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Chemical Modification of Apomorphine to Discover σ Ligands: 6*H*-Dibenzo[*b*,*d*]pyran and Carbazole Analogues

Atsuro Nakazato,* Yoshinori Sekiguchi, Kohmei Ohta, Shigeyuki Chaki and Shigeru Okuyama

1st Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Ohmiya, Saitama 330-8530, Japan

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Abstract—It seems that many σ ligands have been designed from known sigma ligands. We focused on a difference in structural flexibility between haloperidol and apomorphine, and studied chemical modification of apomorphine, a compound with high affinity for dopamine D_2 receptors but not for σ receptors, for discovery of σ ligands. The first modification yielded good results with 6*H*-dibenzo[*b*,*d*]pyran analogues with weak affinity for σ receptors but not D_2 receptors. Furthermore, carbazole analogues, compounds designed from 6*H*-dibenzo[*b*,*d*]pyran analogues, potentially acted at σ receptors with high selectivity. This paper describes the design, synthesis and sigma/D_2 selectivity of 6*H*-dibenzo[*b*,*d*]pyran and carbazole analogues.

Introduction

Interest in σ receptors, which were postulated by Martin et al.[1] to account for the actions of (±)-*N*-allylnormetazocine (SKF10047 (**1**)), has grown since they are bound by both typical and atypical antipsychotics. Along with the relationship between σ receptors and schizophrenia, the molecular properties and signaling mechanisms mediated through σ receptors have not been fully elucidated, although recent molecular cloning experiments[2,3] have suggested that the σ binding protein does not appear to be related to either cytochrome P-450 or neuropeptide Y receptors, which has long been postulated to be the σ receptor.[4,5] These ambiguities might be due to the lack of potent and selective ligands for σ receptor currently available. Discovery of potent and selective σ ligands might thus be important for determining the physiological and clinical significance of σ ligands.

Various σ ligands have been reported. It seems that these ligands have been designed on the basis of known σ ligands,[6] including SKF10047 (**1**), 3-PPP (**2**), DTG (**3**), haloperidol (**4**), and/or BMY14802 (**5**)[7] (Chart 1).

Our interest was focused on structural differences between haloperidol and apomorphine (**6**) in study to discover new types of σ ligands. Both haloperidol and apomorphine have a basic nitrogen atom and benzene rings and difference in the distances between the nitrogen atom and benzene ring(s) of the two compounds might be small, since both compounds have high affinity for dopamine D_2 (D_2) receptors. Haloperidol has high affinity for both σ and D_2 receptors, but apomorphine has no affinity for σ receptors.[6] The lack of understanding why apomorphine has no affinity for σ receptors led us to attempt chemical modification of apomorphine.

Several structural changes of apomorphine[8] have been made in attempts to discover D_2 receptor agonists or antagonists (Scheme 1). Our first approach involved both elimination of two bonds of apomorphine to obtain structural flexibility for the nitrogen atom and bridging two benzene rings with a -CH_2O-bond to retain planar structure, yielding 6*H*-dibenzo[*b*,*d*]pyran analogues **7** (Scheme 2). Based on the elevated σ affinity of 6*H*-dibenzo[*b*,*d*]pyran analogues **7**, our interest was shifted to a second chemical modification, in which the -CH_2O- was changed to a -NH- moiety (Scheme 2). The carbazole analogue **8a** (FH-510) exhibited high and selective affinity for σ receptors.

This paper describes a design based on a qualitative difference in structural flexibility between haloperidol

Key words: Sigma ligands; structure–affinity relationships; 6*H*-dibenzo-[*b*,*d*]pyrans; carbazoles.

* Corresponding author. Tel.: +81-(0)48-663-1111; fax: +81-(0)48-652-7254; e-mail: s10968@ccm.taisho.co.jp

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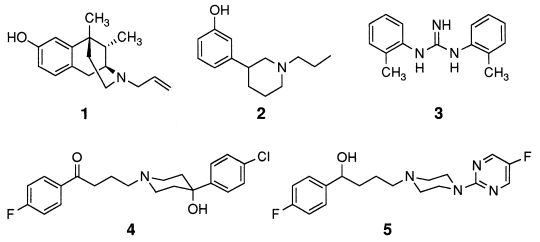
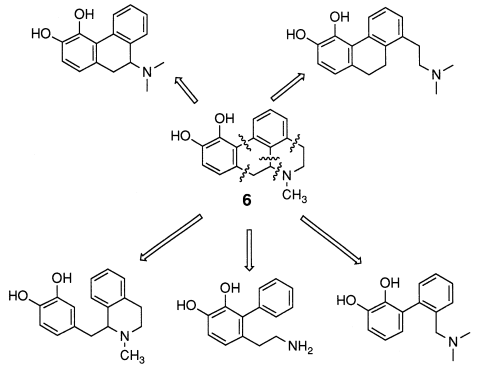
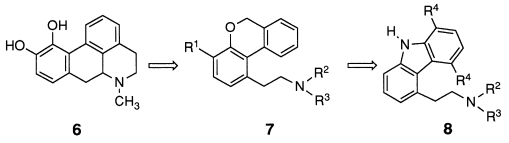


Chart 1.



Scheme 1.



Scheme 2.

and apomorphine, and the synthesis and structure–affinity relationships (SAR) of 6*H*-dibenzo[*b*,*d*]pyran and carbazole analogues.

Chemistry

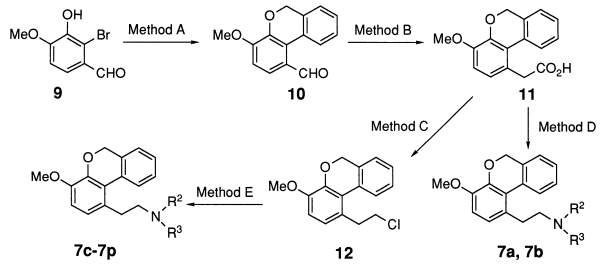
Synthetic procedures of compounds **10**, **11**, **7a** and **7s** have been already reported.[13]

6*H*-Dibenzo[*b*,*d*]pyran analogues **7a**–**7s** were prepared via a key intermediate, aldehyde **10** (Schemes 3–5).

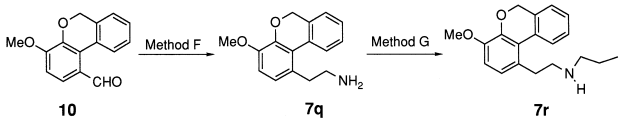
Aldehyde **10** was derived by Ullmann reaction of 2-bromo-3-(2-iodobenzyloxy)-4-methoxybenzaldehyde, a compound obtained by treatment of 2-bromo-3-hydroxy-4-methoxybenzaldehyde[9] with 2-iodobenzyl bromide (Method A). Carboxylic acid **11** was derived from aldehyde **10** in four generic steps: reduction, chloro-replacement, and cyano-substitution, followed by hydrolysis (Method B).

6*H*-Dibenzo[*b*,*d*]pyran analogues **7a** and **7b** were obtained by reduction of the corresponding amides derived from carboxylic acid **11** via acyl chloride (Method D).

