Synthesis and Blocking Activities of Isoindolinone- and Isobenzofuranone-Containing Phenoxylalkylamines as Potent α_1-Adrenoceptor Antagonists

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This paper describes the synthesis and blocking activities of twelve new isoindolinone- and isobenzofuranone-containing phenoxylalkylamines as potent α_1-Adrenoceptor antagonists. These compounds were synthesized in moderate to good yields starting from 3,4-dimethylphenol, and characterized with ^{1}H-NMR, MS, IR and elemental analysis. Their blocking activities toward α_1-Adrenoceptors were evaluated on isolated rat anococcygeus muscles. The results indicated that these compounds were very strong in blocking α_1-Adrenoceptors, and most of them exhibited activities that were comparable to that of known potent α_1-Adrenoceptor antagonist 1-(2,6-dimethylphenoxy)-2-(3,4-dimethoxyphenylethylamino)propane hydrochloride (DDPH).

Key words α_1-Adrenoceptor antagonist; phenoxylalkylamine; synthesis; blocking activity

During the past decades, considerable interests have been attracted in the development of potent α_1-Adrenoceptor (α_1-AR) antagonists.[1—3] These efforts have been prompted primarily by their wide applications, for example, in the treatment of benign prostatic hyperplasia (BPH)[4] and high blood pressure.[5] To date, several types of α_1-AR antagonists, such as prazosin,[6] terazosin,[7] tamsuolosin,[8] have been developed as effective antihypertensive and BPH therapeutic drugs. In these respects, we have keenly become interested in the design and synthesis of promising α_1-AR antagonists by using readily available phenoxylalkylamines. Noteworthy among them is 1-(2,6-dimethylphenoxy)-2-(3,4-dimethoxyphenylethylamino)propane hydrochloride (DDPH) (Fig. 1), which is very effective in blocking α_1-ARs, and presently under Phase II clinic trials in China.[9—11] From the viewpoint of new drug discovery, however, it is of highly practical importance to synthesize α_1-AR antagonists that have diverse structures.

In our previous study on the structure–activity relationship of DDPH and its analogs, we have shown that the sizes of the substituents in aromatic ring A (Fig. 1) play a crucial role in the blocking activity.[12] That is, introducing bulky groups into the 3- or 4-positions of aromatic ring A may significantly ameliorate the activity, while Bremner's work on the pharmacophores of α_1-ARs has suggested that the oxygen atom of the carbonyl group in KMD-3213 (Fig. 1) could interact as an H-bonding acceptor with α_1-ARs.[13] On the other hand, it is known that isoindolinones and isobenzofuranones that are widely distributed in nature, exhibit multiple pharmacological properties, such as antibacterial activity against Gram-positive and Gram-negative bacteria, anticancer activity and cardiovascular activity.[14—17] These observations, taken together, make us reason that incorporating of isoindolinones and isobenzofuranones into phenoxylalkylamines may lead to strong α_1-AR antagonists. With this rationale in mind, we describe herein the synthesis and blocking activities toward α_1-ARs of isoindolinone- and isobenzofuranone-containing phenoxylalkylamines **1**—**12** (Chart 1, Table 1). In these compounds, the bulkiness and/or the potential H-bonding ability of isoindolinone and isobenzofuranone subunits are expected to impart enhanced interaction with α_1-AR. To the best of our knowledge, this represents an unprecedented example of α_1-AR antagonists containing isoindolinones and isobenzofuranones.

Results and Discussion

Synthesis of Compounds 1—12 The synthetic approaches that were used to synthesize compounds **1**—**12** are outlined in Chart 1. Compounds **13**—**16** were prepared starting from 3,4-dimethylphenol according to reported procedures.[18—22] Demethylation of **15** by HI and **16** by HBr and subsequent reaction with bromoacetone afforded compounds **17** and **18** in good yields, respectively. It should be noted that demethylation of compound **15** by HI proceeded in a higher yield than by HBr. Reductive amination of **17** and **18** with substituted phenylethylamines gave **1**—**12** in moderate to good yields. Among them, compounds **1**, **2**, **7**—**10** and **12** were oily and therefore converted into hydrochloric acid salts by treating with gaseous HCl. Compounds **1**—**12** were fully characterized with ^{1}H-NMR, MS, IR and elemental analysis. They afforded MS spectra with the *m*/*z* values corresponding to $[M+H]^+$. Their NMR spectra were also in full agreement with the given structures (see Experimental). The purity of each compound was judged from NMR and TLC.

