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Synthesis, SAR studies, and evaluation of 1,4-benzoxazepine derivatives as selective 5-HT_{1A} receptor agonists with neuroprotective effect: Discovery of Piclozotan

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Abstract—A new series of 1,4-benzoxazepine derivatives was designed, synthesized, and evaluated for binding to 5-HT_{1A} receptor and cerebral anti-ischemic effect. A lot of compounds exhibited nanomolar affinity for 5-HT_{1A} receptor with good selectivity over both dopamine D_2 and α_1-adrenergic receptors. Among these compounds, 3-chloro-4-[4-[4-(2-pyridinyl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-1, 4-benzoxazepin-5(4*H*)-one (**50**: SUN N4057 (Piclozotan) as 2HCl salt) showed remarkable neuroprotective activity in a transient middle cerebral artery occlusion (t-MCAO) model.

1. Introduction

Serotonin (5-HT) and its receptors are known to play important roles in various physiological and pathophysiological processes.[1,2] Of these receptors, the 5-HT_{1A} receptor subtype is generally accepted to be involved in psychiatric disorders such as depression,[3] anxiety,[4] and psychosis.[5] In the past decade, cerebral serotonergic neuron has been suggested to be involved in cerebral ischemic conditions. It has been reported that 5-HT_{1A} receptor agonists have protective effects in cerebral ischemic conditions,[6–11] due to hyperpolarization of cell membrane[12] and glutamate release inhibition.[13] At the present day, acute ischemic stroke is one of the major causes of death in advanced nations. Though many pharmacological treatments by means of so-called neuroprotective drugs have been tried, they have not been successful to improve clinical outcome in patients.[14] Our goal is to develop a 5-HT_{1A} receptor agonist for a therapeutic agent against ischemic stroke. We have already reported novel 5-HT_{1A} receptor agonists possessing 1,4-benzoxazepine scaffold.[15,16] In this issue, we have provided a full account of design, synthesis, SAR, and biological evaluation of 1,4-benzoxazepine derivatives in detail.

2. Chemistry

2.1. Design

Buspirone, tandospirone, and ipsapirone are well recognized as 5-HT_{1A} receptor agonists (Fig. 1), and the former two compounds have been useful in treatment of anxiety and depression.[17,18] However, three compounds show a poor selectivity for 5-HT_{1A} receptor; that is to say buspirone and tandospirone exhibit affinity for dopamine D_2 receptor and ipsapirone does show affinity for α_1-adrenergic receptor (Table 1). It has been said that dopamine D_2 antagonists might cause undesirable side effects such as prolactin stimulation[19] and extrapyramidal symptoms,[20] and α_1-adrenergic receptor antagonists cause hypotensive effect and worsen clinical state. We have aspired after a selective 5-HT_{1A} receptor agonist over both dopamine D_2 and α_1-adrenergic receptors. We have considered that a selectivity for 5-HT_{1A} receptor over both dopamine D_2 and α_1-adrenergic receptors is attributable to the difference of lipophilic

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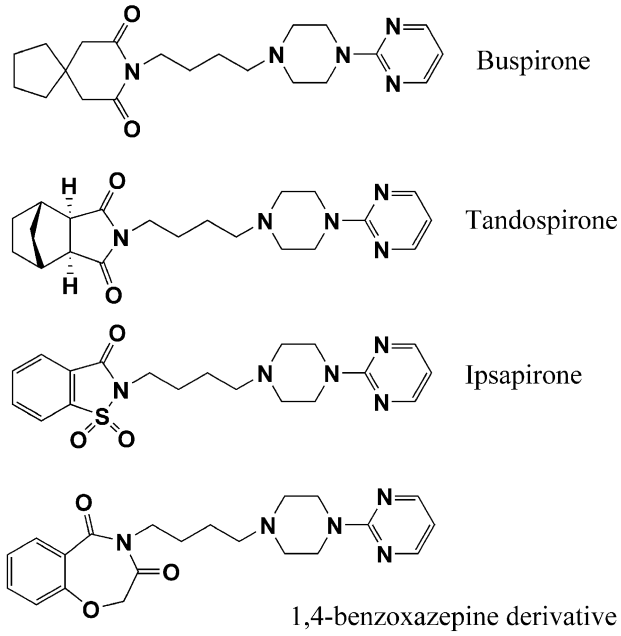


Figure 1.

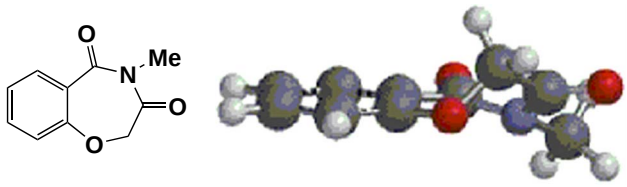


Figure 2. Structure of 4-methyl-1,4-benzoxazepin-3,5-dione.

moiety, i.e., imide structure. Buspirone and tandospirone possess aliphatic and steric volume imide moiety and show an affinity for dopamine D_2 receptor. On the contrary, ipsapirone possesses planar aromatic imide moiety and shows an affinity for α_1-adrenergic receptor. To reduce affinities for both dopamine D_2 and α_1-adrenergic receptors, we have designed some compounds possessing benzazepine scaffold which have an aromatic ring and a little steric volume imide moiety based on puckered conformation for 7-membered ring (Fig. 2).[21] In addition to imide compounds, some vinyl-amide compounds have been designed because vinyl-carbon is sp2 carbon as the same imide carbonyl-one. We have also challenged a transformation of amine part, because 1-(2-pyrimidinyl)piperazine (1-PP), which is a major metabolite of buspirone, tandospirone, and ipsapirone, exhibits blood-pressure fall[22] and it might worsen clinical states.

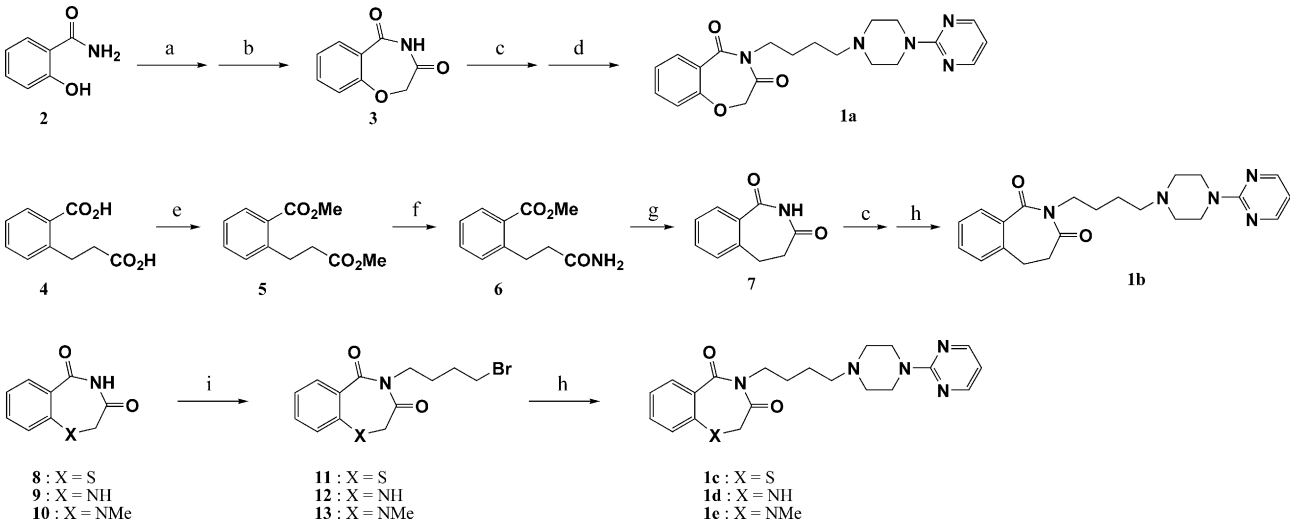
2.2. Synthesis

4-Benzazepine-3,5-dione derivatives **1a**–**e** were prepared using the pathway shown in Scheme 1. 1,4-Benzoxazapine-3,5-dione scaffold **3** was synthesized by *O*-alkylation of salicylamide **2** with ethyl 2-bromoacetate in the presence of K_2CO_3 followed by cyclization with NaOEt in excellent yield. Compound **1a** was obtained by *N*-alkylation of **3** with 1-bromo-4-chlorobutane and subsequent amination with 1-PP. Methylene analogue **1b** of 1,4-benzoxazepine derivative **1a** was prepared from dicarboxylic acid **4**. Methyl 3-(2-methoxycarbonyl)phenylpropionate **5** which was prepared from **4** with H_2SO_4 in MeOH was converted to monoamide **6**. Cyclization of **6** with NaH gave 2-benzazepine-1,3-dione **7** in 88% yield. Other imide intermediates **8**–**10** were prepared by the same procedure described for the synthesis of imide derivatives **3** or **7**. Compounds **7**–**10** were *N*-alkylated with 1-bromo-4-chlorobutane or 1,4-dibromobutane and subsequently substituted by 1-PP by the same way as **1a** in moderate yield (respectively, 61–82%, 52–89%).

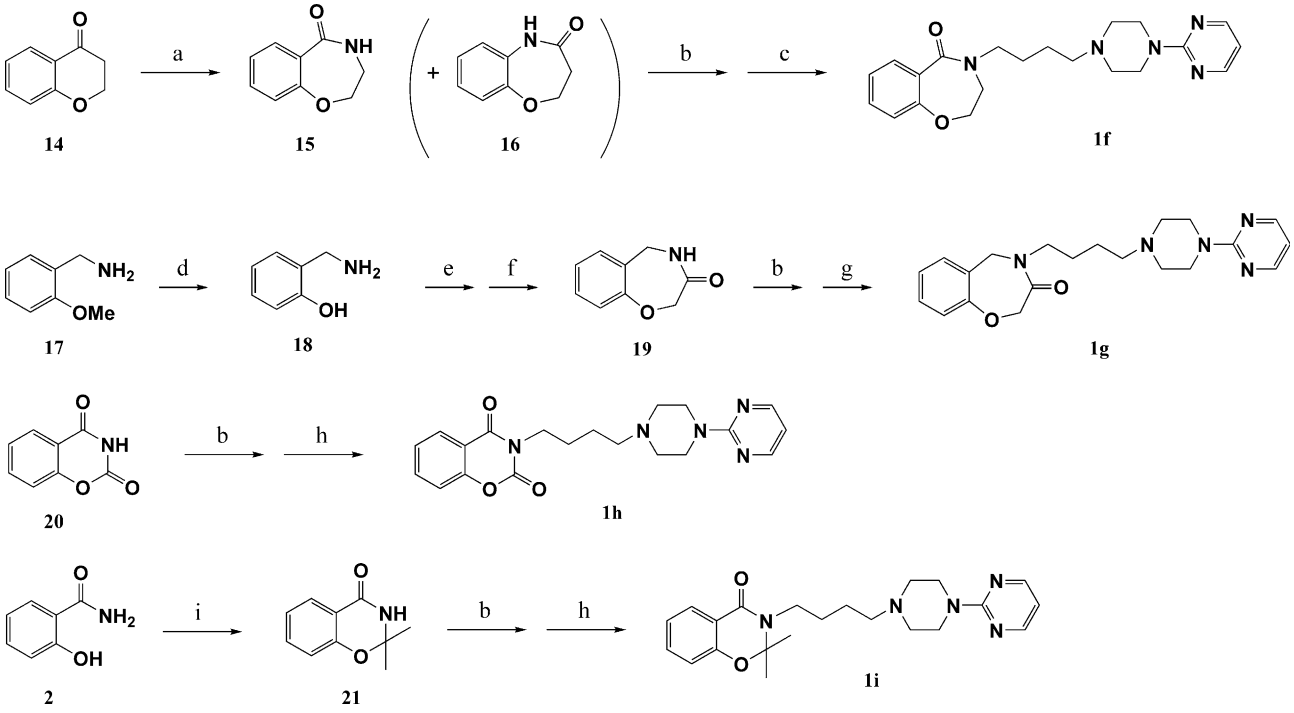
Amide analogues **1f** and **1g** and 1,3-benzoxazine derivatives **1h** and **1i** were prepared by the pathway shown in Scheme 2. Synthesis of each scaffold was described as follows. 3,4-Dihydro-1,4-benzoxazepin-5(2*H*)-one **15**, which is a 3-decarbonyl analogue of imide derivative **1a**, was synthesized by the Schmidt rearrangement of 4-chromanone **14** with sodium azide in methanesulfonic acid. Though 1,5-benzoxazepine isomer **16** was generated in 2.6% yield, it was separated off by column chromatography with SiO_2. 4,5-Dihydro-1,4-benzoxazepin-3(2*H*)-one **19**, which is a 5-decarbonyl analogue of imide derivative **1a**, was obtained from 2-methoxybenzylamine **17**. Treatment by demethylation of **17** with 48% aqueous HBr gave aminoalcohol derivative **18**. Selective *N*-acylation of **18** and cyclization in the presence of K_2CO_3 gave amide derivative **19**. 2,2-Dimethyl-2,3-dihydro-1,3-benzoxazin-4-one **21** was obtained by acetal formation of **2** with 2,2-dimethoxypropane in the presence of *p*-TsOH. Compounds **1f**–**i** were prepared from **15** and **19**–**21** by *N*-alkylation with 1,4-dibromobutane and subsequent substitution by 1-PP.

