2a-[4-(Tetrahydropyridoindol-2-yl)butyl]tetrahydrobenzindole Derivatives: New Selective Antagonists of the 5-Hydroxytryptamine$_7$ Receptor

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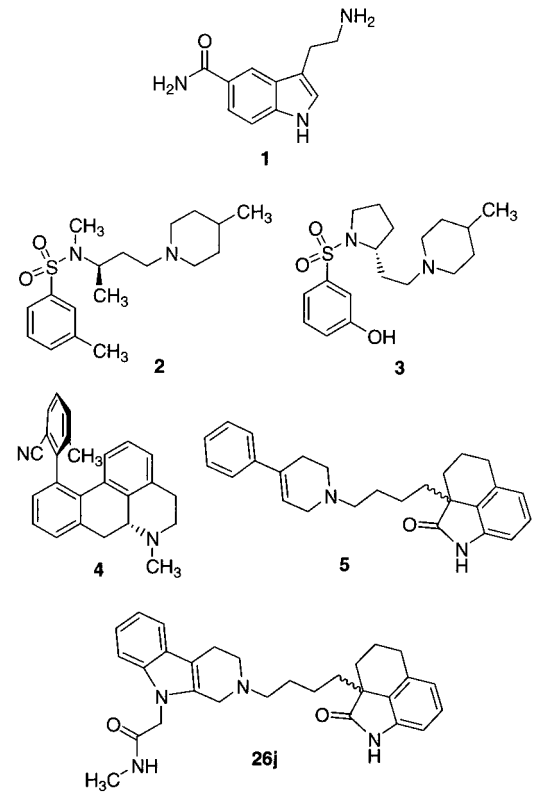
A series of tetrahydrobenzindoles was prepared, and the affinity of these compounds for the 5-hydroxytryptamine$_7$ (5-HT$_7$) receptor and other receptors was evaluated. Most of the compounds showed high affinity for the 5-HT$_7$ receptor, and 2a-[4-(tetrahydropyridoindol-2-yl)butyl]tetrahydrobenzindole derivatives (**26a**−**j**) exhibited high selectivity for this receptor. The nature of the substituent at the 9-position of the tetrahydropyridindole ring affected the affinity for the 5-HT$_7$ receptor, and the 9-carbamoyl moiety afforded increased selectivity. Compound **26j** exhibited high affinity for the 5-HT$_7$ receptor, with at least 280-fold selectivity over the 5-HT$_2$ receptor. In a functional model of 5-HT$_7$ receptor activation, this compound was confirmed to have 5-HT$_7$ receptor antagonist activity. It should be a useful tool for clarifying the biological role of the 5-HT$_7$ receptor.

Introduction

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is involved in a variety of pharmacological effects in the central and peripheral nervous system. Seven classes of 5-HT receptor subtypes (5-HT$_1$−5-HT$_7$) have been characterized by molecular biological techniques. The 5-HT$_7$ receptor is the most recent addition to the family of G-protein-coupled 5-HT receptors and has been cloned from rat,[1−3] mouse,[4] human,[5] and guinea pig.[6] The deduced amino acid sequences of 5-HT$_7$ receptors show a high degree of interspecies homology but only a limited homology with other types of 5-HT$_7$ receptors. All four species homologues of the 5-HT$_7$ receptor have high affinity for 5-HT, 5-carboxyamidotryptamine (5-CT, **1**) (Chart 1), 5-methoxytryptamine (5-MeOT), and methiothepin and have moderate affinity for 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT), clozapine, and a number of other psychoactive drugs.[7] Four 5-HT$_7$ splice variants exist in human and rat. Both the long (5-HT$_{7a}$) and short (5-HT$_{7b}$) forms of the human receptor exhibit similar distribution patterns and pharmacology.[8−10]

The biological functions of the 5-HT$_7$ receptor are poorly understood. High levels of 5-HT$_7$ receptor mRNA have been observed in the brain where it is localized in the thalamus, hypothalamus, brainstem, and hippocampus.[1,3,5,11] The distribution of 5-HT$_7$ receptor binding sites in rat and guinea pig brain was essentially the same as the mRNA distribution.[11−13] The 5-HT$_7$ receptor is involved in the control of circadian rhythms of spontaneous electrical activity in the suprachiasmatic nucleus (SCN) of the hypothalamus.[3,14−16] It may be involved in the disturbance of circadian rhythms, such as jet lag, delayed sleep-phase syndrome (DSPS), and non-24-hour sleep−wake disorder (non-24).[17] In addition, the decrease of 5-HT$_7$ receptors in dorsal raphe nuclei with aging suggests that these receptors may have a role of in age-related changes of the circadian timing system.[18] The affinity of a number of antipsychotic agents for the 5-HT$_7$ receptor also led to the speculation that this receptor may mediate the therapeutic actions of these compounds.[7] The 5-HT$_7$ receptor may be of value as a novel therapeutic target.

Chart 1



Only a few selective antagonists for the 5-HT$_7$ receptor, **2**−**5** (Chart 1), have been reported to date,[19−22] and no selective agonist is yet available. In the previous paper, we reported the synthesis and the affinities for the 5-HT$_7$ receptor and other receptors of a novel series

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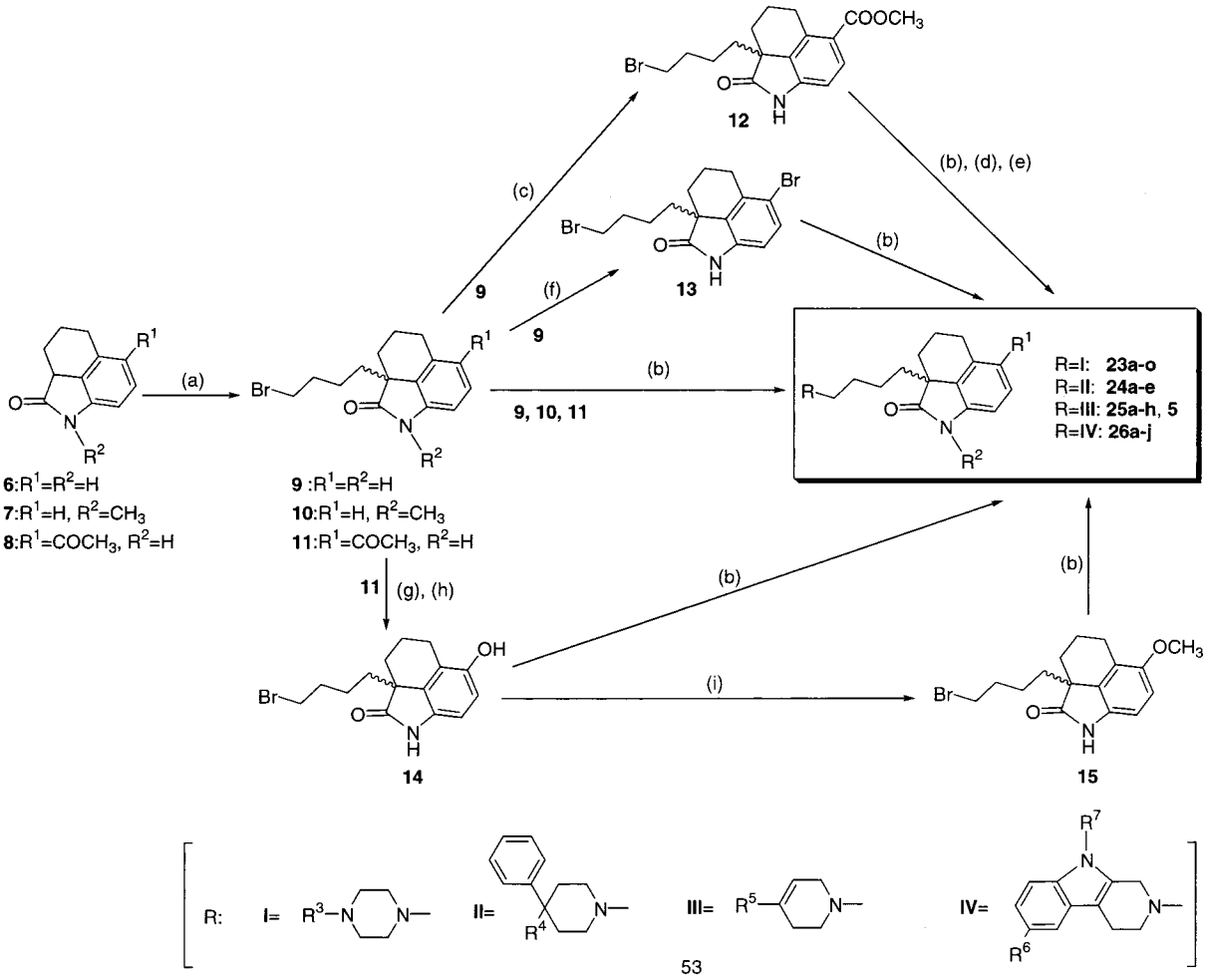
Scheme 1[a]



[a] Reagents: (a) 1,4-dibromobutane, NaH (55%), DMF, −40 to 0 °C; (b) corresponding amine, K_2CO_3, DMF, 60 °C; (c) bis(trichloromethyl)carbonate, $AlCl_3$, 1,2-dichloroethane, MeOH, 0 °C to room temp; (d) LiOH(aq), MeOH, reflux; (e) NH_3(aq), DCC, HOBt, DMF; (f) Br_2, 1,2-dichloroethane, −20 °C; (g) mCPBA, TFA; (h) NaOMe, MeOH, 0 °C; (i) MeI, K_2CO_3, acetone.

of tetrahydrobenzindoles. Compound **5** is a highly potent antagonist for the 5-HT_7 receptor, with 50-fold selectivity over 5-HT_2 receptor.[22] In the present paper, we report the synthesis and the binding affinity for the 5-HT_7 and 5-HT_2 receptors of 2a-(4-substituted)butyltetrahydrobenzindole derivatives **23a**−**26j**. The structure−activity relationship of these derivatives is also discussed. On the basis of the relative affinity for the 5-HT_7 and 5-HT_2 receptors, we selected compound **26j** for further evaluation of the in vitro agonist or antagonist activity. We also evaluated its affinity for the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_6 receptors.