Blocking Activities of Compounds 1—12 The blocking

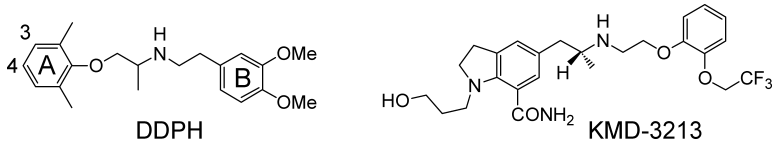

Fig. 1. Chemical Structures of DDPH and KMD-3213

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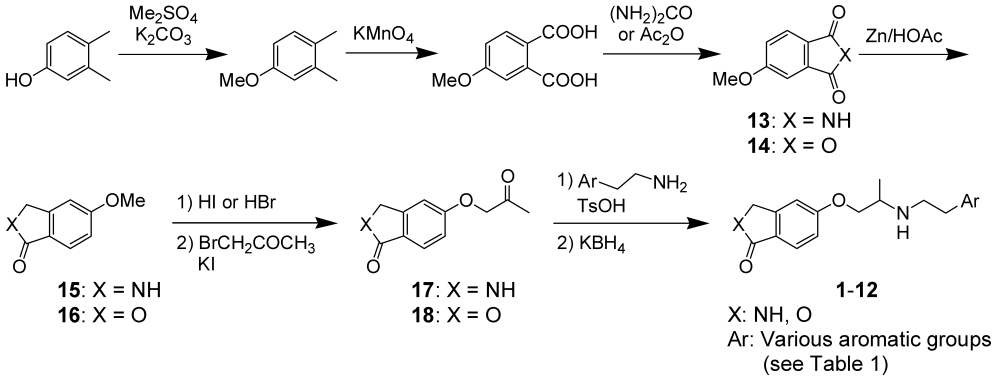
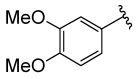
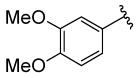
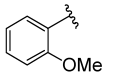
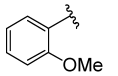
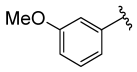
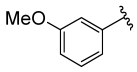
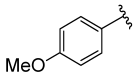
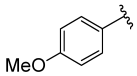
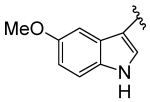
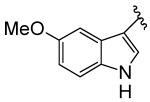
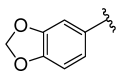
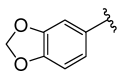


Chart 1. The Synthetic Route for Compounds **1**—**12**

Table 1. Structures and Blocking Activities (pA_2) of Compounds **1**—**12** and DDPH[a)]

Compound	X	Ar	pA_2	Compound	X	Ar	pA_2
1	NH		8.09±0.17	**7**	O		8.18±0.19
2	NH		7.86±0.20	**8**	O		7.69±0.37
3	NH		8.07±0.18	**9**	O		8.21±0.40
4	NH		8.14±0.32	**10**	O		7.51±0.22
5	NH		7.92±0.23	**11**	O		8.29±0.25
6	NH		8.11±0.59	**12**	O		7.59±0.38
DDPH			8.07±0.29				

a) pA_2 values, expressed as means±S.E.M. of three different concentrations, each tested at least three times.

activities of compounds **1**—**12** were then evaluated, by using methods similar to those described in the literatures.[23—26)] Here, anococcygeus smooth muscles, because of their selective contraction to α_1-AR agonists and long *in vitro* survival, were used as the isolated tissues. The blocking activity is expressed as p$A_2 = -\log[\mathbf{1}—\mathbf{12}]_2$, in which $[\mathbf{1}—\mathbf{12}]_2$ is defined as the molar concentrations (M) of **1**—**12**. These concentrations were measured according to Schild's methods.[27)] The obtained pA_2 values of compounds **1**—**12**, together with that of DDPH as a positive control, are listed in Table 1.