A preparation of 1,4-benzoxazepin-5(4*H*)-one derivatives **28**–**30** is shown in Scheme 3. 3-Methyl-1,4-benzoxazepin-5(4*H*)-one scaffold **23** was obtained by *O*-alkylation of **2** with chloroacetone and subsequent cyclization with *p*-TsOH. 3-Unsubstituted-1,4-benzoxazepin-5(4*H*)-one scaffold **25** was also synthesized by *O*-alkylation of salicylamide **2** with bromoacetaldehyde diethyl acetal and the subsequent cyclization with HCl gas and dehydration of alcohol compound **24** with MsCl. Compounds **28** and **29** were obtained by the same method as **1a**. Synthesis of 3-chloro-1,4-benzoxazepin-5(4*H*)-one scaffold **30** was described as follows. Imide compound **26** was converted to a vinyl chloride analogue **27** with $POCl_3$ in the presence of HCl gas in 54% yield. Replacement of terminal chloride of **27** by 1-PP gave **30**.

New pyrimidine derivatives **34**, **36**, and **38**–**40** and pyridine analogues **43**–**45** were prepared by the pathway shown in Scheme 4. Tin-lithium exchange of **32**, which was converted from 2-chloropyrimidine **31** by treatment with *n*-Bu_3SnLi at $-78\,^{\circ}C$,[23] and subsequent alkylation with *N*-Boc-4-piperidone gave alcohol product **33**. Dehydration of **33** with $POCl_3$ converted 1,2,3,6-tetrahydropyridine derivative **35**, and then hydrogenation of **35** in the presence of Pd/C gave **37**. Pyrimidine derivatives **34**, **36**, and **38** were



Scheme 1. Reagents: (a) $BrCH_2CO_2Et$, K_2CO_3, acetone; (b) NaOEt, DMF; (c) NaH, $Br(CH_2)_4Cl$, DMF; (d) 1-PP, NaI, K_2CO_3, CH_3CN; (e) cH_2SO_4, MeOH, (f) NH_3aq, NH_4Cl, 1,4-dioxane; (g) i—NaH, 1,4-dioxane; ii—citric acid; (h) 1-PP, 1,4-dioxane; (i) NaH, $Br(CH_2)_4Br$, DMF.



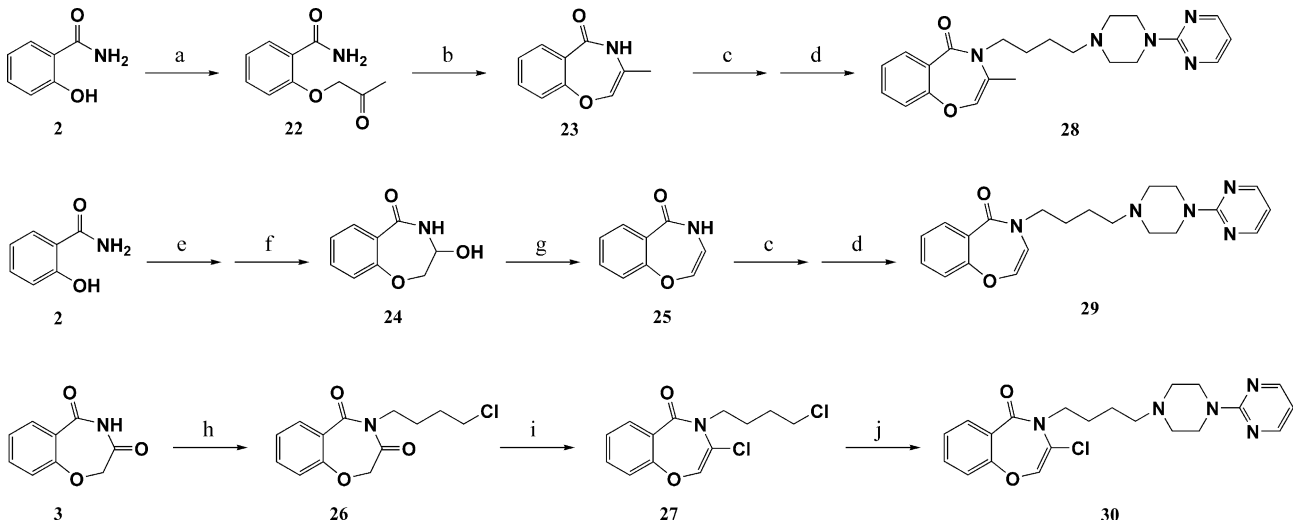
Scheme 2. Reagents: (a) NaN_3, CH_3SO_3H; (b) NaH, $Br(CH_2)_4Br$, DMF; (c) 1-PP, Et_3N, CH_3CN; (d) HBr, H_2O; (e) $ClCOCH_2Cl$, K_2CO_3, CH_2C1_2; (f) K_2CO_3, acetone; (g) 1-PP, 1,4-dioxane; (h) 1-PP, NaI, Et_3N, DMF; (i) $(H_3C)_2C(OCH_3)_2$, *p*-TsOH, PhH.

obtained by deprotection of the corresponding Boc derivatives **33**, **35**, and **37** with TFA in 83–96% yield. Regio-isomers **39** and **40** of compounds **36** and **38** were synthesized the same way as described above from *N*-Boc-3-piperidone instead of *N*-Boc-4-piperidone. Pyridine derivatives **43**–**45** were prepared from 2-bromopyridine **41** via alcohol intermediate **42**. Assessed compounds **30** and **46**–**54** were obtained by substitution of chlorobutyl compound **27** with the corresponding amines (Scheme 5). Later during our study, we successfully made an improvement in the synthesis of **50**, which was synthesized by reduction with $NaBH_4$ of the quaternary ammonium intermediate **55** in 97% yield.

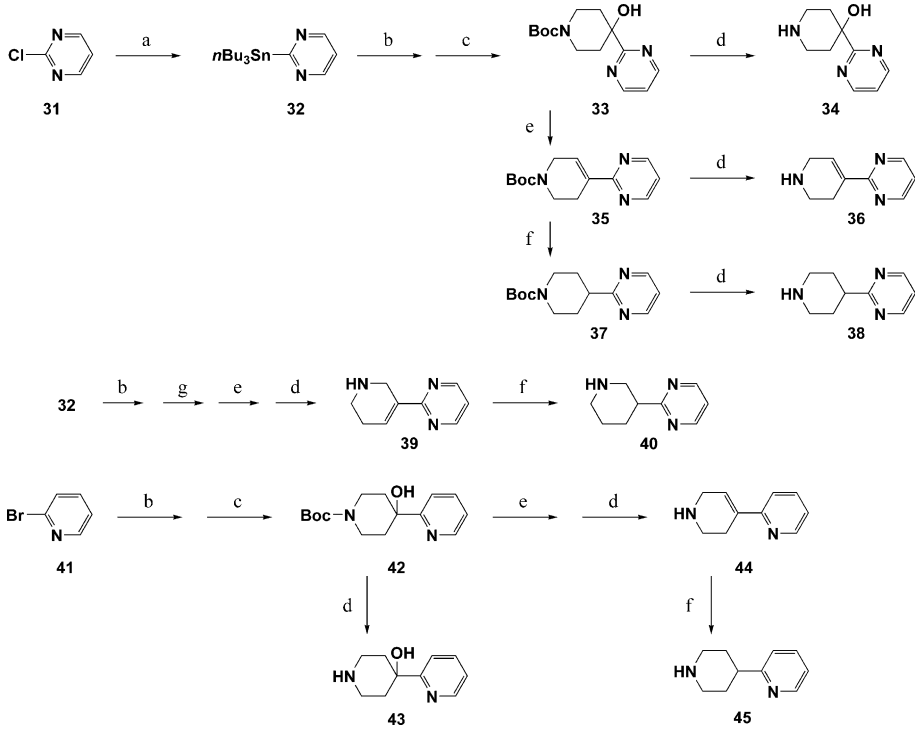
3. Result and discussion

3.1. In vitro binding assay

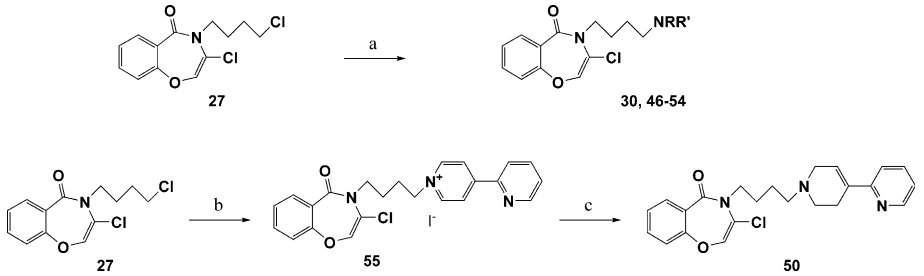
Compounds were evaluated for their binding affinities to 5-HT_{1A}, dopamine D_2, and α_1-adrenergic receptors by radioligand binding assays (Tables 1, 2). The specific ligands and tissue sources were used as follows;



Scheme 3. Reagents: (a) $C1CH_2COCH_3$, K_2CO_3, acetone; (b) *p*-TsOH, $PhCH_3$; (c) K_2CO_3, $Br(CH_2)_4Br$, acetone; (d) 1-PP, K_2CO_3, 1,4-dioxane; (e) $BrCH_2CH(OEt)_2$, K_2CO_3, acetone; (f) HC1, 1,4-dioxane; (g) MsCl, Et_3N, CH_2C1_2; (h) K_2CO_3, $Br(CH_2)_4Cl$, acetone; (i) $POC1_3$, HC1, 1,4-dioxane; (j) 1-PP, Nal, Et_3N, DMF.

