Succinimide Derivatives. II.[1] Synthesis and Antipsychotic Activity of *N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2-*cis*-cyclohexanedicarboximide (SM-9018) and Related Compounds[2,3]

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Cyclic imides bearing ω-(4-benzisothiazol-3-yl-1-piperazinyl)alkyl moieties were synthesized and tested for antipsychotic activity. The *in vitro* binding affinities of these compounds were examined for dopamine 2 (D_2) and serotonin 2 (5-HT_2) receptor sites. Structure–activity relationships within these series are discussed. One of these compounds, *N*-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2-*cis*-cyclohexanedicarboximide (SM-9018), was found to be more potent and more selective *in vivo* than tiospirone in its antipsychotic activity. SM-9018 (17) is currently undergoing clinical evaluation as a selective antipsychotic agent.

Key words cyclohexanedicarboximide; SM-9018; dopamine 2 receptor; serotonin 2 receptor; structure–activity relationship

Drug therapy of schizophrenia has traditionally involved the use of neuroleptics which pharmacologically act as dopamine 2 (D_2) antagonists. While these classical neuroleptics are effective in alleviating the delusion, hallucination, or paranoia known as positive symptoms of schizophrenia, the flattening affect and social withdrawal which characterize the negative symptoms of this disease are refractory to drug treatment. Moreover, their use is frequently attended by the development of extrapyramidal side effects.[4] Chronic administration of neuroleptics can cause the serious and often irreversible syndrome of tardive dyskinesia.[5] Thus, there is compelling need to develop newer atypical agents which would retain efficacy for both positive and negative symptoms of schizophrenia, but have a much lower incidence of debilitating side effects.

The pharmacological blockade of central D_2 receptors in limbic areas and the frontal cortex, sites of action of known neuroleptics, is held to be responsible for the marked control of positive symptoms.[6,7] However, this action in the striatum produces extrapyramidal side effects.[8] On the other hand, the mechanism of the negative symptoms is still unclear. It has nevertheless been reported that the selective serotonin 2 (5-HT_2) receptor antagonists ritanserin (A) and setoperone (B) alleviate negative symptoms and reduce the incidence of extrapyramidal side effects caused by neuroleptic maintenance therapy.[9–11]

On the basis of these findings, compounds which have 5-HT_2 antagonistic activity with D_2 antagonistic activity may be useful atypical agents which would retain efficacy for both positive and negative symptoms of schizophrenia and have a much lower incidence of debilitating side effects.

Initial research and development of psychotropic cyclic imide derivatives was conducted by the Bristol–Myers research group around 1970,[12] and buspirone (C) was proposed as a candidate drug. Buspirone was initially screened as a neuroleptic with D_2 antagonistic activity, but it was found later through clinical studies to have anxiolytic properties rather than neuroleptic properties.[13]

Our study program on cyclic imide derivatives was initiated in the early 1980s with the aim of finding new and useful psychotropic agents by applying receptor-binding assay as a major tool. As a result, tandospirone (**1**) has been developed as an anxio-selective agent with more selective serotonin 1A (5-HT_{1A}) agonistic activity and without any appreciable D_2 antagonistic activity compared to buspirone.[1a] Clinical studies of tandospirone have confirmed its potency as an anti-anxiety agent.

Our screening studies were next focussed on discovering new neuroleptics with more characteristic properties. In 1983, it was proposed that cyclic imide derivatives with a benzisothiazole ring, such as tiospirone (D), might be atypical neuroleptics.[14] We started to synthesize succinimide derivatives with various heteroaromatic moieties containing a benzisothiazole ring and to screen the compounds through systematic receptor-binding assay. In the course of our studies, some derivatives with a benzisothiazole moiety, such as SM-9018 (**17**), were found to show strong binding affinities to both D_2 and 5-HT_2 receptors. Pharmacological studies, furthermore, showed that these derivatives had both potent D_2 and 5-HT_2 antagonistic activities *in vivo*. In the present report, we describe the synthesis and D_2 antagonistic and 5-HT_2 antagonistic activity of succinimide derivatives.

Chemistry

Most of the *N*-substituted cyclic imides (I) listed in Table 1 were prepared by modifications of the reported methods,[14b,15] from anhydrides (II) (method A) or imides (III) (method B or C), as outlined in Chart 1. Method A involved condensation of anhydrides (II) with 4-[4-(benzisothiazol-3-yl)-1-piperazinyl]butylamine (**52**) prepared from 1-(1,2-benzisothiazol-3-yl)piperazine (**54**). Method B involved condensation of the imide (III) with the spiro-fused quaternary salt (**53**) prepared from **54** and dimesylate. In method C, the imides (III) were converted to *N*-(ω-haloalkyl)imides (IV), followed by reaction with V.

Carbinol derivatives (**12**, **13**) were prepared with combinations of three moieties, *i.e.*, 1-(1,2-benzisothiazol-3-yl)piperazine (**54**), the imide (**55**) and 3,4-epoxybutyl

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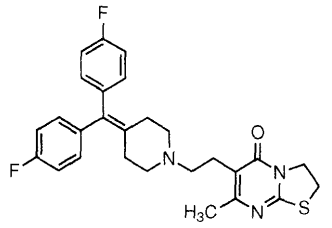
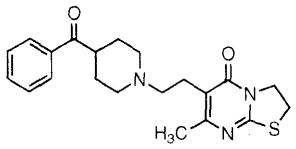
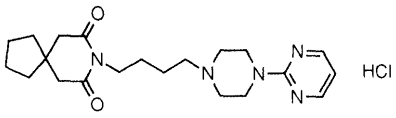


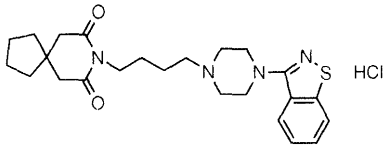
ritanserin (A)



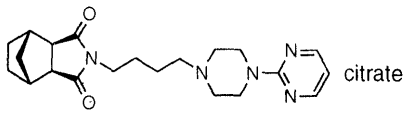
setoperone (B)



buspirone (C)



tiospirone (D)



tandospirone (1)

Fig. 1

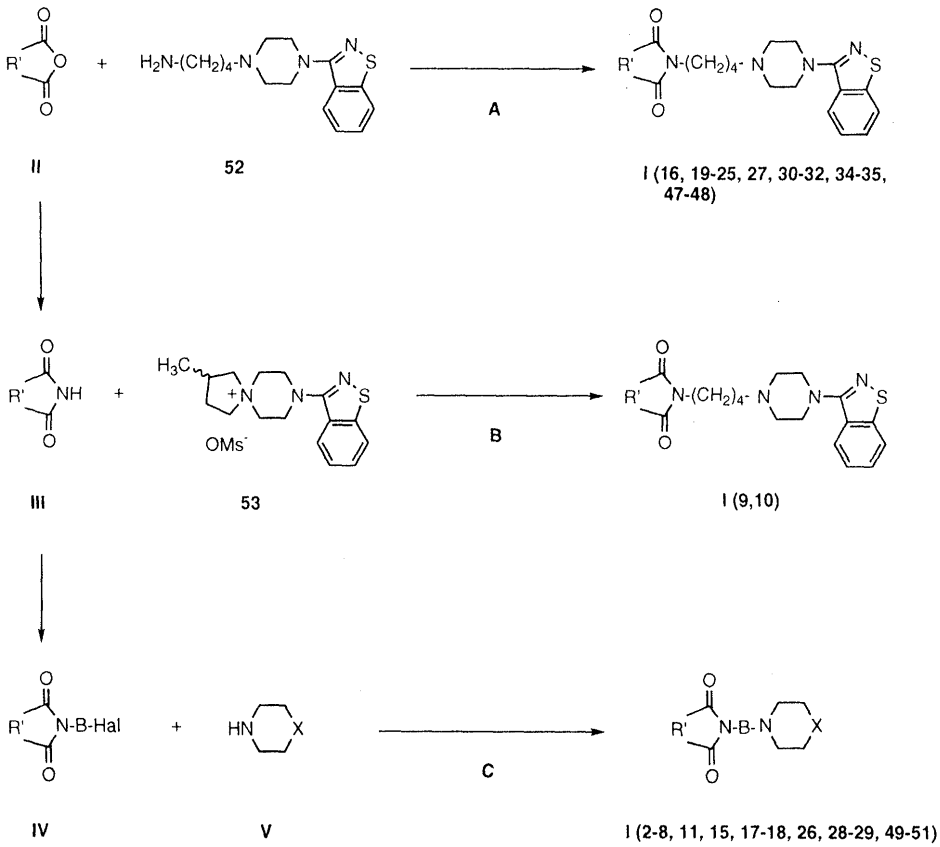


Chart 1

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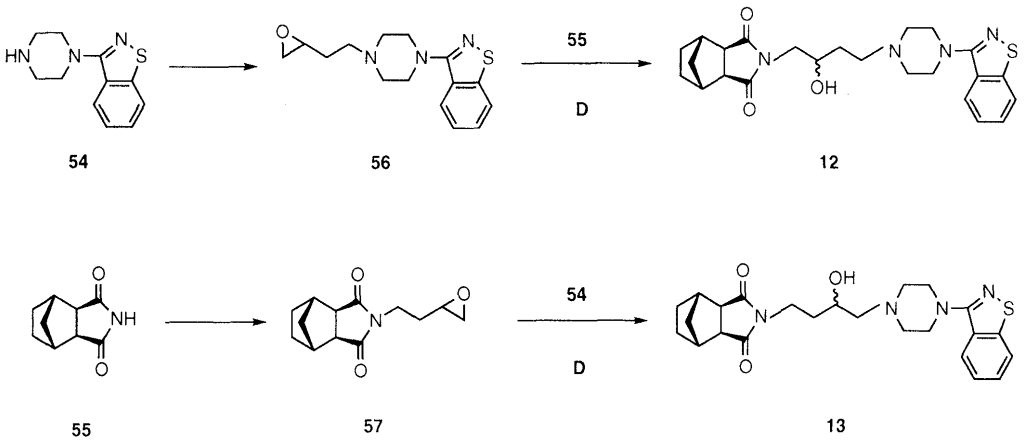

Chart 2

halide (Chart 2). Alkylation of **54** with 3,4-epoxybutyl halide, followed by the reaction of the resulting epoxide (**56**) with **55**, afforded **12** (method D), while initial alkylation of **55** with 3,4-epoxybutyl halide and subsequent treatment of the resulting epoxide (**57**) with **54** led to **13** (method D).

As shown in Chart 3, reduction of the imide moiety in I with $NaBH_4$ or $LiAlH_4$ gave the hydroxylactam derivatives (VI),[16] which were allowed to react with triethylsilane in the presence of trifluoroacetic acid to give the lactam derivative (**38**) (method E).[17] The pyrrolidine derivative (**39**), corresponding to the complete reduction product of the imide moiety in **17**, was prepared by the condensation of the dimesylate (**58**) with **52** in the presence of base (method F).

As shown in Chart 4, the amide derivative (**14**) was prepared by the condensation of γ-aminobutyric acid with the anhydride (**59**), followed by reaction with thionyl chloride, and then with **54** (method G). The amide derivatives (VII) were prepared by the condensation of the amine (**52**) with the corresponding acid halide (VIII) (method H). Method J involved condensation of the halide (**61**) with **54**.

The ester derivative (**43**) was prepared by condensation of the corresponding alcohol (**62**) with cyclohexanecarbonyl chloride in the usual manner as shown in Chart 5 (method K).