Some interesting observations can be extracted from Table 1. The first observation was that all the compounds exhibited strong blocking activities, and most of them were very similar with potent DDPH. It is remarkable that compounds **1**—**12** were much more active than DDPH analogs we have reported to date.[23,28)] This result indicates that incorporating of naturally occurring isoindolinones and isobenzofuranones into phenoxylalkylamines may serve as one sophisticated approach to improve the blocking efficiency. According to the reports by us[12)] and others,[13)] the bulkiness and H-bond forming ability of the substituents of DDPH analogs may make substantial contributions to the blocking activity. Given the fact that compounds **1** and **7** showed comparable activity with DDPH, bulkiness may be the predominant factor for the potency of compounds **1**—**12**. In addition, introducing at the aromatic group B of bulky groups, for example, 3,4-dihydro-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide, led to a dramatic decrease in the activity,[23)] suggesting that bulkiness at the aromatic group A may be preferable, which is in agreement with our structure–activity correlation study.[12)] Secondly, isoindolinone-containing compounds **1**—**6** did not consistently show higher blocking activities than isobenzofuranone-conjugated compounds **7**—**12**, and *vice versa*. For example, isoindolinonyl derivative **4** was more potent than isobenzofuranonyl derivative **10**, however, isobenzofuranone-containing compound **11** was better than isoindolinone-containing compound **5**. Thirdly, for the same series, *i.e.* compounds **1**—**6** or **7**—**12**, the pA_2 values also varied with the structures of aromatic group B (Fig. 1), but with a very small range. Since aromatic group B is an essential group for the activity of

DDPH analogs, this result suggested that its substituents in this case had minor effects on the interaction with α_1-ARs.

Concluding Remarks

Twelve new isoindolinone- and isobenzofuranone-containing phenoxylalkylamines were successfully synthesized as α_1-AR antagonists, and characterized with IR, ^{1}H-NMR, MS and elemental analysis. All the compounds were strong in blocking α_1-ARs ($pA_2 > 7.5$). compared with potent DDPH, most of them exhibited similar activities, suggesting that they may be exploitable as a new class of α_1-AR antagonists.

Experimental

General ^{1}H-NMR spectra were recorded in DMSO-d_6 using a Bruker unity ACF-400 spectrometer, and TMS as an internal reference. IR spectra were measured on Nieolet Impact 410 (KBr). Electrospray ionization (ESI) Mass spectra were measured on HP 1100 spectrometer. Elemental analysis was conducted on Elementar Vario EL III. Melting points (mp) were measured on RDCSY-I, and the temperature was uncorrected. Thin-layer chromatography (TLC) was performed on an aluminum plate precoated with silica gel and a fluorescence indicator (Merck, U.S.A.). Detection on TLC was made by UV (254 nm). Compounds **13**—**16** were prepared according to reported protocols.[18—22] All the other reagents and chemicals were obtained from commercial sources and used as received unless otherwise stated.

Synthesis of 5-Oxypropoxy-1-isoindolinone 17 A solution of 5-methoxyisoindolin-1-one **15** (0.8 g, 4.9 mmol) in hydroiodic acid (20 ml) was heated at 100 °C for 12 h. After the reaction mixture was concentrated under reduced pressure, the obtained residue was dissolved in acetone (50 ml), followed by addition of anhydrous potassium carbonate (2.0 g, 14.5 mmol), bromoacetone (0.5 ml) and a catalytic amount of potassium iodide. The resulting mixture was refluxed for 3 h and then filtered. The filtrate was concentrated under reduce pressure and purified by chromatography on a silica-gel column (CH_2Cl_2/CH_3OH, 60/1 by volume) to give compound **17** (0.3 g, 30%) as a white solid having mp 156.9—157.9 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.16 (s, 3H, $COCH_3$), 4.28 (s, 2H, $ArCH_2NH$), 4.91 (s, 2H, $ArOCH_2$), 6.97—7.54 (m, 3H, 3×ArH), 8.33 (s, 1H, CONH). IR (KBr) cm^{-1}: 3472, 2962, 2849, 1751, 1612, 1485, 1431, 1155, 773, 603. MS (ESI) *m/z*: 206 $[M+H]^+$, 411 $[2M+H]^+$. *Anal.* Cacld for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.38; N, 6.89.