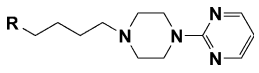


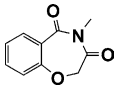
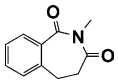
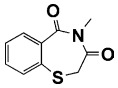
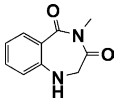
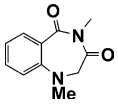
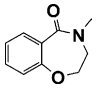
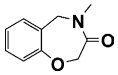
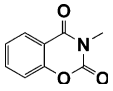
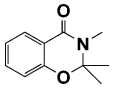
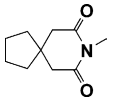
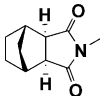
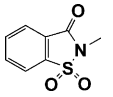
Scheme 4. Reagents and conditions: (a) *n*-Bu_3SnLi, THF, −78 °C to rt; (b) *n*-BuLi, THF, −78 °C; (c) *N*-Boc-4-piperidone, THF, −78 °C to rt; (d) TFA, CH_2C1_2; (e) $POC1_3$, pyridine; (f) H_2, 10% Pd/C, EtOH; (g) *N*-Boc-3-piperidone, THF, −78 °C to rt.



Scheme 5. Reagents: (a) amine (HNRR′), NaI, Et_3N, DMF; (b) 2,4′-dipyridyl, NaI, CH_3CN; (c) $NaBH_4$, EtOH.

Table 1. Structure and their receptor binding data



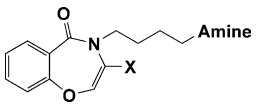
Compound	R	IC_{50} (nM)			IC_{50} ratio	
		5-HT_{1A}	D_2	α_1	D_2/5-HT_{1A}	α_1/5-HT_{1A}
1a[b]		3.75	14500	850	3866	227
1b[c]		58.4	N.T.[a]	398	—	6.8
1c[c]		15.1	N.T.[a]	909	—	60
1d[c]		67.3	N.T.[a]	510	—	7.6
1e[c]		270	N.T.[a]	1550	—	5.7
1f[d]		52.2	N.T.[a]	4510	—	86
1g[e]		101	N.T.[a]	3270	—	32
1h[b]		23.8	N.T.[a]	580	—	24
1i[f]		20.8	N.T.[a]	1100	—	53
Buspirone		11.0	55	2920	5.0	265
Tandspirone		7.7	59	2780	8.0	362
Ipsapirone		5.8	371	457	65	79

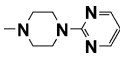
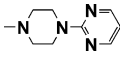
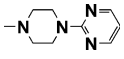
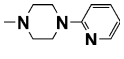
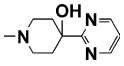
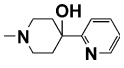
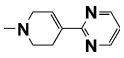
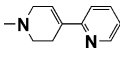
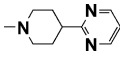
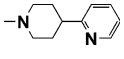
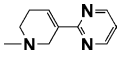
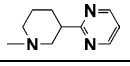
[a] Not tested.
[b] Dihydrochloride.
[c] Maleinate.
[d] Trihydrochloride.
[e] Hydrochloride.
[f] Fumarate.

(a) 5-HT_{1A} serotonergic receptor:[24] [^{3}H]8-OH-DPAT (8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin), rat hippocampus membranes; (b) dopamine D_2 receptor:[25] [^{3}H]Raclopride, rat striatum membranes; (c) α_1-adrenergic receptor:[26] [^{3}H]prazosin, rat cerebral cortex membranes.

All benzazepine derivatives **1a**–**e** showed affinity for 5-HT_{1A} receptor. Among these analogues, 1,4-benzoxazepine **1a** displayed higher 5-HT_{1A} receptor affinity and better selectivity over both dopamine D_2 and α_1-adrenergic receptors than buspirone, tandospirone, and ipsapirone being up to our expectations. We have also

Table 2. Structure and their receptor binding data



Compound	X	Amine	IC_{50} (nM)			IC_{50} ratio	
			5-HT_{1A}	D_2	α_1	D_2/5-HT_{1A}	α_1/5-HT_{1A}
28[b]	Me		10.2	N.T.[a]	1100	—	108
29[b]	H		18.0	N.T.[a]	N.T.[a]	—	—
30[b]	Cl		1.59	199	544	125	342
46[b]	Cl		0.77	51	43	66	55
47[c]	Cl		2650	N.T.[a]	9560	—	3.6
48[c]	Cl		2790	N.T.[a]	4340	—	1.6
49[c]	Cl		1.38	494	924	358	670
50[d]	Cl		0.47	84	128	179	272
51[c]	Cl		5.81	1800	2000	310	344
52[c]	Cl		1.03	229	150	222	146
53[b]	Cl		79.6	893	384	11	4.8
54[b]	Cl		314	N.T.[a]	N.T.[a]	—	—

[a] Not tested.
[b] Fumarate.
[c] Hydrochloride.
[d] Dihydrochloride.

confirmed the advantage of imide moiety and 7-membered scaffold as compared with amide compounds (**1a** vs **1f** and **1g**) and 6-membered analogues (**1a** vs **1h** and **1i**). 3-Substituted-1,4-benzoxazepine-5(4*H*)-one derivatives **28**–**30** also exhibited binding affinity for 5-HT_{1A} receptor. Especially vinylchloride derivative **30** showed emphasized affinity for 5-HT_{1A} receptor with 100-fold selectivity over both dopamine D_2 and α_1-adrenergic receptors. As imide derivative **1a** and vinylchloride compound **30** showed similar binding affinities for 5-HT_{1A} and α_1-adrenergic receptors, we have considered that vinylchloride-amide moiety is a good bioisostere for imide conformer. 3-Chloro-1,4-benzoxazepin-5(4*H*)-one scaffold also showed a puckered conformation for 7-membered ring. Though steric conformation of **30** does not necessarily correspond to **1a**, steric volume of both sides is very similar (Fig. 3).

Next, we investigated effects of various amine moieties. Pyridine derivatives enhanced affinities for not only 5-HT_{1A} receptor but also dopamine D_2 and α_1-adrenergic receptors as compared with pyrimidinyl derivatives (**30**

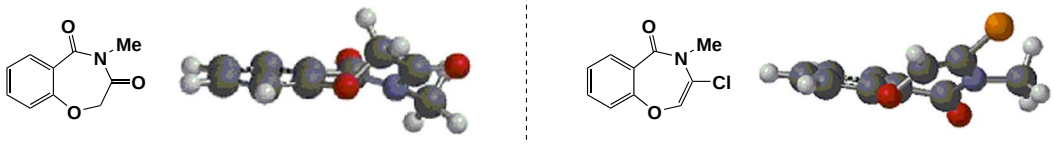


Figure 3. Structure of 4-methyl-1,4-benzoxazepin-3,5-dione and 3-chloro-4-methyl-1,4-benzoxazepin-5-one.

vs **46**, **49** vs **50**, and **51** vs **52**). Alcohol derivatives **47** and **48** showed a very weak affinity for 5-HT_{1A} receptor. 1,2,3,6-Tetrahydropyridine derivatives **49** and **50** exhibited strong affinity for 5-HT_{1A} receptor and good selectivity over both dopamine D_2 and α_1-adrenergic receptors. Piperidine analogues **51** and **52** slightly weaken affinity for 5-HT_{1A} receptor compared with piperazine derivatives **30**, **46** and tetrahydropyridine derivatives **49**, **50**. A slight difference of angle between basic amine and aromatic plane could pave the way for better selectivities for 5-HT_{1A} over both dopamine D_2 and α_1-adrenergic receptors. Regio-isomers **53** and **54** of pyrimidine derivatives **49** and **51** showed reduced affinity for 5-HT_{1A} receptor. As a whole 3-chloro-4-[4-[4-(2-pyridinyl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one **50** exhibited remarkable affinity for 5-HT_{1A} receptor and moderate selectivity over both dopamine D_2 and α_1-adrenergic receptors.

3.2. In vitro 5-HT_{1A} receptor agonist activity

It is known that 5-HT_{1A} receptor agonists inhibit adenylate cyclase activity via Gi protein conjugated with 5-HT_{1A} receptor.[27] Adenylate cyclase activity was determined according to the modified method of De Vivo et al.[27] The amount of cAMP produced was measured by a radioimmunoassay. Compound **50** inhibited forskolin-stimulated adenylate cyclase activity in plasma membrane prepared from the rat hippocampus ($IC_{50} = 2.67 \pm 0.74$ nM), and this effect was perfectly blocked by the treatment with WAY-100635,[28] which is a selective 5-HT_{1A} receptor antagonist. These results indicated that compound **50** acted as a 5-HT_{1A} receptor agonist at postsynaptic receptors in rat hippocampal membranes.

3.3. In vivo neuroprotective assay

We investigated in vivo neuroprotective effect of 1,4-benzoxazepine derivatives and buspirone in a rat model of transient focal cerebral ischemia (Table 3). Male Wistar rats were subjected to t-MCAO using the intraluminal suture method of Koizumi et al.[29] The evaluated compounds and vehicle (saline) were administered immediately after the occlusion. The measurement of peripheral type benzodiazepine binding sites (PTBBS) in ipsilateral cortical and striatal homogenates was carried out as an index for quantification of neuronal damage 10 days after recirculation.[30,31] All compounds caused reduction of the increase in PTBBS levels at a dose of 1 mg/kg sc.[32] Among these compounds, **46**, **49**, and **50** exhibited a highly potent anti-ischemic effect (>60% inhibition; $^{**}p < 0.01$ vs vehicle). In this model, rectal temperature was found to increase during ischemia to above 38.5 °C, but tested compounds reduced the ischemic hyperthermia at the neuroprotective doses. It has been reported that 5-HT_{1A} receptor agonists possess a hypothermic effect.[33] We have investigated a hypothermic effect in this t-MCAO model. 4-Dimethylaminoantipyrine, an antipyretic drug, at a dose of 200 mg/kg ip immediately after t-MCAO did not affect PTBBS levels by only 21% inhibition, although it caused hypothermia to the same degree as each 5-HT_{1A} receptor agonist (1 mg/kg sc). These results indicate that pharmacological effects in addition to the hypothermic effect are involved in the mechanism of neuroprotective effect of 5-HT_{1A} receptor agonist.

Table 3. Neuronal protective effects of compounds against ischemic brain damage in the rat t-MCAO model

Compound	% inhibition	
	1 mg/kg	0.3 mg/kg
1a	33	
30	29	
46	68**	42*
49	65**	16
50	63**	32*
52	22	
Buspirone	53	

See experimental section for details.
* $P < 0.05$ versus vehicle (one-way ANOVA followed by Dunnest's multiple comparisons test).
** $P < 0.01$.