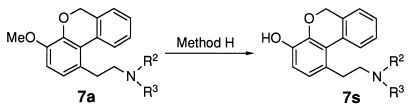
6*H*-Dibenzo[*b*,*d*]pyran analogues **7c**–**7p** were derived from carboxylic acid **11** in three steps: reduction and



Scheme 3. Method A: 2-l-$PhCH_2Cl$, K_2CO_3, NaI, DMF, rt; Cu, DMF, heat. Method B: $LiAlH_4$, THF, 0°C; $SOCl_2$. THF, HMPA, rt; KCN, 18-Crown-6, CH_3CN, rt; KOH, EtOH, H_2O, reflux. Method C: $LiAlH_4$, THF, 0°C; $SOCl_2$, THF, HMPA, rt. Method D: $SOCl_2$, PhH, reflux; HNR^1R^2, PhH, 0°C rt; $LiAlH_4$, THF, reflux. Method E: HN R^1R^2, $(iso\text{-}Pr)_2NEt$, 80°C.



Scheme 4. Method F: $LiAlH_4$, THF, 0°C rt; $SOCl_2$, THF, HMPA, rt; KCN, 18-Crown-6, CH_3CN, rt; BH_3·THF, THF. Method G: EtCOCl, Py, CH_2Cl_2; $LiAlH_4$, THF, reflux.



Scheme 5. Method H: HBr, AcOH; K_2CO_3, DMF.

chloro-replacement (Method C), followed by treatment with various corresponding amines (Method E).

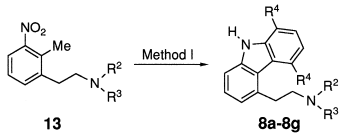
6*H*-Dibenzo[*b*,*d*]pyran analogue **7q**, a primary amine, was derived by reduction of the intermediate nitrile derivative in Method C (Method F). 6*H*-Dibenzo[*b*,*d*]-pyran analogue **7r**, a secondary amine, was obtained by *N*-acylation of **7q** followed by reduction (Method G) (Scheme 4).

6*H*-Dibenzo[*b*,*d*]pyran analogue **7s**, a phenol derivative, was prepared by cleavage of two ether bonds followed by recyclization (Method H) (Scheme 5).

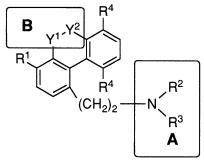
Carbazole analogues **8a**–**8g** were prepared via the corresponding indole derivatives **14** (Scheme 6). The indole derivatives **14** were prepared by Leimgruber–Batcho indole synthesis,[10] and treatment of 2-methyl-3-nitrophenylethyl amine derivatives **13**[11] with *N*,*N*-dimethylformamide dimethyl acetal (DMFDA) followed by hydrogenation. Indole derivatives **14** were treated with hexan-2,4-dione or 2,5-dimethoxytetrahydrofurane under acidic conditions to yield carbazole analogues **8a**–**8g**.

Results and Discussion

All compounds were examined for affinity for σ receptors labeled with [^{3}H]-(+)-3-PPP, and for D_2 receptors labeled with [^{3}H]-sulpiride (Table 1), using the procedure



Scheme 6. Method I: MDFDM, pyrrolidine, DMF, reflux; H_2, Pd/C, AcOH, MeOH, rt; $CH_3CO(CH_2)_2COCH_3$ or 2,5-dimethoxytetrahydrofurane, *p*-TosOH, EtOH, reflux.



Scheme 7.

described in the literature.[12] Binding data of compounds **7a** and **7s** have been already reported.[13]

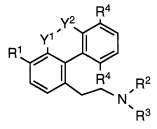
6*H*-Dibenzo[*b*,*d*]pyran analogues **7**, which were designed from apomorphine **6**, had markedly increased selectivity for σ receptors over D_2 receptors (versus **6**). Given this result, the focus of our study shifted to the changes of units on Area A (Scheme 7).

Replacement of the dipropylamino group by other amino moieties on Area A lead to an undesirable but interesting result. Two alkyl groups on the basic nitrogen atom, which were of appropriate length, were required to maintain affinity for σ receptors (**7b** versus **7a** and **7c**). Substitution of cyclic amino moieties for the propylamino group decreased σ affinity (**7d**–**7g**), with the exception of arylpiperazine derivatives (**7h**–**7p**). Arylpiperazine derivatives maintained affinity for σ receptors but not selectivity over D_2 receptors (**7h**–**7p** versus **7a** and **7c**). This phenomenon was observed for 2-methoxyphenylpiperazine **7n**. Compound **7n**, which had 100-fold greater affinity for D_2 receptors than for σ receptors, was a D_2 ligand rather than a σ ligand.

Replacement of the methoxy group by a hydroxyl group for R^1 (Scheme 7) yielded a slight increase in σ affinity (**7a** versus **7s**).

Our strategy to discover σ ligands was changed to consideration of carbazole analogues **8**. Carbazole analogue **8a** (FH-510), a compound in which the -OCH_2- bond of 6*H*-dibenzo[*b*,*d*]pyran analogue **7a** was replaced by an -NH- moiety, had high affinity and selectivity for σ

Table 1. Derivatives **7** and **8**: physical and biological data



No.	R^1	R^4	Y^1–Y^2	-NR^1R^{2a}	Salt[b]	σ(IC_{50}, nM)[c]	D_2(IC_{50}, nM)[c]
7a[d]	MeO	H	OCH_2	N(*n*-Pr)$_2$	HCl	990	> 1000
7b	MeO	H	OCH_2	N(*n*-Hex)$_2$	—	> 1000	NT
7c	MeO	H	OCH_2	N(*n*-Bu)$_2$	Oxa	700	1000
7d	MeO	H	OCH_2	Pyrrolidino	HCl	> 1000	> 1000
7e	MeO	H	OCH_2	Piperidoino	HCl	1000	> 1000
7f	MeO	H	OCH_2	Morpholino	HCl	> 1000	> 1000
7g	MeO	H	OCH_2	Piperazino	2HCl	> 1000	> 1000
7h	MeO	H	OCH_2	Pipe-Ph	HCl	540	990
7i	MeO	H	OCH_2	Pipe-Ph-CF_3-3	2HCl	≥1000	340
7j	MeO	H	OCH_2	Pipe-Ph-Me_2-2,3	HCl	930	180
7k	MeO	H	OCH_2	Pipe-Ph-Cl-2	HCl	410	NT
7l	MeO	H	OCH_2	Pipe-Ph-Cl-3	HCl	790	280
7m	MeO	H	OCH_2	Pipe-Ph-Cl-4	2HCl	> 1000	360
7n	MeO	H	OCH_2	Pipe-Ph-OMe-2	2HCl	980	9.5
7o	MeO	H	OCH_2	Pipe-Ph-OMe-3	HCl	> 1000	260
7p	MeO	H	OCH_2	Pipe-Ph-OMe-4	2HCl	300	660
7q	MeO	H	OCH_2	NH_2	HCl	> 1000	> 1000
7r	MeO	H	OCH_2	NH(*n*-Pr)	HCl	> 1000	> 1000
7s[d]	HO	H	OCH_2	N(*n*-Pr)$_2$	HCl	560	> 1000
8a	H	CH_3	N(H)	N(*n*-Pr)$_2$	HCl	4.6	> 1000
8b	H	CH_3	N(H)	Pyrrolidino	HCl	270	> 1000
8c	H	CH_3	N(H)	Piperidino	HCl	17	> 1000
8d	H	CH_3	N(H)	Morpholino	HCl	> 1000	> 1000
8e	H	CH_3	N(H)	N(*i*-Pr)$_2$	HCl	13	> 1000
8f	H	CH_3	N(H)	N(*n*-Hex)$_2$	Oxa	57	NT
8g	H	H	N(H)	N(*n*-Pr)	HCl	9.2	710

[a] Pipe-Ph, 1-(4-phenylpiperazinyl); Pipe-Ph-CF_3-3, 1-[4-(3-trifluoromethylphenyl)-piperazinyl]; Pipe-Ph-Me_2-2,3, 1-[4-(2,3-dimethylphenyl)-piperazinyl]; Pipe-Ph-Cl-2, 1-[4-(2-chlorophenyl)piperazinyl]; Pip-Ph-Cl-3, 1-[4-(3-chlorophenyl)piperazinyl]; Pipe-Ph-Cl-4, 1-[4-(4-chlorophenyl)piperazinyl]; Pipe-Ph-MeO-2, 1-[4-(2-m-ethoxyphenyl)piperazinyl]; Pipe-Ph-MeO-3, 1-[4-(3-methoxyphenyl)piperazinyl]; Pipe-Ph-MeO-4, 1-[4-(4-methoxyphenyl)piperazinyl].