The elemental analysis and spectral data of these newly synthesized compounds (I, VII, **12**—**14**, **36**—**39** and **42**—**43**) are presented in Tables 1 and 2. Starting materials, such as the acid anhydrides (II), the imides (III, IV), the amines (V), and acid halides (VIII), if not commercially available, were prepared by known methodologies.[1,14b,18]

Biological Results and Discussion

All compounds were screened for *in vitro* binding affinities for rat striatal D_2 receptor labeled with [^{3}H]domperidone[19] and rat whole brain 5-HT_2 receptor labeled with [^{3}H]ketanserin.[20] Binding affinity data are summarized in Table 3.

The high affinities of the cyclic imides toward D_2 and 5-HT_2 receptors were essentially due to the presence of the 1-(1,2-benzisothiazol-3-yl)piperazine moiety. In fact, compounds **1**, **2**, **49**, **50** and **51** proved to have little affinity for these receptors (Table 3).

Variation of the bond length between the imide and arylpiperazine had a significant effect on D_2 binding and little effect on 5-HT_2 binding. Compound **3** with a four-carbon chain had the highest affinities for both D_2 and 5-HT_2 receptors among compounds **3**, **4** and **5** with chains from three to five carbons. Replacement of the saturated four-carbon chain of **3** with unsaturated four-carbon chains showed different effects depending upon the type of unsaturation. Compounds **6** and **18** with the double bond in the *trans* configuration were equipotent with the corresponding saturated derivatives (**3** and **17**, respectively). However, compound **7** with the double bond in the *cis* configuration was significantly less potent than **3**.[21]

Introduction of methyl and hydroxyl groups onto the four-carbon chain in **3** showed a different effect depending upon the site of substitution on the carbon chain. Compounds **8** and **9** which were substituted with a methyl group at positions 1 and 2 on the carbon chain, respectively, had affinities for both receptors similar to those of the unsubstituted compound (**3**), while compounds **10** and **11**, substituted at positions 3 and 4, respectively, had less potent affinities than **3** for both receptors. Compound **12**, substituted with a hydroxyl group at position 2, had weaker affinities for both receptor than the unsubstituted compound (**3**), but tended to be more potent than compound **13** substituted with a hydroxyl group at position 3. Generally, the binding affinities of substituted derivatives tended to decrease as their substituted sites approached position 4 on the carbon chain, substituted with a piperazine group. Introduction of an oxo group at position 4 on the saturated four-carbon chain of **3** resulted in a loss of both binding affinities (compare **14** with **3**). The above results concerning the binding affinities of substituted derivatives of **3** suggest that the nitrogen atom at position 4 on the carbon chain plays an important part in both binding affinities.

As expected,[1] compounds varying in the imide portion of **3** generally retained both binding affinities so long as the lipophilicity of the imide moiety was retained. However, variation of the imide portion showed a more significant effect on D_2 binding than on 5-HT_2 binding. As regards D_2 binding affinity, the stereoisomer (**15**), the homoderivative (**16**), and the norderivative (**17**) of **3**

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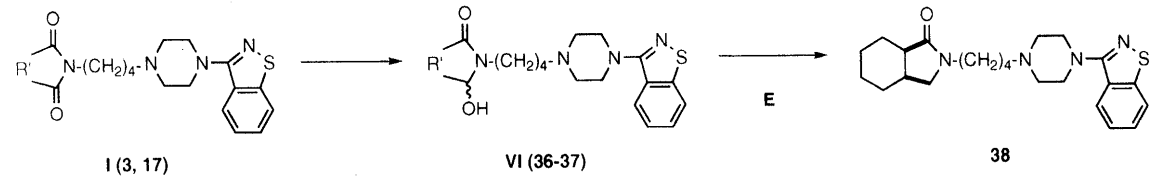


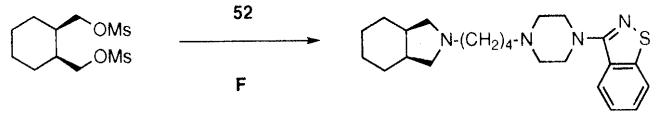
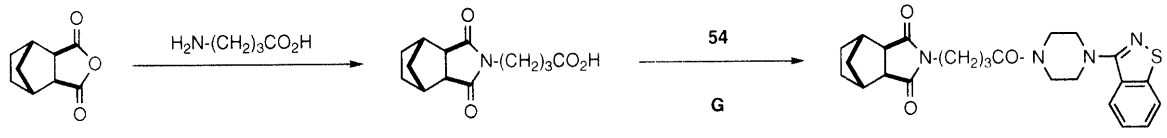
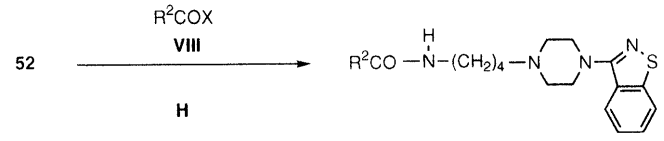


Chart 3





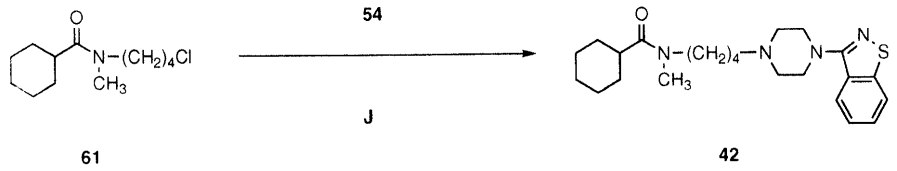


Chart 4

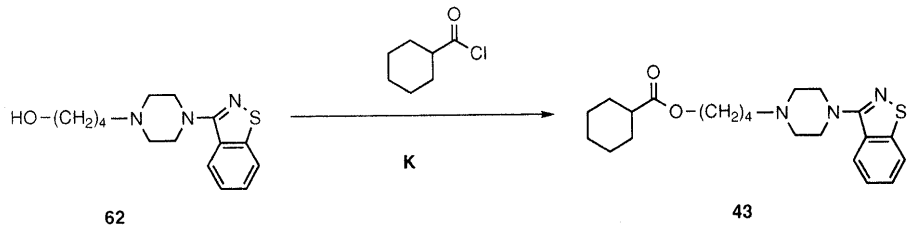


Chart 5

retained the same affinity as **3**, and the oxaderivative (**19**) had a somewhat decreased D_2 binding affinity compared to **3**. However, the 5-HT_2 binding affinities of these compounds were equivalent to that of **3**. The spiroderivatives (**20**, **21**), which had the same lipophilicity as **3**, retained potent affinities for both receptors. Introduction of one methyl group in the cyclic imide moiety of **3** had little effect on either of the binding affinities, while introduction of two methyl groups had a significant effect on binding to both receptors. The monomethyl derivative (**22**) possessed the same affinities for both receptors as **3** and **17**, although the dimethyl derivatives (**23**, **24**, **25**) possessed less potent affinities than **17**. Ring-constriction of the cyclic imide moiety of **3** tended to decrease both binding affinities, probably as a result of decreasing lipophilicity. The succinimide derivative (**26**), which was the simplest cyclic imide derivative tested, had the lowest affinity among **3**, **17**, **26** and **27**. Replacement of the ethylene bond on the cyclic imide portion with a double bond showed a different effect depending on the site of

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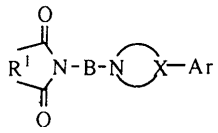
Table 1. Cyclic Imide Derivatives



Compd. No.	—R[1]—	B	N X–Ar[a]	Yield (%)[b] (method)	mp (°C)	Formula	Analysis (%)[c] Calcd (Found)		
							C	H	N
2		$(CH_2)_4$	A-1	34.0 (C)	196—203	$C_{22}H_{29}ClN_4O_2 \cdot 2HCl \cdot 0.5H_2O$	52.96 (52.91)	6.47 (6.41)	11.23 (11.16)
3		$(CH_2)_4$	A-2	57.9 (C)	217—218	$C_{24}H_{30}N_4O_2S \cdot HCl$	60.65 (60.68)	6.74 (6.58)	11.61 (11.80)
4		$(CH_2)_5$	A-2	53.4 (C)	230—232	$C_{25}H_{32}N_4O_2S \cdot HCl \cdot 0.5H_2O$	60.28 (60.54)	6.88 (6.78)	11.25 (11.14)
5		$(CH_2)_3$	A-2	56.5 (C)	245—246	$C_{23}H_{28}N_4O_2S \cdot HCl \cdot 0.3H_2O$	59.23 (59.21)	6.40 (6.31)	12.01 (11.92)
6		$CH_2C(H)=CCH_2$ (H)	A-2	70.0 (C)	214—215	$C_{24}H_{28}N_4O_2S \cdot HCl \cdot H_2O$	58.70 (58.46)	6.36 (6.07)	11.41 (11.28)
7		$CH_2C(H)=C(H)CH_2$	A-2	75.9 (C)	116—118	$C_{24}H_{28}N_4O_2S$	60.94 (60.81)	6.18 (6.28)	11.84 (11.70)
8		$CH(Me)CH_2CH_2CH_2$	A-2	10.2 (C)	184—186	$C_{25}H_{32}N_4O_2S \cdot HCl \cdot 1.2H_2O$	58.80 (58.74)	6.99 (6.87)	10.97 (11.01)
9		$CH_2CH(Me)CH_2CH_2$	A-2	14.9 (B)	234—235	$C_{25}H_{32}N_4O_2S \cdot HCl$	61.40 (61.32)	6.80 (7.02)	11.46 (11.40)
10		$CH_2CH_2CH(Me)CH_2$	A-2	67.8 (B)	205—206	$C_{25}H_{32}N_4O_2S \cdot HCl$	61.40 (61.29)	6.80 (7.07)	11.46 (11.40)
11		$CH_2CH_2CH_2CH(Me)$	A-2	62.7 (C)	257—258	$C_{25}H_{32}N_4O_2S \cdot HCl \cdot 0.3H_2O$	60.73 (60.82)	6.85 (6.91)	11.33 (11.25)
12		$CH_2CH(OH)CH_2CH_2$	A-2	47.7 (D)	166—167	$C_{24}H_{30}N_4O_3S$	63.41 (63.35)	6.65 (6.79)	12.32 (11.90)
13		$CH_2CH_2CH(OH)CH_2$	A-2	80.7 (D)	169—170	$C_{24}H_{30}N_4O_3S$	63.41 (63.61)	6.65 (6.64)	12.32 (12.35)
14		$CH_2CH_2CH_2CO$	A-2	62.8 (G)	133—135	$C_{24}H_{28}N_4O_3S \cdot 0.3H_2O$	62.94 (62.95)	6.29 (6.31)	12.23 (12.25)
15		$(CH_2)_4$	A-2	60.0 (C)	213—214	$C_{24}H_{30}N_4O_2S \cdot HCl \cdot 0.3H_2O$	60.00 (60.05)	6.63 (6.74)	11.66 (11.56)
16		$(CH_2)_4$	A-2	77.3 (A)	229—231	$C_{25}H_{32}N_4O_2S \cdot HCl$	61.40 (61.35)	6.80 (6.96)	11.46 (11.53)
17		$(CH_2)_4$	A-2	70.5 (C)	192—193	$C_{23}H_{30}N_4O_2S \cdot HCl \cdot 2H_2O$	55.35 (55.73)	7.07 (7.03)	11.23 (11.33)
18		$CH_2C(H)=CCH_2$ (H)	A-2	44.2 (C)	209—210	$C_{23}H_{28}N_4O_2S \cdot (CO_2H)_2$	58.19 (58.35)	6.07 (5.88)	10.61 (10.89)
19		$(CH_2)_4$	A-2	94.8 (A)	243—244	$C_{23}H_{28}N_4O_3S \cdot HCl$	57.91 (57.39)	6.13 (6.41)	11.75 (11.88)

