Studies on the Synthesis of Condensed Pyridazine Derivatives. IV.[1] Synthesis and Anxiolytic Activity of 2-Aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones and Related Compound[2]

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A series of 2-aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones and related compounds were synthesized and evaluated for their ability to displace ^{3}H-diazepam from rat brain membranes *in vitro*, and to prevent bicuculline induced convulsions in mice *in vivo*.

Compounds with a 4′-methoxyphenyl (36) or 4′-chlorophenyl group (37, 39—42) as 2-aryl substituents showed prominent activities in both the *in vitro* and *in vivo* tests. Among them, 2-(4′-chlorophenyl)-5,6-dihydro- (37) and 2-(4′-chlorophenyl)-5,6-dihydro-10-fluoro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-one 7-oxides (41) showed activity twice as potent as diazepam in an anticonflict test (Vogel type, rats) while exhibiting less muscle relaxation (rotarod test, mice) and augmentation of γ-aminobutyric acid-induced chloride current (I_{Cl}) in isolated frog sensory neurones than diazepam. Compound 37 (Y-23684) was selected from this series as a candidate for further development. The structure–activity relationships are discussed.

Keywords benzodiazepine receptor; binding assay; antibicuculline test; anticonflict test; anxiolytic activity; sulfoxide; γ-aminobutyric acid; (1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-one; structure–activity relationship

Since the discovery of chlordiazepoxide and diazepam (DZ), the 1,4-benzodiazepines (BZs) have been the most widely used anxiolytics. In addition to their anxiolytic activity, the BZs possess undesirable effects, *e.g.*, muscle relaxation, sedation, and a hypnotic effect. Recently, research of anxiolytics has focused on discovering potent anxioselective agents[3] which do not exhibit the undesirable effects. Anxioselective activity may be achieved by partial agonists[4] at the BZ receptor (BZR) complex. Most of the ligands which are characterized as partial agonists to BZR are approximately planar shaped,[5] constructing a rigidly condensed ring system; β-carboline,[5c] pyrazolo[4,3-*c*]-quinoline,[6] imidazo[1,5-*a*][1,4]benzodiazepine,[7] triazolo-[4,3-*b*]pyridazine,[8] and imidazo[1,2-*a*]pyrimidine.[9]

We have previously reported that (4a*R**,6*R**)-2-(4-chlorophenyl)-4a,5-dihydro-2*H*-(1)benzothiopyrano[4,3-*c*]pyridazin-3(4*H*)-one 6-oxide (**1**), which has a six–six–six tricyclic condensed ring system, possesses an anxioselective property and behaves as a BZR partial agonist.[10] In the course of the research program on anxioselective compounds, we synthesized 2-aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones and related compounds, which have a six–seven–six tricyclic ring system designated as the general formula **2**. We describe here the detailed

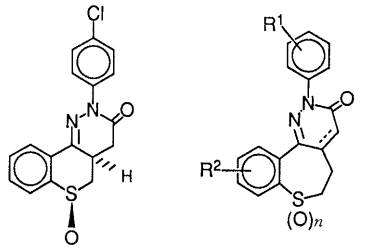

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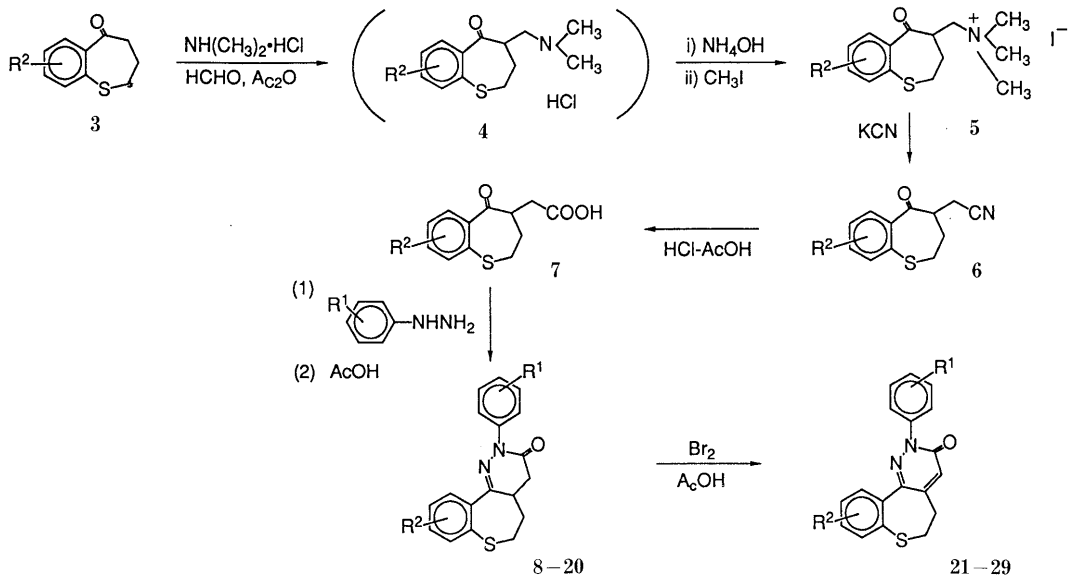
Chart 1



3 4 5 6 7 8–20 21–29

Chart 2

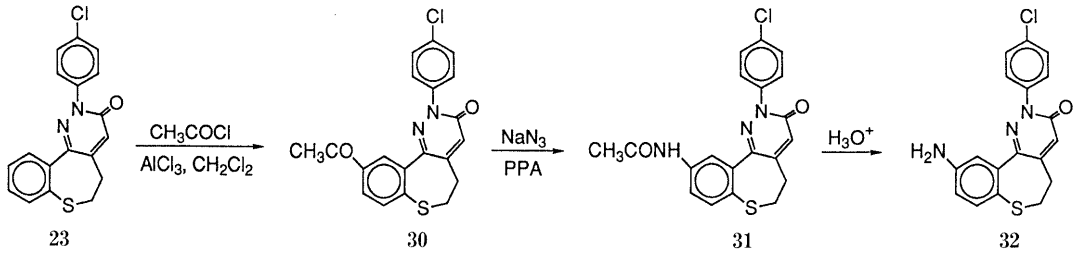


Chart 3

synthesis, biological activity, and structure–activity relationships of the (1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones (**2**).