[b] Oxa, oxalate.

[c] IC_{50} values from duplicate determinations.

[d] Binding data have been already reported (ref 13).

receptors. Displacement of the dipropylamino group of analogue **8a** with cyclic amino groups (**8b**–**8d**), diisopropyl group (**8e**) or a longer alkyl group (**8f**) decreased σ receptor affinity, as was also the case for 6*H*-dibenzo[*b*,*d*]pyran analogues **7**. Furthermore, methyl groups were superior to a proton for R^4 (Scheme 7) in yielding higher σ receptors affinity (**8a** versus **8g**).

Conclusions

Carbazole analogue **8a** (FH-510), a high-affinity and selective σ ligand, was designed from 6*H*-dibenzo[*b*,*d*]-pyran analogue **7**, which was discovered by modification based on the difference in structural flexibility between apomorphine and haloperidol. This design based on the qualitative difference in structural freedom among ligands might be generally useful for drug design.

The physiological functions of σ receptors have not yet been determined. Carbazole analogue **8a** (FH-510) might be useful for determining the physiological and clinical significance of σ ligands.

Experimental

Chemistry

Melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin–Elmer 1760 spectrometer. Proton nuclear magnetic resonance (NMR) spectra were obtained using a Varian VXR-200 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Simazu/Kratos HV-300. Elemental analyses were performed by a Perkin–Elmer 240C (for carbon, hydrogen, and nitrogen) or Yokokawadenki IC7000P (for halogens and sulfur). Chromatography was performed on a silica gel C-200, 100–200 mesh (Wako Pure Chemical) using the solvent systems (volume ratios) indicated below.

Method A: 1-formyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran 10. A mixture of 2-bromo-3-hydroxy-4-methoxybenzaldehyde **9** (106.3 g, 0.46 mol), 2-iodobenzyl chloride (117.6 g, 0.47 mol), K_2CO_3 (71.0 g, 0.51 mol) and KI (7.64 g, 46 mmol) in *N,N*-dimethylformamide (DMF) (800 mL) was stirred at room temperature for 22 h. After concentration in vacuo, the residue was partitioned between CH_2Cl_2 and water. The separated water layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), concentrated in vacuo and then recrystallized from MeOH to obtain 2-bromo-3-(2-iodobenzyloxy)-4-methoxybenzaldehyde (198.0 g, 96% yield).

A mixture of 2-bromo-3-(2-iodobenzyloxy)-4-methoxybenzaldehyde (197.6 g, 0.44 mol) and powdered copper (201.7 g, 3.17 atom) in DMF (600 mL) was stirred and heated under reflux for 4 h. To the cooled reaction mixture was added water and AcOEt, followed by filtration through Celite. The separated organic layer was washed with 1 N HCl, water and saturated brine, dried (Na_2SO_4), and concentrated in vacuo. The residual semisolid was recrystallized from AcOEt to give **10** as colorless crystal (61.0 g, 57% yield). Mp 113–114°C; IR (KBr) 1672, 1592, 1567, 1301, 1283, 1255, 1220, 1099, 1013 cm^{-1}; MS (EI) *m*/*z* 240 (M^+, 100%), 225 (M^+-CH_3); ^1H NMR ($CDCl_3$) δ 3.99 (3H, s, CH_3O), 5.13 (2H, s, CH_2O), 6.99 (1H, d, $J = 8.6$ Hz, ArH), 7.30–7.48 (4H, m, ArH), 7.73 (1H, d, $J = 8.6$ Hz, ArH), 10.27 (1H, s, CHO); Anal. ($C_{15}H_{12}O_3$) C, H.

Method B: 1-hydroxycarbonylmethyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran 11. To a solution of **10** (41.24 g, 0.17 mol) in a mixture of tetrahydrofuran (THF)–MeOH (400 mL–50 mL), $NaBH_4$ (1.79 g, 47 mol) was added over 10 min, followed by stirring for 1.5 h with ice-cooling. To the solution was added dropwise 1 N HCl, followed by extraction with AcOEt. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated in vacuo to obtain crude 4-methoxy-l-hydroxymethyl-6*H*-dibenzo[*b*,*d*]pyran, which was carried on to the next step.

To a solution of crude 4-methoxy-1-hydroxymethyl-6*H*-dibenzo-[*b*,*d*]pyran in a mixture of THF-hexamethyl phosphoric amide (HMPA) (300 mL–60 mL), $SOCl_2$ (18.8 mL, 0.26 mol) was added at room temperature, and stirred for 1.5 h. The concentrated reaction mixture was partitioned between AcOEt and water. The separated organic layer was washed with saturated $NaHCO_3$, saturated brine, dried ($MgSO_4$), and concentrated in vacuo to give crude 4-methoxy-l-chloromethyl-6*H*-dibenzo[*b*,*d*]pyran, which was carried on to the next step.

To a solution of crude 4-methoxy-1-chloromethyl-6*H*-dibenzo[*b*,*d*]-pyran in a CH_3CN (600 mL) was added 18-Crown-6 (4.54 g, 17 mmol) and KCN (22.36 g, 0.34 mol), with stirring for 1 day at room temperature. The concentrated reaction mixture was partitioned between AcOEt and water. The separated organic layer was washed with saturated $NaHCO_3$, saturated brine, dried ($MgSO_4$), concentrated in vacuo, and recrystallized from AcOEt to obtain 4-methoxy-1-cyanomethyl-6*H*-dibenzo[*b*,*d*]pyran (32.05 g, 74% yield). Mp 131–132°C; IR (KBr) 2246, 1505, 1417, 1277, 1268, 1139, 1102, 1016 cm^{-1}; MS (EI) *m*/*z* 251 (M^+, 100%), 236 (M^+-Me), 211 (M^+-CH_2CN), 196 (M^+-Me, CH_2CN); ^1H NMR ($CDCl_3$) δ 3.93 (3H, s, CH_3O), 4.03 (2H, s, CH_2CO), 5.01 (2H, s, CH_2O), 6.91 (1H, d, $J = 7.2$ Hz, ArH), 7.18 (1H, d, $J = 7.2$ Hz, ArH), 7.25–7.56 (4H, m, ArH), 7.36 (1H, m, ArH); Anal. ($C_{16}H_{13}NO_2$) C, H, N.

A solution of 4-methoxy-1-cyanomethyl-6*H*-dibenzo-[*b*,*d*]pyran (20.0 g) in a mixture of acetic acid, H_2O and sulfuric acid (400 mL–120 mL–40 mL) was heated at reflux for 20 h and then concentrated in vacuo. The residue was poured onto ice. The resulting precipitate was collected by filtration, and recrystallized from AcOEt to obtain **11** as colorless crystal (18.28 g, 85% yield). Mp 142–143°C; IR (KBr) 1691, 1479, 1418, 1270, 1223, 1139, 1106, 1022 cm^{-1}; MS (EI) *m*/*z* 270 (M^+,

100%), 225 (M^+-CO_2H), 210 (M^+-CO_2H, CH_3), 194 (M^+-CO_2H, OCH_3); ^1H NMR ($CDCl_3$) δ 3.91 (3H, s, CH_3O), 4.00 (2H, s, CH_2CO), 5.01 (2H, s, CH_2O), 6.89 (1H, d, $J=8.5$ Hz, ArH), 7.02 (1H, d, $J=8.5$ Hz, ArH), 7.26–7.41 (3H, m, ArH), 7.36 (1H, m, ArH); Anal. ($C_{16}H_{14}O_4$) C, H.