It has been considered that a 5-HT_{1A} receptor agonist hyperpolarizes the cell membrane as well as inhibits glutamic acid release in the hippocampus. So it is thought that during ischemia 5-HT_{1A} receptor agonists inhibit excessive excitation of the cell membrane and the release of glutamic acid.[12,13]

4. Conclusion

We presented the synthesis and biological evaluation of a novel class of 1,4-benzoxazepine derivatives. 3-Chloro-1,4-benzoxazepin-5(4*H*)-one derivatives showed not only highly potent affinity for 5-HT_{1A} receptor but good selectivity over dopamine D_2 and α_1-adrenergic receptors. Since compound **50** was a potent and selective 5-HT_{1A} receptor agonist compared with buspirone and showed a desirable neuroprotective effect in the in vivo t-MCAO model, we have selected it as a clinical candidate. Now compound **50** (SUN N4057 (Piclozotan) as 2HCl salt) is currently being developed for treatment of acute phase of cerebral infarction at phase IIb in clinical trial.

5. Experimental

5.1. General

Melting points were measured with a Yanagimoto or Büchi 535 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker ARX-400 using TMS as an internal reference. IR spectra were recorded on a Perkin-Elmer 1640 instrument. Mass spectra were obtained on a JEOL JMX-AX500 by the FAB ionization method. All compounds were routinely checked by TLC using Merck Kieselgel 60 F254 plates (detection at 254 nm). Column chromatography separations were carried out on Merck Kieselgel 60. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer.

5.2. Chemistry

5.2.1. 1,4-Benzoxazepine-3,5(2*H*, 4*H*)-dione (3). A mixture of salicylamide **2** (13.7 g, 0.10 mol), K_2CO_3 (15.2 g, 0.11 mol), and ethyl bromoacetate (11.1 mL, 0.10 mol) in 300 mL acetone was heated at reflux for 4 h. The reaction mixture was cooled down to room temperature, and then the insoluble solid was removed by filtration. The filtrate was concentrated in vacuo, and then the given residue was washed with Et_2O to give 2-(ethoxycarbonylmethyloxy)benzamide (20.5 g, 92%).

To a stirred solution of 2-(ethoxycarbonylmethyloxy)benzamide (20.5 g, 92 mmol) in 200 mL DMF was added dropwise a solution of 28% sodium methoxide of MeOH (19 mL) at 0 °C. The resultant reaction mixture was stirred at room temperature for 3 h. An aqueous solution of 150 mL citric acid hydrate (21 g, 0.10 mol) was added to the reaction mixture at 0 °C, and then stirring was continued for 2 h. The precipitate was collected by filtration, washed with diisopropylether, and dried to give the title compound (16.1 g, 99%). White solid; mp 144–145 °C. ^{1}H NMR ($CDCl_3$) δ 4.72 (s, 2H), 7.15 (d, 1H, J = 8 Hz), 7.29 (t, 1H, J = 8 Hz), 7.56 (t, 1H, J = 8 Hz), 8.14 (d, 1H, J = 8 Hz), 8.36 (br s, 1H); IR ($CHCl_3$) cm^{-1}: 3222, 3005, 2887, 1722, 1706, 1634, 1588, 1480, 1460; FAB-MS m/z: 178 $(M+H)^+$.

5.2.2. 4-[4-[4-(2-Pyrimidinyl)piperazin-1-yl]butyl]-1,4-benzoxazepine-3,5(2*H*,4*H*)-dione (1a). To a stirred solution of **3** (10.0 g, 0.056 mol) and 1-bromo-4-chlorobutane (10.6 g, 0.062 mol) in 100 mL DMF was added 60% dispersion of NaH on mineral oil (2.71 g, 0.067 mol) at 0 °C. After 1 h, the reaction mixture was poured into an aqueous solution of citric acid at 0 °C, and then the products were extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using *n*-hexane/EtOAc (6:1) as an eluent to give 4-(4-chlorobutyl)-1,4-benzoxazepine-3,5(2*H*,4*H*)-dione (12.6 g, 84%).

A mixture of 4-(4-chlorobutyl)-1,4-benzoxazepine-3,5(2*H*,4*H*)-dione (1.5 g, 5.6 mmol), sodium iodide (1.3 g, 8.4 mmol), 1-(2-pyrimidinyl)piperazine (1.1 g, 6.7 mmol), and K_2CO_3 (1.5 g, 11.2 mmol) in 50 mL CH_3CN was heated at reflux overnight. The reaction mixture was concentrated in vacuo, and then the residue was dissolved into AcOEt and water. An organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using CH_2Cl_2/MeOH (30:1) as an eluent to give the title compound (2.0 g, 91%). This compound was subsequently converted to its dihydrochloride. White solid; mp 145–147 °C (recryst solvent: MeOH–Et_2O). ^{1}H NMR (DMSO-d_6) δ 1.52–1.70 (m, 4H), 2.52–2.73 (m, 6H), 3.82–4.07 (m, 6H), 4.76 (s, 2H), 6.51 (t, 1H, J = 5 Hz), 7.10 (d, 1H, J = 8 Hz), 7.25 (t, 1H, J = 8 Hz), 7.52 (t, 1H, J = 8 Hz), 8.16 (d, 1H, J = 8 Hz), 8.31 (d, 2H, J = 5 Hz); IR (KBr) cm^{-1}: 2900, 2750, 1700, 1640, 1580, 1480, 1440; Anal. Calcd for $C_{21}H_{25}N_5O_3{\cdot}2HCl{\cdot}\ 1/2H_2O$: C, 52.83; H, 5.91; N, 14.67. Found: C, 52.70; H, 5.73; N, 14.78.

5.2.3. 4,5-Dihydro-2*H*-benzazepine-1,3-dione (7). A mixture of 3-ortho(hydroxycarbonyl)phenylpropionic acid (2.0 g, 10.3 mmol) and five drops of conc. sulfuric acid in 10 mL MeOH was heated at reflux for 30 min. The reaction mixture was diluted with AcOEt and washed with brine. After being dried over $MgSO_4$, removal of the solvent gave **5** (2.2 g, 97%).

A mixture of **5** (4.36 g, 20.0 mmol), NH_4Cl (2.0 g, 38.1 mmol), and 120 mL of 28% aqueous NH_3 in 120 mL of 1,4-dioxane was stirred for 3 weeks. After the reaction mixture was concentrated in vacuo, the residue was dissolved into CH_2Cl_2 and washed with brine. After being dried over $MgSO_4$, removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using CH_2Cl_2/MeOH (97:3) as an eluent to give **6** (1.1 g, 27%).

To a stirred solution of **6** (1.1 g, 5.3 mmol) in 60 mL of 1,4-dioxane was added 60% dispersion of NaH on mineral oil (271 mg, 6.4 mmol) at 0 °C. The reaction mixture was stirred at 100 °C for 10 min and poured into an aqueous solution of citric acid at 0 °C, and then the aqueous mixtures were extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave the title compound (866 mg, 88%). White solid; mp 103–105 °C. ^{1}H NMR ($CDCl_3$) δ 2.88–2.92 (m, 2H), 3.09–3.13 (m, 2H), 7.23 (d, 1H, J = 7 Hz), 7.42 (t, 1H, J = 8 Hz), 7.52 (ddd, 1H, J = 1 Hz, 7 Hz, 8 Hz), 8.12 (dd, 1H, J = 1 Hz, 8 Hz); IR ($CHCl_3$) cm^{-1}: 3180, 3070, 2880, 1700, 1660, 1595, 1450, 1370; FAB-MS m/z: 176 $(M+H)^+$.

5.2.4. 2-[4-[4-(2-Pyrimidinyl)piperazin-1-yl]butyl]-4,5-dihydro-2*H*-benzazepine-1,3-dione (1b). The title compound was prepared from **7**, using a method similar to that described for **1a**, in 53% yield (in two steps). This compound was subsequently converted to its maleinate. White solid; mp 137-140 °C (recryst solvent: MeOH–Et_2O). ^{1}H NMR (DMSO-d_6) δ 1.53–1.73 (m, 4H), 2.43 (t, 2H, J = 8 Hz), 2.50 (t, 4H, J = 5Hz), 2.99 (s, 4H), 3.83 (t, 4H, J = 5 Hz), 4.03 (t, 2H, J = 8 Hz), 6.47 (t, 1H, J = 5 Hz), 7.16 (d, 1H, J = 7 Hz), 7.36 (t, 1H, J = 7 Hz), 7.44 (dt, 1H, J = 1, 7 Hz), 7.96 (dd, 1H,

J = 1, 7 Hz), 8.29 (d, 2H, J = 5 Hz); IR (KBr) cm^{-1}: 2940, 2800, 1695, 1640, 1580, 1540, 1490, 1445; Anal. Calcd for $C_{22}H_{27}N_5O_2 \cdot C_4H_4O_4$: C, 61.28; H, 6.13; N, 13.75. Found: C, 61.01; H, 6.26; N, 13.64.

5.2.5. 4-(4-Bromobutyl)-1,4-benzothiazepine-3,5(2*H*,4*H*)-dione (11). The title compound was prepared from **8**,[34] using a method similar to that described for the above 4-(4-chlorobutyl)-1,4-benzoxazepine-3,5(2*H*, 4*H*)-dione, in 61% yield. Colorless oil. ^1H NMR ($CDCl_3$) δ 1.75–1.96 (m, 4H), 3.43 (t, 2H, J = 6 Hz), 3.68 (s, 2H), 4.03 (t, 2H, J = 6 Hz), 7.31 (m, 3H), 8.17 (m, 1H); IR (KBr) cm^{-1}: 2950, 2860, 1690, 1630, 1580, 1430; HRMS: Calcd for $C_{13}H_{14}BrNO_2S$: 326.9927. Found: 326.9921.

5.2.6. 4-(4-Bromobutyl)-1,2-dihydro-4*H*-1,4-benzodiazepine-3,5-dione (12). The title compound was prepared from **9**, using a method similar to that described for the above 4-(4-chlorobutyl)-1,4-benzoxazepine-3,5(2*H*, 4*H*)-dione, in 64% yield. Colorless solid; mp 60–61 °C. ^1H NMR ($CDCl_3$) δ 1.77-1.93 (m, 4H), 3.40 (t, 2H, J = 7 Hz), 3.92 (d, 2H, J = 5 Hz), 3.93 (t, 2H, J = 7 Hz), 4.77 (t, 1H, J = 5 Hz), 6.79 (d, 1H, J = 7 Hz), 6.95 (t, 1H, J = 7 Hz), 7.35 (dt, 1H, J = 1, 7 Hz), 8.25 (dd, 1H, J = 1, 7 Hz); IR (KBr) cm^{-1}: 3300, 2850, 1690, 1630, 1600, 1480, 1420; HRMS: Calcd for $C_{13}H_{15}BrN_2O_2$: 310.0316. Found: 310.0312.

5.2.7. 4-(4-Bromobutyl)-1-methyl-1,2-dihydro-4*H*-1,4-benzodiazepine-3,5-dione (13). The title compound was prepared from **10**, using a method similar to that described for the above 4-(4-chlorobutyl)- 1,4-benzoxazepine-3,5(2*H*, 4*H*)-dione, in 82% yield. Colorless oil. ^1H NMR ($CDCl_3$) δ 1.74–1.96 (m, 4H), 3.22 (s, 3H), 3.41 (t, 2H, J = 6 Hz), 3.86 (s, 2H), 3.92 (t, 2H, J = 6 Hz), 6.94 (d, 1H, J = 8 Hz), 6.96 (t, 1H, J = 8 Hz), 7.45 (dt, 1H, J = 1, 8 Hz), 8.32 (dd, 1H, J = 1, 8 Hz); IR ($CHCl_3$) cm^{-1}: 2950, 2880, 1700, 1640, 1600, 1500, 1435; HRMS: Calcd for $C_{14}H_{17}BrN_2O_2$: 324.0473. Found: 324.0487.