Chemistry The 2-aryl-4,4a,5,6-tetrahydro- (**8**—**20**) and 2-aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones (**21**—**29**) were prepared by the synthetic route shown in Chart 2.

The key intermediates **7**, 5-oxo-2,3,4,5-tetrahydro-1-benzothiepin-4-acetic acids, were prepared according to the method in our previous paper.[1] The ketones **3** were converted to the Mannich products **4**. Reaction of **4** with iodomethane gave the quaternary salts **5**, which were converted to the γ-ketonitrile derivatives **6** in a reaction with an aqueous methanolic solution of potassium cyanide. The intermediates **7** were obtained by hydrolysis of **6** (Table IV).

The desired 2-aryl-4,4a,5,6-tetrahydro-(1)benzothiepino-[5,4-*c*]pyridazin-3(2*H*)-ones (**8**—**20**) were furnished by treatment of **7** with an ethanolic solution of phenylhydrazine derivatives followed by cyclization in acetic acid under reflux.

The 2-aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones (**21**—**29**) were prepared by oxidation of the corresponding 4,4a,5,6-tetrahydro compounds with bromine in acetic acid.

The 10-acetyl (**30**), 10-acetylamino (**31**), and 10-amino (**32**) compounds were prepared by the synthetic sequence shown in Chart 3. The Friedel–Crafts reaction of **23** with acetyl chloride in dichloromethane afforded **30**, which underwent the Schmidt rearrangement reaction with sodium azide in polyphosphoric acid (PPA) to give **31**. Compound **32** was obtained from **31** in good yield by hydrolysis with hydrochloric acid under reflux. The 10-hydroxy compound (**33**) was prepared by treating the 10-methoxy compound (**28**) with butylmercaptan and $AlCl_3$ in dichloromethane according to the method of Node *et al.*[11] as shown in Chart 4.

The sulfoxide (7-oxide) derivatives (**35**—**43**) were prepared by oxidation of the corresponding sulfides (**21**—**28**, **30**) with hydrogen peroxide in formic acid (Chart 5).

The 3-thioxo compound (**34**) was obtained by treatment of **23** with Lawesson's reagent in benzene (Chart 6). Physicochemical properties of compounds **2** are summarized in Tables I and II.

The structural assignment of compound **37** was also confirmed by X-ray analysis as shown in Fig. 1.

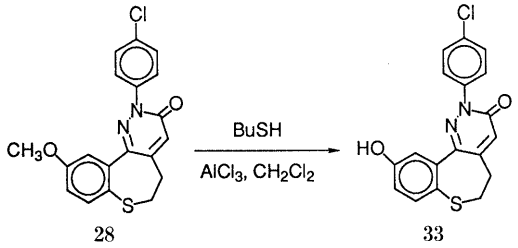


Chart 4

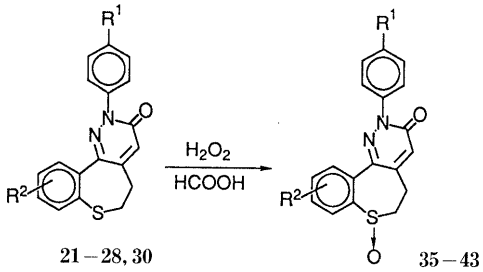


Chart 5

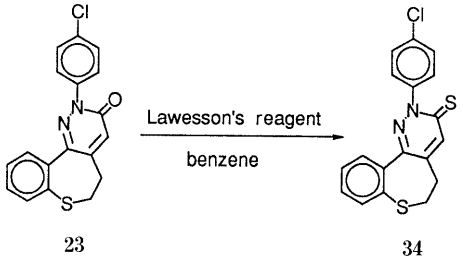


Chart 6

Results and Discussion

Pharmacology The (1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones were primarily examined for their ability to displace ^{3}H-diazepam from rat brain membranes *in vitro* and to prevent bicuculline-induced convulsions (anti-BCL)

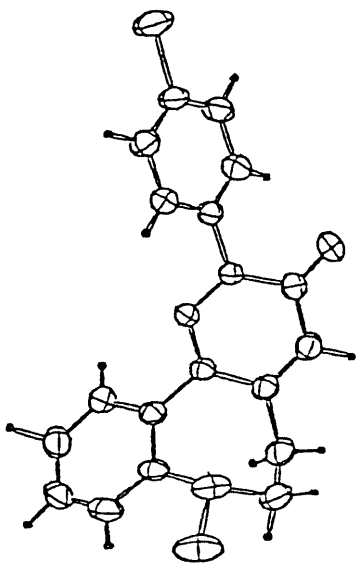
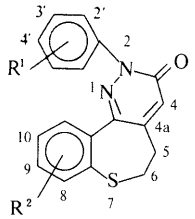


Fig. 1. X-Ray Crystal Structure of **37** by ORTEP Drawing

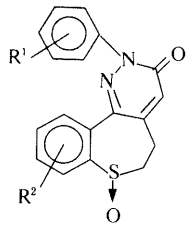
TABLE I. Physicochemical and Biological Data for 2-Aryl-4,4a,5,6-tetrahydro- and 2-Aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones



Compd. No.	R^1	R^2	4–4a[b] Bond	Yield (%)	mp (°C)[c] Recryst. solv.	Formula	Analysis (%) Calcd (Found) C	H	N	[^{3}H]Diazepam binding assay K_i (nM)	Antibicu.[d] ED_{50} mg/kg, *p.o.*
8	4′-OCH_3	H	1	53	143—145 EtOH	$C_{19}H_{18}N_2O_2S$	67.43 (67.48)	5.36 (5.38)	8.28 (8.24)	46	>100
9	H	H	1	67	138–140 EtOH	$C_{18}H_{16}N_2OS$	70.10 (70.27)	5.23 (5.25)	9.08 (9.06)	670	>100
10	4′-Cl	H	1	85	140—142 EtOH	$C_{18}H_{15}ClN_2OS$	63.06 (63.10)	4.41 (4.41)	8.17 (8.04)	70	36.2
11	3′-Cl	H	1	43	122—123 MeOH	$C_{18}H_{15}ClN_2OS$	63.06 (63.09)	4.41 (4.35)	8.17 (8.09)	>1000	N.T.
12	2′-Cl	H	1	18	148—150 EtOH	$C_{18}H_{15}ClN_2OS$	63.06 (62.85)	4.41 (4.40)	8.17 (8.11)	>1000	N.T.
13	4′-CH_3	H	1	53	143—145 EtOH	$C_{19}H_{18}N_2OS$	70.78 (71.07)	5.63 (5.63)	8.69 (8.52)	160	>100
14	4′-Br	H	1	50	135—137 MeOH	$C_{18}H_{15}BrN_2OS$	55.82 (56.06)	3.90 (3.80)	7.23 (7.24)	110	49.9
15	4′-F	H	1	47	146—147 EtOH	$C_{18}H_{15}FN_2OS$	66.24 (65.70)	4.63 (4.60)	8.58 (8.55)	610	>100
16	4′-Cl	10-Cl	1	66	141—143 MeOH	$C_{18}H_{14}Cl_2N_2OS$	57.30 (57.54)	3.74 (3.79)	7.43 (7.48)	200	>100
17	4′-Cl	10-CH_3	1	40	151—153 EtOH	$C_{19}H_{17}ClN_2OS$	63.95 (64.17)	4.80 (4.78)	7.85 (7.80)	180	>100
18	4′-Cl	10-OCH_3	1	64	137—138 EtOH–$CHCl_3$	$C_{19}H_{17}ClN_2O_2S$	61.20 (61.23)	4.60 (4.61)	7.51 (7.42)	38	38.4
19	4′-Cl	10-F	1	47	141—142 EtOH	$C_{18}H_{14}ClFN_2OS$	59.92 (59.93)	3.91 (4.02)	7.76 (7.73)	90	12.5
20	4′-OCH_3	10-Cl	1	34	159—161 EtOH	$C_{19}H_{17}ClN_2OS$	61.20 (61.18)	4.60 (4.52)	7.51 (7.43)	56	>100
21	4′-OCH_3	H	2	80	134—135 EtOH	$C_{19}H_{16}N_2O_2S$	67.84 (67.89)	4.79 (4.97)	8.33 (8.25)	3	4.8
22	4′-Br	H	2	44	208—209 MeOH	$C_{18}H_{13}BrN_2OS$	56.12 (56.27)	3.40 (3.58)	7.27 (7.20)	16	29.5
23	4′-Cl	H	2	88	185—186 EtOH	$C_{18}H_{13}ClN_2OS$	63.43 (63.48)	3.84 (3.79)	8.22 (8.18)	11	5.5
24	4′-Cl	10-Cl	2	80	215—217 EtOH–$CHCl_3$	$C_{18}H_{12}Cl_2N_2OS$	57.61 (57.72)	3.22 (3.21)	7.47 (7.53)	11	22.0
25	4′-Cl	9-Cl	2	88	191—193 EtOH–$CHCl_3$	$C_{18}H_{12}Cl_2N_2OS$	57.61 (57.52)	3.22 (3.47)	7.47 (7.40)	63	7.9
26	4′-Cl	8-Cl	2	50	166—168 EtOH	$C_{18}H_{12}Cl_2N_2OS$	57.61 (57.72)	3.22 (3.24)	7.47 (7.40)	29	29.4
27	4′-Cl	10-F	2	80	162—163 IPA	$C_{18}H_{12}ClFN_2OS$	60.25 (60.38)	3.37 (3.35)	7.81 (7.80)	14	2.2
28	4′-Cl	10-OCH_3	2	87	205—206 MeOH	$C_{19}H_{15}ClN_2O_2S$	61.55 (61.79)	4.08 (4.15)	7.55 (7.55)	2.3	8.1
29	4′-Cl	10-CH_3	2	67	182—184 EtOH	$C_{19}H_{15}ClN_2OS \cdot 1/2H_2O$	62.72 (62.54)	4.44 (4.05)	7.70 (7.58)	13	19.7
30	4′-Cl	10-Ac	2	47	178—179 EtOH–$CHCl_3$	$C_{20}H_{15}ClN_2O_2S \cdot 1/3H_2O$	61.77 (61.79)	4.06 (3.92)	7.20 (7.15)	22	11.4
31	4′-Cl	10-NHAc	2	71	258—260 EtOH–$CHCl_3$	$C_{20}H_{16}ClN_3O_2S$	60.37 (60.08)	4.05 (3.96)	10.56 (10.50)	750	>100
32	4′-Cl	10-NH_2	2	67	242—244 EtOH–$CHCl_3$	$C_{18}H_{14}ClN_3OS$	60.76 (60.63)	3.97 (3.86)	11.81 (11.81)	30	>100
33	4′-Cl	10-OH	2	65	233—235 MeOH	$C_{18}H_{13}ClN_2O_2S$	60.59 (60.31)	3.67 (3.69)	7.85 (7.64)	17	>100
34[e]	4′-Cl	H	2	64	258—259 $CHCl_3$–EtOH	$C_{18}H_{13}ClN_2S_2$	60.58 (60.64)	3.67 (3.63)	7.85 (7.42)	490	>100

a) Ac, acetyl; AcNH, acetylamino. *b*) 1, single bond; 2, double bond. *c*) IPA, isopropyl alcohol. *d*) Antibicu., antibicuculline. N.T., no test. *e*) 3-Thioxo compound.

TABLE II. Physicochemical and Biological Data for 2-Aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-one 7-Oxides



Compd. No.	R^1	$R^{2a)}$	Yield (%)	mp (°C) Recryst. solv.	Formula	Analysis (%) Calcd (Found) C	H	N	[^{3}H]Diazepam binding assay K_i (nM)	Antibicu.[b] ED_{50} mg/kg, *p.o.*
35	4′-Br	H	73	227 MeOH–$CHCl_3$	$C_{18}H_{13}BrN_2O_2S$	53.88 (53.81)	3.27 3.31	6.98 7.00)	34	5.9
36	4′-OCH_3	H	86	200—201 MeOH	$C_{19}H_{16}N_2O_3S$	64.76 (64.77)	4.58 4.75	7.95 7.82)	18	0.7
37	4′-Cl	H	74	233—234 EtOH	$C_{18}H_{13}ClN_2O_2S$	60.59 (60.79)	3.67 3.64	7.85 7.86)	41	1.2
38	4′-Cl	10-Cl	40	239—241 MeOH	$C_{18}H_{12}Cl_2N_2O_2S$	55.26 (55.47)	3.10 3.30	7.16 7.02)	11	3.2
39	4′-Cl	9-Cl	78	208—209 EtOH	$C_{18}H_{12}Cl_2N_2O_2S$	55.26 (55.17)	3.10 3.35	7.16 7.06)	97	0.8
40	4′-Cl	8-Cl	78	217—219 MeOH	$C_{18}H_{12}Cl_2N_2O_2S$	55.26 (55.01)	3.10 3.08	7.16 7.09)	11	0.7
41	4′-Cl	10-F	77	233—235 MeOH	$C_{18}H_{12}ClFN_2O_2S$	57.68 (57.69)	3.23 3.26	7.47 7.44)	36	0.7
42	4′-Cl	10-OCH_3	48	209—210 MeOH	$C_{19}H_{15}ClN_2O_3S$	59.00 (58.80)	3.91 4.14	7.24 7.12)	3.9	1.0
43	4′-Cl	10-Ac	53	231—232 EtOH–$CHCl_3$	$C_{20}H_{15}ClN_2O_3S \cdot 1/3H_2O$	59.33 (59.31)	3.90 3.73	6.92 6.83)	40	7.9
Diazepam									5.8	0.4