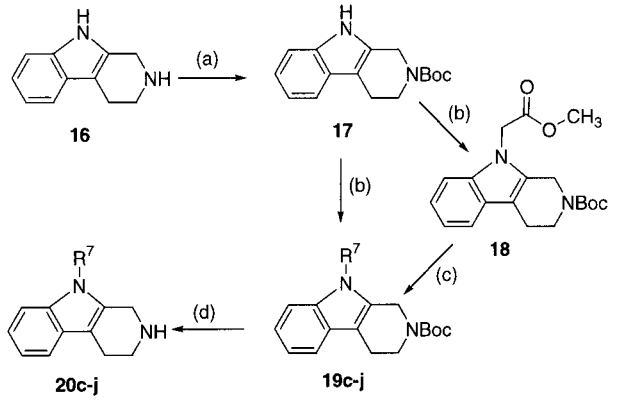
Chemistry

The synthetic procedures to the target compounds are illustrated in Scheme 1. Compound **6** is commercially available. Compound **9** was prepared by treating tetrahydrobenzindole **6** with sodium hydride and 1,4-dibromobutane.[22] This alkylation procedure did not provide the N-alkylated product. A previous paper described that the 3-position of a 3-monosubstituted oxindole was about 30 times as reactive as the 1-position.[23] In view of the report, our result that compound **6** was not N-alkylated was reasonable. Compound **12** was prepared from compound **9** by Friedel−Crafts reaction. Compound **13** was obtained from compound **9** by reaction with bromine at −20 °C. The reaction furnished 6-bromobenzindole **13** in high yield, with none of the alternative 8-bromobenzindole detectable. Bromination of compound **9** at 0 °C mainly provided the 6,8-dibrominated compound. Compound **14** was prepared from compound **11** by treatment with mCPBA followed by hydrolysis. Compound **15** was prepared from **14** by reaction with iodomethane in the presence of K_2CO_3. Compounds **23a**−**26j** were obtained from **9**−**15** by reaction with the corresponding amines in the presence of K_2CO_3.

The tetrahydropyridindoles substituted at the 9-position were synthesized starting from 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (**16**). Compound **16** is commercially available. Protection of the basic nitrogen of compound **16** gave compound **17**, which was reacted with the corresponding alkyl halide or acid halide. After removal of the protective group, compounds **20c**−**j** were obtained (Scheme 2).[24]

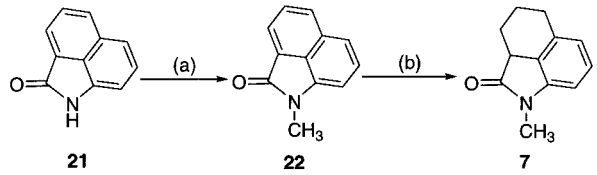
Compound **7** could not be prepared via N-alkylation of compound **6**, so it was synthesized starting from benzindole **21** (Scheme 3). Compound **22** was prepared by reacting compound **21** with sodium hydride and iodomethane, and the tetrahydrobenzindole **7** was obtained from compound **22** by catalytic hydrogenation using Raney Ni.

Scheme 2[a]



[a] Reagents: (a) $(Boc)_2O$, K_2CO_3, 2-propanol/H_2O; (b) corresponding halide or acid halide, NaH (55%), DMF; (c) (i) NaOH(aq), THF, (ii) methylamine(aq), DCC, HOBt, CH_3CN; (d) TFA, anisole, $CHCl_3$.

Scheme 3[a]



[a] Reagents: (a) MeI, NaH (55%), DMF, 0 °C to room temp; (b) Raney Ni, EtOH, H_2.

Pharmacology

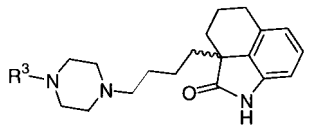
Compounds **23a**−**26j** were evaluated for in vitro affinity for 5-HT_7 and 5-HT_2 receptors by means of radioligand binding assays. Compound **26j** was also evaluated for in vitro affinity for 5-HT_7, 5-HT_2, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_6 receptors by means of radioligand binding assays. The specific ligands and tissue sources used were as follows: (a) 5-HT_7 receptors, [^{3}H]5-CT, human recombinant receptors in mammalian cells; (b) 5-HT_2 receptors, [^{3}H]-ketanserin, rat cerebral cortex membranes;[25] (c) 5-HT_{1A} receptors, [^{3}H]8-OH-DPAT, human recombinant receptors in mammalian cells;[26] (d) 5-HT_{1B} receptors, [^{125}I]-(−)-iodocyanopindolol, rat striatal;[27] (e) 5-HT_{2C} receptors, [^{3}H]mesulergine, pig choroids plexus;[27] (f) 5-HT_3 receptors, [^{3}H]GR-65630, N1E-115 cells;[28] (g) 5-HT_4 receptors, [^{3}H]GR-113808, guinea-pig striatum;[29] (h) 5-HT_6 receptors, [^{3}H]LSD, human recombinant receptors in mammalian cells.[30]

The agonist and antagonist activity of compound **26j** at the 5-HT_7 receptor was evaluated in terms of the influence on 5-HT-induced stimulation of cAMP accumulation in HEK293 cells transfected with an expression vector containing human 5-HT_7 receptor cDNA.

Results and Discussion

The results of the in vitro binding studies of compounds **23a**−**26j**, expressed as pK_i, are summarized in Tables 1−4. Most of compounds **23a**−**26j** exhibited moderate to high affinity for the 5-HT_7 receptor.

Table 1. 5-HT_7 and 5-HT_2 Receptor Affinities for Compounds **23a**−**o**

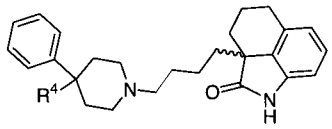


compd	R^3	pK_i[a] 5HT_7[b]	pK_i[a] 5HT_2[c]
23a	phenyl	8.48 ± 0.02	7.37 ± 0.05
23b	2-methoxyphenyl	8.29 ± 0.08	6.95 ± 0.10
23c	3-methoxyphenyl	8.63 ± 0.02	7.19 ± 0.10
23d	4-methoxyphenyl	7.69 ± 0.11	6.69 ± 0.05
23e	2-chlorophenyl	7.91 ± 0.06	7.01 ± 0.16
23f	2-cyanophenyl	8.42 ± 0.67	6.98 ± 0.07
23g	2-carbamoylphenyl	7.76 ± 0.14	6.05 ± 0.06
23h	2-acetylphenyl	8.10 ± 0.08	6.45 ± 0.06
23i	2-trifluoromethylphenyl	7.13 ± 0.11	5.86 ± 0.14
23j	2-nitrophenyl	7.62 ± 0.15	7.34 ± 0.07
23k	2-methylphenyl	7.98 ± 0.08	7.35 ± 0.07
23l	2,6-dimethylphenyl	6.83 ± 0.10	5.85 ± 0.09
23m	2-pyridyl	8.73 ± 0.09	7.27 ± 0.06
23n	2-pyrimidinyl	7.34 ± 0.10	6.91 ± 0.08
23o	cyclohexyl	<6	<6
1		9.31 ± 0.06	<6

[a] The pK_i values are means ± SEM of 8−12 values. [b] Binding affinity (human recombinant receptors in mammalian cells; [^{3}H]5-CT). [c] Binding affinity (rat cerebral cortex membranes; [^{3}H]ketanserin).

Some of the piperazine derivatives **23a**−**o** showed high affinity for the 5-HT_7 receptor (Table 1). The phenylpiperazine derivative **23a** and the 2-methoxyphenylpiperazine **23b** showed high affinity for the 5-HT_7 receptor with selectivity over the 5-HT_2 receptor. The 3-substituted phenylpiperazine **23c** also showed high affinity for the 5-HT_7 receptor, but the 4-substituted phenylpiperazine **23d** had lower affinity than **23b**,**c**. These results suggested that substituent position is important in determining 5-HT_7 receptor affinity. The other 2-substituted phenylpiperazines **23e**−**k** also had moderate to high affinity for the 5-HT_7 receptor (pK_i = 7.13−8.42), with selectivity over the 5-HT_2 receptor. There was no marked difference between the effects on 5-HT_7 receptor affinity of an electron-donating substituent and those of an electron-withdrawing substituent on the phenyl ring. The 2,6-disubstituted phenylpiperazine **23l** showed lower affinity for the 5-HT_7 receptor compared with the 2-substituted phenylpiperazines **23b**,**e**−**k**. This may be due to a conformational difference generated by rotation around the bond between the phenyl ring and the piperazine ring. Although pyridylpiperazine **23m** was a highly potent 5-HT_7 ligand, pyrimidinylpiperazine **23n** was not. The cyclohexylpiperazine **23o** showed affinity for neither the 5-HT_7 receptor nor the 5-HT_2 receptor. Thus, affinity for the 5-HT_7 receptor would appear to depend on the aromaticity of these compounds. The carbamoylphenyl derivative **23g** and the acetylphenyl derivative **23h** were the most selective ligands for the 5-HT_7 receptor among the series of piperazine derivatives **23a**−**o**. 5-CT (**1**), which has a carbamoyl moiety, is also a highly selective ligand for the 5-HT_7 receptor over the 5-HT_2 receptor. Thus, a carbamoyl moiety would appear to be important for high 5-HT_7 receptor selectivity over the 5-HT_2 receptor. The carbamoyl group and the acetyl group are the hydrogen

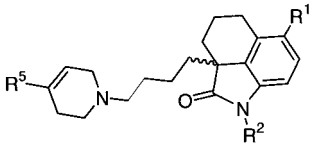
Table 2. 5-HT_7 and 5-HT_2 Receptor Affinities of Compounds **24a**−**e**



compd	R^4	pK_i[a] 5HT_7[b]	pK_i[a] 5HT_2[c]
24a	H−	8.40 ± 0.11	6.84 ± 0.12
24b	HO−	7.36 ± 0.14	6.35 ± 0.08
24c	CH_3O−	7.66 ± 0.09	6.43 ± 0.19
24d	H_2NCO−	6.65 ± 0.24	7.80 ± 0.09
24e	CH_3CO−	7.14 ± 0.12	7.01 ± 0.10

[a] The pK_i values are means ± SEM of 8−12 values. [b] Binding affinity (human recombinant receptors in mammalian cells; [^{3}H]5-CT). [c] Binding affinity (rat cerebral cortex membranes; [^{3}H]ketanserin).

Table 3. 5-HT_7 and 5-HT_2 Receptor Affinities of Compounds **25a**−**h**



compd	R^1	R^2	R^5	pK_i[a] 5HT_7[b]	pK_i[a] 5HT_2[c]
25a	H−	H−	4-fluorophenyl	8.45 ± 0.05	7.10 ± 0.04
25b	H−	H−	4-methylphenyl	8.32 ± 0.10	6.94 ± 0.11
25c	H−	CH_3−	phenyl	7.60 ± 0.06	6.88 ± 0.06
25d	CH_3OC−	H−	phenyl	7.01 ± 0.13	7.12 ± 0.11
25e	CH_3O−	H−	phenyl	6.96 ± 0.12	7.55 ± 0.23
25f	H_2NOC−	H−	phenyl	6.38 ± 0.10	6.80 ± 0.09
25g	Br−	H−	phenyl	7.91 ± 0.13	6.54 ± 0.09
25h	HO−	H−	phenyl	8.09 ± 0.06	7.40 ± 0.13
5	H−	H−	phenyl	8.67 ± 0.07	7.01 ± 0.05

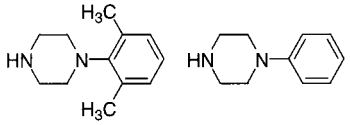
[a] The pK_i values are means ± SEM of 8−12 values. [b] Binding affinity (human recombinant receptors in mammalian cells; [^{3}H]5-CT). [c] Binding affinity (rat cerebral cortex membranes; [^{3}H]ketanserin).

bond acceptors, and this nature may contribute to high 5-HT_7 selectivity.