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Table 1. (continued)

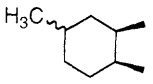
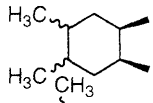
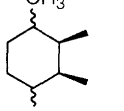
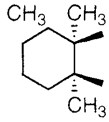
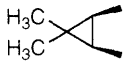
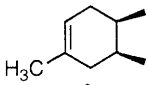
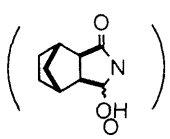
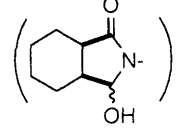
Compd. No.	—R¹—	B	N X–Ar[a]	Yield (%)[b] (method)	mp (°C)	Formula	Analysis (%)[c] Calcd (Found) C	H	N
20		$(CH_2)_4$	A-2	57.6 (A)	215—216	$C_{26}H_{34}N_4O_2S \cdot HCl$	62.07 (61.62	7.01 7.06	11.14 10.88)
21		$(CH_2)_4$	A-2	73.6 (A)	220—221	$C_{25}H_{32}N_4O_2S \cdot HCl \cdot H_2O$	59.22 (59.27	6.96 6.77	11.05 11.04)
22		$(CH_2)_4$	A-2	84.1 (A)	180—181	$C_{24}H_{32}N_4O_2S \cdot HCl$	60.42 (60.25	6.97 7.07	11.74 11.83)
23		$(CH_2)_4$	A-2	49.7 (A)	208—210	$C_{25}H_{34}N_4O_2S \cdot HCl \cdot 0.2H_2O$	60.70 (60.71	7.21 7.20	11.33 11.05)
24		$(CH_2)_4$	A-2	61.8 (A)	200—201	$C_{25}H_{34}N_4O_2S \cdot HCl \cdot 0.3H_2O$	60.48 (60.54	7.23 7.10	11.28 11.16)
25		$(CH_2)_4$	A-2	55.6 (A)	245—247	$C_{25}H_{34}N_4O_2S \cdot HCl \cdot 0.5H_2O$	60.04 (60.05	7.26 7.26	11.20 10.91)
26		$(CH_2)_4$	A-2	71.9 (C)	204—205	$C_{19}H_{24}N_4O_2S \cdot HCl \cdot 0.3H_2O$	55.08 (55.11	6.23 6.30	13.52 13.52)
27		$(CH_2)_4$	A-2	61.4 (A)	204—205	$C_{22}H_{28}N_4O_2S \cdot HCl \cdot (CH_3)_2CHOH$	58.98 (59.06	7.33 7.32	11.01 11.02)
28		$(CH_2)_4$	A-2	52.9 (C)	222—224 (dec.)	$C_{24}H_{28}N_4O_2S \cdot HCl$	60.94 (60.87	6.18 6.18	11.85 11.66)
29		$(CH_2)_4$	A-2	59.2 (C)	214—216 (dec.)	$C_{24}H_{28}N_4O_2S \cdot HCl$	60.94 (60.60	6.18 6.21	11.85 11.74)
30		$(CH_2)_4$	A-2	49.0 (A)	141—142	$C_{25}H_{30}N_4O_2S$	66.64 (66.86	6.71 6.80	12.44 12.15)
31		$(CH_2)_4$	A-2	74.4 (A)	92.5—94	$C_{23}H_{28}N_4O_2S$	65.07 (64.89	6.65 6.74	13.20 12.86)
32		$(CH_2)_4$	A-2	32.4 (A)	154—156 (dec.)	$C_{24}H_{30}N_4O_3S \cdot (CO_2H)_2$	59.08 (58.71	6.10 6.24	10.60 10.28)
33		$(CH_2)_4$	A-2	68.4 (A)	226—227	$C_{23}H_{28}N_4O_2S \cdot HCl$	59.92 (59.62	6.34 6.33	12.15 12.09)
34		$(CH_2)_4$	A-2	87.0 (A)	142—145 (Base)	$C_{23}H_{24}N_4O_2S \cdot HCl$	60.45 (60.18	5.51 5.60	12.26 12.36)
35		$(CH_2)_4$	A-2	57.2 (A)	253—254	$C_{22}H_{23}N_5O_2S \cdot HCl \cdot 0.3H_2O$	57.02 (57.02	5.35 5.47	15.11 15.30)
36		$(CH_2)_4$	A-2	63 (E)	129—130	$C_{24}H_{32}N_4O_2S \cdot 0.5H_2O$	64.11 (64.25	7.40 7.27	12.46 12.30)
37		$(CH_2)_4$	A-2	52.1 (E)	206—208	$C_{23}H_{32}N_4O_2S \cdot 0.5HCl$	61.83 (61.78	7.33 7.00	12.54 12.46)

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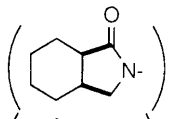
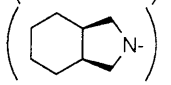
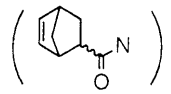
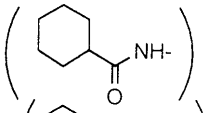
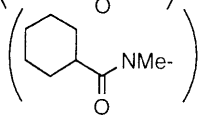
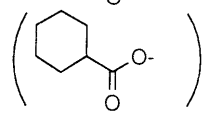
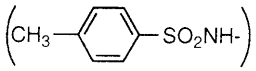
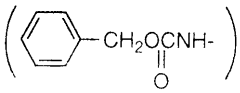
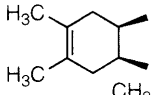
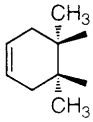
Table 1. (continued)

Compd. No.	—R[1]—	B	N⌒X–Ar[a]	Yield (%)[b] (method)	mp (°C)	Formula	Analysis (%)[c] Calcd (Found) C	H	N
38		$(CH_2)_4$	A-2	47.2 (E)	176—177	$C_{23}H_{32}N_4OS \cdot HCl$	61.52 (61.46	7.41 7.27	12.48 12.49)
39		$(CH_2)_4$	A-2	46.9 (F)	258—259	$C_{23}H_{34}N_4S \cdot 2HClH_2O$	54.43 (54.11	7.94 7.89	11.04 10.95)
40		$(CH_2)_4$	A-2	56.4 (H)	147.5—149	$C_{23}H_{30}N_4OS \cdot (CO_2H)_2 \cdot 0.5H_2O$	58.92 (58.87	6.53 6.51	10.99 10.80)
41		$(CH_2)_4$	A-2	67.7 (H)	128—129	$C_{22}H_{32}N_4OS \cdot 0.2H_2O$	65.38 (65.12	8.08 7.80	13.86 13.56)
42		$(CH_2)_4$	A-2	43.5 (J)	202—202.5	$C_{23}H_{34}N_4OS \cdot HCl \cdot H_2O$	58.89 (59.05	7.95 7.60	11.94 11.94)
43		$(CH_2)_4$	A-2	87.1 (K)	166—168	$C_{22}H_{31}N_3O_2S \cdot HCl \cdot 0.2H_2O$	59.83 (59.89	7.39 7.43	9.51 9.62)
44		$(CH_2)_4$	A-2	77.5 (H)	95—97 (Base)	$C_{17}H_{24}N_4OS \cdot (CO_2H)_2 \cdot 0.5H_2O$	52.89 (53.13	6.31 6.25	12.99 12.18)
45		$(CH_2)_4$	A-2	75.0 (H)	171—173 (dec.)	$C_{22}H_{28}N_4O_2S \cdot (CO_2H)_2$	53.92 (53.65	5.66 5.85	10.48 10.39)
46		$(CH_2)_4$	A-2	74.8 (H)	143—144	$C_{23}H_{28}N_4O_2S \cdot (CO_2H)_2 \cdot 0.5H_2O$	57.35 (57.01	5.97 5.98	10.70 10.52)
47		$(CH_2)_4$	A-2	77.0 (A)	85—86	$C_{25}H_{32}N_4O_2S$	66.34 (66.20	7.13 7.18	12.38 12.29)
48		$(CH_2)_4$	A-2	73.3 (A)	102.5—104	$C_{25}H_{32}N_4O_2S \cdot 0.3H_2O$	65.56 (65.38	7.17 7.21	12.23 12.47)
49		$(CH_2)_4$	A-3	62.5 (C)	258—259 (dec.)	$C_{21}H_{31}ClN_2O_3 \cdot HCl$	61.67 (61.77	6.90 6.90	5.99 6.04)
50		$(CH_2)_4$	A-4	66.4 (C)	276—278	$C_{25}H_{32}N_4O_3 \cdot HCl$	63.48 (63.42	7.03 6.80	11.85 11.90)
51		$(CH_2)_4$	A-5	53.3 (C)	193—196 (Base)	$C_{26}H_{34}N_4O_3 \cdot HCl \cdot 0.3H_2O$	63.74 (64.12	7.27 7.24	11.24 11.50)

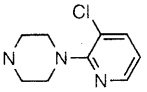
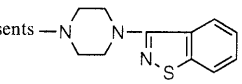
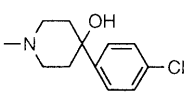
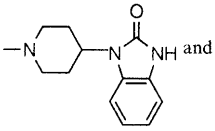
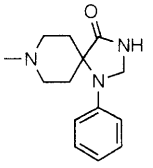
a) A-1 represents  , A-2-represents  , A-3 represents  , A-4 represents  and A-5 represents  . *b*) Yield of free base. *c*) Analytical results are within ±0.4% of the theoretical values in C, H, N analysis.