Method C: 1-(2-chloroethyl)-4-methoxy-6*H*-dibenzo-[*b*,*d*]-pyran 12. To a suspension of $LiAlH_4$ (8.85 g, 0.23 mol) in THF (300 mL) was added dropwise a solution of **11** (42.00 g, 0.16 mol) in THF (100 mL), with stirring and cooling in an ice-bath. After stirring in the ice-bath for 5 h, a saturated aqueous Na_2SO_4 was added dropwise to the reaction mixture, which was filtered through Celite and concentrated in vacuo. Chlorination of the residue with $SOCl_2$ (17.0 mL, 0.23 mol) in a mixture of THF–HMPA (300 mL–60 mL), using the procedure described in the second step of Method B, yielded **12** as yellow oil (40.55 g, 95% yield), which was carried on to the next step. IR (neat) 2960, 2837, 1571, 1504, 1478, 1417, 1277, 1021 cm^{-1}; MS (EI) *m*/*z* 276 ($m^+ + 2$), 274 (M^+), 225 (M^+-CH_2Cl, 100%); ^1H NMR (DMSO-d_6) δ 3.39 (2H, d, $J=7.5$ Hz, CH_2), 3.78 (3H, s, CH_3O), 3.90 (2H, d, $J=7.5$ Hz, CH_2), 4.91 (2H, s, CH_2O), 6.97 (1H, d, $J=8.3$ Hz, ArH), 7.05 (1H, d, $J=8.3$ Hz, ArH), 7.31–7.50 (3H, in, ArH), 7.68 (1H, m, ArH).

Method D: 1-(2-dipropylaminoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran hydrochloride 7a. To a suspension of **11** (780 mg, 2.87 mmol) in benzene (20 mL) was added $SOCl_2$ (0.42 mL, 5.76 mmol), followed by heating at reflux for 30 min and concentration in vacuo.

A solution of the above residue in benzene (10 mL) was added dropwise to a solution of Et_3N (321 mg, 3.17 mmol) and dipropylamine (321 mg, 3.17 mmol) in benzene (20 mL), with stirring and cooling in an ice-bath. After stirring for 1.5 h at room temperature, the reaction mixture was washed with 1 N HCl, saturated $NaHCO_3$ and saturated brine, dried ($MgSO_4$), and concentrated in vacuo to obtain crude amide.

A mixture of the amide and $LiAlH_4$ (153 mg, 4.03 mmol) in THF (20 mL) was heated at reflux for 1 h. After cooling in an ice-bath, to the mixture was added dropwise saturated aqueous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The residue was column chromatographed ($CHCl_3$:MeOH, 50:1), treated with 4 N HCl in AcOEt, and then recrystallized from isopropanol/AcOEt to obtain **7a** as colorless crystal (557 mg, 51% yield). Mp 162–164°C; IR (KBr) 3436, 2966, 2594, 2525, 2423, 1472, 1280, 1144, 1022 cm^{-1}; MS (CI) *m*/*z* 340 ($M^+ + 1$), 114 (100%); ^1H NMR (DMSO-d_6) δ 0.89 (6H, t, $J=7.4$ Hz, CH_3C), 1.53–1.80 (4H, m, CCH_2C), 2.93–3.13 (4H, m), 3.16–3.34 (2H, m, CH_2), 3.36–3.51 (2H, m, CH_2), 3.79 (3H, s, CH_3O), 4.92 (2H, s, CH_2O), 6.99 (1H, d, $J=8.3$ Hz, ArH), 7.04 (1H, d, $J=8.3$ Hz, ArH), 7.33–7.53 (3H, m, ArH), 7.79 (1H, d, $J=7.1$ Hz, ArH), 10.65 (1H, br s, HCl); Anal. ($C_{22}H_{29}NO_2$·HCl) C, H, N.

In a corresponding fashion, the following compound **7b** was prepared.

1-(2-Dihexylaminoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran 7b. 63% yield; oily; IR (neat) 2928, 2857, 2798, 1504, 1477, 1466, 1276, 1023 cm^{-1}; MS (EI) *m*/*z* 437 (M^+, 100%), 336 (M^+-C_5H_{11}), 198 ($CH_2N(C_6H_{13})_2$); ^1H NMR ($CDCl_3$) δ 0.88 (6H, t, $J=6.0$ Hz, CH_3C), 1.13–1.54 (16H, m, CH_2), 1.87 (2H, m, CH_2), 2.27–2.60 (6H, m, CH_2), 2.97 (2H, t, $J=8.0$ Hz, CH_2), 3.89 (3H, s, CH_3O), 4.98 (2H, s, CH_2O), 6.84 (1H, d, $J=9.0$ Hz, ArH), 6.95 (1H, d, $J=9.0$ Hz, ArH), 7.20–7.43 (3H, m, ArH), 7.71 (1H, br d, $J=8.0$ Hz, ArH); Anal. ($C_{29}H_{43}NO_2$) C, H, N.

Method E: 1-(2-dibutylaminoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran hydrochloride 7c. A solution of **12** (3.30 g, 12.0 mmol) and dibutylamine (4.66 g, 36.1 mmol) in toluene (8.5 mL) was heated at reflux for 10 h. The cooled reaction mixture was poured into saturated $NaHCO_3$, and separated. The separated organic layer was washed with saturated $NaHCO_3$, saturated brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was column chromatographed ($CHCl_3$:MeOH, 50:1), treated with oxalic acid in MeOH, and then recrystallized from isopropanol to obtain **7c** as colorless crystal (2.63 g, 52% yield). Mp 129–131°C; IR (KBr) 3436, 2961, 2613, 1417, 1279 cm^{-1}; MS (CI) *m*/*z* 368 ($M^+ + 1$), 142 (100%); ^1H NMR (DMSO-d_6) δ 0.88 (6H, t, $J=7.1$ Hz, CH_3C), 1.15–1.40 (4H, m, CH_2), 1.40–1.65 (4H, m, CH_2), 2.92–3.10 (4H, m, CH_2), 3.10–3.43 (4H, m, CH_2), 3.78 (3H, s, CH_3O), 4.91 (2H, s, CH_2O), 6.98 (1H, d, $J=8.7$ Hz, ArH), 7.04 (1H, d, $J=8.7$ Hz, ArH), 7.32–7.48 (3H, m, ArH), 7.75 (1H, br d, $J=7.4$ Hz, ArH); Anal. ($C_{24}H_{33}NO_2$·$C_2H_2O_4$) C, H, N.

In a corresponding fashion, the following compounds **7d**–**7p** were prepared.