The 4-phenylpiperidine **24a** showed high potency for the 5-HT_7 receptor, and **24a** had higher selectivity than the phenylpiperazine derivative **23a**. To find the derivatives with high selectivity for the 5-HT_7 receptor, the R^4 group was modified and **24b**−**e** were synthesized (Table 2). However, these 4,4-disubstituted piperidine derivatives **24b**−**e** were less potent and less selective than **24a** for the 5-HT_7 receptor. The hydroxyl derivative **24b** and the methoxyl derivative **24c** showed moderate affinity for the 5-HT_7 receptor, while the carbamoyl derivative **24d** showed low affinity for the 5-HT_7 receptor. The carbamoyl derivative **24d** and the acetyl derivative **24e** did not show selectivity for the 5-HT_7 receptor. Thus, the 4,4-disubstituted piperidine derivatives **24b**−**e** did not have high affinity for the 5-HT_7 receptor. These results suggested that the size of the R^4 group influences the binding to the 5-HT_7 receptor. The small R^4 groups may be preferred for the 5-HT_7 receptor binding.

Table 3 summarized the affinities for the 5-HT_7 and 5-HT_2 receptors of the 4-phenyltetrahydropyridine derivatives **25a**−**h**. The 4-phenyltetrahydropyridine derivative **5** (DR4004) has high affinity and selectivity for the 5-HT_7 receptor, so the 4-phenyltetrahydropyridines **25a**−**h** were evaluated for affinity for the 5-HT_7 and 5-HT_2 receptors. The 4-fluorophenyl derivative **25a** and the 4-methylphenyl derivative **25b** were as potent as compound **5**. This information will be applicable to the improvement of the pharmacokinetic property.

Chart 2



27 **28**

As the next step, the tetrahydrobenzindole moiety was modified. The *N*-methyltetrahydrobenzindole **25c** showed a lower affinity for the 5-HT_7 receptor compared with the unsubstituted tetrahydrobenzindole **5**. The 6-substituted tetrahydrobenzindoles **25d**−**h** showed a lower selectivity than **5** for the 5-HT_7 receptor. The acetyl derivative **25d**, the methoxyl derivative **25e**, and the carbamoyl derivative **25g** lacked selectivity for the 5-HT_7 receptor and also had low affinity for this receptor. There was no appreciable difference between the effect on 5-HT_7 receptor affinity of an electron-donating substituent and that of an electron-withdrawing substituent. The bromo derivative **25f** had moderate affinity and selectivity for the 5-HT_7 receptor. Although the hydroxyl derivative **25h** showed high affinity for the 5-HT_7 receptor, this derivative had lower selectivity than **5**. These results suggested that a large substituent at the 6-position reduces the affinity for the 5-HT_7 receptor. This series **25c**−**h** thus showed lower selectivity than compound **5** for the 5-HT_7 receptor, so it was not further evaluated.

The 4-phenyltetrahydropyridine **5** has higher affinity and selectivity than the phenylpiperazine **23a** and the phenylpiperidine **24a** for the 5-HT_7 receptor. This could be due to the influence of the conjugated double bond on the conformation of the 4-phenyltetrahydropyridine. The 4-phenyltetrahydropyridine can be presumed to adopt a planar conformation, which may be important for the 5-HT_7 receptor affinity and selectivity.

Further Modification. We mentioned that the low 5-HT_7 affinity of 2,6-disubstituted phenylpiperazine **23l** might be due to the conformational difference generated by rotation around the bond between the phenyl ring and the piperazine ring. To rationalize the hypothesis, we carried out the energy minimization of model compounds and superimposed their lowest energy conformations. The 2,6-dimethylphenylpiperazine **27** and the phenylpiperazine **28** were chosen as the model compounds (Chart 2). As can be seen in Figure 1, 2,6-disubstitued phenylpiperazine **27** showed no planar conformation and the superimposition of **27** and **28** did not show a good match. This conformational difference may have a critical influence on the affinity and selectivity of these derivatives for the 5-HT_7 receptor.

To test this idea, the tetrahydropyridoindole derivatives **26a**−**j** were synthesized and evaluated (Table 4). The tetrahydropyridoindoles have the phenyl ring fixed to the tetrahydropyridine ring by C−N bonds (Scheme 4). All of the tetrahydropyridoindole derivatives **26a**−**j**

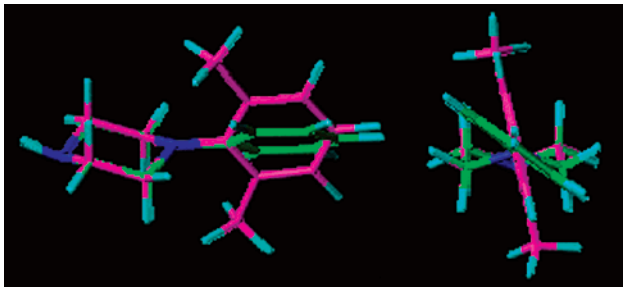
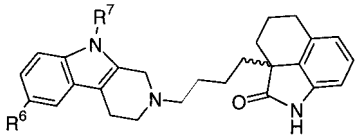


Figure 1. Superimposition of the lowest energy conformation of the model compound **27** (pink carbons) and **28** (green carbons): front view (left) and side view (right).

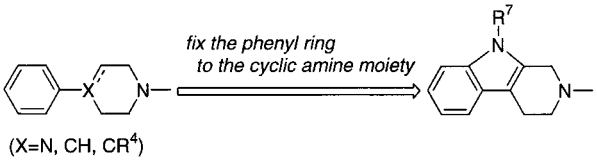
Table 4. 5-HT_7 and 5-HT_2 Receptor Affinities for Compounds **26a**−**j**



compd	R^6	R^7	pK_i[a] 5HT_7[b]	pK_i[a] 5HT_2[c]
26a	H−	H−	8.24 ± 0.08	6.62 ± 0.09
26b	CH_3O−	H−	7.53 ± 0.14	6.17 ± 0.06
26c	H−	CH_3−	7.72 ± 0.12	6.28 ± 0.06
26d	H−	CH_3OCH_2−	7.77 ± 0.13	6.24 ± 0.06
26e	H−	CH_3CO−	8.19 ± 0.06	6.27 ± 0.06
26f	H−	CH_2=$CHCH_2$−	8.22 ± 0.09	6.55 ± 0.16
26g	H−	$(CH_3)_2NCO$−	8.15 ± 0.09	6.12 ± 0.05
26h	H−	H_2NCOCH_2−	8.06 ± 0.16	6.09 ± 0.10
26i	H−	$(CH_3)_2NCOCH_2$−	7.72 ± 0.12	<6
26j	H−	$(CH_3)HNCOCH_2$−	8.45 ± 0.04	<6

[a] The pK_i values are means ± SEM of 8−12 values. [b] Binding affinity (human recombinant receptors in mammalian cells; [^{3}H]5-CT). [c] Binding affinity (rat cerebral cortex membranes; [^{3}H]ketanserin).

Scheme 4



showed high selectivity for the 5-HT_7 receptor. The 6-methoxy derivative **26b** had lower affinity for the 5-HT_7 receptor than the unsubstituted derivative **26a**, and the 9-methyl derivative **26c** and the 9-methoxymethyl derivative **26d** also had lower affinity compared with **26a**. The 9-acetyl derivative **26e** and the 9-allyl derivative **26f** were as potent and selective as compound **26a**. The 9-dimethylcarbamoyl derivative **26g** had higher selectivity than **26a** for the 5-HT_7 receptor. To find derivatives with higher selectivity for the 5-HT_7 receptor, we modified the carbamoyl moiety. The 9-carbamoylmethyl derivative **26h** was as potent and selective as compound **26g**, and the 9-dimethylcarbamoylmethyl derivative **26i** had lower affinity than compound **26g**. The dimethylcarbamoylmethyl group may be too large to show high affinity. Finally, the 9-methylcarbamoylmethyl derivative **26j** showed both high affinity and high selectivity. Compound **26j** had a pK_i of 8.45 for the 5-HT_7 receptor, with more than 280-fold selectivity over the 5-HT_2 receptor. This result also suggested that a carbamoyl moiety is important for high selectivity for the 5-HT_7 receptor over the 5-HT_2 receptor.

Table 5. Receptor Binding Profile of **26j**[a]

receptor	affinity (pK_i)[b]	receptor	affinity (pK_i)[b]
5-HT_{1A}	6.89 ± 0.13	5-HT_3	<6
5-HT_{1B}	<6	5-HT_4	6.31 ± 0.06
5-HT_{2C}	<6	5-HT_6	<6
5-HT_2	<6	5-HT_7	8.45 ± 0.04

[a] See Pharmacology section. [b] The pK_i values are means ± SEM of 8−12 values.

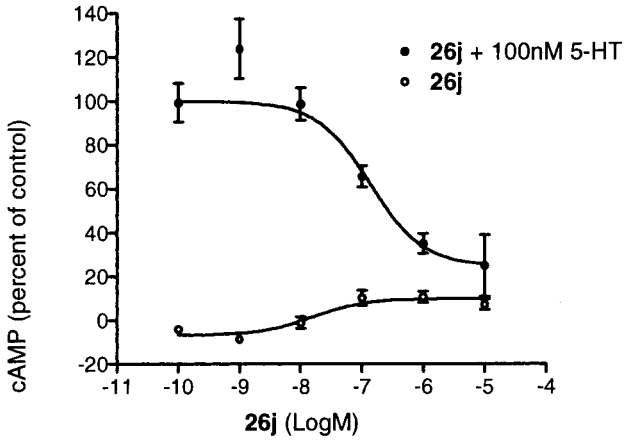


Figure 2. 5-HT-induced stimulation of cAMP accumulation in HEK293 cells expressing the 5-HT_7 receptor and its inhibition by compound **26j**. Data represent the mean ± SEM of at least three determinations.

As can be seen in Table 4, compounds **26a**−**j** showed high 5-HT_7 receptor selectivity. These results support the idea that the conformational difference generated by rotation around the bond between the phenyl ring and the cyclic amine moiety is important for 5-HT_7 receptor affinity and selectivity. The tetrahydropyridoindoles have the phenyl ring fixed to the tetrahydropyridine ring by C−N bonds, and this planar structure may impair the binding ability to the 5-HT_2 receptor.