Synthesis of 5-Oxypropoxy-1-isobenzofuranone 18 A solution of 5-methoxy-1-isobenzo furanone **16** (2.8 g, 3.6 mmol) in 48% hydrobromic acid (50 ml) was heated at 100 °C for 24 h. After the reaction mixture was concentrated under reduced pressure, the obtained residue was dissolved in acetone (50 ml) and then anhydrous potassium carbonate (7.1 g, 51.4 mmol), bromoacetone (1.7 ml, 20.2 mmol) and a catalytic amount of potassium iodide were added. The resulting mixture was refluxed for 3 h, and then filtered. The filtrate was concentrated under reduced pressure and purified by chromatography on a silica-gel column (CH_2Cl_2/CH_3OH, 60/1 by volume), followed by re-crystallization (acetone/petroleum ether, 1/3 by volume), to afford compound **18** (1.7 g, 48%) as a white solid having mp 135.0—135.8 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.28 (s, 3H, $COCH_3$), 4.64 (s, 2H, $ArOCH_2$), 5.22 (s, 2H, OCH_2Ar), 6.87—7.82 (m, 3H, 3×ArH). IR (KBr) cm^{-1}: 3444, 3197, 3078, 2896, 1914, 1706, 1462, 1362, 1163. MS (ESI) *m/z*: 207 $[M+H]^+$. *Anal.* Cacld for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.15; H, 4.86.

Synthesis of 5-(2-(3,4-Dimethoxyphenylethylamino)propoxy)-1-isoindolinone Hydrochloride 1·HCl To a solution of 5-oxypropoxy-1-isoindolinone **17** (0.3 g, 1.46 mmol) in methanol (20 ml) were added 3,4-dimethoxyphenylethylamine (0.3 ml, 1.75 mmol) drop wise and a catalytic amount of TsOH. The resulting mixture was refluxed under the atmosphere of nitrogen for 3 h, and cooled to room temperature. Then KBH_4 (0.3 g) was added in portions, while keeping the temperature below 30 °C. The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The obtained residue was partitioned between water (15 ml) and ethyl acetate (15 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (15 ml×2). The organic layer was combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by chromatography on a silica-gel column (ethyl acetate/methanol, 5/1 by volume). The obtained oily product was dissolved in a mixture of methanol–ether (1 : 3 by volume) and saturated with anhydrous HCl gas. After filtered, the obtained solid was washed with ethyl acetate and re-crystallized with a mixture of methanol–ethyl acetate (2/5 by volume) to give **1** (0.2 g, 34%) as a white hydrochloride salt having mp 196.8—197.4 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.42 (d, J=6.4 Hz, 3H, $CHCH_3$), 3.01—2.97 (t, J=8.0 Hz, 2H, $ArCH_2$), 3.21 (m, 2H, $NHCH_2$), 3.69 (m, 1H, CH_2CHCH_3), 3.73 and 3.75 (2s, 6H, 2×$ArOCH_3$), 4.23—4.35 (m, 4H, $ArCH_2NH$, $ArOCH_2$), 6.78—7.62 (m, 6H, 6×ArH), 8.39 (s, 1H, CONH), 9.50 (br s, 2H, NH_2^+). IR (KBr) cm^{-1}: 3237, 2940, 2450, 1679, 1519, 1262, 1141, 1022. MS (ESI) *m/z*: 371 $[M+H]^+$. *Anal.* Cacld for $C_{21}H_{27}ClN_2O_4$: C, 61.99; H, 6.69; N, 6.88. Found: C, 61.93; H, 6.74; N, 6.83.

5-(2-(2-Methoxyphenylethylamino)propoxy)-1-isoindolinone Hydrochloride 2·HCl (18%) as a white solid having mp 189.5—190.3 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.39 (d, J=6.4 Hz, 3H, $CHCH_3$), 2.97—3.01 (t, J=8.0 Hz, 2H, $ArCH_2$), 3.17 (m, 2H, $NHCH_2$), 3.71 (m, 1H, CH_2CHCH_3), 3.77 (s, 3H, $ArOCH_3$), 4.24—4.34 (m, 4H, $ArCH_2NH$, $ArOCH_2$), 6.91—7.61 (m, 7H, 7×ArH), 8.36 (s, 1H, CONH), 9.21 (br s, 2H, NH_2^+). IR (KBr) cm^{-1}: 3448, 2741, 2468, 1704, 1653, 1615, 1494, 1250. MS (ESI) *m/z*: 341.2 $[M+H]^+$. *Anal.* Cacld for $C_{20}H_{25}ClN_2O_3$: C, 63.74; H, 6.69; N, 7.43. Found: C, 63.71; H, 6.70; N, 7.48.