1-(2-Pyrrolidinoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran hydrochloride 7d. 59% yield; mp 225–227°C (EtOH); IR (KBr) 3436, 2959, 2443, 1416, 1275, 1016 cm^{-1}; MS (EI) *m*/*z* 309 (M^+), 165, 152, 84 (100%); ^1H NMR (DMSO-d_6) δ 1.76–2.10 (4H, m, CH_2 of pyrrolidine), 2.91–3.13 (2H, m, CH_2), 3.38 (4H, br s, CH_2), 3.34–3.63 (2H, m, CH_2), 3.78 (3H, s, CH_3O), 4.92 (2H, s, CH_2O), 7.02 (2H, s, ArH), 7.31–7.54 (3H, m, ArH), 7.75 (1H, d, $J=6.7$ Hz, ArH), 11.09 (1H, br s, NH^+); Anal. ($C_{20}H_{23}NO_2$·HCl) C, H, N.

1-(2-Piperidinoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran hydrochloride 7e. 36% yield; mp 197–199°C (EtOH); IR (KBr) 3436, 2945, 2437, 1504, 1277, 1018 cm^{-1}; MS (EI) *m*/*z* 323 (M^+), 165, 152, 98 (100%); ^1H NMR (DMSO-d_6) δ 1.21–1.56 (1H, m, CH_2 of piperidine), 1.61–1.97 (5H, m, CH_2 of piperidine), 2.78–3.03 (2H, m, CH_2), 3.20–3.57 (6H, m, CH_2), 3.78 (3H, s, CH_3O), 4.91 (2H, s, CH_2O), 7.01 (2H, s, ArH), 7.31–7.50 (3H, m, ArH), 7.76 (1H, d, $J=7.4$ Hz, ArH), 10.73 (1H, br s, NH^+); Anal. ($C_{21}H_{25}NO_2$·HCl) C, H, N.

1-(2-Morphorinoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran hydrochloride 7f. 44% yield; mp 214–217°C (EtOH); IR (KBr) 3436, 2927, 2447, 1478, 1416, 1279, 1104, 1018 cm^{-1}; MS (EI) *m*/*z* 325 (M^+), 165, 100 (100%); ^1H NMR (DMSO-d_6) δ 3.00–3.25 (2 H, m, CH_2 of

morphorine), 3.30–3.57 (6H, m, CH_2), 3.73–4.51 (4H, m, CH_2), 3.78 (3H, s, CH_3O), 4.92 (2H, s, CH_2O), 7.02 (2H, s, ArH), 7.32–7.56 (3H, m, ArH), 7.74 (1H, d, $J=6.7$ Hz, ArH); Anal. ($C_{20}H_{23}NO_3\cdot HCl$) C, H, N.

1-(2-Piperazinoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran 2 hydrochloride 7g. 72% yield; mp 253–255°C (MeOH); IR (KBr) 3411, 2980, 2933, 2645, 2559, 1420, 1276, 1020 cm^{-1}; MS (EI) *m*/*z* 324 (M^+), 99 (100%); ^1H NMR (DMSO-d_6) δ 3.20–3.90 (12H, m, CH_2), 3.30–3.57 (6H, m, CH_2), 3.79 (3H, s, CH_3O), 4.93 (2H, s, CH_2O), 7.02 (1H, d, $J=8.5$ Hz, ArH), 7.08 (1H, d, $J=8.5$ Hz, ArH), 7.35–7.54 (3H, m, ArH), 7.73 (1H, d, $J=6.5$ Hz, ArH), 9.88 (1H, br s, NH_2^+), 12.23 (1H, br s, NH_2^+); Anal. ($C_{20}H_{24}N_2O_2\cdot 2HCl$) C, H, N.

1-(2-(4-Phenylpiperazino)ethyl)-4-methoxy-6*H*-dibenzo-[*b*,*d*]pyran hydrochloride 7h. 69% yield; mp 241–245°C (MeOH); IR (KBr) 3436, 2837, 2536, 2447, 1504, 1498, 1016 cm^{-1}; MS (EI) *m*/*z* 400 (M^+), 175 ($CH_2N((CH_2)_2)_2NPh$, 100%); ^1H NMR (DMSO-d_6) δ 3.05–3.50 (8H, m, CH_2), 3.65 (2H, m, CH_2), 3.80 (3H, s, CH_3O), 3.86 (2H, m, CH_2), 4.93 (2H, s, CH_2O), 6.88–7.82 (11H, m, ArH), 10.85 (1H, br s, NH^+); Anal. ($C_{26}H_{28}N_2O_2\cdot HCl$) C, H, N.

1-(2-(4-(3-Trifluoromethylphenyl)piperazino)ethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran 2 hydrochloride 7i. 69% yield; mp 205–207°C (MeOH); IR (KBr) 3480, 3419, 2522, 2439, 1335, 1323, 1141, 1126, 1108, 1077, 1018 cm^{-1}; MS (EI) *m*/*z* 468 (M^+), 243 ($CH_2N((CH_2)_2)_2NPhCF_3$, 100%); ^1H NMR (DMSO-d_6) δ 3.15–3.40 (4H, m, CH_2), 3.48 (4H, s, CH_2), 3.65 (2H, br d, $J=10.0$ Hz, CH_2), 3.80 (3H, s, CH_3O), 4.00 (2H, br d, $J=10.0$ Hz, CH_2), 4.93 (2H, s, CH_2O), 7.00–7.53 (9H, m, ArH), 7.77 (1H, d, $J=8.0$ Hz, ArH), 11.60 (1H, br s, NH^+); Anal. ($C_{27}H_{27}F_3N_2O_2\cdot 2HCl$) C, H, N.

1-(2-(4-(2,3-Dimethylphenyl)piperazino)ethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran hydrochloride 7j. 8% yield; mp 218–223°C (MeOH); IR (KBr) 3436, 2525, 2423, 1475, 1278, 1019 cm^{-1}; MS (EI) *m*/*z* 428 (M^+), 203 ($CH_2N((CH_2)_2)_2NPhMe_2$, 100%); ^1H NMR (DMSO-d_6) δ 3.05–3.21 (4H, m, CH_2), 3.25–3.35 (2H, m, CH_2), 3.31 (6H, s, CH_3Ar), 3.40–3.58 (4H, m, CH_2), 3.61–3.73 (2H, m, CH_2), 3.80 (3H, s, CH_3O), 4.92 (2H, s, CH_2O), 6.89–6.98 (2H, m, ArH), 7.03–7.15 (3H, m, ArH), 7.38–7.56 (3H, m, ArH), 7.75 (1H, d, $J=8.5$ Hz, ArH), 10.72 (1H, br s, NH^+); Anal. ($C_{28}H_{32}N_2O_2\cdot HCl$) C, H, N.

1-(2-(4-(2-Chlorophenyl)piperazino)ethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran hydrochloride 7k. 49% yield; mp 239–240°C (MeOH); IR (KBr) 3436, 2320, 1481, 1445, 1283, 1018 cm^{-1}; MS (EI) *m*/*z* 436 ($M^+ + 2$), 434 (M^+), 225 (M^+-$CH_2N((CH_2)_2)_2NPhCl$), 211 ($CH_2N((CH_2)_2)_2$-$NPhCl + 2$), 209 ($CH_2N((CH_2)_2)_2NPhCl$, 100%); ^1H NMR (DMSO-d_6) δ 3.05–3.80 (12H, m, CH_2), 3.82 (3H, s, CH_3O), 4.94 (2H, s, CH_2O), 7.02–7.80 (10H, m, ArH), 10.70 (1H, br s, NH^+); Anal. ($C_{26}H_{27}ClN_2O_2$ ·HCl) C, H, N.