On the basis of its relative affinity for the 5-HT_7 and 5-HT_2 receptors, compound **26j** was selected for further evaluation. As can be seen in Table 5, compound **26j** had high selectivity over a number of other key receptors. Thus, compound **26j** was confirmed to be a high-affinity ligand for the 5-HT_7 receptor with high selectivity.

Compound **26j** was next evaluated for influence on 5-HT-induced stimulation of cAMP accumulation in HEK293 cells expressing the human 5-HT_7 receptor. Intracellular cAMP formation was measured by enzyme immunoassay. Compound **26j** on its own did not stimulate basal activity (i.e., it lacked agonist activity), but it inhibited 5-HT-induced stimulation of cAMP accumulation (Figure 2). Compound **26j** is thus a 5-HT_7 receptor antagonist.

Conclusion

Tetrahydrobenzindoles were prepared, and the affinities of these compounds for the 5-HT_7 and 5-HT_2 receptors were evaluated. Most of the tetrahydrobenzindole derivatives showed high affinity for the 5-HT_7 receptor. The tetrahydropyridindolylbutyltetrahydrobenzindole derivatives (**26a**−**j**) had high selectivity for the 5-HT_7 receptor. The nature of the substituent at the 9-position of the tetrahydropyridindole ring affected the affinity for the 5-HT_7 receptor, and the 9-carbamoyl

derivatives showed increased selectivity. Compound **26j** (DR4365) exhibited high affinity for the 5-HT_7 receptor, with high selectivity over the 5-HT_2 receptor and other related receptors. In a functional model of 5-HT_7 receptor activation, compound **26j** was confirmed to be a 5-HT_7 receptor antagonist. This compound should be a useful tool for clarifying the biological role of the 5-HT_7 receptor.

Experimental Section

Melting points were determined on a Yanaco melting point apparatus. Elemental analyses were performed by the Toray Research Center and were within ±0.4% of calculated values. The ^{1}H NMR spectra were recorded on JEOL JNM-GX400 and JNM-LA400 spectrometers with chemical shifts reported in ppm relative to internal tetramethylsilane. Electron-impact (EI) mass spectra were recorded on a Hitachi M-80B instrument. Fast-atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-700 instrument. Thermospray (TSP) mass spectra were recorded on a Hewlett-Packard 5989A instrument.

1-Methyl-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (7). A mixture of benz[*cd*]indole-2(1*H*)-one (5.1 g, 30 mmol) and NaH (55% oil suspension, 1.2 g, 30 mmol) in DMF (100 mL) was stirred at 0 °C for 20 min. Methyl iodide (2.6 mL, 42 mmol) was added dropwise to the mixture, and the whole was stirred at room temperature for 1 h and then was added to H_2O. This mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated to afford **22** as yellow solid (4.7 g, 74% yield). A mixture of **22** (4.5 g, 25 mmol) and Raney Ni in EtOH (100 mL) was stirred under 1 atm of H_2 for 30 h. Raney Ni was removed by filtration, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (eluent: diisopropyl ether) to afford **7** as a colorless solid (3.8 g, 83% yield). ^{1}H NMR ($CDCl_3$) δ 1.22−1.40 (1H, m), 1.80−2.00 (1H, m), 2.06−2.20 (1H, m), 2.36−2.50 (1H, m), 2.53−2.70 (1H, m), 2.81−2.99 (1H, m), 3.20−3.32 (4H, m), 6.60 (1H, d, J = 7.9 Hz), 6.80 (1H, d, J = 7.9 Hz), 7.16 (1H, dd); EIMS m/z 187 (M^+).

2a-(4-Bromobutyl)-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (9). A mixture of 2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (10 g, 58 mmol) and NaH (55% oil suspension, 2.5 g, 58 mmol) in DMF (100 mL) was stirred at 0 °C for 1 h. 1,4-Dibromobutane (35 mL, 290 mmol) in dry DMF (50 mL) was added dropwise to the reaction mixture at −40 °C. The mixture was stirred at 0 °C for 30 min and then was added to H_2O. The whole was extracted with AcOEt. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 4/1) to afford **9** as crystals (9.5 g, 54% yield). Mp 81 °C;^{1}H NMR ($CDCl_3$) δ 1.17−1.28 (1H, m), 1.32−1.51 (2H, m), 1.72−1.90 (5H, m), 2.06−2.19 (2H, m), 2.60−2.70 (1H, m), 2.80−2.89 (1H, m), 3.30 (2H, t, J = 7.0 Hz), 6.67 (1H, d, J = 7.4 Hz), 6.81 (1H, d, J = 7.8 Hz), 7.12 (1H, dd), 7.34 (1H, br s); EIMS m/z 309, 307 (M^+). Anal. ($C_{15}H_{18}BrNO$) C, H, N.

6-Methoxycarbonyl-2a-(4-bromobutyl)-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (12). Bis(trichloromethyl)-carbonate (1.4 g, 4.9 mmol) was added to a suspension of $AlCl_3$ (3.0 g, 15 mmol) in 1,2-dichloroethane (30 mL) at 0 °C. A solution of **9** (1.5 g, 1.6 mmol) in 1,2-dichloroethane (30 mL) was added to the mixture, and the whole was stirred for 2 h at 0 °C. MeOH (50 mL) was added, and stirring was continued for 1 h at room temperature. The reaction mixture was poured into 1 N aqueous HCl and extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 1/1) and then recrystallized from hexane/AcOEt = 1/1 to afford **12** as colorless crystals (0.63 g, 35% yield). Mp 127 °C; ^{1}H NMR ($CDCl_3$) δ 1.13−1.30 (1H, m), 1.34−1.51 (2H, m), 1.62−1.96 (5H, m), 2.07−2.22 (2H, m), 3.01−3.12 (1H, m), 3.23−3.37 (3H, m), 3.87 (3H, s), 6.81 (1H, d, J = 8.1 Hz), 7.94 (1H, d), 8.76 (1H, br s); TSPMS m/z 368, 366 ($M + H^+$).

6-Bromo-2a-(4-bromobutyl)-2a,3,4,5-tetrahydrobenzo-[*cd*]indol2(1*H*)-one (13). Br_2 (0.57 mL, 11 mmol) was added to **9** (3.1 g, 10 mmol) in 1,2-dichloroethane (120 mL) at −20 °C. The mixture was stirred at −20 °C for 30 min and then was added to saturated aqueous $NaHCO_3$. The whole was extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 4/1) to afford **13** as a colorless solid (3.4 g, 88% yield). ^{1}H NMR ($CDCl_3$) δ 1.20−1.53 (3H, m), 1.68−1.89 (4H, m), 1.89−2.00 (1H, m), 2.08−2.20 (2H, m), 2.74 (2H, t, J = 7.0 Hz), 3.32 (2H, t, J = 6.8 Hz), 6.59 (1H, d, J = 7.2 Hz), 7.23 (1H, br s), 7.34 (1H, d); EIMS m/z 389, 387, 385 (M^+).

6-Hydroxy-2a-(4-bromobutyl)-2a,3,4,5-tetrahydrobenzo-[*cd*]indol2(1*H*)-one (14). A mixture of **11** (2.9 g, 8.3 mmol), mCPBA (3.6 g, 21 mmol), and trifluoroacetic acid (0.64 mL, 8.3 mmol) in CH_2Cl_2 (60 mL) was stirred at 0 °C for 45 min and then at room temperature for 2 h. It was poured into $CHCl_3$ and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated to afford a residue. Sodium methoxide (1.9 mL, 33 mmol) was added to a suspension of the residue in MeOH (90 mL) at 0 °C, and the mixture was stirred for 1 h. Aqueous HCl (5 N, 4 mL) was added to the reaction mixture, and the whole was evaporated. The residue was dissolved in $CHCl_3$, and the organic layer was washed with 0.1 N aqueous HCl and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 2/1) to afford **14** as a colorless solid (1.2 g, 44% yield). ^{1}H NMR ($CDCl_3$) δ 1.30−1.52 (3H, m), 1.70−1.98 (5H, m), 2.03−2.19 (2H, m), 2.60−2.80 (2H, m), 3.31 (2H, t, J = 6.8 Hz), 4.66 (1H, s), 6.56 (1H, d, J = 8.0 Hz), 6.59 (1H, d), 7.23 (1H, br s); EIMS m/z 325, 323 (M^+).

6-Methoxy-2a-(4-bromobutyl)-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (15). A solution of **14** (520 mg, 1.6 mmol), methyl iodide (2.0 mL, 3.2 mmol), and K_2CO_3 (450 mg, 3.3 mmol) in acetone (4 mL) was stirred at room temperature for 17 h. The reaction mixture was poured into AcOEt and was washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 2/1) to afford **15** as colorless solid (310 mg, 56% yield). ^{1}H NMR ($CDCl_3$) δ 1.16−1.50 (3H, m), 1.67−1.95 (5H, m), 2.12−2.16 (2H, m), 2.54−2.65 (1H, m), 2.72−2.82 (1H, m), 3.07 (2H, t, J = 7.2 Hz), 3.79 (3H, s), 6.61 (1H, d, J = 8.3 Hz), 6.65 (1H, d), 8.22 (1H, br s); TSPMS m/z 340, 338 ($M + H^+$).

2-*tert*-Butoxycarbonyl-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole (17). A mixture of 1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole (2.5 g, 15 mmol), di-*tert*-butyl dicarbonate (4.0 mL, 17 mmol), and K_2CO_3 (2.4 g, 17 mmol) in 2-propanol/H_2O = 5/6 (55 mL) was stirred at room temperature for 17 h. The reaction mixture was poured into AcOEt and was washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated. The residue was recrystallized from hexane/AcOEt = 1/1 to afford **17** as colorless crystals (3.9 g, 98% yield). Mp 151 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 2.80 (2H, br s), 3.77 (2H, br s), 4.64 (2H, br s), 7.09−7.18 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.48 (1H, d, J = 7.8 Hz).

2-*tert*-Butoxycarbonyl-9-methoxycarbonylmethyl-1,2,-3,4-tetrahydropyrido[3,4-*b*]indole (18). A mixture of **17** (0.99 g, 3.6 mmol) and NaH (55% oil suspension, 0.22 g, 5.0 mmol) in DMF (12 mL) was stirred at room temperature for 30 min. Methyl bromoacetate (0.52 mL, 5.5 mmol) was added dropwise to the reaction mixture. The mixture was stirred at room temperature for 17 h and then was added to H_2O. The whole was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 1/3) to afford **18** as a solid (0.96 g, 77% yield). ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 2.79 (2H, br s),

3.72 (3H, s), 3.74 (2H, br s), 4.56 (2H, s), 4.68 (2H, s), 7.08−7.18 (3H, m), 7.48 (1H, d, J = 7.5 Hz).