5.2.8. 4-[4-[4-(2-Pyrimidinyl)piperazin-1-yl]butyl]-1,4-benzothiazepine-3,5(2*H*,4*H*)-dione (1c). A mixture of **11** (53.8 mg, 0.16 mmol) and 1-(2-pyrimidinyl)piperazine (84.3 mg, 0.49 mmol) in 10 mL of 1,4-dioxane was heated at reflux for 6 h. The reaction mixture was concentrated in vacuo, and then the residue was dissolved into CH_2Cl_2 and water. An organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using *n*-hexane/EtOAc (1:3) as an eluent to give the title compound (35.2 mg, 52%). This compound was subsequently converted to its maleinate. White solid; mp 153–154 °C (recryst solvent: CH_2Cl_2–Et_2O). ^1H NMR (DMSO-d_6) δ 1.54–1.72 (m, 4H), 2.40 (t, 2H, J = 8 Hz), 2.47 (t, 4H, J = 5 Hz), 3.68 (s, 2H), 3.81 (t, 4H, J = 5 Hz), 4.03 (t, 2H, J = 8 Hz), 6.47 (t, 1H, J = 5 Hz), 7.27–7.49 (m, 3H), 8.17–8.20 (m, 1H); IR (KBr) cm^{-1}: 2930, 2800, 1730, 1690, 1655, 1635, 1580, 1540, 1490, 1440; Anal. Calcd for $C_{21}H_{25}N_5O_2S \cdot C_4H_4O_4$: C, 56.91; H, 5.54; N, 13.28. Found: C, 56.75; H, 5.56; N, 13.26.

5.2.9. 4-[4-[4-(2-Pyrimidinyl)piperazin-1-yl]butyl]-1,2-dihydro-4*H*-1,4-benzodiazepine-3,5-dione (1d). The title compound was prepared from **12**, using a method similar to that described for **1c**, in 87% yield. This compound was subsequently converted to its maleinate. White solid; mp 126–133 °C (recryst solvent: CH_2Cl_2–Et_2O). ^1H NMR (DMSO-d_6) δ 1.47–1.72 (m, 4H), 2.38 (t, 2H, J = 7 Hz), 2.45 (t, 4H, J = 5 Hz), 3.80 (t, 4H, J = 5 Hz), 3.91 (d, 2H, J = 5 Hz), 3.94 (t, 2H, J = 7 Hz), 4.78 (t, 1H, J = 5 Hz), 6.46 (t, 1H, J = 5 Hz), 6.78 (t, 1H, J = 9 Hz), 6.94 (t, 1H, J = 9 Hz), 7.34 (dt, 1H, J = 2, 9 Hz), 8.27 (dd, 1H, J = 2, 9 Hz), 8.33 (d, 2H, J = 5 Hz); IR (KBr) cm^{-1}: 3250, 2850, 1690, 1630, 1580, 1540, 1480, 1440; Anal. Calcd for $C_{21}H_{26}N_6O_2 \cdot C_4H_4O_4 \cdot 1H_2O$: C, 56.81; H, 6.10; N, 15.90. Found: C, 56.82; H, 5.96; N, 15.76.

5.2.10. 1-Methyl-4-[4-[4-(2-pyrimidinyl)piperazin-1-yl]butyl]-1,2-dihydro-4*H*-1,4-benzodiazepine-3,5-dione (1e). The title compound was prepared from **13**, using a method similar to that described for **1c**, in 89% yield. This compound was subsequently converted to its maleinate. White solid; mp 160-162 °C (recryst solvent: CH_2Cl_2–Et_2O). ^1H NMR (DMSO-d_6) δ 1.53–1.73 (m, 4H), 2.17 (s, 3H), 2.37 (t, 2H, J = 8 Hz), 2.45 (t, 4H, J = 5 Hz), 3.22 (s, 2H), 3.80 (t, 4H, J = 5 Hz), 3.91 (t, 2H, J = 8 Hz), 6.48 (t, 1H, J = 5 Hz), 6.93 (d, 1H, J = 9 Hz), 6.95 (t, 1H, J = 9 Hz), 7.44 (dt, 1H, J = 1, 9 Hz), 8.29 (d, 2H, J = 5 Hz), 8.32 (dd, 1H, J = 1, 9 Hz); IR (KBr) cm^{-1}: 2920, 2760, 1675, 1635, 1580, 1540, 1495, 1440; Anal. Calcd for $C_{22}H_{28}N_6O_2 \cdot C_4H_4O_4 \cdot 1/4H_2O$: C, 59.02; H, 6.19; N, 15.89. Found: C, 59.04; H, 6.19; N, 15.85.

5.2.11. 4-[4-[4-(2-Pyrimidinyl)piperazin-1-yl]butyl]-1,2-dihydro-4*H*-1,4-benzoxazepin-5-one (1f). The title compound was prepared from **15**, using a method similar to that described for **1a**, in 35% yield (in two steps). This compound was subsequently converted to its trihydrochloride. White solid; mp 171-172 °C (recryst solvent: EtOH-Et_2O). ^1H NMR (DMSO-d_6) δ 1.63–1.71 (m, 4H), 2.47 (t, 2H, J = 7 Hz), 2.52–2.55 (m, 4H), 3.50 (t, 2H, J = 5 Hz), 3.65 (t, 2H, J = 7 Hz), 3.83–3.87 (m, 4H), 4.37 (t, 2H, J = 5 Hz), 6.48 (t, 1H, J = 5 Hz), 6.99 (d, 1H, J = 8 Hz), 7.16 (t, 1H, J = 8 Hz), 7.38 (dt, 1H, J = 2, 8 Hz), 7.79 (dd, 1H, J = 2, 8 Hz), 8.30 (d, 2H, J = 5 Hz); IR (KBr) cm^{-1}: 2930, 2850, 2800, 1630, 1585, 1540, 1470, 1445; Anal. Calcd for $C_{21}H_{27}N_5O_2 \cdot 3HCl$: C, 51.38; H, 6.16; N, 14.27. Found: C, 51.28; H, 6.18; N, 13.91.

5.2.12. 4,5-Dihydro-1,4-benzoxazepin-3(2*H*)-one (19). A mixture of 2-methoxybenzylamine (**17**) (5.0 g, 0.036 mol) in 50 mL of 48% aqueous hydrobromic acid was heated at reflux for 3 h. The reaction mixture was neutralized with 3N NaOH at 0 °C, and then the product was extracted with $CHCl_3$ and the extract was washed with brine. After being dried over $MgSO_4$, removal of the solvent in vacuo gave **18** (3.78 g, 84%), which was used for next step without further purification.

To a stirred mixture of **18** (3.78 g, 0.031 mol) and K_2CO_3 (12.7 g, 0.093 mol) in 50 mL CH_2Cl_2 was added dropwise chloroacetyl chloride (2.69 ml, 0.034 mol) at 0 °C. After being stirred for 30 min, the reaction mixture was diluted with CH_2Cl_2 and washed with brine. After being dried over $MgSO_4$, removal of the solvent in vacuo gave a residue. A mixture of this residue and K_2CO_3 (9.25 g, 0.067 mol) in 400 mL acetone was heated at reflux for 6 h. The reaction mixture was concentrated in vacuo, and then a residue was dissolved into CH_2Cl_2 and water. An organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave the residue, which was chromatographed over SiO_2 using CH_2Cl_2/MeOH (98:2) as an eluent to give the title compound (1.28 g, 35%) as a white solid. mp 113–114 °C (recryst solvent: CH_2Cl_2–EtOH-Et_2O). ^{1}H NMR ($CDCl_3$) δ 4.38 (d, 2H, J = 5 Hz), 4.62 (2H, s), 6.64 (1H, s), 7.11–7.15 (2H, m), 7.21 (dd, 1H, J = 1, 8 Hz), 7.34 (dt, 1H, J = 2, 8 Hz); IR ($CHCl_3$) cm^{-1}: 2916, 1671, 1482, 1409; FAB-MS *m*/*z*: 164 (M+H)$^+$.

5.2.13. 4-[4-[4-(2-Pyrimidinyl)piperazin-1-yl]butyl]-4,5-dihydro-1,4-benzoxazepin-3(2*H*)-one (1g). The title compound was prepared from **19**, using a method similar to that described for **1a**, in 51% yield (in two steps). This compound was subsequently converted to its hydrochloride. White solid; mp 198–199 °C (recryst solvent: CH_2Cl_2–Et_2O). ^{1}H NMR (DMSO-d_6) δ 1.54–1.70 (m, 4H), 2.47–2.54 (m, 6H), 3.58 (t, 2H, J = 7 Hz), 3.84–3.95 (m, 4H), 4.51 (s, 2H), 4.70 (s, 2H), 6.50 (t, 1H, J = 5 Hz), 7.03–7.09 (m, 2H), 7.17 (d, 1H, J = 7 Hz), 7.29 (t, 1H, J = 7 Hz), 8.31 (d, 2H, J = 5 Hz); IR (KBr) cm^{-1}: 2930, 2850, 2800, 1665, 1635, 1590, 1545, 1490, 1445; Anal. Calcd for $C_{21}H_{27}N_5O_2 \cdot 1HCl \cdot 1H_2O$: C, 57.85; H, 6.94; N, 16.07. Found: C, 57.58; H, 6.49; N, 16.04.

5.2.14. 3-[4-[4-(2-Pyrimidinyl)piperazin-1-yl]butyl]-1,3-3*H*-benzoxazine-2,4-dione (1h). The title compound was prepared from 1,3-benzoxazine-2,4-dione **20**, using a method similar to that described for **1a**, in 19% yield (in two steps). This compound was subsequently converted to its dihydrochloride. White solid; mp 206–208 °C (recryst solvent: MeOH–$CHCl_3$–Et_2O). ^{1}H NMR (DMSO-d_6) δ 1.63–1.84 (m, 4H), 2.94–3.19 (m, 4H), 3.30–3.42 (m, 2H), 3.57 (t, 2H, J = 5 Hz), 3.93 (t, 2H, J = 5 Hz), 4.64–4.74 (m, 2H), 6.75 (t, 1H, J = 5 Hz), 7.42 (d, 1H, J = 8 Hz) , 7.44 (t, 1H, J = 8 Hz), 7.81 (t, 1H, J = 8 Hz), 8.00 (d, 1H, J = 8 Hz), 8.44 (d, 2H, J = 5 Hz), 10.42–10.56 (m, 2H); IR (KBr) cm^{-1}: 3476, 2717, 1754, 1688, 1621, 1540, 1489, 1433, 1404; Anal. Calcd for $C_{20}H_{23}N_5O_3 \cdot 2HCl \cdot 2H_2O$: C, 48.99; H, 5.96; N, 14.28. Found: C, 48.91; H, 5.81; N, 14.67.