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Table 2. Spectral Data for Cyclic Imide Derivatives

Compd. No.	Mass spectra *m/z*	IR spectra cm^{-1} (KBr)	^{1}H-NMR spectra δ (ppm) ($CDCl_3$)[a,b]
2	416 (M^+), 381, 288, 275, 263	1770, 1690, 1575, 1540, 1435, 1400	8.17 (1H, dd, J=4.5, 2.0 Hz), 7.57 (1H, dd, J=7.5, 2.0 Hz), 6.78 (1H, dd, J=7.5, 4.5 Hz), 3.32—3.53 (6H, m), 2.28—2.71 (10H, m), 1.17—1.72 (10H, m)
3	438 (M^+), 423, 302, 288, 275, 263, 232	1765, 1695, 1490, 1450, 1425, 1395	7.70—7.97 (2H, m), 7.23—7.57 (2H, m), 3.37—3.67 (6H, m), 2.53—2.77 (8H, m), 2.30—2.53 (2H, m), 1.07—1.83 (10H, m)
4	452 (M^+), 437, 316, 302, 289, 287	1769, 1699, 1590, 1560, 1488, 1460	7.89 (1H, d, J=8.0 Hz), 7.8 (1H, d, J=8.0 Hz), 7.46 (1H, t, J=8.0 Hz), 7.34 (1H, d, J=8.0 Hz), 3.49—3.63 (6H, m), 2.57—2.75 (8H, m), 2.46 (2H, t, J=8.0 Hz), 1.79 (2H, t, J=8.0 Hz), 1.68 (2H, d, J=8.0 Hz), 1.34 (2H, d, J=8.0 Hz), 1.22 (1H, d, J=11.0 Hz), 1.1 (1H, d, J=11.0 Hz)
5	424 (M^+), 409, 288, 274, 266, 249	1764, 1693, 1495, 1465, 1426, 1404	7.9 (1H, d, J=8.0 Hz), 7.8 (1H, d, J=8.0 Hz), 7.46 (1H, t, J=8.0 Hz), 7.34 (1H, d, J=8.0 Hz), 3.51—3.61 (4H, m), 3.48 (2H, t, J=8.0 Hz), 2.61—2.74 (6H, m), 2.59 (2H, s), 2.41 (2H, t, J=8.0 Hz), 1.47—1.73 (6H, m), 1.27—1.43 (4H, m), 1.22 (1H, d, J=11.0 Hz), 1.1 (1H, d, J=11.0 Hz)
6	436 (M^+), 421, 300, 286, 273, 258	1760, 1700, 1580, 1560, 1480, 1450	7.70—8.05 (2H, m), 7.20—7.60 (2H, m), 5.7 (2H, d, J=6.0 Hz), 4.05 (2H, d, J=6.0 Hz), 3.45—3.68 (4H, m), 3.02 (2H, d, J=6.0 Hz), 2.55—2.75 (4H, m), 1.10—1.80 (10H, m)
7	436 (M^+), 421, 286, 273, 258, 218	1770, 1700, 1600, 1560, 1500, 1340	7.67—8.0 (2H, m), 7.17—7.57 (2H, m), 5.32—5.92 (2H, m), 4.1 (2H, d, J=6.0 Hz), 3.58 (4H, t, J=5.3 Hz), 3.26 (2H, d, J=6.0 Hz), 2.53—2.9 (8H, m), 1.03—1.93 (6H, m)
8	452 (M^+), 437, 316, 302, 289	1762, 1691, 1560, 1491, 1447, 1424	7.90 (1H, d, J=8.3 Hz), 7.81 (1H, d, J=8.3 Hz), 7.32—7.49 (2H, m), 4.1—4.25 (1H, m), 3.5—3.65 (4H, m), 2.4—2.8 (10H, m), 1.35 (3H, t, J=6.9 Hz), 1.1—2.1 (10H, m)
9	452 (M^+), 437, 316, 302, 289	1766, 1689	7.90 (1H, d, J=7.9 Hz), 7.80 (1H, d, J=7.9 Hz), 7.32—7.49 (2H, m), 3.55 (4H, t, J=5.0 Hz), 3.41 (1H, dd, J=13.2, 8.0 Hz), 3.33 (1H, dd, J=13.2, 8.0 Hz), 2.61—2.70 (8H, m), 2.37—2.56 (2H, m), 1.11—2.0 (9H, m), 0.90 (3H, d, J=6.8 Hz)
10	452 (M^+), 437, 316, 302, 289	1767, 1690	7.91 (1H, d, J=7.9 Hz), 7.81 (1H, d, J=7.9 Hz), 7.32—7.49 (2H, m), 3.51—3.58 (6H, m), 2.59—2.70 (8H, m), 2.16—2.31 (2H, m), 1.08—1.68 (9H, m), 0.99 (3H, d, J=6.6 Hz)
11	452 (M^+), 437, 316, 302, 289	1750, 1680, 1480, 1440, 1390, 1370	7.91 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.25—7.53 (2H, m), 3.35—3.65 (6H, m), 2.5—2.85 (9H, m), 0.93—1.8 (13H, m)
12	454 (M^+), 439, 318, 291	1760, 1690, 1590, 1560, 1490, 1420	7.87 (1H, d, J=8.0 Hz), 7.80 (1H, d, J=8.0 Hz), 7.39—7.61 (2H, m), 5.55 (1H, br), 4.0—4.17 (1H, m), 3.37—3.75 (6H, m), 2.51—2.93 (10H, m), 1.51—1.81 (4H, m), 1.15—1.41 (4H, m)
13	454 (M^+), 439, 421, 391, 304	1765, 1695, 1495, 1450, 1430	7.90 (1H, d, J=8.0 Hz), 7.82 (1H, d, J=8.0 Hz), 7.33—7.53 (2H, m), 3.47—3.80 (8H, m), 2.81—2.92 (2H, m), 2.72 (2H, s), 2.63 (2H, s), 2.62—2.74 (4H, m), 2.58—2.72 (2H, m), 2.40—2.48 (2H, m), 1.31—1.41 (2H, m), 1.12—1.27 (2H, m)
14	451 (M^+-1), 234, 176, 163	1760, 1700, 1640, 1580, 1560, 1490	7.89 (1H, d, J=8.0 Hz), 7.83 (1H, d, J=8.0 Hz), 7.36—7.53 (2H, m), 3.80—3.90 (2H, m), 3.61—3.72 (2H, m), 3.50—3.61 (6H, m), 2.70 (2H, s), 2.60 (2H, s), 2.39 (2H, t, J=7.0 Hz), 1.95 (2H, qi, J=7.0 Hz), 1.68 (2H, d, J=6.0 Hz), 1.35 (2H, d, J=6.0 Hz), 1.23 (1H, d, J=11.0 Hz), 1.12 (1H, d, J=11.0 Hz)
15	438 (M^+), 423, 302, 288, 275, 263	1764, 1695, 1496, 1432, 1388	7.67—7.93 (2H, m), 7.20—7.53 (2H, m), 3.30—3.67 (6H, m), 2.96—3.13 (2H, m), 2.30—2.83 (8H, m), 1.06—1.89 (10H, m)
16	452 (M^+), 436, 316, 302, 294, 277	1760, 1700, 1590, 1560, 1490, 1450	7.67—7.97 (2H, m), 7.2—7.53 (2H, m), 3.43—3.67 (6H, m), 2.08—2.9 (10H, m), 1.38—1.83 (12H, m)
17	426 (M^+), 290, 263, 177, 163	1773, 1670, 1588, 1560, 1489, 1460	7.90 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.46 (1H, t, J=8.0 Hz), 7.35 (1H, t, J=8.0 Hz), 3.45—3.60 (6H, m), 2.77—2.91 (2H, m), 2.56—2.74 (4H, m), 2.45 (2H, t, J=7.0 Hz), 1.3—1.97 (12H, m)
18	424 (M^+), 288, 258, 206	1760, 1700, 1490, 1420, 1400	7.89 (1H, d, J=7.9 Hz), 7.81 (1H, d, J=7.9 Hz), 7.46 (1H, t, J=7.9 Hz), 7.36 (1H, t, J=7.9 Hz), 6.2—6.31 (1H, m), 5.59—5.82 (2H, m), 4.11 (2H, m), 4.11 (2H, d, J=5.3 Hz), 3.4—3.67 (4H, m), 3.07 (2H, d, J=5.6 Hz), 2.8—3.0 (2H, m), 2.5—2.8 (4H, m), 1.6—2.0 (4H, m), 1.2—1.6 (6H, m)
19	440 (M^+), 425, 304, 290, 277, 265	1775, 1700, 1595, 1495, 1460, 1450	7.7—8.0 (2H, m), 7.18—7.55 (2H, m), 4.76—4.90 (2H, m), 3.35—3.65 (6H, m), 2.82 (2H, s), 2.28—2.72 (6H, m), 1.33—2.0 (8H, m)
20	452 (M^+), 437, 316, 302, 289, 277	1760, 1700, 1590, 1560, 1490, 1450	7.67—7.97 (2H, m), 7.2—7.53 (2H, m), 3.43—3.67 (6H, m), 2.08—2.9 (10H, m), 1.38—1.83 (12H, m)
21	452 (M^+), 437, 316, 302, 289, 277	1770, 1700, 1595, 1565, 1495, 1460	7.74—8.03 (2H, m), 7.24—7.63 (2H, m), 3.43—3.67 (6H, m), 1.97—2.88 (12H, m), 1.03—1.80 (10H, m)
22	440 (M^+), 425, 304, 295, 277, 265	1770, 1710, 1595, 1560, 1495, 1450	7.89 (1H, d, J=8.0 Hz), 7.80 (1H, d, J=8.0 Hz), 7.45 (1H, t, J=8.0 Hz), 7.33 (1H, t, J=8.0 Hz), 3.46—3.62 (6H, m), 2.72—2.96 (2H, m), 2.56—2.72 (4H, m), 2.45 (2H, t, J=7.0 Hz), 2.06—2.20 (2H, m), 1.16—1.60 (8H, m), 0.74—1.06 (4H, m)
23	454 (M^+), 439, 318, 304, 291, 279	1770, 1710, 1595, 1560, 1495, 1450	7.6—7.9 (2H, m), 7.28—7.52 (2H, m), 3.46—3.62 (6H, m), 2.74—2.92 (2H, m), 2.54—2.74 (4H, m), 2.36—2.52 (2H, m), 1.44—1.92 (10H, m), 0.7—0.96 (6H, d, J=7.0 Hz)
24	454 (M^+), 439, 318, 304, 291, 279	1765, 1700, 1590, 1560, 1495, 1450	7.78—8.00 (2H, m), 7.20—7.57 (2H, m), 3.36—3.70 (6H, m), 2.77—2.93 (2H, m), 1.87—2.77 (8H, m), 1.03—1.77 (14H, m)
25	454 (M^+), 439, 318, 304, 291, 279	1770, 1710, 1595, 1565, 1495, 1465	7.73—8.00 (2H, m), 7.26—7.60 (2H, m), 3.37—3.67 (6H, m), 2.30—2.80 (6H, m), 1.26—2.13 (12H, m), 1.16 (6H, s)
26	372 (M^+), 357, 236, 222, 209	1770, 1700, 1600, 1560, 1500	7.90 (1H, d, J=8.0 Hz), 7.80 (1H, d, J=8.0 Hz), 7.3—7.53 (2H, m), 3.45—3.65 (6H, m), 2.6—2.8 (8H, m), 2.4—2.53 (2H, m), 1.48—1.75 (4H, m)
27	412 (M^+), 398, 278, 262, 249, 236	1760, 1690, 1490, 1440	7.90 (1H, d, J=8.0 Hz), 7.80 (1H, d, J=8.0 Hz), 7.48 (1H, t, J=8.0 Hz), 7.36 (1H, t, J=8.0 Hz), 2.50—3.60 (4H, m), 3.42 (2H, t, J=6.0 Hz), 2.60—2.70 (4H, m), 2.36 (2H, t, J=6.0 Hz), 2.34 (2H, s), 1.50—1.67 (4H, m), 1.25 (3H, s), 1.21 (3H, s)

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Table 2. (continued)