2-*tert*-Butoxycarbonyl-9-methylcarbamoylmethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (19j). A mixture of **18** (0.62 g, 1.8 mmol) and aqueous NaOH (2.7 N, 5 mL) in THF (10 mL) was stirred at room temperature for 17 h. Aqueous HCl (1 N, 10 mL) was added dropwise to the reaction mixture. The whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue, DCC (560 mg, 2.7 mmol), and HOBT (370 mg, 2.7 mmol) in CH_3CN (12 mL) was stirred at room temperature for 2 h. Then 40% aqueous methylamine (2.0 mL, 23 mmol) was added to the mixture at 0 °C and the whole was stirred at room temperature for 30 min. The reaction mixture was filtrated and evaporated. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH = 30/1) to afford **19j** as a solid (0.54 g, 88% yield). ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 2.70 (3H, s), 2.80 (2H, br s), 3.76 (2H, br s), 4.54 (2H, s), 4.58 (2H, s), 5.66 (1H, br s), 7.13 (3H, m), 7.50 (1H, d, J = 7.5 Hz).

9-Methylcarbamoylmethyl-1,2,3,4-tetrahydropyrido-[3,4-*b*]indole (20j). A mixture of **19j** (0.54 g, 1.6 mmol), anisole (1 mL), and trifluoroacetic acid (1 mL) in CH_3Cl (10 mL) was stirred at room temperature for 17 h. The reaction mixture was evaporated. The residue was washed with acetone and diisopropyl ether to afford **20j** trifluoroacetate as a solid (0.47 g, 89% yield). ^{1}H NMR ($CDCl_3$) δ 2.75 (3H, s), 3.10 (2H, t, J = 6.0 Hz), 3.59 (2H, t), 4.49 (2H, s), 4.78 (2H, s), 7.12 (1H, dd, J = 8.0, 7.2 Hz), 7.22 (1H, dd, J = 7.6 Hz), 7.33 (1H, d), 7.52 (1H, d); EIMS m/z 243 (M^+).

General Procedure for the Synthesis of Compounds 23a−o, 24a−e, 25a−e, 25f,g, and 26a−i. 2a-[4-(9-Methylcarbamoylmethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indol-2-yl)butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (26j). A mixture of the bromide **9** (0.31 g, 1.0 mmol), 9-methylcarbamoylmethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole trifluoroacetate (0.33 g, 1.0 mmol), and K_2CO_3 (0.42 g, 3.0 mmol) in DMF (6 mL) was stirred at room temperature for 4 days and evaporated. The residue was added to AcOEt, and the solution was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH = 30/1) to afford **26j** as crystals (0.40 g, 85% yield). ^{1}H NMR ($CDCl_3$) δ 1.17−1.20 (1H, m), 1.30−1.42 (2H, m), 1.43−1.59 (2H, m), 1.78−1.95 (3H, m), 2.06−2.21 (2H, m), 2.47−2.60 (2H, m), 2.60−2.74 (4H, m), 2.74−2.90 (5H, m), 3.52 (2H, s), 4.61 (2H, s), 5.42 (1H, br s), 6.67 (1H, d, J = 7.8 Hz), 6.81 (1H, d, J = 7.8 Hz), 7.09−7.24 (4H, m), 7.44 (1H, br s), 7.50 (1H, d, J = 7.6 Hz); TSPMS m/z 471 ($M + H^+$). Fumarate. Mp 184 °C (EtOH). Anal. ($C_{29}H_{34}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

2a-[4-(4-Phenylpiperazinyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23a). This compound was prepared from **9** and 1-phenylpiperazine hydrochloride (91% yield). ^{1}H NMR ($CDCl_3$) δ 1.03−1.15 (1H, m), 1.25−1.51 (4H, m), 1.75−1.92 (3H, m), 2.07−2.20 (2H, m), 2.24−2.36 (2H, m), 2.49−2.56 (4H, m), 2.60−2.69 (1H, m), 2.80−2.88 (1H, m), 3.13−3.19 (4H, m), 6.67 (1H, d, J = 7.6 Hz), 6.79−6.86 (2H, m), 6.91 (2H, d, J = 8.4 Hz), 7.11 (1H, dd), 7.22−7.29 (2H, m), 7.50 (1H, br s); EIMS m/z 389 (M^+). Hydrochloride. Mp 165−166 °C (IPE/MeOH). Anal. ($C_{25}H_{31}N_3O \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

2a-[4-[4-(2-Methoxyphenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23b). This compound was prepared from **9** and 1-(2-methoxyphenyl)piperazine (94% yield). ^{1}H NMR ($CDCl_3$) δ 1.04−1.15 (1H, m), 1.26−1.51 (4H, m), 1.76−1.92 (3H, m), 2.07−2.20 (2H, m), 2.25−2.38 (2H, m), 2.54−2.68 (5H, m), 2.80−2.90 (1H, m), 3.05 (4H, br s), 3.85 (3H, s), 6.84 (1H, d, J = 8.2 Hz), 6.66 (1H, d, 7.6 Hz), 6.80 (1H, d, 7.6 Hz), 6.88−7.00 (3H, m), 7.12 (1H, dd), 7.42 (1H, br s); TSPMS m/z 420 ($M + H^+$). Hydrochloride. Mp 170−171 °C (AcOEt/MeOH). Anal. ($C_{26}H_{33}N_3O_2 \times e1 \cdot 2HCl \cdot {}^1/_4H_2O$) C, H, N.

2a-[4-[4-(3-Methoxyphenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23c). This compound was prepared from **9** and 1-(3-methoxyphenyl)piperazine hydrochloride (85% yield). ^{1}H NMR ($CDCl_3$) δ 1.03−1.15 (1H, m), 1.24−1.50 (4H, m), 1.75−1.92 (3H, m), 2.05−2.20 (2H, m), 2.22−2.35 (2H, m), 2.47−2.55 (4H, m), 2.60−2.69 (1H, m), 2.79−2.89 (1H, m), 3.12−3.18 (4H, m), 3.78 (3H, s), 6.40 (1H, dd, J = 8.2, 2.3 Hz), 6.44 (1H, d, J = 2.3 Hz), 6.52 (1H, dd, J = 8.4 Hz), 6.66 (1H, d, J = 7.6 Hz), 6.81 (1H, d, J = 7.6 Hz), 7.09−7.17 (2H, m), 7.31 (1H, br s); EIMS m/z 419 (M^+). Hydrochloride. Mp 232 °C (dec) (AcOEt/MeOH). Anal. ($C_{26}H_{33}N_3O_2 \cdot 2HCl \cdot {}^2/_5H_2O$) C, H, N.

2a-[4-[4-(4-Methoxyphenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23d). This compound was prepared from **9** and 1-(4-methoxyphenyl)piperazine hydrochloride (61% yield). ^{1}H NMR ($CDCl_3$) δ 1.03−1.14 (1H, m), 1.25−1.52 (4H, m), 1.75−1.91 (3H, m), 2.05−2.20 (2H, m), 2.23−2.35 (2H, m), 2.50−2.57 (4H, m), 2.60−2.70 (1H, m), 2.80−2.90 (1H, m), 3.01−3.09 (4H, m), 3.76 (3H, s), 6.66 (1H, dd, J = 7.8 Hz), 6.79−6.89 (5H, m), 7.11 (1H, dd, J = 7.4 Hz), 7.29 (1H, br s); EIMS m/z 419 (M^+). Hydrochloride. Mp 165−166 °C (MeOH). Anal. ($C_{26}H_{33}N_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$) C, H, N.

2a-[4-[4-(2-Chlorophenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23e). This compound was prepared from **9** and 1-(2-chlorophenyl)piperazine hydrochloride (95% yield). ^{1}H NMR ($CDCl_3$) δ 1.03−1.16 (1H, m), 1.29−1.51 (4H, m), 1.76−1.92 (3H, m), 2.06−2.20 (2H, m), 2.26−2.39 (2H, m), 2.51−2.69 (5H, m), 2.80−2.90 (1H, m), 3.00−3.08 (4H, m), 6.67 (1H, d, J = 8.0 Hz), 6.81 (1H, d, J = 7.6 Hz), 6.95 (1H, ddd, J = 8.0, 7.2, 1.5 Hz), 7.03 (1H, dd), 7.12 (1H, dd), 7.20 (1H, ddd), 7.26 (1H, br s), 7.34 (1H, dd); EIMS m/z 425, 423 (M^+). Hydrochloride. Mp 153−154 °C (AcOEt/MeOH). Anal. ($C_{25}H_{30}N_3O \cdot 2HCl$) C, H, N.

2a-[4-[4-(2-Cyanophenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23f). This compound was prepared from **9** and 1-(2-cyanophenyl)piperazine (97% yield). ^{1}H NMR ($CDCl_3$) δ 1.03−1.14 (1H, m), 1.30−1.50 (4H, m), 1.75−1.92 (3H, m), 2.07−2.19 (2H, m), 2.28−2.38 (2H, m), 2.55−2.70 (5H, m), 2.80−2.90 (1H, m), 3.17−3.22 (4H, m), 6.67 (1H, d, J = 7.6 Hz), 6.81 (1H, d, J = 7.8 Hz), 6.96−7.00 (2H, m), 7.12 (1H, dd), 7.36 (1H, br s), 7.44−7.49 (1H, m), 7.54 (1H, dd, J = 7.8, 1.5 Hz); EIMS m/z 414 (M^+). Hydrochloride. Mp 184−185 °C. Anal. ($C_{26}H_{30}N_4O \cdot HCl \cdot {}^9/_{10}H_2O$) C, H, N.

2a-[4-[4-(2-Carbamoylphenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23g). This compound was prepared from **9** and 1-(2-carbamoylphenyl)piperazine (98% yield). ^{1}H NMR ($CDCl_3$) δ 1.07−1.17 (1H, m), 1.31−1.49 (4H, m), 1.75−1.92 (4H, m), 2.05−2.14 (2H, m), 2.27−2.36 (2H, m), 2.50−2.70 (5H, m), 2.80−2.90 (1H, m), 2.98−3.03 (4H, m), 5.85 (1H, br s), 6.68 (1H, d, J = 7.8 Hz), 6.81 (1H, d, J = 7.8 Hz), 7.12 (1H, dd), 7.19−7.28 (2H, m), 7.45−7.60 (2H, m), 8.15 (1H, dd, J = 8.2, 1.7 Hz), 9.51 (1H, br s); EIMS m/z 432 (M^+). Hydrochloride. Mp 145−146 °C (AcOEt/MeOH). Anal. ($C_{26}H_{33}N_4O_2 \cdot HCl \cdot {}^{11}/_4H_2O$) C, H, N.