5.2.15. 2,2-Dimethyl-2,3-dihydro1-1,3-benzoxazin-4-one (21). A mixture of salicylamide **2** (1.08 g, 7.88 mmol), 2,2-dimethoxypropane (1.94 mL, 15.76 mmol), and *p*-TsOH (20 mg, 0.10 mmol) in 30 mL benzene was heated at reflux for 3 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine. After being dried over $MgSO_4$, removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using hexane/EtOAc (4:1) as an eluent to give the title compound (1.39 g, 100%) as a white solid. mp 121–124 °C. ^{1}H NMR ($CDCl_3$) δ 3.30 (s, 1H), 6.96 (d, 1H, J = 8 Hz), 7.09 (t, 1H, J = 8 Hz), 7.50 (t, 1H, J = 8 Hz), 7.77 (d, 1H, J = 8 Hz); IR ($CHCl_3$) cm^{-1}: 3064, 1675, 1614, 1469; FAB-MS *m*/*z*: 178 (M+H)$^+$.

5.2.16. 2,2-Dimethyl-3-[4-[4-(2-pyrimidinyl)piperazin-1-yl]butyl]-2,3-dihydro1,3-benzoxazin-4-one (1i). The title compound was prepared from **21**, using a method similar to that described for **1a**, in 61% yield (in two steps). This compound was subsequently converted to its fumarate. White solid; mp 184–185 °C (recryst solvent: MeOH–Et_2O). ^{1}H NMR (DMSO-d_6) δ 1.45–1.66 (m, 4H), 1.64 (s, 6H), 2.35–2.48 (m, 6H), 3.55–3.67 (m, 2H), 3.70–3.74 (m, 4H), 6.70 (t, 1H, J = 5 Hz), 6.61 (s, 2H), 6.95 (d, 1H, J = 8 Hz) , 7.09 (t, 1H, J = 7 Hz), 7.49 (dt, 1H, J = 1, 8 Hz), 7.76 (dd, 1H, J = 1, 7 Hz), 8.33 (d, 2H, J = 5 Hz); IR (KBr) cm^{-1}: 3596, 2990, 2554, 1718, 1644, 1613, 1586, 1548, 1470; Anal. Calcd for $C_{22}H_{29}N_5O_2$: C, 61.04; H, 6.50; N, 13.69. Found: C, 60.96; H, 6.51; N, 13.72.

5.2.17. 2-(2-Oxa-*n*-propyloxy)benzamide (22). To a stirred solution of salicylamide **2** (14.6 g, 0.11 mol) in 500 mL of acetone were added K_2CO_3 (30.0 g, 0.22 mol) and chloroacetone (17 mL, 0.22 mol). The reaction mixture was heated at reflux for 2 h and then cooled down to room temperature. After the generated precipitate was removed by filtration, the filtrate was concentrated in vacuo and the residue was washed with Et_2O to give the title compound (17.1 g, 83%). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H), 4.89 (s, 2H), 6.62 (br s, 1H), 6.91 (d, 1H, J = 8 Hz), 7.08 (t, 1H, J = 8 Hz), 7.46 (t, 1H, J = 8 Hz), 8.12 (d, 1H, J = 8 Hz), 8.39 (br s, 1H); IR ($CHCl_3$) cm^{-1}: 3088, 1710, 1669, 1587, 1560, 1477, 1446; FAB-MS *m*/*z*: 194 (M+H)$^+$.

5.2.18. 3-Methyl-1,4-benzoxazepin-5(4*H*)-one (23). A mixture of **22** (17.1 g, 88 mmol) and *p*-toluenesulfonic acid monohydrate (220 mg, 1.2 mmol) in 100 mL toluene was heated at reflux overnight with removal of the generated water with a Dean–Stark trap. The reaction mixture was diluted with EtOAc, washed with water and brine, and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using hexane/EtOAc (5:1) as an eluent to give the title compound (12.4 g, 80%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3H), 6.56 (s, 1H), 6.77 (br s, 1H), 6.89 (d, 1H, J = 8 Hz), 7.10 (t, 1H, J = 8 Hz), 7.34 (t, 1H, J = 8 Hz), 7.89 (d, 1H, J = 8 Hz); IR ($CHCl_3$) cm^{-1}: 2998, 1684, 1652, 1451; FAB-MS *m*/*z*: 176 (M+H)$^+$.

5.2.19. 3-Methyl-4-[4-[4-(2-pyrimidinyl)piperazin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one (28). The title compound was prepared from **23**, using a method similar to that described for **1a**, in 66% yield (in two steps). This compound was subsequently converted to its fumarate. White solid; mp 141–142 °C (recryst solvent: MeOH–Et_2O). ^{1}H NMR (DMSO-d_6) δ 1.50–1.76 (m, 4H), 1.81 (s, 3H), 2.38 (t, 2H, J = 7 Hz), 2.43 (t, 4H, J = 5 Hz),

3.71–3.78 (m, 6H), 6.55–6.60 (m, 2H), 6.61 (s, 2H), 7.05 (d, 1H, $J = 8$ Hz), 7.23 (t, 1H, $J = 8$ Hz), 7.48 (t, 1H, $J = 8$ Hz), 7.69 (d, 1H, $J = 8$ Hz), 8.33 (d, 2H, $J = 5$ Hz); IR (KBr) cm^{-1}: 3438, 2956, 1684, 1634, 1584, 1482; Anal. Calcd for $C_{26}H_{31}N_5O_6$: C, 61.28; H, 6.13; N, 13.74. Found: C, 61.02; H, 6.22; N, 13.69.

5.2.20. 3-Hydroxy-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (24). To a stirred solution of salicylamide **2** (5.0 g, 36 mmol) in 100 mL acetone were added K_2CO_3 (7.5 g, 54 mmol) and 2-bromomethyl-1,3-dioxolane (6.7 g, 40 mmol). The resulting mixture was heated at reflux for 5 h and then cooled down to room temperature. After the solid was removed by filtration, the filtrate was concentrated in vacuo to afford a solid that was crystallized from EtOAc/*n*-hexane to give 2-(1,3-dioxolan-2-ylmethyl)benzamide (6.2 g, 79%).

A mixture of 2-(1,3-dioxolan-2-ylmethyl)benzamide (6.2 g, 28 mmol) and 10% aqueous HCl (5 mL) in 10 mL of 1,4-dioxane was heated at reflux for 2 h. The reaction mixture was diluted with water and extracted with EtOAc, and then the organic layer was washed with water and brine. After drying over $MgSO_4$, removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using CH_2Cl_2/EtOAc (1:2) as an eluent to give the title compound (3.6 g, 65%). White solid; mp 102–103 °C. ^1H NMR ($CDCl_3$) δ 3.15–3.21 (br s, 1H), 4.09 (d, 1H, $J = 12$ Hz), 4.42–4.47 (m, 1H), 4.97–5.03 (m, 1H), 6.82 (br s, 1H), 6.97 (d, 1H, $J = 8$ Hz), 7.03 (t, 1H, $J = 8$ Hz), 7.34 (t, 1H, $J = 8$ Hz), 7.82 (d, 1H, $J = 8$ Hz); IR (KBr) cm^{-1}: 3387, 3290, 3200, 2998, 1661, 1615, 1492; FAB-MS *m*/*z*: 180 $(M+H)^+$.

5.2.21. 1,4-Benzoxazepin-5(4*H*)-one (25). To a stirred solution of **24** (3.6 g, 18 mmol) in 50 mL CH_2Cl_2 were added methanesulfonyl chloride (1.7 mL, 22 mmol) and triethylamine (7.6 mL, 55 mmol) at 0 °C, and then stirring was continued for 2 h. The reaction mixture was diluted with $CHCl_3$ (200 mL) and washed with 0.5 N HCl, a saturated solution of $NaHCO_3$ and brine. After drying over $MgSO_4$, removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using CH_2Cl_2/EtOAc (1:1) as an eluent to give the title compound (2.8 g, 87%). Yellow oil; ^1H NMR ($CDCl_3$) δ 5.23 (d, 1H, $J = 7$ Hz), 6.14 (d, 1H, $J = 7$ Hz), 6.81 (br s, 1H), 6.93 (d, 1H, $J = 8$ Hz), 7.04 (t, 1H, $J = 8$ Hz), 7.35 (t, 1H, $J = 8$ Hz), 7.91 (d, 1H, $J = 8$ Hz); IR ($CHCl_3$) cm^{-1}: 2985, 1688, 1653, 1445; FAB-MS *m*/*z*: 162 $(M+H)^+$.

5.2.22. 4-[4-[4-(2-Pyrimidinyl)piperazin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one (29). The title compound was prepared from **25**, using a method similar to that described for **1a**, in 93% yield (in two steps). Pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.57–1.80 (m, 4H), 2.44 (t, 2H, $J = 7$ Hz), 2.54 (t, 4H, $J = 5$ Hz), 3.54 (t, 4H, $J = 5$ Hz), 3.67 (t, 2H, $J = 7$ Hz), 5.57 (d, 1H, $J = 5$ Hz), 6.35 (d, 1H, $J = 5$ Hz), 6.45 (t, 1H, $J = 5$ Hz), 6.75 (d, 1H, $J = 8$ Hz), 7.06 (t, 1H, $J = 8$ Hz), 7.23 (t, 1H, $J = 8$ Hz), 7.69 (d, 1H, $J = 8$ Hz), 8.18 (d, 2H, $J = 5$ Hz); IR (neat) cm^{-1}: 2941, 1682, 1651, 1485; FAB-MS *m*/*z*: 380 $(M+H)^+$; This compound was subsequently converted to its fumarate. mp 152–154 °C (recryst solvent: MeOH–Et_2O). Anal. Calcd for $C_{25}H_{29}N_5O_6$: C, 60.60; H, 5.90; N, 14.13. Found: C, 60.45; H, 6.01; N, 14.01.

5.2.23. 3-Chloro-4-(4-chlorobutyl)-1,4-benzoxazepin-5(4*H*)-one (27). A mixture of **3** (5.0 g, 28 mmol), K_2CO_3 (7.8 g, 56 mmol), and 1-bromo-4-chlorobutane (6.5 mL, 56 mmol) in 100 mL acetone was heated at reflux for 8 h. The reaction mixture was cooled down to room temperature, and then the insoluble solid was removed off by filtration. The filtrate was concentrated in vacuo, and then the resultant residue was dissolved into 50 mL of phosphorus oxychloride. A solution of 4 N HCl in dioxane (30 mL) was added dropwise, and then the resultant reaction mixture was stirred at 90 °C for 24 h. After the remaining phosphorus oxychloride was removed in vacuo, the residue was basified to pH 8 by addition of 10% NaOH solution at 0 °C and extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using hexane/EtOAc (6:1) as an eluent to give the title compound (4.3 g, 54%). Colorless oil; ^1H NMR ($CDCl_3$) δ 1.86–1.89 (m, 4H), 3.57–3.60 (m, 2H), 3.94 (t, 2H, $J = 6$ Hz), 6.73 (s, 1H), 7.02 (d, 1H, $J = 8$ Hz), 7.22–7.26 (m, 1H), 7.43–7.47 (m, 1H), 7.86-7.89 (m, 1H); IR (NaCl) cm^{-1}: 2956, 1704, 1644, 1605, 1574; FAB-MS *m*/*z*: 287 $(M+H)^+$.