1-(2-(4-(3-Chlorophenyl)piperazino)ethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran hydrochloride 7l. 65% yield; mp 242–243°C (MeOH); IR (KBr) 3436, 2438, 1597, 1569, 1504, 1477, 1462, 1414, 1287, 1277, 1104, 1015 cm^{-1}; MS (EI) *m*/*z* 436 ($M^+ + 2$), 434 (M^+, 100%), 211 ($CH_2N((CH_2)_2)_2NPhCl + 2$), 209 ($CH_2N((CH_2)_2)_2NPhCl$); ^1H NMR (DMSO-d_6) δ 3.12–3.51 (8H, m, CH_2), 3.55–3.70 (2H, m, CH_2), 3.78 (3H, s, CH_3O), 3.85–4.00 (2H, m, CH_2), 4.93 (2H, s, CH_2O), 6.85–7.12 (5H, m, ArH), 7.27 (1H, t, $J=7.5$ Hz, ArH), 7.35–7.55 (3H, m, ArH), 7.75 (1H, d, $J=8.0$ Hz, ArH), 11.25 (1H, br s, NH^+); Anal. ($C_{26}H_{27}ClN_2O_2\cdot HCl$) C, H, N.

1-(2-(4-(4-Chlorophenyl)piperazino)ethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran 2 hydrochloride 7m. 51% yield; mp 282–285°C (MeOH); IR (KBr) 3436, 2441, 1497, 1243, 1012 cm^{-1}; MS (EI) *m*/*z* 436 ($M^+ + 2$), 434 (M^+), 211 ($CH_2N((CH_2)_2)_2NPhCl + 2$), 209 ($CH_2N((CH_2)_2)_2$ NPhCl, 100%); ^1H NMR (DMSO-d_6) δ 3.06–3.50 (8H, m, CH_2), 3.59–3.73 (2H, m, CH_2), 3.78 (3H, s, CH_3O), 3.76–3.93 (2H, m, CH_2), 4.93 (2H, s, CH_2O), 7.03 (2H, s, ArH), 7.03 (2H, d, $J=8.5$ Hz, ArH), 7.30 (2H, d, $J=8.5$ Hz, ArH), 7.36–7.55 (3H, m, ArH), 7.75 (1H, d, $J=7.6$ Hz, ArH); Anal. ($C_{26}H_{27}ClN_2O_2\cdot 2HCl$) C, H, N.

1-(2-(4-(2-Methoxyphenyl)piperazino)ethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran hydrochloride 7n. 41% yield; mp 223–224°C (MeOH); IR (KBr) 3436, 2348, 1503, 1456, 1415, 1276, 1017 cm^{-1}; MS (EI) *m*/*z* 430 (M^+, 100%), 205 ($CH_2N((CH_2)_2)_2NPhOMe$), 190 ($CH_2N((CH_2)_2)_2$ NPhO); ^1H NMR (DMSO-d_6) δ 3.05–3.37 (4H, m, CH_2), 3.40–3.73 (6H, m, CH_2), 3.78 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 4.94 (2H, s, CH_2O), 6.85–7.12 (6H, m, ArH), 7.35–7.57 (3H, m, ArH), 7.80 (1H, d, $J=6.5$ Hz, ArH), 11.50 (1H, br s, NH^+); Anal. ($C_{27}H_{30}N_2O_3\cdot HCl$) C, H, N.

1-(2-(4-(3-Methoxyphenyl)piperazino)ethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran hydrochloride 7o. 27% yield; mp 198–199°C (acetone); IR (KBr) 3435, 2526, 2418, 1604, 1455, 1276, 1216, 1169, 1016 cm^{-1}; MS (EI) *m*/*z* 430 (M^+), 205 ($CH_2N((CH_2)_2)_2NPhOMe$, 100%); ^1H NMR (DMSO-d_6) δ 3.04–3.25 (4H, m, CH_2), 3.39–3.92 (8H, m, CH_2), 3.73 (3H, s, CH_3O), 3.79 (3H, s, CH_3O), 4.93 (2H, s, CH_2O), 6.64 (1H, dd, $J=7.5$, 2.5 Hz, ArH), 6.52–6.65 (2H, m, ArH), 7.03 (2H, s, ArH), 7.18 (1H, t, $J=8.3$ Hz, ArH), 7.39–7.55 (3H, m, ArH), 7.72 (1H, d, $J=9.0$ Hz, ArH), 10.62 (1H, br s, NH^+); Anal. ($C_{27}H_{30}N_2O_3\cdot HCl$) C, H, N.

1-(2-(4-(4-Methoxyphenyl)piperazino)ethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran 2 hydrochloride 7p. 27% yield; mp 246–247°C (MeOH); IR (KBr) 3436, 3315, 1511, 1259, 1016 cm^{-1}; MS (EI) *m*/*z* 430 (M^+), 205 ($CH_2N((CH_2)_2)_2$ NPhOMe, 100%); ^1H NMR (DMSO-d_6) δ 3.00–3.36 (4H, m, CH_2), 3.46 (4H, br s, CH_2), 3.60–3.75 (4H, m, CH_2), 3.68 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 4.92 (2H, s, CH_2O), 6.87 (2H, d, $J=8.0$ Hz, ArH), 6.98 (2H, d, $J=8.0$ Hz, ArH), 7.04 (2H, s, ArH), 7.35–7.55 (3H, m, ArH), 7.75 (1H, d, $J=6.5$ Hz, ArH), 11.20 (1H, br s, NH^+); Anal. ($C_{27}H_{30}N_2O_3\cdot 2HCl$) C, H, N.

Method F: 1-(2-aminoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran hydrochloride 7q. To a suspension of 4-methoxy-

l-cyanomethyl-6*H*-dibenzo[*b*,*d*]pyran (14.25 g, 56.9 mmol) and $NaBH_4$ (1.64 g, 42.8 mmol) in 1,2-dimethoxyethane (86 mL), $BF_3{\cdot}Et_2O$ (7.0 mL, 56.9 mmol) was added dropwise at room temperature, followed by heating at reflux for 3 h. To the cooled reaction mixture was added dropwise MeOH (20 mL), and stirred at room temperature for 30 min. After concentration of the reaction mixture, to the residue was cautiously added concentrated HCl (86 mL) at room temperature and heated at reflux for 2 h. To the concentrated reaction mixture was added 40% aqueous NaOH to basidify, followed by extraction with $CHCl_3$. The extract was dried (Na_2SO_4), concentrated in vacuo, treated with 4 N HCl in AcOEt and recrystallized from EtOH to obtain **7q** as colorless crystal (7.45 g, 62% yield). Mp 266–270°C; IR (KBr) 3436, 3002, 2967, 2906, 1504, 1286, 1276, 1139, 1018 cm^{-1}; MS (CI) *m*/*z* 226 ($M^+ + 1$, 100%); ^1H NMR (DMSO-d_6) δ 3.02–3.18 (2H, m, CH_2), 3.18–3.34 (2H, m, CH_2), 3.79 (3H, s, CH_3O), 4.92 (2H, s, CH_2O), 6.99 (2H, s, ArH), 7.30–7.53 (3H, m, ArH), 7.68 (1H, d, *J* = 7.5 Hz, ArH), 8.14 (3H, br s, NH_3); Anal. ($C_{16}H_{17}NO_2{\cdot}HCl$) C, H, N.

Method G: 1-(2-propylaminoethyl)-4-methoxy-6*H*-dibenzo-[*b*,*d*]pyran hydrochloride 7r. To a solution of **7q** (6.22 g, 21.3 mmol) in pyridine (52 mL) was added dropwise propionyl chloride (2.17 g, 23.5 mmol), with stirring and cooling in an ice-bath. After stirring in the ice-bath for 1 h and at room temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ and 1 N HCl. The separated organic layer was washed with saturated $NaHCO_3$, saturated brine, dried (Na_2SO_4) and concentrated in vacuo.