Compd. No.	Mass spectra m/z	IR spectra cm^{-1} (KBr)	^{1}H-NMR spectra δ (ppm) ($CDCl_3$)[a,b]
28	436 (M^+), 421, 300, 286, 273, 261	1767, 1695, 1483, 1448, 1394	7.73—8.00 (2H, m), 7.13—7.57 (2H, m), 6.17—6.37 (2H, m), 3.40—3.73 (6H, m), 3.20—3.40 (2H, m), 2.30—2.80 (8H, m), 1.13—1.87 (6H, m)
29	436 (M^+), 421, 300, 286, 273, 261	1762, 1694, 1495, 1382, 1337	7.73—7.98 (2H, m), 7.20—7.57 (2H, m), 6.03—6.20 (2H, m), 3.17—3.70 (10H, m), 2.27—2.80 (6H, m), 1.33—1.83 (6H, m)
30	450 (M^+), 435, 314, 300, 287, 275	1770, 1695, 1595, 1560, 1495, 1465	7.77—8.03 (2H, m), 7.23—7.63 (2H, m), 6.17—6.27 (2H, m), 3.33—3.70 (6H, m), 3.05—3.33 (2H, m), 2.73—2.83 (2H, m), 2.55—2.73 (4H, m), 2.33—2.55 (2H, m), 1.25—1.73 (8H, m)
31	424 (M^+), 409, 388, 374, 361, 349	1770, 1700, 1595, 1560, 1495, 1465	7.73—7.98 (2H, m), 7.20—7.60 (2H, m), 5.80—5.99 (2H, m), 3.37—3.70 (6H, m), 2.97—3.20 (2H, m), 2.23—2.89 (10H, m), 1.37—1.67 (2H, m)
32	438 (M^+), 423, 302, 289, 275, 263	1760, 1695, 1620, 1590, 1555, 1485	7.76—8.00 (2H, m), 7.30—7.53 (2H, m), 5.50—5.93 (1H, m), 3.45—3.66 (6H, m), 2.93—3.18 (2H, m), 2.57—2.78 (4H, m), 2.36—2.57 (3H, m), 1.40—2.30 (10H, m)
33	424 (M^+), 409, 288, 261, 232, 164	1762, 1710, 1499, 1402	7.90 (1H, d, J=8.0 Hz), 7.84 (1H, d, J=8.0 Hz), 7.46 (1H, t, J=8.0 Hz), 7.35 (1H, t, J=8.0 Hz), 3.45—3.62 (6H, m), 2.66 (4H, t, J=5.0 Hz), 2.41 (2H, t, J=5.0 Hz), 2.26—2.39 (4H, m), 1.45—1.83 (8H, m)
34	420 (M^+), 405, 284, 270, 257, 245	1760, 1710, 1610, 1590, 1560, 1490	7.60—7.97 (6H, m), 7.20—7.60 (2H, m), 3.43—3.87 (6H, m), 2.37—2.80 (6H, m), 1.43—1.97 (4H, m)
35	421 (M^+), 406, 285, 271, 258, 246	1775, 1720, 1600, 1590, 1485, 1465	8.91 (1H, d, J=6.0 Hz), 8.13 (1H, d, J=8.0 Hz), 7.18—7.98 (5H, m), 3.78 (2H, t, J=8.0 Hz), 3.33—3.65 (4H, m), 2.32—2.80 (6H, m), 1.33—2.00 (4H, m)
36	440 (M^+), 304, 295, 277, 258, 247	1650, 1490, 1460, 1420, 1380	7.89 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.47 (1H, t, J=8.0 Hz), 7.35 (1H, t, J=8.0 Hz), 4.72 (1H, s), 3.2—3.7 (6H, m), 2.2—2.8 (10H, m), 2.0 (1H, d, J=7.0 Hz), 1.45—1.82 (6H, m), 0.95—1.37 (4H, m)
37	410 (M^+-18), 395, 275, 260, 247, 232, 221	1653, 1495, 1457, 1457	7.89 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.46 (1H, t, J=8.0 Hz), 7.35 (1H, t, J=8.0 Hz), 4.71 (1H, s), 3.30—3.63 (6H, m), 2.35—2.81 (7H, m), 2.12—2.25 (1H, m), 1.81—2.09 (1H, m), 1.41—1.87 (8H, m), 0.93—1.32 (3H, m)
38	412 (M^+), 397, 276, 262, 249, 232	1664, 1561, 1491, 1447	7.91 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.47 (1H, t, J=8.0 Hz), 7.36 (1H, t, J=8.0 Hz), 3.56 (4H, t, J=5.0 Hz), 3.28—3.41 (3H, m), 2.89 (1H, d, J=10.0 Hz), 2.39—2.52 (3H, m), 2.26—2.39 (1H, m), 1.98—2.09 (1H, m), 1.42—1.83 (8H, m), 1.12—1.32 (3H, m)
39	398 (M^+), 234, 209	1492, 1442, 1421, 1384	7.91 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.46 (1H, t, J=8.0 Hz), 7.35 (1H, t, J=8.0 Hz), 3.57 (4H, t, J=5.0 Hz), 2.79 (2H, t, J=7.0 Hz), 2.68 (4H, t, J=5.0 Hz), 2.38—2.61 (6H, m), 2.06—2.21 (2H, m), 1.70—2.00 (2H, m), 1.22—1.65 (12H, m)
40	410 (M^+), 395, 326, 247, 232	1720, 1640, 1500	7.91 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.47 (1H, t, J=8.0 Hz), 7.37 (1H, t, J=8.0 Hz), 6.2—6.31 (1H, m), 5.96—6.05 (1H, m), 5.61 (1H, br), 3.42—3.67 (4H, m), 3.19—3.37 (2H, m), 3.15 (1H, br), 2.8—3.0 (2H, m), 2.63—2.8 (4H, m), 2.4—2.55 (2H, m), 1.85—2.06 (2H, m), 1.41—1.69 (4H, m), 1.21—1.41 (2H, m)
41	400 (M^+), 385, 264, 250, 237, 232	1636, 1550, 1488, 1446, 1422, 1386	7.90 (1H, d, J=8.0 Hz), 7.82 (1H, d, J=8.0 Hz), 7.47 (1H, t, J=8.0 Hz), 7.36 (1H, t, J=8.0 Hz), 5.82 (1H, br), 3.60 (4H, t, J=5.0 Hz), 3.28 (2H, q, J=6.0 Hz), 2.72 (4H, t, J=5.0 Hz), 2.56 (2H, t, J=7.0 Hz), 1.17—2.20 (15H, m)
42	414 (M^+), 399, 278, 264, 251, 239	1613, 1494, 1450, 1421, 1383	7.91 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.47 (1H, t, J=8.0 Hz), 7.35 (1H, t, J=8.0 Hz), 3.64 (4H, t, J=5.0 Hz), 3.29—3.44 (2H, q, J=6.0 Hz), 2.97 (3H, d, J=18.0 Hz), 2.67 (4H, t, J=5.0 Hz), 2.89—2.53 (3H, m), 1.16—1.87 (15H, m)
43	424 (M^+), 409, 288, 274, 261, 249	1728, 1560, 1497, 1467, 1448, 1426	7.90 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.47 (1H, t, J=8.0 Hz), 7.35 (1H, t, J=8.0 Hz), 4.10 (2H, t, J=6.0 Hz), 3.59 (4H, t, J=5.0 Hz), 2.71 (4H, t, J=5.0 Hz), 2.48 (2H, t, J=7.0 Hz), 2.20—2.36 (1H, m), 1.11—1.99 (14H, m)
44	332 (M^+), 317, 232, 196	1640, 1550, 1480, 1420, 1370	7.91 (1H, d, J=8.0 Hz), 7.82 (1H, d, J=8.0 Hz), 7.49 (1H, t, J=8.0 Hz), 7.37 (1H, t, J=8.0 Hz), 6.19 (1H, br), 3.5—3.65 (4H, m), 3.33—3.45 (2H, m), 2.63—2.78 (4H, m), 2.52 (2H, t, J=7.0 Hz), 1.98 (3H, s), 1.67—1.8 (2H, m)
45	444 (M^+), 429, 308, 294, 289, 281	2592, 1719, 1630, 1494, 1422, 1323	7.68—7.93 (4H, m), 7.26—7.52 (4H, m), 7.04 (1H, br), 3.51—3.67 (4H, m), 2.90—3.05 (2H, m), 2.58—2.70 (4H, m), 2.30—2.44 (5H, m), 1.49—1.69 (4H, m)
46	424 (M^+), 316, 301, 288, 275, 261	3300, 1680, 1580, 1530, 1480, 1440	7.75—8.00 (2H, m), 7.20—7.54 (7H, m), 5.67 (1H, br), 5.10 (1H, s), 3.48—3.68 (4H, m), 3.13—3.33 (2H, m), 2.56—2.80 (4H, m), 2.32—2.56 (2H, m), 1.43—1.71 (4H, m)
47	452 (M^+), 437, 316, 302, 289, 277	1770, 1700, 1590, 1560, 1490, 1450	7.73—7.99 (2H, m), 7.13—7.57 (2H, m), 3.37—3.67 (6H, m), 2.93—3.10 (2H, m), 2.50—2.73 (4H, m), 2.20—2.50 (6H, m), 1.60—1.80 (6H, m), 1.37—1.60 (4H, m)
48	452 (M^+), 437, 316, 302, 289, 277	1760, 1695, 1590, 1490	7.67—7.97 (2H, m), 7.17—7.57 (2H, m), 5.77—5.93 (2H, m), 3.33—3.67 (6H, m), 2.30—2.83 (6H, m), 1.00—2.00 (14H, m)
49	430 (M^+), 224, 192, 139, 105	3430, 2200—2800, 1765, 1690, 1405	7.45 (2H, d, J=8.9 Hz), 7.31 (2H, d, J=8.9 Hz), 3.49 (2H, t, J=7.0 Hz), 2.74—2.87 (2H, m), 2.7 (2H, s), 2.6 (2H, s), 2.34—2.49 (4H, m), 2.05—2.20 (2H, m), 1.45—1.80 (9H, m), 1.35 (2H, d, J=9.6 Hz), 1.22 (1H, d, J=11.2 Hz), 1.09 (1H, d, J=9.6 Hz)
50	436 (M^+), 381, 355, 301, 261, 230, 187	3440, 1765, 1695, 1485, 1400, 1380	9.31 (1H, s), 7.24—7.33 (1H, m), 7.00—7.13 (3H, m), 4.28—4.43 (1H, m), 3.50 (2H, t, J=7.1 Hz), 3.0—3.1 (1H, m), 2.71 (2H, s), 2.60 (2H, s), 2.33—2.55 (4H, m), 2.11 (2H, t, J=11.9 Hz), 1.75—1.82 (2H, m), 1.40—1.75 (6H, m), 1.34 (2H, d, J=9.2 Hz), 1.22 (1H, d, J=11.2 Hz), 1.10 (1H, d, J=11.2 Hz)
51	450 (M^+), 328, 301, 275, 244, 187	3420, 2200—2800, 1760, 1690, 1600	7.23—7.35 (2H, m), 6.81—6.97 (3H, m), 6.40 (1H, s), 4.73 (2H, s), 3.5 (2H, t, J=7.1 Hz), 2.55—2.87 (8H, m), 2.39—2.49 (2H, m), 1.43—1.77 (10H, m), 1.34 (2H, d, J=9.2 Hz), 1.22 (1H, d, J=11.2 Hz), 1.10 (1H, d, J=11.2 Hz)

a) All compounds were subjected to the measurement of their NMR spectra in basic form. *b*) Abbreviations: s, singlet; d, doublet; t, triplet; qi, quintet; m, multiplet; dd, double doublet.