2a-[4-[4-(2-Acethylphenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23h). This compound was prepared from **9** and 1-(2-acetylphenyl)piperazine (87% yield). ^{1}H NMR ($CDCl_3$) δ 1.03−1.14 (1H, m), 1.29−1.48 (4H, m), 1.75−1.91 (3H, m), 2.06−2.19 (2H, m), 2.23−2.36 (2H, m), 2.48−2.55 (4H, m), 2.60−2.70 (4H, m), 2.78−2.89 (1H, m), 2.95−3.00 (4H, m), 6.67 (1H, d, J = 7.6 Hz), 6.80 (1H, d, J = 7.8 Hz), 7.12−7.14 (3H, m), 7.36−7.42 (3H, m); EIMS m/z 431 (M^+). Hydrochloride. Mp 130 °C (AcOEt/MeOH). Anal. ($C_{27}H_{33}N_3O_2 \cdot 2HCl \cdot {}^3/_2H_2O$) C, H, N.

2a-[4-[4-(2-Trifluorophenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23i). This compound was prepared from **9** and 1-(2-trifluorophenyl)piperazine (62% yield). ^{1}H NMR ($CDCl_3$) δ 1.01−1.15 (1H, m), 1.22−1.50 (4H, m), 1.71−1.91 (3H, m), 2.03−2.20 (2H, m), 2.25−2.39 (2H, m), 2.42−2.70 (5H, m), 2.80−3.00 (5H, m), 6.67 (1H, d, J = 7.6 Hz), 6.81 (1H, d, J = 7.8 Hz), 7.11 (1H, dd), 7.16−7.23 (2H, m), 7.35 (1H, d, J = 8.3 Hz), 7.49 (1H, t), 7.60 (1H, d); EIMS m/z 457 (M^+). Hydrochloride. Mp 233−234 °C (AcOEt/MeOH). Anal. ($C_{26}H_{30}N_3OF_3 \cdot HCl \cdot {}^2/_5H_2O$) C, H, N.

2a-[4-[4-(2-Nitrophenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23j). This compound was prepared from **9** and 1-(2-nitrophenyl)piperazine (47% yield). ^{1}H NMR ($CDCl_3$) δ 1.02−1.14 (1H, m), 1.26−1.46 (4H,

m), 1.76−1.92 (3H, m), 2.04−2.20 (2H, m), 2.22−2.38 (2H, m), 2.44−2.58 (5H, m), 2.60−2.70 (1H, m), 2.80−2.90 (1H, m), 3.00−3.10 (4H, m), 6.67 (1H, d, J = 7.8 Hz), 6.81 (1H, d, J = 7.6 Hz), 7.02 (1H, d, J = 7.7, 1.2 Hz), 7.09−7.14 (2H, m), 7.33 (1H, br s), 7.46 (1H, td, J = 1.7 Hz), 7.74 (1H, dd); EIMS m/z 434 (M^+). Hydrochloride. Mp 228−229 °C. Anal. ($C_{25}H_{30}N_4O_3$·HCl·$^1/_2H_2O$) C, H, N.

2a-[4-[4-(2-Methylphenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23k). This compound was prepared from **9** and 1-(2-methylphenyl)piperazine hydrochloride (91% yield). ^{1}H NMR ($CDCl_3$) δ 1.04−1.14 (1H, m), 1.28−1.51 (4H, m), 1.76−1.93 (3H, m), 2.06−2.19 (2H, m), 2.25−2.38 (5H, m), 2.44−2.70 (5H, m), 2.80−2.93 (5H, m), 6.67 (1H, d, J = 7.8 Hz), 6.81 (1H, d, J = 7.4 Hz), 6.95−7.01 (3H, m), 7.10−7.17 (2H, m), 7.28 (1H, br s); EIMS m/z 403 (M^+). Hydrochloride. Mp 244 °C (MeOH). Anal. ($C_{26}H_{33}N_3O$·2HCl·$^1/_2H_2O$) C, H, N.

2a-[4-[4-(2,6-Dimethylphenyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23l). This compound was prepared from **9** and 1-(2,6-dimethylphenyl)piperazine (86% yield). ^{1}H NMR ($CDCl_3$) δ 1.03−1.17 (1H, m), 1.26−1.53 (4H, m), 1.77−1.92 (3H, m), 2.08−2.20 (2H, m), 2.21−2.38 (8H, m), 2.42−2.50 (4H, m), 2.60−2.70 (1H, m), 2.80−2.90 (1H, m), 3.03−3.11 (4H, m), 6.67 (1H, d, J = 7.8 Hz), 6.81 (1H, d, J = 7.8 Hz), 6.90−7.00 (3H, m), 7.12 (1H, dd), 7.40 (1H, br s); TSPMS m/z 418 (M + H^+). Hydrochloride. Mp 235−236 °C (IPE/MeOH). Anal. ($C_{27}H_{35}N_3O$·HCl·H_2O) C, H, N.

2a-[4-[4-(2-Pyridyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23m). This compound was prepared from **9** and 2-pyridylpiperazine hydrochloride (100% yield). ^{1}H NMR ($CDCl_3$) δ 1.03−1.52 (5H, m), 1.75−1.92 (5H, m), 2.06−2.19 (2H, m), 2.32−2.34 (2H, m), 2.45−2.51 (4H, m), 2.60−2.69 (1H, m), 2.79−2.89 (1H, m), 3.47−3.52 (4H, m), 6.59−6.63 (2H, s), 6.67 (1H, d, J = 7.4 Hz), 6.80 (1H, d, J = 7.8 Hz), 7.17 (1H, dd), 7.46 (1H, ddd, J = 8.0, 7.6, 2.0 Hz), 7.62 (1H, br s), 8.17 (1H, m); TSPMS m/z 391 (M + H^+). Hydrochloride. Mp 170 °C (IPE/MeOH). Anal. ($C_{24}H_{30}N_4O$·2HCl·$^5/_4H_2O$) C, H, N.

2a-[4-[4-(2-Pyrimidinyl)piperazinyl]butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23n). This compound was prepared from **9** and 2-pyrimidylpiperazine hydrochloride (79% yield). ^{1}H NMR ($CDCl_3$) δ 1.02−1.14 (1H, m), 1.26−1.51 (4H, m), 1.75−1.92 (3H, m), 2.06−2.18 (2H, m), 2.22−2.34 (2H, m), 2.39−2.48 (4H, m), 2.60−2.70 (1H, m), 2.80−2.90 (1H, m), 3.77−3.79 (4H, m), 6.47 (1H, t, J = 4.7 Hz), 6.66 (1H, d, J = 7.8 Hz), 6.80 (1H, d, J = 7.8 Hz), 7.11 (1H, dd), 7.28 (1H, br s), 8.29 (2H, dd, J = 1.6 Hz); FABMS m/z 392 (M + H^+). Hydrochloride. Mp 219−220 °C (AcOEt/MeOH). Anal. ($C_{23}H_{29}N_5O$·HCl·$^1/_2H_2O$) C, H, N.

2a-[4-(4-Cyclohexylpiperazinyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (23o). This compound was prepared from **9** and 1-cyclohexylpiperazine (100% yield). ^{1}H NMR ($CDCl_3$) δ 0.97−1.49 (11H, m), 1.57−1.65 (1H, m), 1.71−1.93 (7H, m), 2.03−2.29 (5H, m), 2.33−2.69 (8H, m), 2.79−2.89 (1H, m), 6.66 (1H, d, J = 7.4 Hz), 6.80 (1H, d, J = 7.8 Hz), 7.11 (1H, dd), 7.86 (1H, br s); FABMS m/z 395 (M + H^+). Hydrochloride. Mp 246 °C (dec) (AcOEt/MeOH). Anal. ($C_{25}H_{37}N_3O$·2HCl·$^1/_2H_2O$) C, H, N.

2a-[4-(4-Phenylpiperidinyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (24a). This compound was prepared from **9** and 4-phenylpiperidine hydrochloride (91% yield). ^{1}H NMR ($CDCl_3$) δ 1.02−1.14 (1H, m), 1.22−1.54 (4H, m), 1.75−1.93 (7H, m), 1.94−2.07 (2H, m), 2.07−2.20 (2H, m), 2.23−2.36 (2H, m), 2.41−2.51 (1H, m), 2.60−2.70 (1H, m), 2.80−2.90 (1H, m), 2.95−3.04 (2H, m), 6.67 (1H, d, J = 7.8 Hz), 6.81 (1H, d, J = 7.8 Hz), 7.12 (1H, dd), 7.16−7.24 (3H, m), 7.25−7.33 (3H, m); TSPMS m/z 389 (M + H^+). Hydrochloride. Mp 148−149 °C (IPE/AcOEt). Anal. ($C_{26}H_{32}N_2O$·HCl·H_2O) C, H, N.

2a-[4-(4-Hydroxy-4-phenylpiperidinyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (24b). This compound was prepared from **9** and 4-hydroxy-4-phenylpiperidine (99% yield). ^{1}H NMR ($CDCl_3$) δ 1.02−1.15 (1H, m), 1.28−1.91 (9H, m), 2.05−2.20 (4H, m), 2.25−2.43 (4H, m), 2.54−2.69 (1H, m), 2.71−2.90 (3H, m), 6.67 (1H, d, J = 7.6 Hz), 6.81 (1H, d, J = 7.6 Hz), 7.12 (1H, dd), 7.23−7.51 (6H, m); EIMS m/z 404 (M^+). Hydrochloride. Mp 258 °C (AcOEt/MeOH). Anal. ($C_{26}H_{32}N_2O_2$·HCl) C, H, N.

2a-[4-(4-Methoxy-4-phenylpiperidinyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (24c). This compound was prepared from **9** and 4-methoxy-4-phenylpiperidine (96% yield). ^{1}H NMR ($CDCl_3$) δ 1.04−1.16 (1H, m), 1.25−1.31 (2H, m), 1.36−1.50 (1H, m), 1.76−1.92 (4H, m), 1.99−2.20 (6H, m), 2.38−2.53 (4H, m), 2.60−2.69 (1H, m), 2.77−2.89 (3H, m), 2.95 (3H, s), 6.67 (1H, d, J = 7.4 Hz), 6.80 (1H, d, J = 7.8 Hz), 7.11 (1H, dd), 7.24−7.40 (5H, m), 7.43 (1H, br s); EIMS m/z 418 (M^+). Hydrochloride. Mp 243 °C (AcOEt/MeOH). Anal. ($C_{27}H_{34}N_2O_2$·HCl·$^1/_4H_2O$) C, H, N.