A solution of the above residue in THF (80 mL) was added dropwise to a suspension of $LiAlH_4$ (3.71 g, 97.8 mmol) in THF (20 mL), while being stirred and cooled in an ice-bath. After heating at reflux for 2 h, to the mixture was added dropwise a saturated aqueous Na_2SO_4, filtered through Celite, and concentrated in vacuo. Treatment of the residue with 4 N HCl and recrystallization from a mixture of MeOH and isopropanol yielded **7r** as colorless crystal (5.39 g, 81% yield). Mp 198–200°C, IR (KBr) 3436, 2973, 2944, 2770, 2723, 1572, 1478, 1461, 1278, 1021 cm^{-1}; MS (CI) *m*/*z* 298 ($M^+ + 1$, 100%); ^1H NMR (DMSO-d_6) δ 0.92 (3H, t, *J* = 7.4 Hz, CH_3), 1.55–1.78 (2H, m, CH_2), 2.88 (2H, br t, *J* = 7.8 Hz, CH_2), 3.10–3.26 (2H, m, CH_2), 3.26–3.44 (2H, m, CH_2), 3.79 (3H, s, CH_3O), 4.92 (2H, s, CH_2O), 7.00 (2H, s, ArH), 7.31–7.54 (3H, m, ArH), 7.72 (1H, d, *J* = 7.5 Hz, ArH), 9.13 (2H, br s, NH_2^+); Anal. ($C_{19}H_{23}NO_2{\cdot}HCl$) C, H, N.

Method H: 1-(2-dipropylaminoethyl)-4-hydroxy-6*H*-dibenzo[*b*,*d*]-pyran hydrochloride 7s. A solution of **7a** (1.00 g, 2.66 mmol) in 37% HBr in acetic acid (15 mL) was heated at reflux for 8 h, and then concentrated in vacuo. A suspension of the above residue and K_2CO_3 (1.10 g, 7.24 mmol) in DMF (10 mL) was stirred at room temperature for 1 day, and filtered. The filtrate was concentrated in vacuo, column chromatographed ($CHCl_3$:MeOH, 50:1), treated with 4 N HCl in AcOEt, and then recrystallized from EtOH to obtain **7s** as colorless crystal (0.50 g, 52% yield). Mp 242–244°C, IR (KBr) 3220, 3150, 2968, 2943, 2666, 1478, 1285, 1096, 1026 cm^{-1}; MS (CI) *m*/*z* 368 ($M^+ + 1$), 142 (100%); ^1H NMR (DMSO-d_6) δ 0.89 (6 H, t, *J* = 7.0 Hz, CH_3C), 1.53–1.78 (4H, m, CH_2), 2.93–3.13 (4H, m, CH_2), 3.13–3.50 (4H, m, CH_2), 4.90 (2H, s, CH_2O), 6.81 (1H, d, *J* = 8.7 Hz, ArH), 6.92 (1H, d, *J* = 8.7 Hz, ArH), 7.30–7.51 (3H, m, ArH), 7.78 (1H, br d, *J* = 8.4 Hz, ArH), 9.18 (1H, br s, HO), 10.59 (1H, br s, NH^+); Anal. ($C_{21}H_{27}NO_2{\cdot}HCl$) C, H, N.

Method I: 5,8-dimethyl-4-(2-dipropylaminoethyl)carbazole hydrochloride 8a. A solution of 1-(2-dipropylaminoethyl)-2-methyl-3-nitrobenzene (100.5 g, 0.38 mol), *N*,*N*-dimethylformamide dimethyl acetal (113.2 g, 0.95 mol) and pyrrolidine (67.6 g, 0.95 mol) in DMF (380 mL) was heated at reflux for 12 h, and then poured into H_2O. The mixture was extracted with AcOEt, and washed with H_2O and saturated brine, dried ($MgSO_4$), and concentrated in vacuo.

A suspension of the above residue and 5% Pd/C (57.0 g) in a mixture of MeOH and acetic acid (210 mL–210 mL) was stirred at 55°C under an atmosphere of hydrogen. After the theoretical amount of hydrogen had taken up, the suspension was filtered through Celite. The filtrate was concentrated in vacuo, and partitioned between AcOEt and 1 M Na_2CO_3. The separated organic layer was washed with 1 M Na_2CO_3 and saturated brine, dried ($MgSO_4$), and concentrated in vacuo to obtain the crude indole compound.

A solution of the crude indole compound, 2,4-hexandione (69.7 g, 0.61 mol) and *p*-TosOH·H_2O (116.1 g, 0.61 mol) in EtOH (150 mL) was heated at reflux for 10 h, and then concentrated in vacuo. The residue was partitioned between AcOEt and 1 M Na_2CO_3. The organic layer was washed 1 M Na_2CO_3, H_2O and saturated brine, dried ($MgSO_4$), concentrated in vacuo, column chromatographed (hexanes:AcOEt, 6:1), treated with 4 N HCl in AcOEt, and then recrystallized from EtOH to obtain **8a** as colorless crystal (71.8 g, 53% yield). Mp 240–241°C; IR (KBr) 3170, 2972, 2598, 2534, 2485, 1616, 1480, 1320 cm^{-1}; MS (EI) *m*/*z* 322 (M^+), 208 (M^+-CH_2NPr_2), 114 (CH_2NPr_2, 100%); ^1H NMR (DMSO-d_6) δ 0.90 (6H, t, *J* = 7.6 Hz, CH_3C), 1.60–1.80 (4H, m, CH_2), 2.51 (3H, s, CH_3), 2.93 (3H, s, CH_3), 2.96–3.18 (4H, m, CH_2), 3.36–3.53 (2H, m, CH_2), 3.75–3.93 (2H, m, CH_2), 6.89 (1H, d, *J* = 7.3 Hz, ArH), 7.06 (1H, br d, *J* = 7.7 Hz, ArH), 227.10 (1H, d, *J* = 7.3 Hz, ArH), 7.35 (1H, t, *J* = 7.7 Hz, ArH), 7.49 (1H, br d, *J* = 7.7 Hz, ArH), 10.75 (1H, brs, NH^+), 11.35 (1H, s, NH); Anal. ($C_{22}H_{30}N_2{\cdot}HCl$) C, H, N.

In a corresponding fashion, the following compounds **8b**–**8g** were prepared.

5,8-Dimethyl-4-(2-pyrrolidinoethyl)carbazole hydrochloride 8b. 35% yield; mp 269–270°C (EtOH); IR (KBr) 3436, 3236, 2948, 2570, 2483, 1447, 1332, 1318 cm^{-1}; MS (EI) *m*/*z* 292 (M^+), 208 (M^+-$CH_2NC_4H_8$), 84 ($CH_2NC_4H_8$, 100%); ^1H NMR (DMSO-d_6) δ 1.78–2.10 (4H, m, CH_2), 2.51 (3H, s, CH_3), 2.92 (3H, s,

CH_3), 2.92–3.14 (2H, m, CH_2), 3.42–3.67 (4H, m, CH_2), 3.67–3.90 (2H, m, CH_2), 6.88 (1H, d, $J=7.5$ Hz, ArH), 6.99 (1H, br d, $J=7.3$ Hz, ArH), 7.09 (1H, d, $J=7.5$ Hz, ArH), 7.33 (1H, t, $J=7.3$ Hz, ArH), 7.48 (1H, br d, $J=7.3$ Hz, ArH), 11.19 (1H, br s, NH^+), 11.33 (1H, s, NH); Anal. ($C_{21}H_{24}N_2$·HCl) C, H, N.