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Table 3. *In Vitro* Binding Data for Cyclic Imide Derivatives

Compound No.	D_2 (10^{-8} M) %	5-HT_2 (10^{-8} M) %
1	<10	<10
2	<10	10
3	95	85
4	48	77
5	11	61
6	80	75
7	21	27
8	90	85
9	93	81
10	67	70
11	47	49
12	81	60
13	72	55
14	13	<10
15	81	82
16	85	84
17	81	88
18	60	75
19	57	81
20	65	73
21	84	77
22	79	79
23	46	63
24	64	70
25	55	64
26	54	55
27	74	76
28	95	80
29	78	72
30	77	82
31	95	81
32	72	78
33	39	59
34	36	61
35	20	51
36	83	79
37	76	90
38	80	81
39	25	64
40	76	80
41	73	87
42	61	80
43	24	80
44	15	64
45	37	61
46	77	63
47	NT	NT
48	76	85
49	10	14
50	14	<10
51	19	11
Tiospirone (D)	90	78

NT, not tested.

the replacement. Compounds **28**, **29**, **30**, **31** and **32**, which were unsaturated at a region away from the imide radical, retained the potent affinities of the corresponding saturated derivatives (**3**, **15**, **16**, **17**, **22**, respectively) for binding to both receptors, although the unsaturated derivatives (**33**, **34**, **35**), in which the unsaturated bonds were conjugated with the imide radical, decreased both binding affinities, especially that to the D_2 receptor.

The cyclic imide moiety of **3** and **17** seemed not to be essential for potent affinity to either receptor. The hydroxylactam derivatives (**36**, **37**) and the lactam derivative (**38**) had potent affinities for both receptors, while the cyclic amine derivative (**39**) showed decreased binding affinity for both, but especially for the D_2 receptor. The ring-opened amide derivatives (**40**, **41**) had potent affinities for both receptors, but the amide derivative (**42**) and ester derivative (**43**) showed a tendency toward decreased D_2 binding affinity. Although the simple acetamide derivative (**44**) and sulfonamide derivative (**45**) also had decreased binding affinity for both receptors, especially for the D_2 receptor, the carbamate derivative (**46**) retained potent affinities for both receptors.

Table 4. *In Vivo* D_2 Antagonistic Activity of Selected Compounds

Compound	Inhibition of climbing behavior[22] (ED_{50}, mg/kg)
3	0.21
12	0.5
17 (SM-9018)	0.11
18	0.31

Table 5. Pharmacology of SM-9018, Haloperidol and Tiospirone

Pharmacological activity[22]	SM-9018	Haloperidol	Tiospirone
D_2 antagonistic activity (ED_{50}, mg/kg, *p.o.*, rats)	2.2	0.6	18.2
5-HT_2 antagonistic activity (ED_{50}, mg/kg, *p.o.*, rats)	1.4	13.6	4.7
Cataleptogenic activity (ED_{50}, mg/kg, *p.o.*, rats)	153	11.9	216
Central depressant activity (ED_{50}, mg/kg, *p.o.*, mice)	15	0.73	NT

NT, not tested.

The representative cyclic imide derivatives **3**, **12**, **17** and **18**, which possessed potent affinities for both D_2 and 5-HT_2 receptors, were examined with regard to their *in vivo* D_2 antagonistic activity to inhibit apomorphine-induced climbing behavior in mice.[22] The results are summarized in Table 4. SM-9018 (**17**) was the most potent *in vivo* D_2 antagonist among these four derivatives. The pharmacological profile of SM-9018 was more precisely evaluated by examining the *in vivo* D_2 antagonistic activity to inhibit methamphetamine-induced hyperactivity in rats,[22] the *in vivo* 5-HT_2 antagonistic activity to inhibit triptamine-induced clonic seizure in rats,[23] the cataleptogenic activity in rats,[22] and the central depressant activity to inhibit spontaneous locomotor activity in mice,[22] and the results are summarized in Table 5 in comparison with those of tiospirone and the classical neuroleptic haloperidol. SM-9018 strongly inhibited both D_2 receptor-mediated and 5-HT_2 receptor-mediated behaviors. SM-9018 possessed only weak cataleptogenic activity, which may be clinically related to the lower incidence of its extrapyramidal side effects, despite its potent D_2 antagonistic activity. Moreover, SM-9018 induced a weak central depressant effect, as compared with that of haloperidol. These results suggest that SM-9018 is a new neuroleptic drug with efficacy for both positive and negative symptoms of schizophrenia and with a lower incidence of debilitating side effects. SM-9018 is now

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undergoing clinical trials as a selective atypical neuroleptic. In addition, a follow-up study of cyclic imide derivatives is in progress to identify more selective atypical neuroleptics.

Experimental

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with the assigned structures. Nuclear magnetic resonance (NMR) spectra were recorded on JEOL GX-270 instruments with tetramethylsilane as an internal standard; chemical shifts are given on the d scale (ppm), coupling constants (J values) are expressed in hertz (Hz), and the following abbreviations are used. s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, m = multiplet, dd = double doublet and br = broad. Mass spectra (MS) were recorded with a Hitachi DF/GC/MS M-80 mass spectrometer. Infrared (IR) spectra were recorded with a Hitachi 260-10 IR spectrophotometer. Elemental analysis was done with a Heraeus elemental analyzer. For column chromatography, Merck Kieselgel 60 (70—230 mesh) was used.

3-(1-Piperazinyl)-1,2-benzisothiazole (54) Anhydrous piperazine (36.6 g, 0.42 mol) was added to 3-chloro-1,2-benzisothiazole (4.80 g, 0.028 mol), and the resultant mixture was stirred at 120 °C for 12 h. Excess piperazine was removed by distillation, and dilute sodium hydroxide (NaOH) solution was added to the residue, followed by extraction with dichloromethane (CH_2Cl_2). The extract was washed with a saturated sodium chloride (NaCl) solution and dried over anhydrous magnesium sulfate ($MgSO_4$). The solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel to give **54** (3.50 g, 56.4%), mp 87—91 °C.

3-[4-(4-Aminobutyl)-1-piperazinyl]-1,2-benzisothiazole (52) A mixture of 3-(1-piperazinyl)-1,2-benzisothiazole (**54**) (1.00 g, 4.60 mmol), anhydrous potassium carbonate (K_2CO_3) (0.76 g, 5.5 mmol), potassium iodide (KI) (0.090 g, 0.55 mmol), *N*-(4-bromobutyl)phthalimide (1.56 g; 5.5 mmol) and anhydrous dimethylformamide (DMF) (10 ml) was stirred at 90—100 °C for 3 h. After removal of insoluble materials by filtration, the filtrate was evaporated under reduced pressure, and the residue was chromatographed on silica gel to give *N*-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]phthalimide (**34**) (1.70 g, 87.0%), mp 142—145 °C.

A solution of **34** (1.00 g, 2.38 mmol) and hydrazine hydrate (0.20 g, 3.75 mmol) in methanol (10 ml) was refluxed for 2.5 h. After cooling, the reaction mixture was combined with a 10% aqueous hydrochloric acid solution and stirred. The resultant crystals were removed by filtration, and the filtrate was neutralized with a 10% NaOH solution and extracted with chloroform ($CHCl_3$). The extract was washed with a saturated NaCl solution and dried over anhydrous $MgSO_4$. The solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel to give **52** (0.60 g, 86.2%) as an oily substance, IR (neat): 2925, 2830, 1585, 1555, 1485, 1455, 1445, 1420, 1375 cm^{-1}.

2-Methyl-1,4-butanediol A solution of methylsuccinic anhydride (22.80 g, 0.20 mol) in tetrahydrofuran (THF, 400 ml) was added dropwise to a mixture of lithium aluminum hydride ($LiAlH_4$) (11.40 g, 0.30 mol) in THF (100 ml) at room temperature. The reaction mixture was refluxed for 3 h, then a mixture of water and THF was added dropwise. Insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure to give 2-methyl-1,4-butanediol (11.36 g, 54.6%), ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J = 7.0 Hz), 1.5—1.9 (3H, m), 3.4—3.8 (4H, m).

1,4-Bis(methanesulfonyloxy)-2-methylbutane Methanesulfonyl chloride (22.9 g, 0.200 mol) was added dropwise to a solution of 2-methyl-1,4-butanediol (10.4 g, 0.100 mol) and triethylamine (30.3 g, 0.300 mol) in $CHCl_3$ (150 ml) at room temperature. The reaction mixture was stirred at room temperature for 15 h, then washed with water, dried and evaporated under reduced pressure to give 1,4-bis(methanesulfonyloxy)-2-methylbutane (20.23 g, 77.8%). ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J = 7.0 Hz), 1.5—1.7 (1H, m), 1.9—2.2 (2H, m), 3.03 (6H, s), 4.06—4.19 (2H, m), 4.28—4.35 (2H, m).

8-(1,2-Benzisothiazol-3-yl)-2-methyl-8-aza-5-azoniaspiro[4.5]decane Methanesulfonate (53) A mixture of **54** (7.58 g, 34.6 mmol), 1,4-bis-(methanesulfonyloxy)-2-methylbutane (10.00 g, 38.5 mmol), anhydrous Na_2CO_3 (4.08 g; 38.5 mmol) and acetonitrile (300 ml) was stirred under reflux for 28 h. After completion of the reaction, insoluble materials were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was washed with acetone (50 ml) to give **53** (7.86 g, 60.4%), mp 198—199 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J = 7.0 Hz), 1.99—2.10 (1H, m), 2.41—2.54 (1H, m), 2.75 (3H, s) 2.71—2.91 (1H, m), 3.44 (1H, m), 3.87—4.09 (11H, m), 7.37—7.54 (2H, m), 7.83 (1H, d, J = 8.0 Hz), 7.93 (1H, d, J = 8.0 Hz).

(1*R*,2*S*,3*R*,4*S*)-2,3-Bicyclo[2.2.1]heptanedicarboxylic Anhydride (59) A mixture of (1*R*,2*S*,3*R*,4*S*)-2,3-bicyclo[2.2.1]hept-5-enedicarboxylic anhydride (16.4 g, 0.100 mol) and 50% water-containing 10% palladium on charcoal (0.82 g) in THF (296 ml) was hydrogenated at room temperature for 1.5 h. The precipitate was removed by filtration, and the filtrate was evaporated under reduced pressure to give **59** (15.93 g, 95.9%), mp 74—78 °C. IR (KBr): 2980, 2960, 2895, 1865, 1835, 1790, 1230, 1195 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.8 (6H, m), 2.7—2.8 (4H, m).

(1*R*,2*S*,3*R*,4*S*)-2,3-Bicyclo[2.2.1]heptanedicarboximide (55) A 7% aqueous ammonia solution (133 ml) was added to a stirred solution of (1*R*,2*S*,3*R*,4*S*)-2,3-bicyclo[2.2.1]heptanedicarboxylic anhydride (**59**) (59.3 g, 0.357 mol) in THF (120 ml) at room temperature. The mixture was slowly heated to 190 °C, kept for 2 h at the same temperature and cooled. The resulting precipitate was collected by filtration and washed with *n*-hexane to give **55** (47.5 g, 80.5%), mp 153—154 °C. IR (Nujol): 3180, 3060, 1770, 1690, 1360, 1305, 1295, 1279 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.75 (6H, m), 2.67 (4H, s), 9.0—9.6 (1H, br).

(1*R*,2*S*,3*R*,4*S*)-*N*-(4-Bromobutyl)-2,3-bicyclo[2.2.1]heptanedicarboximide A mixture of **55** (24.8 g, 0.15 mol), 1,4-dibromobutane (162 g, 0.750 mol) and anhydrous K_2CO_3 (30.9 g, 0.225 mol) in acetone (250 ml) was refluxed for 7 h, cooled and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel to give (1*R*,2*S*,3*R*,4*S*)-*N*-(4-bromobutyl)-2,3-bicyclo[2.2.1]heptanedicarboximide (40.6 g, 90.2%) as an oil. IR (neat): 1765, 1700, 1430, 1395, 1360, 1345, 1295, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.1 (10H, m), 2.4—2.9 (4H, m), 3.1—3.7 (4H, m).