a) Ac, acetyl. *b*) Antibicu., antibicuculline.

TABLE III. Comparative Biological Data for Representative Compounds

Compd. No.	[^{3}H]Diazepam binding K_i (nM)	Antibicuculline ED_{50} mg/kg, *p.o.*	Anticonflict (Water-lick test) MED mg/kg, *p.o.*	Rota rod ED_{50} mg/kg, *p.o.*	Ratio (Rotarod/anticonflict)	Relative I_{cl}
36	18	0.7	25	157	6	1.54
37	41	1.2	5	158	32	1.64
39	97	0.8	5	35	7	1.61
40	11	0.7	25	>250	>10	1.75
41	36	0.7	5	107	21	1.75
42	3.9	1.0	10	N.T.[a]		1.91
Diazepam	5.8	0.4	10	1.6	0.2	2.40

a) N.T., no test.

in mice *in vivo* (Tables I and II).

Compounds that exhibited activity in both of the primary screens were further studied by the following assays: anticonflict test (water-lick test),[12] rotarod test,[13] and electrophysiological test on the γ-aminobutyric acid (GABA)-induced chloride current (concentration-clamp technique).[14] The results are summarized in Table III.

The tests described above were selected in order to evaluate anxioselectivity. The anticonvulsant properties of the compounds were evaluated by using the $GABA_A$ receptor antagonist bicuculline. The anticonflict test was adapted from Vogel *et al.*,[12] and is considered to be a reliable method for identifying potential anxiolytic activity. The concentration-clamp technique appears to be useful for evaluating the efficacy of the compounds on the responses mediated by the GABA receptor complex.[14b] The details of these tests are given in the experimental section.

Structure–Activity Relationships The K_i (nM) values and anti-BCL activity (ED_{50} values) were used as preliminary selection criteria and a probe for further synthesis. Among the 2-aryl-4,4a,5,6-tetrahydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones (**8**—**15**), compounds which had such substituents for R^1 as a 4′-chloro, 4′-bromo, 4′-methoxy, or 4′-methyl group on the phenyl ring at the 2-position revealed an appreciable affinity for BZR. The unsubstituted compound (**9**) and 4′-fluoro compound (**15**) had a reduced affinity for BZR. In contrast, the 3′-chloro compound (**11**) and 2′-chloro compound (**12**) did not exhibit BZR affinity ($K_i > 10^3$ nM). The 4′-methoxy compound (**8**) showed the highest affinity to BZR among **8**—**15**.

In the *in vivo* test, 4′-chloro (**10**) and 4′-bromo (**14**) compounds showed anti-BCL activities. However, com-

pounds with other substituents for R^1 were inactive in the anti-BCL test, showing no apparent correlation to the affinity to BZR.

Compounds (**16**—**20**) were examined regarding how the substituent R^2 on the benzothiepine ring affected pharmacological activity. The 10-methoxy compound (**18**) seemed to have the best K_i value among them, though a remarkable improvement over the activity of the unsubstituted counterpart (**10**) was not observed. In the anti-BCL test, the 10-fluoro compound (**19**) showed more enhanced activity than compound **10**.

On the basis of the above mentioned structure–activity studies on the 4–4a single bond (s-type) series (**8**—**20**), the 2-aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones (**21**—**33**) having a 4–4a double bond (d-type) were then tested to determine whether the modification of the same series of compounds could improve the affinity to BZR and anti-BCL activity. The d-type compounds (**21**—**24**, **27**—**29**) exhibited a higher affinity to BZR than the corresponding s-type compounds. Among the chloro-substituted compounds at the 8, 9 or 10-position as R^2, the 10-chloro compound (**24**) showed the highest affinity for BZR. The 10-acetyl (**30**), 10-amino (**32**), and 10-hydroxy (**33**) compounds also revealed a high affinity for BZR, whereas the 10-acetylamino compound (**31**) showed low affinity. Among these d-type compounds, the K_i values of compound **21** with a 4′-methoxy group as R^1, and **28** with a 10-methoxy group as R^2, were superior to that of DZ.

Moreover, the d-type compounds revealed a marked improvement in *in vivo* anti-BCL activity. Compounds with a 4′-chloro group as R^1 (**23**—**30**) exhibited remarkable anti-BCL activity. Among them, the unsubstituted compound (**23**), or compounds with a 9-chloro (**25**), 10-fluoro (**27**) or 10-methoxy (**28**) group as R^2 had an oral ED_{50} of less than 10 mg/kg in the anti-BCL test. The 10-amino (**32**) and 10-hydroxy (**33**) compounds, however, did not show *in vivo* activity despite a high affinity for BZR. These results might be attributed to the low penetration of both compounds (**32**, **33**) through the gastrointestinal membrane and/or the blood-brain barrier. The 4′-bromo compound (**22**) as R^1 exhibited moderate activity in the anti-BCL test compared with the 4′-chloro compounds. The 4′-methoxy compound (**21**) showed prominent anti-BCL activity with an oral ED_{50} of 4.8 mg/kg. The thioxo compound (**34**) at the 3-position showed reduced affinity to BZR and exhibited no activity *in vivo*. These results suggest that the carbonyl oxygen at the 3-position in the (1)benzothiepino-[5,4-*c*]pyridazine skeleton is an essential moiety to interact with the BZR complex, for instance, a hydrogen bond acceptor.[5c]