5.2.24. 3-Chloro-4-[4-[4-(2-pyrimidinyl)piperazin-1-yl]-butyl]-1,4-benzoxazepin-5(4*H*)-one (30). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 89% yield. This compound was subsequently converted to its fumarate. White solid; mp 138–140 °C (recryst solvent: EtOH–diisopropylether). ^1H NMR (DMSO-d_6) δ 1.48–1.58 (m, 2H), 1.61–1.70 (m, 2H), 2.36–2.45 (m, 6H), 3.71 (t, 4H, $J = 5$ Hz), 3.85 (t, 2H, $J = 7$ Hz), 6.61 (t, 1H, $J = 5$ Hz), 6.62 (s, 2H), 7.15 (s, 1H), 7.17 (d, 1H, $J = 7$ Hz), 7.31–7.37 (m, 1H), 7.56–7.63 (m, 1H), 7.77–7.81 (m, 1H), 8.34 (d, 2H, $J = 5$ Hz); IR (KBr) cm^{-1}: 3416, 2588, 1657, 1586, 1558, 1479, 1454; FAB-MS *m*/*z*: 414 $(M+H)^+$. Anal. Calcd for $C_{25}H_{28}ClN_5O_6$: C, 56.66; H, 5.33; N, 13.21. Found: C, 56.61; H, 5.26; N, 13.23.

5.2.25. *N*-*tert*-Butoxycarbonyl-4-hydroxy-4-(2-pyrimidinyl)piperidine (33). To a stirred solution of 2-tri-*n*-butyltinpyrimidine **32**[23] (4.74 g, 0.013 mol) in 30 mL THF was added dropwise 12 mL of 1.6 N *n*-butyllithium in hexane under nitrogen atmosphere at −78 °C. After being stirred for 30 min, a solution of *N*-Boc-4-piperidone (3.06 g, 0.016 mol) in 30 mL THF was added dropwise, and the reaction temperature was gradually brought to room temperature. Ice water was added to the reaction solution, and extraction was performed by EtOAc. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using hexane/EtOAc (2:1) as an eluent to give the title compound (2.6 g, 61%). Yellow oil; ^1H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.16–2.25 (m, 2H), 3.11–3.32 (m, 4H), 4.02–4.15 (m, 2H), 7.22 (t, 1H, $J = 5$ Hz), 8.74 (d, 2H,

J = 5 Hz); IR ($CHCl_3$) cm^{-1}: 3022, 1681, 1561, 1424; FAB-MS m/z: 280 $(M+H)^+$.

5.2.26. 4-Hydroxy-4-(2-pyrimidinyl)piperidine (34). To a stirred solution of **33** (380 mg, 1.36 mmol) in 3 mL CH_2Cl_2 was added dropwise 2 mL trifluoroacetic acid. After being stirred for 30 min, the reaction mixture was concentrated in vacuo, and then an aqueous 10% NaOH and brine were added and extraction was performed by $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave the title compound (202 mg, 83%). Yellow oil; ^1H NMR ($CDCl_3$) δ 1.58–1.65 (m, 2H), 2.19–2.29 (m, 2H), 2.41 (t, 1H, J = 6 Hz), 2.85–3.30 (m, 4H), 7.21 (t, 1H, J = 5 Hz), 8.75 (d, 2H, J = 5 Hz); IR ($CHCl_3$) cm^{-1}: 3022, 2956, 1570, 1440; FAB-MS m/z: 180 $(M+H)^+$.

5.2.27. 4-(2-Pyrimidinyl)-1,2,3,6-tetrahydropyridine (36). A mixture of **33** (2.11 g, 7.56 mmol) and phosphorus oxychloride (1.0 mL, 10.6 mmol) in 30 mL pyridine was stirred for 15 h. The pyridine was distilled off in vacuo, and then an aqueous 10% NaOH was added and extraction was performed by $CHCl_3$. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using hexane/EtOAc (2:1) as an eluent to give **35** (1.4 g, 69%) as a colorless oil.

4-(2-Pyrimidinyl)-1,2,3,6-tetrahydropyridine **36** was prepared from **35**, using a method similar to that described for **34**, in 96% yield as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.62–2.66 (m, 2H), 3.12 (t, 2H, J = 6 Hz), 3.62–3.64 (m, 2H), 7.09 (t, 1H, J = 5 Hz), 7.27–7.29 (m, 2H), 8.68 (d, 2H, J = 5 Hz); IR ($CHCl_3$) cm^{-1}: 2984, 1557, 1423, 1210; FAB-MS m/z: 162 $(M+H)^+$.

5.2.28. 4-(2-Pyrimidinyl)piperidine (38). A mixture of **35** (310 mg, 1.19 mmol) and 100 mg of 10% palladium on carbon in 10 mL EtOH was stirred under hydrogen atmosphere for 2 days. The catalyst was filtered out, the filtrate was concentrated in vacuo, and the residue was chromatographed over SiO_2 using n-hexane/EtOAc (1:1) as an eluent to give *N-tert*-butoxycarbonyl-4-(2-pyrimidinyl)piperidine **37** (160 mg, 52%) as a colorless oil.

4-(2-Pyrimidinyl)piperidine **38** was prepared from **37**, using a method similar to that described for **34**, in 95% yield as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.76–1.86 (m, 2H), 2.00–2.04 (m, 2H), 2.75–2.82 (m, 2H), 2.99–3.06 (m, 1H), 3.20–3.24 (m, 2H), 7.12 (t, 1H, J = 5 Hz), 8.68 (d, 2H, J = 5 Hz); IR ($CHCl_3$) cm^{-1}: 3017, 1563, 1427, 1228; FAB-MS m/z: 164 $(M+H)^+$.

5.2.29. 5-(2-Pyrimidinyl)-1,2,3,6-tetrahydropyridine (39). The title compound was prepared from **32**, using a method similar to that described for **36**. Colorless oil. ^1H NMR ($CDCl_3$) δ 2.41–2.44 (m, 2H), 3.08 (t, 2H, J = 6 Hz), 3.95 (2H, s), 7.09 (t, 1H, J = 5 Hz), 7.36–7.38 (m, 1H), 8.66 (d, 2H, J = 5 Hz); IR ($CHCl_3$) cm^{-1}: 2952, 1653, 1627, 1424; FAB-MS m/z: 162 $(M+H)^+$.

5.2.30. 3-(2-Pyrimidinyl)piperidine (40). The title compound was prepared from **39**, using a method similar to that described for **38**. Colorless oil. ^1H NMR ($CDCl_3$) δ 1.54–1.59 (m, 2H), 2.05–2.09 (m, 1H), 2.16–2.21 (m, 1H), 2.33–2.35 (m, 2H), 2.74–2.81 (m, 1H), 3.00–3.14 (m, 2H), 7.14 (t, 1H, J = 5 Hz), 8.68 (d, 2H, J = 5 Hz); IR ($CHCl_3$) cm^{-1}: 2929, 2253, 1466, 1148; FAB-MS m/z: 164 $(M+H)^+$.

5.2.31. 3-Chloro-4-[4-[4-(2-pyridinyl)piperazin-1-yl]-butyl]-1,4-benzoxazepin-5(4*H*)-one (46). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 41% yield. This compound was subsequently converted to its fumarate. White solid; mp 158–161 °C (recryst solvent: EtOH–diisopropylether). ^1H NMR (DMSO-d_6) δ 1.48–1.58 (m, 2H), 1.62–1.72 (m, 2H), 2.40 (t, 2H, J = 7 Hz), 2.44–2.50 (m, 4H), 3.47 (t, 4H, J = 5 Hz), 3.85 (t, 2H, J = 7 Hz), 6.60–6.65 (m, 1H), 6.61 (s, 2H), 6.80 (d, 1H, J = 9 Hz), 7.16 (s, 1H), 7.17 (d, 1H, J = 7 Hz), 7.33 (t, 1H, J = 7 Hz), 7.48–7.63 (m, 2H), 7.77–7.81 (m, 1H), 8.08–8.11 (m, 1H); IR (KBr) cm^{-1}: 3430, 2949, 1704, 1657, 1594, 1480; Anal. Calcd for $C_{22}H_{25}ClN_4O_2 \cdot C_4H_4O_4$: C, 59.03; H, 5.53; N, 10.59. Found: C, 58.70; H, 5.54; N, 10.50.

5.2.32. 3-Chloro-4-[4-[4-hydroxy-4-(2-pyrimidinyl)piperidin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one (47). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 29% yield. This compound was subsequently converted to its hydrochloride. Colorless solid; mp 111–114 °C (recryst solvent: acetone); ^1H NMR (DMSO-d_6) δ 1.80–1.59 (m, 4H), 2.09–1.95 (m, 2H), 2.40–2.26 (m, 2H), 3.29–3.11 (m, 4H), 3.51–3.42 (m, 2H), 3.87 (t, 2H, J = 7 Hz), 7.16 (s, 1H), 7.16 (d, 1H, J = 8 Hz), 7.35 (t, 1H, J = 8 Hz), 7.46 (t, 1H, J = 5 Hz), 7.60 (t, 1H, J = 7 Hz), 7.79 (d, 1H, J = 8 Hz), 8.85 (d, 2H, J = 5 Hz), 9.55 (br s, 1H) ; IR (KBr) cm^{-1}: 2558, 1646, 1589, 1453, 1305; HRMS: Calcd for $C_{22}H_{26}ClN_4O_3$ $(M+H)^+$: 429.1693. Found: 429.1683.

5.2.33. 3-Chloro-4-[4-[4-hydroxy-4-(2-pyridinyl)piperidin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one (48). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 84% yield. This compound was subsequently converted to its hydrochloride. White solid; mp 172–175 °C (recryst solvent: acetone). ^1H NMR (DMSO-d_6) δ 1.78–1.82 (m, 6H), 2.43–2.47 (m, 2H), 3.19–3.27 (m, 4H), 3.43–3.45 (m, 2H), 3.87 (t, 2H, J = 7 Hz), 7.16–7.18 (m, 2H), 7.33 (s, 1H), 7.35 (d, 1H, J = 8 Hz), 7.61 (t, 1H, J = 8 Hz), 7.72 (d, 1H, J = 8 Hz), 7.80 (d, 1H, J = 8 Hz), 7.92 (m, 1H), 8.56 (d, 1H, J = 5 Hz), 9.64 (br s, 1H); IR (KBr) cm^{-1}: 3425, 2950, 1653, 1605, 1521, 1454; FAB-MS m/z: 428 $(M+H)^+$. Anal. Calcd for $C_{23}H_{26}ClN_3O_3 \cdot HCl$: C, 59.49; H, 5.86; N, 9.05. Found: C, 59.73; H, 5.77; N, 8.86.

5.2.34. 3-Chloro-4-[4-[4-(2-pyrimidinyl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one (49). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 26% yield. This compound was subsequently converted to its hydrochlo-

ride. Colorless solid; mp 147–151 °C (recryst solvent: MeOH/acetone). ^{1}H NMR (DMSO-d_6) δ 1.10–1.85 (m, 4H), 2.85–2.99 (m, 2H), 3.24–3.27 (m, 3H), 3.65–3.70 (m, 1H), 3.85–3.88 (m, 3H), 4.09–4.13 (m, 1H), 7.13–7.14 (m, 3H), 7.33–7.43 (m, 2H), 7.60 (t, 1H, J = 8 Hz), 7.79 (d, 1H, J = 8 Hz), 8.82 (d, 2H, J = 5 Hz), 10.15 (br s, 1H) ; IR (KBr) cm^{-1}: 3394, 2930, 1661, 1605, 1453, 1422, 1379, 1200; FAB-MS m/z: 411 (M+H)$^+$; Anal. Calcd for $C_{22}H_{23}ClN_4O_2$·HCl · 0.5H_2O : C, 57.90; H, 5.30; N, 12.28. Found: C, 58.10; H, 5.33; N, 12.29.