3-[4-(3,4-Epoxybutyl)-1-piperazinyl]-1,2-benzisothiazole (56) A mixture of 3,4-epoxybutyl bromide (1.06 g, 7.02 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (**54**) (1.65 g, 7.52 mmol), anhydrous K_2CO_3 (1.60 g, 11.3 mmol) and acetone (20 ml) was stirred under reflux for 19 h. After completion of the reaction, insoluble materials were removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel to give **56** (1.50 g, 73.8%) as an oil. IR (neat): 1590, 1560, 1490, 1460, 1420, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.61—2.09 (2H, m), 2.43—2.85 (8H, m), 2.97—3.1 (1H, m), 3.43—3.65 (4H, m), 7.30—7.53 (2H, m), 7.71—7.97 (2H, m).

(1*R*,2*S*,3*R*,4*S*)-*N*-(3,4-Epoxybutyl)-2,3-bicyclo[2.2.1]heptanedicarboximide (57) A mixture of **55** (330 mg, 2.00 mmol), 3,4-epoxybutyl chloride (282 mg, 2.60 mmol) and anhydrous K_2CO_3 (415 mg, 3.00 mmol) in anhydrous acetone (5 ml) was refluxed with stirring under nitrogen for 2 h, then cooled and filtered. The filtrate was evaporated under reduced pressure, and the residue was chromatographed on silica gel to give **57** (406 mg, 90.1%) as an oil. IR (neat): 2970, 1765, 1710, 1580, 1400, 1365, 1190 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15—2.05 (8H, m), 2.42 (1H, dd, J = 3.0, 5.4 Hz), 2.55—2.75 (5H, m), 2.8—3.0 (1H, m), 3.45—3.8 (2H, m).

1,2-*cis*-Bis(methanesulfonyloxymethyl)cyclohexane (58) Methanesulfonyl chloride (32.0 g, 0.280 mol) was added dropwise to a solution of *cis*-1,2-cyclohexanedimethanol (20.0 g, 0.140 mol) and triethylamine (42.0 g, 0.420 mol) in $CHCl_3$ (300 ml) under ice-cooling, and the resultant mixture was stirred at room temperature for 10.5 h. It was then washed with water, dried and evaporated under reduced pressure. The residue was crystallized from ether to give **58** (23.5 g, 55.8%). ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.65 (8H, m), 2.24 (2H, br), 3.04 (6H, s), 4.16—4.32 (4H, m).

(1*R*,2*S*,3*R*,4*S*)-*N*-(3-Carboxypropyl)-2,3-bicyclo[2.2.1]heptanedicarboximide (60) A mixture of **59** (10.0 g, 0.060 mol) and γ-aminobutyric acid (6.20 g, 0.060 mol) was stirred at 150 °C for 30 min and then cooled. The resultant crude product was recrystallized from ether to give **60** (9.30 g, 61.6%), mp 82—83 °C.

***N*-(4-Chlorobutyl)-*N*-methylcyclohexanecarboxamide (61)** A solution of cyclohexanecarbonyl chloride (7.30 g, 0.050 mol) in THF (36.5 ml) was added dropwise to a solution of 30% monomethylamine in ethanol (156.8 g, 1.50 mol) at 5 °C. The mixture was stirred at the same temperature for 1.5 h and at room temperature for 1 h, then poured into 1N aqueous hydrochloric acid solution and extracted with ethyl acetate (AcOEt). The extract was washed with saturated sodium bicarbonate ($NaHCO_3$) solution and saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to give *N*-methylcyclohexanecarboxamide (5.40 g, 77.5%). ^{1}H-NMR ($CDCl_3$) δ: 1.10—1.91 (10H, m), 1.98—2.13 (1H, m), 2.80 (3H, d, J = 5.0 Hz), 5.51 (1H, br).

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A 60% suspension of NaH in mineral oil (0.48 g, 0.012 mol) was added to a solution of *N*-methylcyclohexanecarboxamide (1.40 g, 0.010 mol) in THF (28 ml) at room temperature. The reaction mixture was stirred at the same temperature for 1.5 h. A solution of 1-bromo-4-chlorobutane (3.40 g, 0.020 mol) in THF (6.8 ml) was added dropwise to the reaction mixture, and the resultant mixture was refluxed with stirring for 19.5 h. After it had cooled, the reaction mixture was poured into water and extracted with AcOEt. The extract was washed with a saturated NaCl solution and dried over anhydrous $MgSO_4$. The solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel to give **61** (0.900 g, 39.0%). ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.92 (14H, m), 2.39—2.56 (1H, m), 2.91, 3.02 (3H, each s), 3.29—3.50 (3H, m), 3.50—3.64 (1H, m).

3-[4-(4-Hydroxybutyl)-1-piperazinyl]-1,2-benzisothiazole (62) A mixture of **54** (2.20 g, 0.010 mol), 4-chlorobutanol (1.30 g, 0.012 mol), anhydrous K_2CO_3 (1.70 g, 0.012 mol), KI (0.20 g, 1.20 mmol) and CH_3CN (44 ml) was refluxed for 13 h, then poured into water (100 ml) and extracted with AcOEt (300 ml). The organic layer was washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel to give **62** (1.60 g, 55.2%). ^{1}H-NMR ($CDCl_3$) δ: 1.59—1.78 (4H, m), 2.40—2.55 (2H, m), 2.64—2.79 (4H, m), 3.51—3.67 (4H, m), 7.35 (1H, t, J=8.0 Hz), 7.47 (1H, t, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.89 (1H, d, J=8.0 Hz).

***N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-2,3-*cis*-bicyclo-[2.2.2]octanedicarboximide (16)** Method A: A mixture of 2,3-*cis*-bicyclo[2.2.2]octanedicarboxylic anhydride (1.00 g, 5.60 mmol), **52** (1.30 g, 4.60 mmol) and dry pyridine (13 ml) was refluxed for 4.5 h. After completion of the reaction, the reaction mixture was poured into H_2O (100 ml) and extracted with AcOEt (500 ml). The organic layer was washed with water (150 ml) and brine, dried and evaporated. The residue was chromatographed on silica gel to give **16** (1.60 g, 77.3%), mp 127—130 °C.

(1*R*,2*S*,3*R*,4*S*)-*N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-2-methylbutyl]-2,3-bicyclo[2.2.1]heptanedicarboximide (9) and (1*R*,-2*S*,3*R*,4*S*)-*N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-3-methylbutyl]-2,3-bicyclo[2.2.1]heptanedicarboximide (10) Method B: A mixture of 8-(1,2-benzisothiazol-3-yl)-8-aza-5-azoniaspiro[4.5]decane methanesulfonate (4.21 g, 11.0 mmol), **55** (1.82 g, 11.0 mmol), anhydrous K_2CO_3 (1.52 g; 11.0 mmol), dibenzo-18-crown-6 (10 mg) and xylene (60 ml) was stirred under reflux for 10 h. After completion of the reaction, insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel to give **9** (0.850 g, 17.2%) and **10** (4.110 g, 82.7%).

(1*R*,2*S*,3*R*,4*S*)-*N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-2,3-bicyclo[2.2.1]heptanedicarboximide (3) Method C: (1*R*,2*S*,3*R*,4*S*)-*N*-(4-Bromobutyl)-2,3-bicyclo[2.2.1]heptanedicarboximide (1.20 g, 4.10 mmol) was added to a mixture of **54** (0.75 g, 3.40 mmol), anhydrous K_2CO_3 (1.20 g; 8.60 mmol) and KI (140 mg, 0.86 mmol) in CH_3CN (30 ml) with stirring and the mixture was refluxed for 8 h. After completion of the reaction, insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel and treated with HCl in isopropyl alcohol to give the hydrochloride of **3** (940 mg, 57.9%).

***N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2-*cis*-cyclohexanedicarboximide (17)** Method C: *N*-(4-Bromobutyl)-1,2-*cis*-cyclohexanedicarboximide (2.37 g, 8.22 mmol) was added to a mixture of **54** (1.50 g, 6.84 mmol), anhydrous K_2CO_3 (1.13 g; 8.21 mmol) and KI (113 mg, 0.68 mmol) in anhydrous DMF (15 ml) with stirring, and the mixture was heated at 90—100 °C for 7 h. After completion of the reaction, insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel to give **17** (2.48 g, 84.9%).

(1*R*,2*S*,3*R*,4*S*)-*N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-2-hydroxybutyl]-2,3-bicyclo[2.2.1]heptanedicarboximide (12) Method D: A mixture of **56** (0.50 g, 1.73 mmol), **55** (0.57 g, 3.46 mmol), anhydrous K_2CO_3 (0.72 g; 5.19 mmol) and *n*-butanol (13 ml) was stirred under reflux for 9 h. After completion of the reaction, the reaction mixture was combined with AcOEt (100 ml), washed with water and dried over anhydrous $MgSO_4$. The solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel to give **12** (375 mg, 47.7%).

(1*R*,2*S*,3*R*,4*S*)-*N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-3-hydroxybutyl]-2,3-bicyclo[2.2.1]heptanedicarboximide (13) Method D: A solution of **57** (1.07 g, 4.60 mmol) and **54** (1.00 g, 4.60 mmol) in *n*-butanol (20 ml) was stirred under reflux for 12 h. After completion of the reaction, the solution was evaporated under reduced pressure. The resultant crystals were washed with isopropyl alcohol to give **13** (1.67 g, 80.7%).

(1*R,2*S**,6*R**,7*S**)-5-Hydroxy-4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-4-azatricyclo[5.2.1.0^{2,6}]decan-3-one (36)** Method E-1: Sodium borohydride ($NaBH_4$) (0.35 g, 9.10 mmol) in 0.1% aqueous NaOH solution (2.8 ml) was added to a solution of **3** (2.00 g, 4.60 mmol) in isopropanol (IPA) (40 ml) and water (10 ml) at room temperature. The mixture was refluxed for 2 h and cooled in an ice bath. Cold water was added to the reaction mixture and the resulting mixture was extracted with $CHCl_3$. The organic layer was washed with water and brine, dried, evaporated, and the residue was chromatographed on silica gel to give **36** (1.27 g, 63.0%).

(1*R,6*S**)-9-Hydroxy-8-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-butyl]-8-azabicyclo[4.3.0]octan-7-one (37)** Method E-1: A solution of **17** (2.10 g, 4.92 mmol) in THF (21 ml) was added dropwise to a mixture of $LiAlH_4$ (374 mg, 9.85 mmol) and THF (42 ml) at 0 °C and the resultant mixture was allowed to react for 10 min. Water was added dropwise into the reaction mixture, insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel to give **37** (1.10 g, 52.1%).

(1*R,6*S**)-8-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-8-azabicyclo[4.3.0]octane-7-one (38)** Method E-2: A solution of **37** (550 mg, 1.30 mmol), triethylsilane (0.21 ml) and trifluoroacetic acid (4.6 ml) in CH_2Cl_2 (70 ml) was stirred at room temperature for 6 h. After completion of the reaction, the solution was evaporated under reduced pressure, then CH_2Cl_2 was added to the residue. The solution was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure, then the residue was chromatographed on silica gel to give **38** (250 mg, 47.2%).

