the supernatant solution. The bottom layer was further centrifuged to give platelet-poor plasma (PPP) as the supernatant solution. Platelet counts were adjusted to about 4×10^5/mm^3 by dilution with PPP. PRP (200 ml) was preincubated with 25 ml of test compound solution at 37 °C for 2 min in the cell of an aggregometer (Hema tracer 1, model PAT-4A, M. C. Medical) and then 25 ml suspension of collagen (Hormon-Chemie) was added to activate the

platelets. The platelet aggregation was measured by the method of Born[12] and the percentage inhibition of platelet aggregation was calculated therefrom.

The inhibitory effect of the test compounds on collagen-induced platelet aggregation was estimated in term of IC_{50} (*i.e.*, the concentration of a test compound required to induce 50% inhibition of collagen-induced platelet aggregation). The results are summarized in Table 8.

X-Ray Structure Determination of (−)-13e·Maleate A colorless prismatic crystal of (−)-**13e**·maleate with dimensions of 0.5×0.5×0.3 mm was obtained by recrystallization from an aqueous solution. The intensity data were collected on a Rigaku AFC5R diffractometer using graphite monochromated CuK_α (λ=1.5418 Å) radiation by the ω-2θ scan technique. Unit cell dimensions were determined by a least-squares refinement using the setting angles of 25 reflections in the range of $35° < \theta < 45°$. Crystal data are: $C_{27}H_{32}N_2O_7S$, M_r=528.61, orthorhombic, space group $P2_12_12_1$, a=10.911(1) Å, b=23.851(3) Å, c=10.419(1) Å, V=2711.4(5) Å^3, Z=4, D_c=1.295 g·cm^{-3}, μ=1.459 mm^{-1}. The intensities of 2891 reflections, including Bijvoet pairs, with $3.7° < \theta < 60.1°$, $-6 \leqq h \leqq 12$, $-12 \leqq k \leqq 26$, $-6 \leqq l \leqq 11$ were measured. Three standard reflections were monitored every 200 reflections measured and showed insignificant fluctuations. The data were corrected for Lorentz and polarization effects, but not for absorption.

The structure was solved by a direct method using SHELXS-86[13] and structure refinement on F^2 was carried out using SHELXL-93[14] with anisotropic temperature factors for all non-hydrogen atoms. All hydrogen atoms were found in the difference Fourier map and were refined riding with the atoms to which they were bonded. The full-matrix least-squares refinement varied 343 parameters and used all 2601 independent reflections weighted by $w = 1/[\sigma^2(F_O^2) + (0.0571P)^2 + 0.5087P]$ where $P = (F_O^2 + 2F_C^2)/3$. Final $R1$=0.0355, $wR2$=0.0876 and Goodness of Fit=1.063 for all data; $R1$=0.0322 for 2490 reflections with $I > 2\sigma(I)$. Absolute structure parameter by Flack[15] converged to the value of −0.04. The final difference Fourier map showed maximum and minimum values of 0.184 eÅ^{-3} and −0.175 eÅ^{-3}.[16]

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References and Notes

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