2a-[4-(4-Carbamoyl-4-phenylpiperidinyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (24d). This compound was prepared from **9** and 4-carbamoyl-4-phenylpiperidine (75% yield). Mp 224 °C ; ^{1}H NMR ($CDCl_3$) δ 0.99−1.10 (1H, m), 1.21−1.44 (4H, m), 1.70−1.88 (3H, m), 2.01−2.26 (6H, m), 2.30−2.42 (4H, m), 2.48−2.68 (3H, m), 2.78−2.88 (1H, m), 5.22 (2H, br s), 6.65 (1H, d, J = 7.8 Hz), 6.80 (1H, d, J = 7.8 Hz), 7.10 (1H, dd), 7.22−7.41 (6H, m); EIMS m/z 431 (M^+). Anal. ($C_{27}H_{33}N_3O_2$·$^3/_{10}H_2O$) C, H, N.

2a-[4-(4-Acetyl-4-phenylpiperidinyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (24e). This compound was prepared from **9** and 4-acethyl-4-phenylpiperidine (24% yield). Mp 224 °C ; ^{1}H NMR ($CDCl_3$) δ 0.98−1.11 (1H, m), 1.22−1.45 (5H, m), 1.72−1.93 (7H, m), 1.98−2.27 (6H, m), 2.37−2.49 (2H, m), 2.58−2.71 (3H, m), 2.77−2.87 (1H, m), 6.66 (1H, d, J = 7.6 Hz), 6.79 (1H, d, J = 7.8 Hz), 7.10 (1H, dd), 7.22−7.36 (5H, m), 7.48 (1H, br s); EIMS m/z 430 (M^+). Anal. ($C_{28}H_{34}N_3O_2$·$^1/_5H_2O$) C, H, N.

2a-[4-[4-(4-Fluorophenyl)-1,2,3,6-tetrahydropyridyl]-butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (25a). This compound was prepared from **9** and 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (32% yield). Mp 165−166 °C ; ^{1}H NMR ($CDCl_3$) δ 1.04−1.19 (1H, m), 1.29−1.56 (4H, m), 1.74−1.93 (3H, m), 2.06−2.18 (2H, m), 2.29−2.41 (2H, m), 2.45−2.53 (2H, m), 2.58−2.69 (3H, m), 2.80−2.89 (1H, m), 3.04−3.09 (2H, m), 5.69 (1H, s), 6.67 (1H, d, J = 7.6 Hz), 6.80 (1H, d, J = 7.8 Hz), 6.94−7.01 (2H, m), 7.11 (1H, dd), 7.28−7.34 (2H, m), 7.69 (1H, br s); EIMS m/z 404 (M^+). Anal. ($C_{26}H_{29}N_2OF$·$^1/_5H_2O$) C, H, N.

2a-[4-[4-(4-Methylphenyl)-1,2,3,6-tetrahydropyridyl]-butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (25b). This compound was prepared from **9** and 4-(4-methylphenyl)-1,2,3,6-tetrahydropyridine (26% yield). ^{1}H NMR ($CDCl_3$) δ 1.04−1.16 (1H, m), 1.29−1.39 (2H, m), 1.51−1.64 (2H, m), 1.77−1.92 (3H, m), 2.04−2.18 (2H, m), 2.33 (3H, s), 2.51−2.69 (5H, m), 2.80−2.90 (3H, m), 3.27−3.34 (2H, br s), 5.95 (1H, s), 6.67 (1H, d, J = 7.6 Hz), 6.80 (1H, d, J = 7.9 Hz), 7.09−7.14 (3H, m), 7.23−7.28 (2H, m), 7.63 (1H, br s); EIMS m/z 400 (M^+). Hydrochloride. Mp 170−171 °C (AcOEt/MeOH). Anal. ($C_{27}H_{32}N_2O$·HCl·$^1/_{10}H_2O$) C, H, N.

1-Methyl-2a-[4-(4-phenyl-1,2,3,6-tetrahydropyridyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (25c). This compound was prepared from **10** and 4-phenyl-1,2,3,6-tetrahydropyridine hydrocloride (14% yield). Mp 110−111 °C; ^{1}H NMR ($CDCl_3$) δ 0.94−1.10 (1H, m), 1.10−1.35 (3H, m), 1.40−1.96 (7H, m), 2.02−2.20 (2H, m), 2.28−2.42 (1H, m), 2.50−2.58 (1H, m), 2.60−2.71 (2H, m), 2.81−2.91 (1H, m), 3.05−3.24 (5H, m), 6.02 (1H, br s), 6.64 (1H, d, J = 7.8 Hz), 6.82 (1H, d, J = 7.6 Hz), 7.15−7.40 (6H, m); EIMS m/z 400 (M^+). Anal. ($C_{27}H_{32}N_2O$·$^3/_5H_2O$) C, H, N.

6-Acetyl-2a-[4-(4-phenyl-1,2,3,6-tetrahydropyridyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (25d). This compound was prepared from **11** and 4-phenyl-1,2,3,6-tetrahydropyridine hydrocloride (24% yield). ^{1}H NMR ($CDCl_3$) δ 1.01−1.14 (1H, m), 1.29−1.52 (4H, m), 1.76−1.95 (3H, m), 2.05−2.20 (2H, m), 2.28−2.42 (2H, m), 2.49−2.72 (7H, m), 3.04−3.16 (3H, m), 3.18−3.28 (1H, m), 6.01 (1H, m), 6.75 (1H, d, J = 8.0 Hz), 7.19−7.36 (5H, m), 7.72 (1H, d), 8.73 (1H, s); TSPMS m/z 429 (M + H^+). Hydrochloride. Mp 246−247 °C (IPE/MeOH). Anal. ($C_{28}H_{32}N_2O_2$·HCl·$^2/_3H_2O$) C, H, N.

6-Methoxy-2a-[4-(4-phenyl-1,2,3,6-tetrahydropyridyl)-butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (25e). This compound was prepared from **15** and 4-phenyl-1,2,3,6-tetrahydropyridine hydrocloride (50% yield). Mp 134 °C; ^{1}H NMR ($CDCl_3$) δ 1.06−1.19 (1H, m), 1.27−1.55 (4H, m), 1.75−1.90 (3H, m), 2.03−2.17 (2H, m), 2.29−2.41 (2H, m), 2.52−2.64 (5H, m), 2.72−2.82 (1H, m), 3.03−3.13 (2H, m), 3.79 (3H, s), 6.01 (1H, m), 6.56−6.65 (2H, m), 7.19−7.37 (5H, m), 8.07 (1H, br s); TSPMS *m*/*z* 417 (M + H$^+$). Anal. ($C_{27}H_{32}N_2O_2\cdot H_2O$) C, H, N.

6-Carbamoyl-2a-[4-(4-phenyl-1,2,3,6-tetrahydropyridyl)-butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (25f). A solution of **12** (270 mg, 0.74 mmol), 1,2,3,6-tetrahydro-4-phenylpyridine hydrochloride (290 mg, 1.5 mmol), and diisopropylethylamine (0.51 mL, 2.9 mmol) in DMF was stirred at room temperature for 17 h. The reaction mixture was poured into AcOEt, and the whole was washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH = 30/1) to afford colorless crystals. Aqueous LiOH (4 N, 6 mL, 24 mmol) was added to the crystals in THF (6 mL), and the mixture was refluxed for 30 h. Aqueous HCl (5 N) was added, and the mixture was extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated to afford the carboxylic acid derivative as colorless crystals. A solution of the crystals, DCC (270 mg, 1.3 mmol), and HOBT (170 mg, 1.3 mmol) in DMF (12 mL) was stirred at room temperature for 3 h and then was cooled to 0 °C. Aqueous NH_3 (28%, 6 mL) was added, and the mixture was stirred at room temperature for 2 h and then was evaporated. The residue was purified on an HP-20 (Mitsubishi Chemical) (eluent: H_2O/MeOH = 10/1 and then MeOH) to afford **25f** as colorless crystals (150 mg, 48% yield). Mp 119 °C; ^{1}H NMR (CD_3OD) δ 0.96−1.08 (1H, m), 1.08−1.54 (4H, m), 1.54−1.64 (1H, m), 1.65−2.00 (3H, m), 2.00−2.12 (1H, m), 2.12−2.28 (1H, m), 2.30−2.45 (2H, m), 2.51−2.61 (2H, m), 2.63−2.74 (2H, m), 2.95−3.11 (4H, m), 3.40−3.50 (1H, m), 6.07 (1H, m), 6.76 (1H, d, *J* = 8.0 Hz), 7.19−7.50 (6H, m), 7.86 (1H, br s); TSPMS *m*/*z* 430 (M + H$^+$). Anal. ($C_{27}H_{31}N_3O_2\cdot{}^{13}/_5H_2O$) C, H, N.

6-Bromo-2a-[4-(4-phenyl-1,2,3,6-tetrahydropyridyl)butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (25g). This compound was prepared from **13** and 4-phenyl-1,2,3,6-tetrahydropyridine hydrocloride (73% yield). Mp 140−141 °C; ^{1}H NMR ($CDCl_3$) δ 1.03−1.17 (1H, m), 1.24−1.55 (4H, m), 1.72−1.93 (3H, m), 2.03−2.20 (2H, m), 2.28−2.42 (2H, m), 2.48−2.79 (6H, m), 3.03−3.14 (2H, m), 6.01 (1H, s), 6.59 (1H, d, *J* = 8.3 Hz), 7.19−7.31 (6H, m), 9.16 (1H, br s); TSPMS *m*/*z* 465, 467 (M + H$^+$). Anal. ($C_{26}H_{29}N_2OBr\cdot{}^1/_2H_2O$) C, H, N.

6-Hydroxy-2a-[4-(4-phenyl-1,2,3,6-tetrahydropyridyl)-butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (25h). This compound was prepared from **14** and 4-phenyl-1,2,3,6-tetrahydropyridine hydrocloride (89% yield). ^{1}H NMR ($CDCl_3$) δ 1.01−1.14 (1H, m), 1.22−1.37 (2H, m), 1.39−1.54 (2H, m), 1.73−1.93 (3H, m), 2.00−2.22 (3H, m), 2.31−2.42 (2H, m), 2.50−2.82 (6H, m), 3.08−3.14 (2H, m), 6.04 (1H, m), 6.53 (1H, d, *J* = 8.0 Hz), 6.59 (1H, d), 7.19−7.38 (5H, m), 7.98 (1H, br s); TSPMS *m*/*z* 403 (M + H$^+$). Hydrochloride. Mp 120−122 °C (AcOEt/MeOH). Anal. ($C_{26}H_{30}N_2O_3\cdot HCl\cdot{}^3/_5H_2O$) C, H, N.