(1*R*,6*S*)-8-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-8-azabicyclo[4.3.0]octane (39) Method F: A mixture of **58** (2.20 g, 7.23 mmol), **52** (1.40 g, 4.82 mmol), anhydrous K_2CO_3 (2.00 g, 14.5 mmol) and CH_3CN (40 ml) was stirred under reflux for 15 h. DMF (40 ml) was added and the reaction mixture was stirred under reflux for 5 h. After completion of the reaction, the reaction mixture was diluted with AcOEt, washed with water and dried over anhydrous $MgSO_4$. The solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel to give **39** (900 mg, 46.9%).

(1*R*,2*S*,3*R*,4*S*)-*N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-4-oxobutyl]-2,3-bicyclo[2.2.1]heptanedicarboximide (14) Method G: A mixture of **60** (1.00 g, 4.00 mmol), and thionyl chloride (10 ml) was refluxed for 3 h, then evaporated under reduced pressure to give (1*R*,2*S*,3*R*,4*S*)-*N*-(3-chlorocarbonylpropyl)-2,3-bicyclo[2.2.1]heptanedicarboximide (1.00 g, 98.7%).

A solution of the crude (1*R*,2*S*,3*R*,4*S*)-*N*-(3-chlorocarbonylpropyl)-2,3-bicyclo[2.2.1]heptanedicarboximide (1.00 g, 3.90 mmol) in THF (10 ml) was added dropwise to a solution of **54** (0.86 g, 3.93 mmol) and triethylamine (0.800 g, 7.90 mmol) in THF (20 ml) at 5 °C. The reaction mixture was stirred at room temperature for 3 h, then insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel to give **14** (1.12 g, 63.0%).

***N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]acetamide (44)** Method H: A solution of acetyl bromide (1.00 g, 7.80 mmol) in ether (12 ml) was added dropwise to a solution of **52** (1.50 g, 5.20 mmol) and triethylamine (1.00 g, 10.3 mmol) in ether (10 ml) and THF (10 ml) at 5 °C. The reaction mixture was stirred at the same temperature for 2 h, poured into 5% aqueous NaOH solution (100 ml) and extracted with $CHCl_3$ (200 ml). The extract was washed with brine, dried and evaporated to give **44** (1.30 g, 77.5%).

***N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-*N*-methylcyclohexanecarboxamide (42)** Method J: A mixture of **61** (0.900 g, 3.88 mmol), anhydrous K_2CO_3 (0.800 g; 5.82 mmol), **54** (850 mg, 3.88 mmol) and DMF (18 ml) was stirred at 90—100 °C for 13 h, then poured into water and extracted with AcOEt. The extract was washed with water and brine, and dried over anhydrous $MgSO_4$. The solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel and treated with HCl in isopropyl alcohol to give the hydrochloride of **42** (840 mg, 48.0%).

4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butylcyclohexanecarboxyl-

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ate (43) Method K: A solution of cyclohexanecarbonyl chloride (0.60 g, 4.12 mmol) in THF (6 ml) was added dropwise to a solution of **62** (1.00 g, 3.43 mmol) and triethylamine (0.42 g, 4.12 mmol) in THF (20 ml) at room temperature. The reaction mixture was stirred at the same temperature for 1.5 h, then poured into saturated $NaHCO_3$ solution and extracted with AcOEt. The extract was washed with brine, dried and evaporated to give **43** (1.30 g, 77.5%).

Biological Activities Dopamine 2 (D_2) Binding Activity: *In vitro* activities of the target compounds were determined by measuring the ability to displace a dopamine D_2 receptor radioligand ([^{3}H]domperidone) in the rat striatal membrane using the reported method.[19]

Serotonin 2 (5-HT_2) Binding Activity: *In vitro* activities of the target compounds were determined by measuring the ability to displace a serotonin 5-HT_2 receptor radioligand ([^{3}H]ketanserin) in the rat whole brain membrane using the reported method.[20]

In Vivo D_2 Antagonistic Activity: *In vivo* activities of selected compounds were determined by measuring the abilities to inhibit apomorphine-induced climbing behavior in rats using the reported method[23] with a slight modification.[22]

In vivo activities of SM-9018, haloperidol and tiospirone were determined by measuring their abilities to inhibit methamphetamine-induced hyperactivity using the reported method.[22]

In Vivo 5-HT_2 Antagonistic Activity: *In vivo* activities of SM-9018, haloperidol and tiospirone were determined by measuring the ability to inhibit tryptamine-induced clonic seizure using the reported method[24] with a slight modification.[22]

Cataleptogenic Activity: Cataleptogenic activities of SM-9018, haloperidol and tiospirone were determined using the reported method[25] with a slight modification.[22]

Central Depressant Activity: Central depressant activities of SM-9018 and haloperidol were determined by measuring the ability to inhibit spontaneous locomotor activity using the reported method.[22]

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References

1) *a*) Part I: Ishizumi K., Kojima A., Antoku F., *Chem. Pharm. Bull.*, **39**, 2288 (1991); *b*) Ishizumi K., Antoku F., Asami Y., Eur. Pat. Appl. EP 82402 (1983) [*Chem. Abstr.*, **99**, 195000*z* (1983)]; *idem*, Jpn. Kokai Tokkyo Koho JP 59 76059 (1984) [*Chem. Abstr.*, **101**, 191971*d* (1984)]; Ishizumi K., Antoku F., Maruyama I., Kojima A., Eur. Pat. Appl. EP 200968 (1986) [*Chem. Abstr.*, **106**, 84646*h* (1987)]; *c*) Kojima A., Maruyama I., Antoku F., Ishizumi K., Jpn. Kokai Tokkyo Koho JP 63 10760 (1988) [*Chem. Abstr.*, **110**, 23914*e* (1989)]; *idem*, *ibid.*, 63 10786 (1988) [*Chem. Abstr.*, **110**, 231663*z* (1989)].

2) A part of this work was presented in preliminary form at the 112th Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, Mar. 1992 and the 15th Medicinal Chemistry Symposium, Osaka, November 1994.

3) Ishizumi K., Antoku F., Maruyama I., Kojima A., Eur. Pat. Appl. EP 196096 (1986) [*Chem. Abstr.*, **106**, 33119*f* (1987)]; Antoku F., Yoshigi M., Saji I., Kojima A., Ishizumi K., Jpn. Kokai Tokkyo Koho JP 63 83085 (1988) [*Chem. Abstr.*, **109**, 149567*s* (1988)].

4) Grohmann R., Günther W., Rüther E., "Psychopharmacology. Part 2, Clinical Psychopharmacology," ed. by Hippius H., Winokur G., Excepta Medica, Amsterdam, 1983; Chapter 27.

5) Jenner P., Marsden C. D., "Neuroleptics: Neurochemical, Behavioral and Clinical Perspectives," ed. by Coyle J. T., Enna S. J., Raven Press, New York, 1983, pp. 223.

6) Seeman P., Lee T., Chau-Wong M., Wong K., *Nature* (London), **261**, 717 (1976).

7) White F. J., Wang R. Y., *Neuropharmacology*, **25**, 995 (1986).

8) Baldessarini R. J., Tarsy D., *Annu. Rev. Neurosci.*, **3**, 23 (1980).

9) Ceulemans D. L. S., Gelders Y. G., Hoppenbrouwers M.-L. J. A., Reyntjens A. J. M., Janssen P. A. J., *Psychopharmacology* (Berlin), **85**, 329 (1985).

10) Bersani G., Grispini A., Marini S., Pasini A., Valducci M., Ciani N., *World Cong. Biol. Psychiat. Abs., Suppl.* **4**, 1 (1985).

11) Gelders Y. G., Ceulemans D., Reyntjens A., Hoppenbrouwers M.-L. J. A., Ferauge M., *World Cong. Biol. Psychiat. Abs., Suppl.* **4**, 417 (1985).

12) Wu Y. -H., Smith K. R., Rayburn J. M., Kissel J. W., *J. Med. Chem.*, **12**, 876 (1969).

13) Goldberg H. L., *Psychopharmacol. Bull.*, **15**, 90 (1979).

14) *a*) Yevich J. P., Temple D. L., Jr., New J. S., Lobeck W. G., Catt J. D., Taylor D. P., Eison M. S., Riblet L. A., 186th Meeting of American Chemical Society, Washington, August 22—26, 1983, Abst. p. 69; *b*) Temple D. L., Jr., Yevich J. P., Jpn. Kokai Tokkyo Koho JP 58 110576 (1983) [*Chem. Abstr.*, **99**, 212537*z* (1983)].

15) Wu Y.-H., Rayburn J. M., Allen L. E., Ferguson H. C., Kissel J. W., *J. Med. Chem.*, **15**, 477 (1972).

16) Farina F., Martin M. V., Paredes M. C., *Heterocycles*, **22**, 1733 (1984).

17) Hrib N. J., Jurcak J. G., Huger F. P., Errico C. L., Dunn.R. W., *J. Med. Chem.*, **34**, 1068 (1991).

18) Craig D., *J. Am. Chem. Soc.*, **73**, 4889 (1951); Alder K., Stein G., *Justus Liebigs Ann. Chem.*, **504**, 247 (1933); Farmer E. H., Warren F. L., *J. Chem. Soc.*, **1929**, 897; Alder K., Schumacher M., *Justus Liebigs Ann. Chem.*, **571**, 87 (1950); Sah P. P. T., Anderson H. H., *J. Am. Chem. Soc.*, **63**, 3167 (1941); Hill R. K., van Auken T. V., *J. Org. Chem.*, **23**, 626 (1958); Bailey B., Haworth R. D., McKenna J., *J. Chem. Soc.*, **1954**, 967; Clarke H. T., Behr L. D., "Organic Syntheses," Coll. Vol. II, ed. by Blatt A. H., John Wiley and Sons, Inc., New York, 1943, p. 562; Kornfeld E. C., Jones R. G., Parke T. V., *J. Am. Chem. Soc.*, **71**, 150 (1949); Jones E. R. H., Robinson F. A., Strachan M. N., *J. Chem. Soc.*, **1946**, 91; Hurst D. H., McOmie J. F. W., Stracham M. W., *ibid.*, 1965, 7119; Späth E., Koller G., *Chem. Ber.*, **56**, 886 (1923); Böshagen H., *ibid.*, **99**, 2566 (1966); McMillen B. A., *J. Pharmacol. Exp. Ther.*, **233**, 369 (1985); Yevich J. P., New J. S., Smith D. V., Lobeck W. G., Catt J. D., Minielli J. L., Eison M. S., Taylor D. P., Riblet L. A., Temple D. L., Jr., *J. Med. Chem.*, **29**, 359 (1986).

19) Kohler C., Hall H., Ogren S. O., Gawell L., *Biochem. Pharmacol.*, **34**, 2251 (1985).

20) Leysen J. E., Niemegeers C. J. E., Van Nueten J. M., Laduron P. M., *Mol. Pharmacol.*, **21**, 301 (1982).

21) The same replacement shows a similar tendency on 5-HT_{1A} binding affinity.[1]

22) Hirose A., Kato T., Ohno Y., Shimizu H., Tanaka H., Nakamura M., Katsube J., *Jpn. J. Pharmacol.*, **53**, 321 (1990).

23) Protais P., Costentin J., Schwartz J. C., *Psychopharmacology* (Berlin), **50**, 1 (1976).

24) Niemegeers C. J. E., Lenaerts F. M., Artois K. S. K., Janssen P. A. J., *Arch. Int. Pharmacodyn. Ther.*, **227**, 238 (1977).

25) Yamasaki T., Kojima H., Sakurai T., Kasahara A., Watanabe S., Fujiwara M., Ueki S., *Arzneimittelforschung*, **31**, 701 (1981).

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