On the basis of our previous data,[10] compounds with a sulfoxide group at 7-position (**35**—**43**) were synthesized in order to improve the *in vivo* activity of the d-type compounds having potent anti-BCL activity. All sulfoxides synthesized showed 3 to 30 times stronger activity in the anti-BCL test and tended to have less BZR affinity than the corresponding d-type compounds. Compounds with a 4′-chloro group as R^1 in combination with no substituent (**37**) or a 9-chloro (**39**), 8-chloro (**40**), 10-fluoro (**41**), or 10-methoxy (**42**) substituent as R^2 showed prominent anti-BCL activity with an oral ED_{50} of 0.7 to 1.2 mg/kg. The 4′-methoxy compound (**36**) as R^1 also revealed remarkable anti-BCL activity (ED_{50} = 0.7 mg/kg). Also, the solubility of the sulfoxide **37** in water at 25 °C was 1×10^{-3} w/v%, being 10 times higher than that of the corresponding sulfide **23** (1×10^{-4} w/v%). Therefore, it is suggested that the enhanced *in vivo* activity of these sulfoxides reflects their improved oral bioavailability.

Table III gives comparative biological data for the compounds (**36**, **37**, **39**—**42**) chosen for further studies in comparison with those for DZ. Compound **37**, **39** and **41** among those selected showed a remarkable improvement in the ratio of minimum effective dose (MED) values in a model of antianxiety (anticonflict test) to ED_{50} values of muscle relaxant effects (rotarod test) when compared to DZ, as shown in Table III. This data suggests that the above listed compounds have more potent anxiolytic effects and weaker muscle relaxant properties.

Recent electrophysiological studies[14] by use of a concentration-clamp technique in isolated frog sensory neurones showed that (1) all full agonists to BZR increased the peak amplitude of chloride current (I_{cl}) elicited by GABA, and (2) partial agonists showed a dose-dependent augmentation of the GABA response, although at about half the amplitude of full agonists. In the present study, the relative I_{cl} value for DZ was 2.40, but the representative compounds showed reduced efficacy with relative I_{cl} values of 1.54 to 1.91. This data suggests that these compounds have partially agonistic properties.

Compounds **37** and **41** were judged to have especially anxioselective properties because these compounds had higher efficacy in the anticonflict test, more reduced activities in the muscle relaxation test, and a lower I_{cl} value than DZ.

Based on the favorable characteristics described above, as well as on detailed biological[15] and toxicological[16] evaluations, 2-(4′-chlorophenyl)-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-one 7-oxide (**37**, Y-23684) was selected as a candidate for further development. Y-23684 is currently undergoing additional studies to further evaluate its potential as an anxioselective anxiolytic agent, namely as a BZR partial agonist.

Experimental

Melting points were determined on a Buchi 530 melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a JASCO IR-810 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL-FX100 spectrometer unless otherwise noted and chemical shifts were given in ppm with tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a JEOL JMS-01SG-2 spectrometer.

2,3,4,5-Tetrahydro-1-benzothiepin-5-ones (3) 7-Chloro (**3c**),[17] 7-methyl (**3d**),[18] 7-methoxy (**3e**),[19] 7-fluoro (**3f**)[17] and unsubstituted (**3g**)[20] compounds were prepared according to the published methods. 9-Chloro (**3a**) and 8-chloro (**3b**) compounds were synthesized by treating 2-chlorothiophenol and 3-chlorothiophenol, respectively, with γ-butyrolactone in ethanolic sodium ethoxide, followed by cyclization with PPA according to the method of Traynelis and Love.[20]

9-Chloro-2,3,4,5-tetrahydro-1-benzothiepin-5-one (**3a**): Colorless prisms (from hexane), mp 71—72 °C. *Anal.* Calcd for $C_{10}H_9ClOS$: C, 56.47; H, 4.26. Found: C, 56.62; H, 4.35. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). MS *m/z*: 212 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.20—2.47 (2H, m), 2.96—3.10 (4H, m), 7.15 (1H, t, *J*=8 Hz, ArH), 7.45 (1H, dd, *J*=2, 8 Hz, ArH), 7.71 (1H, dd, *J*=2, 8 Hz, ArH).

8-Chloro-2,3,4,5-tetrahydro-1-benzothiepin-5-one (**3b**): Oil. *Anal.* Calcd for $C_{10}H_9ClOS$: C, 56.47; H, 4.26. Found: C, 56.75; H, 4.15. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1680 (C=O). MS *m/z*: 212 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.13—2.42 (2H, m), 2.93—3.12 (4H, m), 7.21 (1H, dd, *J*=2, 8 Hz, ArH), 7.47 (1H, d, *J*=2 Hz, ArH), 7.78 (1H, d, *J*=8 Hz, ArH).

5-Oxo-2,3,4,5-tetrahydro-1-benzothiepin-4-acetic Acids (7) A typical example is given to represent the general procedure.

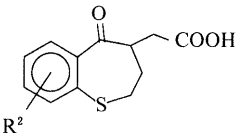
9-Chloro-2,3,4,5-tetrahydro-4-trimethylammoniomethyl-1-benzothiepin-5-one Iodide (**5a**): A solution of 11.3 g (0.139 mol) of dimethylamine hydrochloride in 11.3 g (0.139 mol) of 37% HCHO was stirred at room temperature for 0.5 h. Acetic anhydride (50 ml) was added dropwise at 70—90 °C and the mixture was then kept at 70—75 °C for 1 h. To the solution was added **3a** (20 g, 0.094 mol), and the mixture was stirred at 70—75 °C for 3 h. After removal of the solvent under reduced pressure, acetone (50 ml) and isopropylether (50 ml) were added to the residue and the mixture was allowed to stand at room temperature for 3 h. The crystals formed were collected by filtration, dissolved in chilled water, neutralized with 28% NH_4OH (12 ml), and extracted by $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated below 40 °C. The residue was dissolved in acetone (150 ml), and iodomethane (17 g, 0.12 ml) was added to the resulting solution below 5 °C in an ice bath. After the mixture was allowed to stand at room temperature for 3 h, the crystals formed were collected by filtration and washed with acetone to give **5a** (31 g, 81%). Recrystallization from EtOH gave colorless needles, mp 213—214 °C (dec.). *Anal.* Calcd for $C_{14}H_{19}ClIOS$: C, 40.84; H, 4.65; N, 3.40. Found: C, 40.93; H, 4.71; N, 3.39. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.80—2.73 (3H, m), 2.96 (9H, s, $N(CH_3)_3$), 3.36—3.51 (2H, m), 3.81—4.24 (2H, m), 7.30 (1H, t, J=8 Hz, ArH), 7.56 (1H, dd, J=2, 8 Hz, ArH), 7.67 (1H, dd, J=2, 8 Hz, ArH).