2a-[4-(2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-2-yl)-butyl]-2a,3,4,5-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (26a). This compound was prepared from **9** and 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (38% yield). Mp 151−152 °C; ^{1}H NMR (CD_3OD) δ 1.06−1.10 (1H, m), 1.22−1.36 (2H, m), 1.46−1.60 (2H, m), 1.76−1.95 (3H, m), 2.01−2.08 (1H, m), 2.11−2.24 (2H, m), 2.44−2.57 (2H, m), 2.60−2.70 (1H, m), 2.75−2.90 (5H, m), 3.60 (2H, s), 6.69 (1H, d, *J* = 7.5 Hz), 6.79 (1H, d, *J* = 7.8 Hz), 6.96 (1H, dd, *J* = 7.4, 7.0 Hz), 7.04 (1H, dd, *J* = 6.8 Hz), 7.12 (1H, dd), 7.25 (1H, d), 7.36 (1H, d), 7.85 (1H, br s); TSPMS *m*/*z* 400 (M + H$^+$). Anal. ($C_{26}H_{29}N_2O\cdot{}^9/_5H_2O$) C, H, N.

2a-[4-(6-Methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]-indol-2-yl)butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (26b). This compound was prepared from **9** and 6-methoxy-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (88% yield). Mp 132−133 °C; ^{1}H NMR (CD_3OD) δ 1.00−1.10 (1H, m), 1.22−1.35 (2H, m), 1.45−1.60 (2H, m), 1.77−1.96 (3H, m), 2.00−2.10 (1H, m), 2.11−2.24 (1H, m), 2.43−2.54 (2H, m), 2.59−2.69 (1H, m), 2.72−2.90 (5H, m), 3.60 (2H, s), 3.80 (3H, s), 6.69 (2H, m), 6.79 (1H, d, *J* = 7.8 Hz), 6.88 (1H, d, *J* = 2.2 Hz), 7.12 (2H, m), 7.85 (1H, br s), 7.85 (1H, br s); TSPMS *m*/*z* 430 (M + H$^+$). Anal. ($C_{27}H_{31}N_3O_2\cdot H_2O$) C, H, N.

2a-[4-(9-Methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indol-2-yl)butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (26c). This compound was prepared from **9** and **20c** trifluoroacetate (57% yield). Mp 180−181 °C; ^{1}H NMR ($CDCl_3$) δ 1.03−1.16 (1H, m), 1.27−1.40 (2H, m), 1.44−1.60 (2H, m), 1.74−1.93 (3H, m), 2.02−2.18 (2H, m), 2.45−2.67 (3H, m), 2.70−2.90 (5H, m), 3.53 (3H, s), 3.60 (2H, s), 6.65 (1H, d, *J* = 7.5 Hz), 6.77 (1H, d, *J* = 7.8 Hz), 7.02−7.15 (3H, m), 7.22 (1H, d, *J* = 7.3 Hz), 7.43 (1H, d, *J* = 7.5 Hz), 8.76 (1H, br s); TSPMS *m*/*z* 414 (M + H$^+$). Anal. ($C_{27}H_{31}N_3O\cdot{}^1/_2H_2O$) C, H, N.

2a-[4-(9-Methoxymethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indol-2yl)butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (26d). This compound was prepared from **9** and **20d** trifluoroacetate (39% yield). Mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 1.06−1.16 (1H, m), 1.28−1.40 (2H, m), 1.45−1.60 (2H, m), 1.74−1.93 (3H, m), 2.01−2.18 (2H, m), 2.47−2.64 (3H, m), 2.71−2.88 (5H, m), 3.19 (3H, s), 3.67 (2H, br s), 5.30 (2H, s), 6.66 (1H, d, *J* = 7.8 Hz), 6.77 (1H, d, *J* = 7.8 Hz), 7.05−7.11 (2H, m), 7.16 (1H, dd), 7.37 (1H, d, *J* = 8.1 Hz), 7.43 (1H, d, *J* = 7.5 Hz), 8.56 (1H, br s); TSPMS *m*/*z* 444 (M + H$^+$). Anal. ($C_{28}H_{33}N_3O_2\cdot{}^3/_2H_2O$) C, H, N.

2a-[4-(9-Acetyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indol-2-yl)butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (26e). This compound was prepared from **9** and **20e** trifluoroacetate (56% yield). Mp 141−142 °C; ^{1}H NMR ($CDCl_3$) δ 1.02−1.15 (1H, m), 1.28−1.42 (2H, m), 1.42−1.60 (2H, m), 1.75−1.94 (3H, m), 2.03−2.28 (2H, m), 2.44−2.55 (2H, m), 2.58−2.88 (9H, m), 3.88 (2H, s), 6.67 (1H, d, *J* = 7.5 Hz), 6.77 (1H, d, *J* = 7.8 Hz), 7.08 (1H, dd), 7.20−7.29 (2H, m), 7.37 (1H, d, *J* = 6.8 Hz), 7.78 (1H, d, *J* = 6.8 Hz), 8.55 (1H, s); TSPMS *m*/*z* 442 (M + H$^+$). Anal. ($C_{28}H_{31}N_3O_2\cdot{}^2/_5H_2O$) C, H, N.

2a-[4-(9-Allyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indol-2-yl)-butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (26f). This compound was prepared from **9** and **20f** trifluoroacetate (46% yield). Mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 1.06−1.18 (1H, m), 1.30−1.42 (2H, m), 1.46−1.59 (2H, m), 1.76−1.94 (3H, m), 2.06−2.19 (2H, m), 2.46−2.57 (2H, m), 2.60−2.69 (1H, m), 2.74−2.90 (5H, m), 3.88 (2H, s), 4.54−4.60 (2H, m), 4.88 (1H, dd, *J* = 17.1, 1.3 Hz), 5.09 (1H, dd, *J* = 10.3 Hz), 5.89 (1H, m), 6.67 (1H, d, *J* = 7.8 Hz), 6.77 (1H, d, *J* = 7.7 Hz), 7.04−7.16 (3H, m), 7.22 (1H, d, *J* = 8.0 Hz), 7.36 (1H, br s), 7.46 (1H, d, *J* = 7.5 Hz); EIMS *m*/*z* 439 (M$^+$). Anal. ($C_{29}H_{33}N_3O\cdot{}^1/_2H_2O$) C, H, N.

2a-[4-(9-Dimethylcarbamoyl-1,2,3,4-tetrahydropyrido-[3,4-*b*]indol-2-yl)butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (26g). This compound was prepared from **9** and **20g** trifluoroacetate (90% yield). Mp 141 °C; ^{1}H NMR ($CDCl_3$) δ 1.00−1.13 (1H, m), 1.25−1.38 (2H, m), 1.44−1.58 (2H, m), 1.74−1.92 (3H, m), 2.02−2.18 (2H, m), 2.44−2.65 (3H, m), 2.70−2.86 (5H, m), 3.01 (6H, s), 3.70 (2H, br s), 6.65 (1H, d, *J* = 7.6 Hz), 6.75 (1H, d, *J* = 7.8 Hz), 7.06 (1H, br dd), 7.10−7.21 (3H, m), 7.41 (1H, d, *J* = 7.6 Hz), 8.98 (1H, br s); TSPMS *m*/*z* 471 (M + H$^+$). Anal. ($C_{29}H_{34}N_4O_2\cdot{}^9/_5H_2O$) C, H, N.

2a-[4-(9-Carbamoylmethyl-1,2,3,4-tetrahydropyrido-[3,4-*b*]indol-2-yl)butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (26h). This compound was prepared from **9** and **20h** trifluoroacetate (91% yield). Mp 139−140 °C; ^{1}H NMR ($CDCl_3$) δ 1.01−1.14 (1H, m), 1.20−1.36 (2H, m), 1.40−1.55 (2H, m), 1.75−1.90 (3H, m), 1.99−2.18 (2H, m), 2.42−2.53 (2H, m), 2.55−2.67 (1H, m), 2.70−2.87 (5H, m), 3.52 (2H, s), 4.58 (2H, s), 5.58 (1H, br s), 6.52 (1H, br s), 6.65 (1H, d, *J* = 7.5 Hz), 6.76 (1H, d, *J* = 7.8 Hz), 7.05−7.20 (4H, m), 7.44 (1H, d, *J* = 7.8 Hz), 9.04 (1H, s); TSP *m*/*z* 457 (M + H$^+$). Anal. ($C_{28}H_{32}N_4O_2\cdot H_2O$) C, H, N.

2a-[4-(9-Dimethylcarbamoylmethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indol-2-yl)butyl]-2a,3,4,5-tetrahydrobenz-[*cd*]indol-2(1*H*)-one (26i). This compound was prepared from **9** and **20i** trifluoroacetate (72% yield). Mp 220 °C (dec); ^{1}H

NMR ($CDCl_3$) δ 1.00−1.13 (1H, m), 1.25−1.40 (2H, m), 1.42−1.60 (2H, m), 1.76−1.90 (3H, m), 2.01−2.20 (2H, m), 2.47−2.89 (8H, m), 2.98 (3H, s), 3.09 (3H, s), 3.53 (2H, s), 4.75 (2H, s), 6.66 (1H, d, J = 7.6 Hz), 6.76 (1H, d, J = 8.0 Hz), 7.02−7.15 (4H, m), 7.43 (1H, d, J = 7.6 Hz), 9.11 (1H, br s); EIMS m/z 484 (M^+). Anal. ($C_{30}H_{36}N_4O_2 \cdot {}^1/_2H_2O$) C, H, N.

Computational Methods. All molecular modeling studies were performed on a Silicon Graphics O2 graphic workstation using the molecular modeling software package SYBYL, version 6.7, from Tripos Associates (St. Louis, MO). Geometry optimization was carried out using MMFF94s[31] force field with MMFF94 charge. For the superimposition, the piperazine moiety was used as fitting points.

5-HT_7 Receptor Binding Assay. Radioligand binding assay at human 5-HT_7 receptors were carried out using membranes from COS-7 cells expressed h5-HT_7 receptors. Membranes (10 μg of protein) were incubated with 0.3 nM [^{3}H]5-CT in 50 mM Tris-HCl buffer (pH 7.4), which contained 10 mM $MgCl_2$ and 0.5 mM EDTA, for 30 min at 37 °C in the presence or absence of competing compounds (1 μM to 1 nM). Nonspecific binding was determined with 10 μM metergoline. Membranes were collected by rapid filtration through GF/B filters and washed with 5 mL of ice-cold 50 mM Tris-HCl buffer (pH 7.4). The radioactivity on the filters was counted by liquid scintillation counter (Packard TRI-CARB2000). The concentration displacing 50% of specific [^{3}H]-5-CT binding (IC_{50}) was determined by a computer curve-fitting technique. The inhibition dissociation constant (K_i) of each compound was then determined according to the method of Cheng and Prusoff.[32]

cAMP Assay. HEK293 cells transiently transfected with an expression vector containing human 5-HT_7 receptor cDNA were incubated for 10 min at 37 °C with appropriate drugs in Dulbecco's modified Eagle's medium containing 10 mM HEPES, 100 μM 3-isobutyl-1-methylxanthine, and 100 μM pargyline. Intracellular cAMP formation was measured by enzyme immunoassay.

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