5-(2-(3-Methoxyphenylethylamino)propoxy)-1-isoindolinone 3 (20%) as a white solid having mp 74.3—75.6 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.17 (d, J=6.4 Hz, 3H, $CHCH_3$), 1.64 (br s, 1H, NH), 2.78—2.82 (t, J=6.8 Hz , 2H, $ArCH_2$), 2.86—3.01 (m, 2H, $NHCH_2$), 3.13—3.17 (m, 1H, CH_2CHCH_3), 3.78 (s, 3H, $ArOCH_3$), 3.85—3.93 (m, 2H, $ArOCH_2$), 4.39 (s, 2H, $ArCH_2NH$), 6.77—7.76 (m, 8H, 7×ArH, CONH). IR (KBr) cm^{-1}: 3401, 2930, 1676, 1615, 1454, 1262, 1082, 775. MS (ESI) *m/z*: 341 $[M+H]^+$. *Anal.* Cacld for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.61; H, 7.14; N, 8.20.

5-(2-(4-Methoxyphenylethylamino)propoxy)-1-isoindolinone 4 (34%) as a white solid having mp 113.2—114.9 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.17 (d, J=6.4 Hz, 3H, $CHCH_3$), 1.73 (br s, 1H, NH), 2.76—2.80 (t, 2H, J=6.8 Hz, $ArCH_2$), 2.83—2.99 (m, 2H, $NHCH_2$), 3.12—3.17 (m, 1H, CH_2CHCH_3), 3.79 (s, 3H, $ArOCH_3$), 3.84—3.95 (m, 2H, $ArOCH_2$), 4.39 (s, 2H, $ArCH_2NH$), 6.77—7.75 (m, 8H, 7×ArH, CONH); IR (KBr) cm^{-1}: 3230, 2968, 2484, 1654, 1396, 1247, 1222, 1028. MS (ESI) *m/z*: 341 $[M+H]^+$. *Anal.* Cacld for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.50; H, 7.16; N, 8.27.

5-(2-(2-(5-Methoxy-1*H*-indol-3-yl)ethylamino)propoxy)isoindolin-1-one 5 (18%) as a white solid having mp 197.7—198.6 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.09 (d, J=6.4 Hz, 3H, $CHCH_3$) 1.69 (br s, 1H, NH), 2.79—2.84 (m, 4H, $ArCH_2CH_2NH$), 3.03—3.05 (m, 1H, CH_2CHCH_3), 3.72 (s, 3H, $ArOCH_3$), 3.88—3.90 (m, 2H, $ArOCH_2$), 4.28 (s, 2H, $ArCH_2NH$), 6.71—7.54 (m, 7H, 7×ArH), 8.27 (s, 1H, CONH), 10.61 (s, 1H, ArNH). IR (KBr) cm^{-1}: 3395, 2900, 2826, 1683, 1615, 1485, 1266, 1213. MS (ESI) *m/z*: 380 $[M+H]^+$. *Anal.* Cacld for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.70; H, 6.68; N, 11.01.

5-(2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethylamino)propoxy)isoindolin-1-one 6 (44%) as a white solid having mp 120.4—121.8 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.18 (d, J=6.4 Hz, 3H, $CHCH_3$), 1.67 (br s, 1H, NH), 2.75—2.78 (t, 2H, J=6.8 Hz, $ArCH_2$), 2.85—2.96 (m, 2H, $NHCH_2$), 3.13—3.15 (m, 1H, CH_2CHCH_3), 3.86—3.94 (m, 2H, $ArOCH_2$), 4.40 (s, 2H, $ArCH_2NH$), 5.93 (s, 2H, OCH_2O), 6.68—7.77 (m, 7H, 6×ArH, CONH). IR (KBr) cm^{-1}: 3194, 2485, 1709, 1628, 1488, 1450, 1257, 1094. MS (ESI) *m/z*: 355 $[M+H]^+$. *Anal.* Cacld for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.84; H, 6.29; N, 7.93.