9-Chloro-5-oxo-2,3,4,5-tetrahydro-1-benzothiepin-4-acetonitrile (**6a**): To a solution of **5a** (20.6 g, 0.05 mol) in methanol (300 ml) was added a solution of KCN (3.9 g, 0.06 mol) in water (50 ml) dropwise at room temperature. The solution was stirred at room temperature for 1 h and poured into ice-water. The resulting mixture was extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. After the addition of isoproryl alcohol (IPA) to the residue, the crystals formed were collected by filtration and recrystallized from EtOH to afford **6a** (10.5 g, 83%) as colorless needles, mp 115—116 °C. *Anal.* Calcd for $C_{12}H_{10}ClNOS$: C, 57.27; H, 4.01; N, 5.56. Found: C, 57.27; H, 4.06; N, 5.55. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 2240 (CN). MS m/z: 251 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.96—2.24 (1H, m), 2.33—2.95 (4H, m), 3.11—3.44 (1H, m), 3.70—4.02 (1H, m), 7.18 (1H, t, J=8 Hz, ArH), 7.49 (1H, dd, J=2, 8 Hz, ArH), 7.75 (1H, dd, J=2, 8 Hz, ArH).

9-Chloro-5-oxo-2,3,4,5-tetrahydro-1-benzothiepin-4-acetic Acid (**7a**): To a solution of conc. HCl (10 ml) and acetic acid (10 ml) was added **6a** (5 g, 0.02 mol). The solution was refluxed for 3 h, and poured into ice-water. The precipitate was collected by filtration, washed with water, and recrystallized from IPA to give **7a** (4.3 g, 80%) as colorless needles, mp 195—197 °C. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 1700 (COOH). MS m/z: 270 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.87—3.32 (6H, m), 3.73—4.06 (1H, m), 7.17 (1H, t, J=8 Hz, ArH), 7.45 (1H, dd, J=2, 8 Hz, ArH), 7.63 (1H, dd, J=2, 8 Hz, ArH).

Other compounds (**7b—g**) in Table IV were similarly prepared from the corresponding **3b—g**.

TABLE IV. Physicochemical Data for 5-Oxo-2,3,4,5-tetrahydro-1-benzothiepin-4-acetic Acids



Compd. No.	R^2	Yield[a] (%)	mp (°C) Recryst. solv.[b]	Formula	Analysis (%) Calcd (Found) C	H
7a	9-Cl	57	195—197 IPA	$C_{12}H_{11}ClO_3S$	53.23 (53.02)	4.10 3.89)
7b	8-Cl	54	144—147 IPA	$C_{12}H_{11}ClO_3S$	53.23 (53.48)	4.10 4.20)
7c	7-Cl	53	205—207 EtOH	$C_{12}H_{11}ClO_3S$	53.23 (53.26)	4.10 4.20)
7d	7-CH_3	46	203—205 IPA	$C_{13}H_{14}O_3S$	62.38 (62.57)	5.64 5.75)
7e	7-OCH_3	42	204—206 IPA	$C_{13}H_{14}O_4S$	58.63 (58.78)	5.30 5.37)
7f[c]	7-F	69	193—195 IPA			
7g[c]	H	67	171—173 EtOH			

a) Yield from **3**. *b*) IPA, isopropyl alcohol. *c*) Lit. (reference 1).

2-Aryl-4,4a,5,6-tetrahydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones (8—20) A typical example is given to represent the general procedure.

Method A: 2-(4′-Methoxyphenyl)-4,4a,5,6-tetrahydro-(1)benzothiepino-[5,4-*c*]pyridazin-3(2*H*)-one (**8**): A mixture of **7g** (4 g, 0.017 mol), 4-methoxyphenylhydrazine hydrochloride (2.2 g, 0.02 mol), and sodium acetate (1.8 g, 0.022 mol) in EtOH (100 ml) was refluxed overnight. After evaporation of the solvent, the residue was dissolved in acetic acid (50 ml). The mixture was refluxed for 2 h, poured into ice-water, and extracted with AcOEt. The extract was washed successively with aq. saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column using $CHCl_3$ as an eluent to give **8** (3.0 g, 53%), which was recrystallized from EtOH to give colorless needles, mp 143—145 °C. IR ν_{max}^{KBr} cm^{-1}: 1680 (CON). MS m/z: 338 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.00—3.09 (6H, m), 3.57—3.84 (1H, m), 3.82 (3H, s, OCH_3), 6.93 (2H, d, J=9 Hz, ArH), 7.17—7.39 (3H, m, ArH), 7.72—7.81 (1H, m, ArH).

Other compounds (**9—20**) in Table I were prepared in a similar manner.

2-Aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-ones (21—29) Typical examples are given to represent the general procedure.

Method B: 2-(4′-Chlorophenyl)-5,6-dihydro-(1)benzothiepino[5,4-*c*]-pyridazin-3(2*H*)-one (**23**): To a solution of **10** (16.4 g, 0.048 mol) in acetic acid (500 ml), bromine (9.2 g, 0.057 mol) was added dropwise at 40—50 °C. The reaction mixture was stirred at 40—45 °C for 1 h and poured into ice-water. The precipitate was collected by filtration, washed with water, and recrystallized from EtOH to give **23** (14.4 g, 88%) as colorless needles. mp 185—186 °C. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). MS m/z: 340 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.73 (2H, t, J=7 Hz, $SCH_2\underline{CH_2}$), 3.26 (2H, t, J=7 Hz, $S\underline{CH_2}CH_2$), 6.89 (1H, s, C=C$\underline{H}$CO), 7.43 (2H, d, J=9 Hz, ArH), 7.38—7.64 (4H, m, ArH), 7.70 (2H, d, J=9 Hz, ArH).

Other compounds (**21**, **22**, **24**, **27—29**) in Table I were prepared in a similar manner.