5,8-Dimethyl-4-(2-piperidino)carbazole hydrochloride 8c. 37% yield; mp 249–250°C (EtOH); IR (KBr) 3436, 3233, 2952, 2542, 2511, 1437, 1428, 1332, 1319 cm^{-1}; MS (EI) *m/z* 306 (M^+), 208 (M^+-CH_2N C_5H_{10}), 98 ($CH_2NC_5H_{10}$, 100%); ^1H NMR (DMSO-d_6) δ 1.26–1.54 (1H, m, CH_2), 1.64–2.01 (5 H, m, CH_2), 2.50 (3H, s, CH_3), 2.80–3.06 (2H, m, CH_2), 2.92 (3H, s, CH_3), 3.29–3.45 (2H, m, CH_2), 3.45–3.61 (2H, m, CH_2), 3.76–3.93 (2H, m, CH_2), 6.88 (1H, d, $J=7.5$ Hz, ArH), 7.03 (1H, br d, $J=7.4$ Hz, ArH), 7.09 (1H, d, $J=7.5$ Hz, ArH), 7.34 (1H, t, $J=7.4$ Hz, ArH), 7.48 (1H, br d, $J=7.4$ Hz, ArH), 10.83 (1H, br s, NH^+); 11.32 (1H, s, NH); Anal. ($C_{21}H_{26}N_2$·HCl) C, H, N.

5,8-Dimethyl-4-(2-morpholinoethyl)carbazole hydrochloride 8d. 37% yield; mp 259–260°C (EtOH); IR (KBr) 3526, 3338, 3241, 3202, 2930, 2553, 2451, 1442, 1320, 1093 cm^{-1}; MS (EI) *m/z* 308 (M^+), 208 (M^+-CH_2N C_4H_8O), 100 ($CH_2NC_4H_8O$, 100%); ^1H NMR (DMSO-d_6) δ 2.50 (3H, s, CH_3), 2.93 (3H, s, CH_3), 3.10–3.22 (2H, m, CH_2), 3.32–3.64 (4H, m, CH_2), 3.77–4.08 (6H, m, CH_2), 6.77 (1H, d, $J=7.5$ Hz, ArH), 7.02 (1H, br d, $J=7.4$ Hz, ArH), 7.10 (1H, d, $J=7.5$ Hz, ArH), 7.35 (1H, t, $J=7.4$ Hz, ArH), 7.47 (1H, br d, $J=7.4$ Hz, ArH), 11.33 (1H, br s, NH^+), 11.63 (1H, s, NH); Anal. ($C_{20}H_{24}N_2O$·HCl) C, H, N.

5,8-Dimethyl-4-(2-diisopropylaminoethyl)carbazole hydrochloride 8e. 18% yield; mp 274–275°C; IR (KBr) 3436, 3145, 2971, 2917, 2649, 2514, 1431, 1315 cm^{-1}; MS (EI) *m/z* 322 (M^+), 208 (M^+-$CH_2NisoPr_2$), 114 ($CH_2NisoPr_2$, 100%); ^1H NMR (DMSO-d_6) δ 1.33 (6H, d, $J=7.2$ Hz, CH_3C), 1.38 (6H, d, $J=7.2$ Hz, CH_3C), 2.50 (3H, s, CH_3), 2.93 (3H, s, CH_3), 3.33–3.53 (2H, m, CH_2), 3.63–3.96 (4H, m, CH_2, CH), 6.87 (1H, d, $J=7.3$ Hz, ArH), 7.09 (2H, br d, $J=7.3$ Hz, ArH), 7.36 (1H, t, $J=7.3$ Hz, ArH), 7.47 (1H, br d, $J=7.3$ Hz, ArH), 9.83 (1H, br s, NH^+), 11.30 (1H, s, NH); Anal. ($C_{22}H_{30}N_2$·HCl) C, H, N.

5,8-Dimethyl-4-(2-dihexylaminoethyl)carbazole oxalate 8e. 27% yield; mp 164–165°C; IR (KBr) 3376, 2956, 2937, 2859, 1745, 1626, 1480, 1467, 1319 cm^{-1}; MS (EI) *m/z* 406 (M^+), 208 (M^+-CH_2NHex_2), 198 (CH_2NHex_2, 100%); ^1H NMR (DMSO-d_6) δ 0.86 (6H, d, $J=6.5$ Hz, CH_3C), 1.12–1.42 (12H, m, CH_2), 1.47–1.69 (4H, m, CH_2), 2.50 (3H, s, CH_3), 2.88 (3H, s, CH_3), 2.92–3.10 (4H, m, CH_2), 3.29–3.46 (2H, m, CH_2, CH), 3.64–3.70 (2H, m, CH_2, CH), 6.88 (1H, d, $J=7.4$ Hz, ArH), 7.04 (1H, br d, $J=7.3$ Hz, ArH), 7.10 (1H, t, $J=7.4$ Hz, ArH), 7.34 (1H, br d, $J=7.3$ Hz, ArH), 7.47 (1H, br d, $J=7.3$ Hz, ArH), 11.30 (1H, s, NH); Anal. ($C_{22}H_{30}N_2$·$C_2H_2O_4$) C, H, N.

4-(2-Dipropylaminoethyl)carbazole hydrochloride 8g. 11% yield; mp 204–205°C; IR (KBr) 3195, 2966, 2635, 2575, 2533, 1606, 1460, 1326, 1261 cm^{-1}; MS (EI) *m/z* 294 (M^+), 180 (M^+-CH_2NPr_2), 114 (100%); ^1H NMR (DMSO-d_6) δ 0.94 (6 H, t, $J=7.4$ Hz, CH_3C, 1.60–1.90 (4H, m, CH_2), 3.02–3.26 (4H, m, CH_2), 3.26–3.48 (2H, m, CH_2), 3.62–3.80 (2H, m, CH_2), 7.06 (1H, d, $J=7.4$ Hz, ArH), 7.18 (1H, t, $J=7.5$ Hz, ArH), 7.30–7.48 (3H, m, ArH), 7.52 (1H, d, $J=7.5$ Hz, ArH), 8.39 (1H, d, $J=7.5$ Hz, ArH), 10.99 (1H, br s, NH^+), 11.49 (1H, s, NH); Anal. ($C_{20}H_{26}N_2$·HCl) C, H, N.

In Vitro Study

Radioligand binding study

Male Wistar rats (200–250 g, Japan SLC, Japan) were decapitated and their brains were rapidly removed. The entire brain or striatum (D_2 receptor binding) was homogenized in 20 volumes of 50 mM Tris/HCl (pH 7.7) buffer (Tris buffer), using a Physcotoron homogenizer. The homogenate was centrifuged at 50,000×*g* for 10 min, and the pellet was rehomogenized with Tris buffer and recentrifuged, this procedure was repeated twice. The final pellet was resuspended with Tris buffer and was used for radioligand binding assay.

σ (2 nM [^3H]-(+)-3-PPP) and dopamine D_2 (15 nM [^3H]-sulpiride) receptors were determined according to the method of Tanaka et al.[12] Briefly, 1 mL of membrane suspension and radiolabeled ligand were incubated with various concentrations (at least five) of unlabeled drugs. Incubations were terminated by rapid filtration through a Whatman GF/B glass fiber filter that had been soaked for at least 4 h in a solution of 0.5% polyethylenimine, then washed with Tris buffer. The filter-bound radioactivity was measured using a liquid scintillation spectrometer. IC_{50} values from competitive inhibition experiments were determined using the Marquardt–Levenberg non-linear curve fitting procedure of the RS/1 program (BBN Research System) running on a VAX/VMS system.

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