5.2.35. 3-Chloro-4-[4-[4-(2-pyridinyl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one (50). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 84% yield. This compound was subsequently converted to its dihydrochloride. White solid; mp 133–134 °C (recryst solvent: 2-PrOH-water). ^{1}H NMR (DMSO-d_6) δ 1.70–1.76 (m, 2H), 1.84–1.86 (m, 2H), 2.91–2.93 (m, 2H), 3.21–3.25 (m, 3H), 3.64–3.67 (m, 1H), 3.84–3.87 (m, 3H), 4.03–4.08 (m, 1H), 6.74–6.76 (m, 1H), 7.14–7.17 (m, 2H), 7.34 (t, 1H, J = 8 Hz), 7.42–7.44 (m, 1H), 7.60 (t, 1H, J = 8 Hz), 7.70–7.72 (m, 1H), 7.79 (dd, 1H, J = 2 and 8 Hz), 7.95–7.97 (m, 1H), 8.61–8.63 (m, 1H), 10.74 (br s, 1H); IR (KBr) cm^{-1}: 3320, 3015, 2600, 1644, 1612, 1513, 1455; FAB-MS m/z: 410 (M+H)$^+$; Anal. Calcd for $C_{23}H_{24}ClN_3O_2 \cdot 2HCl \cdot 2H_2O$: C, 53.24; H, 5.83; N, 8.10. Found: C, 53.56; H, 6.04; N, 7.92.

5.2.36. 3-Chloro-4-[4-[4-(2-pyrimidinyl)piperidin-1-yl]-butyl]-1,4-benzoxazepin-5(4*H*)-one (51). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 84% yield. This compound was subsequently converted to its hydrochloride. Colorless solid; mp 110–113 °C (recryst solvent: acetone).; ^{1}H NMR (DMSO-d_6) δ 1.66–1.85 (m, 4H), 2.05–2.20 (m, 4H), 3.03–3.15 (m, 5H), 3.54–3.57 (m, 2H), 3.84–3.87 (m, 2H), 7.14–7.17 (m, 2H), 7.33–7.40 (m, 2H), 7.58–7.62 (m, 1H), 7.80 (d, 1H, J = 8 Hz), 8.78 (d, 2H, J = 5 Hz), 10.15 (br s, 1H) ; IR (KBr) cm^{-1}: 3051, 2946, 1646, 1604, 1564, 1478, 1456, 1426; HRMS: Calcd for $C_{22}H_{26}ClN_4O_2$ (M+H)$^+$: 413.1744. Found: 413.1726.

5.2.37. 3-Chloro-4-[4-[4-(2-pyridinyl)piperidin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one (52). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 85% yield. This compound was subsequently converted to its hydrochloride. White solid; mp 158–161 °C (recryst solvent: acetone). ^{1}H NMR (DMSO-d_6) δ 1.68–1.89 (m, 4H), 2.04–2.15 (m, 4H), 2.95–3.18 (m, 5H), 3.55–3.58 (m, 2H), 3.84–3.87 (m, 2H), 7.14–7.18 (m, 2H), 7.31–7.40 (m, 3H), 7.60 (t, 1H, J = 8 Hz), 7.79 (d, 1H, J = 8 Hz), 7.89–7.91 (m, 1H), 8.55–8.59 (m, 1H), 9.71 (br s, 1H); IR (KBr) cm^{-1}: 3428, 2946, 2672, 1648, 1540, 1454; FAB-MS m/z: 412 (M+H)$^+$; Anal. Calcd for $C_{23}H_{26}ClN_3O_2$·HCl · H $_2$O: C, 54.93; H, 6.01; N, 8.36. Found: C, 54.67; H, 5.64; N, 8.18.

5.2.38. 3-Chloro-4-[4-[5-(2-pyrimidinyl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one (53). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 20% yield. This compound was subsequently converted to its fumarate. Colorless solid; mp 124–126 °C (recryst solvent: acetone). ; ^{1}H NMR (DMSO-d_6) δ 1.61–1.70 (m, 4H), 2.31–2.40 (m, 2H), 2.59–2.62 (m, 4H), 3.42–3.51 (m, 2H), 3.84–3.89 (m, 2H), 6.60 (s, 2H), 7.11–7.15 (m, 2H), 7.23 (s, 1H), 7.29–7.34 (m, 2H), 7.58 (t, 1H, J = 7 Hz), 7.78 (d, 1H, J = 8 Hz), 8.73 (d, 2H, J = 5 Hz); IR (KBr) cm^{-1}: 2926, 2576, 1699, 1649, 1560, 1478, 1422, 1378; HRMS: Calcd for $C_{22}H_{24}ClN_4O_2$ (M+H)$^+$: 411.1588. Found: 411.1583.

5.2.39. 3-Chloro-4-[4-[3-(2-pyrimidinyl)piperidin-1-yl]-butyl]-1,4-benzoxazepin-5(4*H*)-one (54). The title compound was prepared from **27**, using a method similar to that described for **1a**, in 41% yield. This compound was subsequently converted to its fumarate. Amorphous; ^{1}H NMR (DMSO-d_6) δ 1.58–1.95 (m, 8H), 2.21–2.35 (m, 3H), 2.88–3.01 (m, 2H), 3.61–3.65 (m, 2H), 3.82–3.88 (m, 2H), 6.61 (s, 2H), 7.12–7.16 (m, 2H), 7.33–7.38 (m, 2H), 7.50–7.55 (m, 1H), 7.79 (d, 1H, J = 8 Hz), 8.77 (d, 2H, J = 5 Hz); IR (KBr) cm^{-1}: 2947, 1643, 1558, 1480; Anal. Calcd for $C_{22}H_{26}ClN_4O_2$ (M+H)$^+$: 413.1744. Found: 413.1701.

5.2.40. 3-Chloro-4-[4-[4-(2-pyrimidinyl)pyridinio-1-yl]butyl]-1,4-benzoxazepin-5(4*H*)-one iodide (55). A mixture of **27** (200 mg, 0.70 mmol), sodium iodide (210 mg, 1.39 mmol), and 2,4′-dipyridyl (120 mg, 0.77 mmol) in 2 mL CH_3CN was heated at reflux for 30 h. The reaction mixture was allowed to cool, then the precipitated crystal was obtained by filtration and was recrystallized from MeOH/acetone/Et_2O to give the title compound (298 mg, 96%). ^{1}H NMR (DMSO-d_6) δ 1.65–1.71 (m, 2H), 2.01–2.12 (m, 2H), 3.87 (t, 2H, J = 7 Hz), 4.71 (t, 2H, J = 7 Hz), 7.10 (s, 1H), 7.14 (d, 1H, J = 8 Hz), 7.33 (t, 1H, J = 8 Hz), 7.58 (dt, 1H, J = 2 Hz, 8 Hz), 7.66 (dd, 1H, J = 4 Hz, 8 Hz), 7.77 (dd, 1H, J = 2 Hz, 8 Hz), 8.11 (dt, 1H, J = 2 Hz, 8 Hz), 8.44 (d, 1H, J = 8 Hz), 8.81 (d, 2H, J = 7 Hz), 8.87 (d, 1H, J = 4 Hz), 9.21 (d, 2H, J = 7 Hz); IR (KBr) cm^{-1}: 3445, 3008, 1642, 1603, 1561, 1475, 1456; FAB-MS m/z: 406 (M)$^+$.

5.2.41. Different synthetic method of 50 from 55. To a stirred solution of **55** (800 mg, 1.50 mmol) in 20 mL EtOH was added sodium borohydride (140 mg, 3.00 mmol) at 0 °C, and then the resultant mixture was agitated at room temperature for 10 min. Water was added and extraction was performed with EtOAc. An organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over SiO_2 using CH_2Cl_2/MeOH (30:1) as an eluent to give the title compound (718 mg, 97%).

5.3. Biological evaluations

5.3.1. Evaluation of affinity with 5-HT$_{1A}$ serotonergic receptor[24]. The hippocampi dissected from brains of male Wistar rats were homogenized in 50 mM Tris-phosphate buffer (pH 7.7). The homogenate was centrifuged at 4 °C and 35,000g for 10 min. The pellet was suspended in the same buffer, homogenized again, and incubated at 37 °C for 30 min. This mixture was centrifuged at 4 °C and 35,000g for 10 min, and then the same

buffer was added to the obtained precipitate. This homogenization-centrifugation operation was repeated once more to obtain a final precipitate, and then 10 μM *N*-methyl-*N*-2-propynylbenzylamine (Pargyline), 4 mM calcium chloride, and 0.1% ascorbic acid contained in a 50 mM Tris-phosphate buffer (pH 7.7) were added. This was then homogenized to prepare the 5-HT_{1A} receptor. For the binding assay, 0.4 nM [^{3}H]8-OH-DPAT was used, various concentrations of test compounds were added to a system of 0.25 mg/mL protein or a total of 0.25 mL, and these were incubated at 25 °C for 30 min. A Whatman GF/C filter was used to filter each of the reaction solutions, then the filter was washed by 20 mM Tris-phosphate buffer (pH 7.7). The 5-HT_{1A} receptor was trapped on the filter and the radioactivity of the 8-OH-DPAT bound to it was measured to find the degree of binding. The 50% of binding affinity (IC_{50}) was calculated from the degrees of binding in the various sample concentrations.

5.3.2. Evaluation of affinity with dopamine D_2 receptor.[25] The membranes were prepared by the same way as 5-HT_{1A} receptor. The specific ligand and tissue sources were used as follows; [^{3}H]Raclopride, rat striatum membranes.

5.3.3. Evaluation of affinity with α_1-adrenergic receptor.[26] The membranes were prepared by the same way as 5-HT_{1A} receptor. The specific ligand and tissue sources were used as follows; [^{3}H]Prazosin, rat cerebral cortex membranes.

5.3.4. Assay for adenylate cyclase activity. The hippocampus dissected from Wistar rat brain was homogenized and centrifuged at 500*g* for 2 min and then the supernatants were centrifuged at 39,000*g* for 10 min. The pelleted membranes were resuspended in the homogenizing solution and used for the assay. Adenylate cyclase activity was determined according to the modified method of De Vivo et al.[27] The amount of cAMP produced was measured by a radioimmunoassay.

5.3.5. Evaluation of efficacy on experimental ischemic brain tissue damage (t-MCAO model).[29] Ten-to-eleven-week-old Wistar male rats were used and the right middle cerebral artery was temporarily occluded for 60 min. Ten days after reperfusion, the brains were excised and the degree of brain tissue damage of the cerebral cortex, and corpus striatum in the occluded side was evaluated by measuring the density of peripheral type benzodiazepine binding sites (PTBBS).[30] The tested compounds were dissolved in physiological saline and administered subcutaneously at the backs of the rats immediately after the right middle cerebral artery occulusion. As a control, physiological saline of 2 mL/kg body weight was similarly administered.

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