Method C: 9-Chloro-2-(4′-chlorophenyl)-5,6-dihydro-(1)benzothiepino-[5,4-*c*]pyridazin-3(2*H*)-one (**25**): A mixture of **7b** (7 g, 0.026 mol), 4-chlorophenylhydrazine hydrochloride (6.1 g, 0.034 mol), and sodium acetate (2.9 g, 0.034 mol) in EtOH (100 ml) was refluxed overnight. Work-up in a manner similar to that described in method A gave the crude intermediate 9-chloro-2-(4′-chlorophenyl)-4,4a,5,6-tetrahydro-(1)-benzothiepino[5,4-*c*]pyridazin-3(2*H*)-one (**7g**) as a pale yellow oil. To a solution of this crude intermediate in acetic acid (100 ml), bromine (3.3 g, 0.021 mol) was added dropwise at 40—45 °C. Work-up as in method B gave **25** (6.1 g, 63%) as a colorless powder (from EtOH–$CHCl_3$), mp 191—193 °C. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). MS m/z: 375 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.73 (2H, t, J=7 Hz, $SCH_2\underline{CH_2}$), 3.27 (2H, J=7 Hz, $S\underline{CH_2}CH_2$), 6.70 (1H, s, C=C$\underline{H}$CO), 7.42 (2H, d, J=9 Hz, ArH), 7.42—7.68 (3H, m, ArH), 7.67 (2H, d, J=9 Hz, ArH).

Another compound (**26**) in Table I was prepared in a similar manner.

10-Acetyl-2-(4′-chlorophenyl)-5,6-dihydro-(1)benzothiepino[5,4-*c*]-pyridazin-3(2*H*)-one (30) To an ice-cooled solution of $AlCl_3$ (26 g, 0.19 mol) in CH_2Cl_2 (200 ml) was added acetylchloride (10 g, 0.13 mol) and the mixture was stirred at 0—10 °C for 0.5 h. After addition of **23** (20 g, 0.059 mol), the mixture was refluxed for 7 h and then poured onto crushed ice. The resulting mixture was extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column using $CHCl_3$ as an eluent to give **30** (10.5 g, 47%), which was recrystallized from MeOH to afford a colorless powder, mp 178—179 °C. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O), 1685 (C=O). MS m/z: 382 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s, $COCH_3$), 2.75 (2H, t, J=7 Hz, $SCH_2\underline{CH_2}$), 3.31 (2H, t, J=7 Hz, $S\underline{CH_2}CH_2$), 6.92 (1H, s, C=CHCO), 7.43 (2H, d, J=9 Hz, ArH), 7.68 (2H, d, J=9 Hz, ArH), 7.71 (1H, d, J=8 Hz, ArH), 7.97 (1H, dd, J=2, 8 Hz, ArH), 8.12 (1H, d, J=2 Hz, ArH).

10-Acetylamino-2-(4′-chlorophenyl)-5,6-dihydro-(1)benzothiepino[5,4-*c*]-pyridazin-3(2*H*)-one (31) To a suspension of **30** (5.4 g, 0.014 mol) in PPA (55 g) was added NaN_3 (1.4 g, 0.021 mol) by portions, and the mixture was stirred at room temperature for 2 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed successively with aq. saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from EtOH–$CHCl_3$ to give **31** (4.0 g, 71%) as a colorless powder, mp 258—260 °C. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O), 3300 (CONH). MS m/z: 397 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s,

$COCH_3$), 2.70 (2H, t, $J=7$ Hz, SCH_2CH_2), 3.20 (2H, t, $J=7$ Hz, SCH_2CH_2), 6.87 (1H, s, C=CHCO), 7.38 (2H, d, $J=9$ Hz, ArH), 7.64 (2H, d, $J=9$ Hz, ArH), 7.54—7.75 (2H, m, ArH), 7.93 (1H, s, ArH), 7.25—7.75 (1H, br, CONH).

10-Amino-2-(4′-chlorophenyl)-5,6-dihydro-(1)benzothiepino[5,4-*c*]-pyridazin-3(2*H*)-one (32) A mixture of **31** (8.9 g, 0.022 mol) and conc. HCl (90 ml) in EtOH (150 ml) was refluxed for 1 h. The resulting solution was poured into ice-water, neutralized with K_2CO_3, and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from EtOH–$CHCl_3$ to give **32** (5.2 g, 67%) as a colorless powder, mp 242—244 °C. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O), 3330 (NH_2), 3460 (NH_2). MS *m/z*: 355 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.70 (2H, t, $J=7$ Hz, SCH_2CH_2), 3.15 (2H, t, $J=7$ Hz, SCH_2CH_2), 4.04 (2H, br s, NH_2), 6.71 (1H, dd, $J=3$, 8 Hz, ArH), 6.87 (1H, s, C=CHCO), 6.91 (1H, d, $J=3$ Hz, ArH), 7.38 (1H, d, $J=8$ Hz, ArH), 7.42 (2H, d, $J=9$ Hz, ArH), 7.69 (2H, d, $J=9$ Hz, ArH).

2-(4′-Chlorophenyl)-5,6-dihydro-10-hydroxy-(1)benzothiepino[5,4-*c*]-pyridazin-3(2*H*)-one (33) To a suspension of $AlCl_3$ (5 g, 0.038 mol) in CH_2Cl_2 (30 ml), butyl mercaptan (5 ml) was added at 0—5 °C and stirred for on additional 0.5 h. After the addition of **28** (5 g, 0.013 mol), the mixture was stirred at room temperature for 0.5 h and then poured into ice-water. The precipitate was collected by filtration, washed with water, and recrystallized from MeOH to give **33** (3.1 g, 65%) as colorless needles, mp 233—235 °C. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O), 3200 (OH). MS *m/z*: 356 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.71 (2H, t, $J=7$ Hz, SCH_2CH_2), 3.19 (2H, t, $J=7$ Hz, SCH_2CH_2), 3.65 (1H, br s, OH), 6.88 (1H, dd, $J=3$, 8 Hz, ArH), 6.89 (1H, s, C=CHCO), 7.08 (1H, d, $J=3$ Hz, ArH), 7.42 (2H, d, $J=9$ Hz, ArH), 7.49 (1H, d, $J=8$ Hz, ArH), 7.68 (2H, d, $J=9$ Hz, ArH).

2-Aryl-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-one 7-Oxides (35—43) A typical example is given to represent the general procedure.