5-(2-(3,4-Dimethoxyphenethylamino)propoxy)isobenzofuran-1(3*H*)-one hydrochloride 7·HCl (40%) as a white solid having mp 82.5—83.5 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.39 (d, J=6.4 Hz, 3H, $CHCH_3$), 2.93—2.97 (t, 2H, J=7.6 Hz, $ArCH_2$), 3.19 (m, 2H, $NHCH_2$), 3.70—3.73 (m, 7H, 2×OCH_3, CH_2CHCH_3), 4.25—4.38 (m, 2H, $ArOCH_2$), 5.33 (s, 2H, $ArCH_2O$), 6.75—7.78 (m, 6H, 6×ArH), 9.36 (br s, 2H, NH_2^+). IR (KBr) cm^{-1}: 3457, 2942, 2495, 1741, 1630, 1515, 1450, 1260. MS (ESI) *m/z*: 372 $[M+H]^+$. *Anal.* Cacld for $C_{21}H_{26}ClNO_5$: C, 61.84; H, 6.42; N, 3.43. Found: C, 61.79; H, 6.40; N, 3.46.

5-(2-(2-Methoxyphenethylamino)propoxy)isobenzofuran-1(3*H*)-one hydrochloride 8·HCl (34%) as a white solid having mp 216.3—217.6 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.40 (d, J=6.4 Hz, 3H, $CHCH_3$), 2.95—3.06 (t, 2H, J=7.6 Hz, $ArCH_2$), 3.13—3.18 (m, 2H, $NHCH_2$), 3.69—3.71 (m, 1H, CH_2CHCH_3), 3.76 (s, 3H, OCH_3), 4.29—4.44 (m, 2H, $ArOCH_2$), 5.34 (s, 2H, $ArCH_2O$), 6.89—7.78 (m, 7H, 7×ArH), 9.51 (br s, 2H, NH_2^+). IR (KBr) cm^{-1}: 3442, 2939, 2474, 1753, 1612, 1491, 1266, 761. MS (ESI) *m/z*: 342 $[M+H]^+$. *Anal.* Cacld for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.61; H, 6.38; N, 3.67.

5-(2-(3-Methoxyphenethylamino)propoxy)isobenzofuran-1(3*H*)-one hydrochloride 9·HCl (40%) as a white solid having mp 176.2—177.5 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.42 (d, J=6.4 Hz, 3H, CHC$\underline{H}_3$), 2.99—3.03 (t, 2H, J=7.6 Hz, ArC$\underline{H}_2$), 3.17—3.25 (m, 2H, NHC$\underline{H}_2$), 3.69—3.73 (m, 1H, $CH_2C\underline{H}CH_3$), 3.75 (s, 3H, OC$\underline{H}_3$), 4.37—4.39 (m, 2H, ArOC$\underline{H}_2$), 5.36 (s, 2H, ArC$\underline{H}_2$O), 6.81—7.79 (m, 7H, 7×Ar$\underline{H}$), 9.52 (br s, 2H, NH_2^+). IR (KBr) cm^{-1}: 3467, 2945, 2711, 2438, 1742, 1607, 1486, 1274, 1053. MS (ESI) *m/z*: 342 $[M+H]^+$. *Anal.* Cacld for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.51; H, 6.45; N, 3.65.

5-(2-(4-Methoxyphenethylamino)propoxy)isobenzofuran-1(3*H*)-one hydrochloride 10·HCl (35%) as a white solid having mp 159.3—161 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.39 (d, J=6.4 Hz, 3H, CHC$\underline{H}_3$), 2.93—2.97 (t, 2H, J=7.6 Hz, ArC$\underline{H}_2$), 3.14—3.26 (m, 2H, NHC$\underline{H}_2$), 3.66—3.71 (m, 1H, $CH_2C\underline{H}CH_3$), 3.73 (s, 3H, OC$\underline{H}_3$), 4.29—4.39 (m, 2H, ArOC$\underline{H}_2$), 5.36 (s, 2H, ArC$\underline{H}_2$O), 6.90—7.80 (m, 7H, 7×Ar$\underline{H}$), 9.24 (br s, 2H, NH_2^+). IR (KBr) cm^{-1}: 3444, 2933, 2764, 2464, 1772, 1613, 1514, 1252, 1033. MS (ESI) *m/z*: 342 $[M+H]^+$. *Anal.* Cacld for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.55; H, 6.47; N, 3.74.