2-(4′-Chlorophenyl)-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-one 7-Oxide (**37**): To a stirred solution of **23** (6.5 g, 0.019 mol) in formic acid (65 ml) was added dropwise 30% H_2O_2 (2.2 g, 0.019 mol) below 5 °C. The mixture was stirred at 5—10 °C for 1 h and poured into ice-water. The precipitate was collected by filtration and washed with water. Recrystallization from EtOH gave **37** (5.0 g, 74%) as colorless needles, mp 233—234 °C. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). MS *m/z*: 356 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.70—3.25 (3H, m), 3.83—4.11 (1H, m), 6.97 (1H, s, C=CHCO), 7.44 (2H, d, $J=9$ Hz, ArH), 7.60—7.82 (5H, m, ArH), 7.90—7.97 (1H, m, ArH).

Other compounds (**35**, **36**, **38**—**43**) in Table II were prepared in a similar manner.

2-(4′-Chlorophenyl)-5,6-dihydro-(1)benzothiepino[5,4-*c*]pyridazin-3(2*H*)-thione (34) A mixture of **23** (9 g, 0.026 mol) and the Lawesson's reagent (5.7 g, 0.014 mol) in benzene (100 ml) was refluxed for 7 h. After the mixture was allowed to stand at room temperature for 3 h, the precipitated solid was collected by filtration and recrystallized from EtOH–$CHCl_3$ to give **34** (6.0 g, 64%) as a yellow powder, mp 258—259 °C. MS *m/z*: 356 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.71 (2H, t, $J=7$ Hz, SCH_2CH_2), 3.28 (2H, t, $J=7$ Hz, SCH_2CH_2), 7.36—7.68 (8H, m, ArH), 7.76 (1H, s, C=CHCS).

Benzodiazepine Receptor Binding Assay Preparation of a synaptosome fraction and ^{3}H-diazepam (^{3}H-DZ) binding studies were carried out according to the method of Mohler and Okada.[21] Crude synaptosomal membranes were suspended in a 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl and 5 mM KCl. The reaction was started by the addition of a 900 μl aliquot of crude synaptosomal membranes to 100 μl solution containing ^{3}H-DZ (final concentration was 2 nM) and a known concentration of test compounds. After the mixture was incubated for 20 min at 0 °C, the binding was stopped by adding 3 ml of ice-cold 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl and 5 mM KCl. The samples were then filtered under vacuum through Whatman GF/B filters and immediately washed 4 times with 3 ml of ice-cold buffer. The radioactivity on the filters was measured by a liquid scintillation counter. Binding in the presence of 1 μM unlabelled DZ was defined as nonspecific binding. Specific binding was defined as the difference between the total binding and the nonspecific binding. The experiments were carried out in triplicate. The K_i values were determined by the relationship $K_i = IC_{50}/(1+c/K_d)$, where IC_{50} was the concentration of the test compounds which caused a 50% reduction of the specific binding *vs.* the control, c was the concentration of ^{3}H-DZ (2 nM), and K_d was the dissociation constant determined by Scatchard's plot.

Anticonvulsant Test (Antibicuculline Test) The experiment was practiced by a modification of the method of Lippa and Regan.[22] Groups of 7—14 ddY male mice were challenged with bicuculline (0.6 mg/kg i.v.) 1 h after theoral administration of the test compounds. The ED_{50} values were calculated by the probit method as the dose which prevented tonic extension in half of the animals.

Anticonflict Test (Water-Lick Test) The experiment was carried out by a modification of the method of Vogel *et al.*[13] Groups of 10—14 Wister rats were deprived of water for 72 h before the tests began. The rats were placed in a plexiglass conflict test box (light compartment: 38 × 38 × 20 cm, dark compartment: 10 × 10 × 20 cm). A water bottle with a stainless steel spout was fitted to the middle of the outside so that the spout extended 3 cm into the box at 10 cm above the grid floor. A drinkometer circuit (Ohara Inc., Nihon Koden) was connected to the spout and the number of licks was counted. The rats were placed in the apparatus where an electric shock (0.2—0.3 mA, 0.3 s) was given once every 20th lick. After the rats were received the first electric shock, the number of shocks were recorded during the subsequent 3-min test period. The test compounds were administered orally 1 h before the test. The MED was defined as the lowest dose to produce a statistically significant difference in the punished responses from 0.5% methylcellusolve-treated (One-way Anova test; $p<0.05$).

Rotarod Test The experiment was carried out according to the method described by Dunham and Miya.[13] Groups of 10 ddY male mice were used. The mice were gently placed on the rod (2.8 cm in diameter rotating at 11 rpm.) 1 h after oral administration of the test compounds. The ED_{50} value was calculated by the probit method as the dose which caused half of the animals to drop from the rotarod within 1 min.

GABA-Induced Response in Isolated Sensory Neurones of Frogs Sensory neurons of frogs were isolated, and electrophysical experiments were carried out according to the method of Akaike *et al.*[14] Neurones were voltage-clamped at a holding membrane potential of −50 mV with a single-electrode voltage-clamp system. Test compounds were applied by using a concentration-clamp technique. When the peak Cl^- current (I_{Cl}) elicited by 3×10^{-6} M GABA alone was presented as 1, the augmentative I_{Cl} of the test compounds in the presence of 3×10^{-6} M GABA was measured. The results were presented as relative I_{Cl} values.

X-Ray Crystallographic Analysis A crystal of **37** for X-ray crystallographic analysis was obtained from a methanol solution as colorless prisms. The crystal data is as follows: $C_{18}H_{13}ClN_2O_2S$, monoclinic, $P2_1/c$, $a=14.677$ (2), $b=6.946$ (1), $c=16.157$ (2) Å, $\beta=104.56$ (1), $V=1594.2$ (4) Å^3, $Z=4$, D(Calcd) = 1.49, μ(Cu$K\alpha$) = 34.60, F(000) = 736. Intensities were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Cu$K\alpha$ radiation ($\lambda=1.5418$ Å). 2328 unique reflections with $I>2.3\ \sigma(I)$ were used for the refinement. The structure was solved by the direct method. Atomic parameters were refined by a block-diagonal method and the final R value was 0.044.

Supplementary Material Available Tables of final atomic positional parameters, atomic thermal parameters, and bond distances and angles of compound **37** are available. Ordering information is given on the current masthead page.

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