5-(2-(2-(5-Methoxy-1*H*-indol-3-yl)ethylamino)propoxy)isobenzofuran-1(3*H*)-one 11 (35%) as a white solid having mp 124.8—125.8 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.18 (d, J=6.4 Hz, 3H, CHC$\underline{H}_3$) 1.65 (br s, 1H, N$\underline{H}$), 2.95—3.08 (m, 4H, ArC$\underline{H}_2$C$\underline{H}_2$NH), 3.13—3.15 (m, 1H, $CH_2C\underline{H}CH_3$), 3.81 (s, 3H, OCH_3), 3.86—3.92 (m, 2H, ArOC$\underline{H}_2$), 5.20 (s, 2H, ArC$\underline{H}_2$O), 6.74—7.77 (m, 7H, 7×Ar$\underline{H}$), 7.94 (s, 1H, ArNH). IR (KBr) cm^{-1}: 3443, 2827, 1744, 1610, 1487, 1451, 1279, 1061. MS (ESI) *m/z*: 381 $[M+H]^+$. *Anal.* Cacld for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.53; H, 6.34; N, 7.32.

5-(2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethylamino)propoxy)isobenzofuran-1(3*H*)-one Hydrochloride 12·HCl (43%) as a white solid having mp 207.0—208.3 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.40 (d, J=6.4 Hz, 3H, CHC$\underline{H}_3$), 2.93—2.97 (t, 2H, J=7.6 Hz, ArC$\underline{H}_2$), 3.17—3.22 (m, 2H, NHC$\underline{H}_2$), 3.68—3.72 (m, 1H, $CH_2C\underline{H}CH_3$), 4.35 (m, 2H, ArOC$\underline{H}_2$), 5.36 (s, 2H, ArC$\underline{H}_2$O), 5.98 (s, 2H, OCH_2O), 6.86—7.80 (m, 6H, 6×Ar$\underline{H}$), 9.30 (br s, 2H, NH_2^+). IR (KBr) cm^{-1}: 3447, 2961, 2772, 2475, 1766, 1604, 1501, 1448, 1261. MS (ESI) *m/z*: 356 $[M+H]^+$. *Anal.* Cacld for $C_{20}H_{22}ClNO_5$: C, 61.30; H, 5.66; N, 3.57. found: C, 61.35; H, 5.63; N, 3.61.

Determination of pA_2 Value of Each Compound The blocking activity (pA_2) of each compound was measured by using the methods similar to those described previously.[23—26] Specifically, a male Sprague-Dawley rat (300—350 g) was killed by cervical dislocation and its anococcygeus smooth muscles were isolated. The tissues were transferred to Krebs' physiological solution that was aerated with 5% CO_2/95% O_2 at 37 °C. The solution (pH 7.4) was composed of 118.1 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.16 mM $MgSO_4$, 1.0 mM NaH_2PO_4, 25 mM $NaHCO_3$ and 11.1 mM glucose. Then anococcygeus smooth muscles were transferred and suspended in a 20-ml organ chamber containing Krebs solution at 37 °C. The solution was aerated with 5% CO_2/95% O_2. The muscle preparations were set at a resting tension of 1.0 g and allowed to equilibrate for 1 h in the Krebs' solution. During this period, the smooth muscles were replenished with Krebs' solution every 20 min. After equilibration, cocaine hydrochloride, hydrocortisone and propranolol were added to the final concentrations of 30 μmol·l^{-1}, 30 μmol·l^{-1} and 1 μmol·l^{-1}, respectively. After 20 min, concentration–response curves with phenylephrine were obtained by adding phenylephrine to the bath in the cumulative final concentrations of 3, 10, 30 μmol·l^{-1}. Each tissue was tested four times. The first concentration–response curve was the basic one, and the other three with phenylephrine were repeated by adding compounds **1**—**12** or DDPH, respectively. The pA_2 values of compounds **1**—**12** and DDPH were calculated according to Schild's graphical method, and listed in Table 1.

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