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Design, Synthesis and Biological Evaluation of Structurally Constrained Hybrid Analogues Containing Ropinirole Moiety as a Novel Class of Potent and Selective Dopamine D3 Receptor Ligands

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Abstract

Two series of hybrid analogues were designed, synthesized, and evaluated as a novel class of selective ligands for the dopamine D3 receptor. Binding affinities of target compounds were determined (using the method of radioligand binding assay). Compared to comparator agent BP897, compounds **2a** and **2c** were found to demonstrate a considerable binding affinity and selectivity for D3 receptor, and especially compound **2h** was similarly potent and more selective D3R ligand than BP897, a positive reference. Thus they may provide valuable information for the discovery and development of highly potent dopamine D3 receptor ligands with outstanding selectivity.

Key words: Dopamine D3 receptor subtype; Novel ligands; Indoline-2-one; Hybrid compounds; structure-activity relationship

1. Introduction

Since the dopamine 3 (D3) subtype receptor was first reported by Sokoloff et al. in 1990[1], it has been proved to be a promising therapeutic target for the central nervous system (CNS) diseases[2-4], and potent and selective D3 ligands may have the therapeutic potential for the treatment of drug addiction[5-8], Parkinson's disease[9,10], schizophrenia[11,12], restless legs syndrome (RLS) and other CNS disorders[13,14]. Although an enormous amount of work has been done in recent years toward the discovery and development of potent and selective D3 ligands[15-17], a functional study of D3R in

vivo is currently still limited due to the lack of D3 ligands possessing high binding affinity and selectivity.

Dopaminergic neurotransmission is mediated by five dopamine receptors (D1-D5), which can be grouped into the D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptor subtypes. It is a challenging task to develop highly potent and selective ligands for D3R, since the sequences of the D2-like dopamine receptor subtypes are highly similar[18]. In particular, D3R and D2R share 78% sequence identity within the seven transmembrane domains[19-21].

In 2010, Chien et al. reported the crystal structure of the human D3R[19], providing an insight for the rational design of D3R ligands. Chien and coworkers described the structural observation of an extracellular binding pocket highlighting the importance of the extracellular loops that were once thought to provide superficial definition to ligand binding [19].

Ropinirole (**Fig. 1**) has been used as monotherapy or in combination with levodopa for the treatment of parkinsonism and RLS[22,13]. It shows a full agonist activity in the mitogenic functional assay[23]. The efficacy of this compound may be related to its high D3 binding affinity, because a moderate K_i value of 69 nM is obtained for D3 receptor, while only a weak value of 1380 nM is found for D2 receptor at the high affinity binding sites[24]. BP 897 is a potent (K_i <10 nM) dopamine D_3 receptor compound and a high selectivity for the dopamine D_3 versus D_2 receptors (70-fold) developed for the treatment of cocaine abuse and craving[25]. Phenylpiperazine moiety has particularly been developed as an important pharmacophore for the selective D3 receptor ligand[26, 27]. Through the hybridization of the pharmacophores, we hope to get several compounds with high D3R binding affinity and D3/D2 selectivity.

2. Chemistry

As summarized in Table 1, 16 compounds (**1a-2h**) were synthesized. The synthetic routes were illustrated in **Schemes 1** and **2**.

Synthesis of the key intermediate **10** of the target compounds is illustrated in Scheme 1. Treatment of isochroman with benzoyl chloride in the presence of zinc chloride gave **4** with a yield of 99%, which was oxidized by dimethyl sulfoxide to obtain **5** in 67% yield. Compound **5** was converted to nitrostyrene **6** (up to 98%) in the presence of nitromethane and ammonium acetate in acetic acid[28]. Cyclization of **6** using ferric chloride and acetyl chloride in dichloromethane gave **7** in 59% yield. Compound **7** was reduced by hydrazine hydrate in the presence of Pd/C, and subsequently hydrolyzed under basic conditions to produce **8** with a yield of 71%[29]. Treatment of **8** with p-toluenesulfonyl chloride and pyridine in dichloromethane gave **9** in 86% yield, of which subsequent reaction with n-propylamine under N_2 gas gave the key intermediate **10** in 60% yield.

Halogenation of diethanolamine **11** gave **12** in 89% yield. Cyclization of **12** with various substituted aniline produced **13a-13k** that were subsequently neutralized with sodium hydroxide to obtain **14a-14k**. Condensation of **14a-14k** with 1-bromo-2-chloroethane or 1-bromo-3-chloropropane yielded **15a-15h** and **16a-16h**. Aminolysis of **15a-15h** and **16a-16h** was performed using intermediate **10** to afford the corresponding target compounds **1a-2h** (**Scheme 2**).

3. Results and discussion

3.1 Rational design for hybrid analogues

In our effort to design and develop selective and novel ligands for the D3 receptor which was based on the crystal structure of the human D3R[19], we adopted a hybrid approach by merging ropinirole and BP897 and further optimized hybrids by incorporating piperazine fragments with various subtituents into the ropinirole moiety as shown in **Fig. 2**. Interaction of the phenyl piperazine fragment with the dopamine D3 receptor would generate binding affinity, and the ropinirole moiety was expected to impart the selectivity for the D3 receptor by occupying extracellular binding pocket of the D3 receptor[30-31]. Furthermore, arylpiperazine derivatives may enhance the physicochemical properties of compounds to penetrate the blood brain barrier, and show the desired CNS efficacy[32]. On the basis of the crystal structure of the human D3R[19], as well as the basic design principals of combination, we have devised and synthesized novel indoline-2-ones derivatives (**Fig. 2**): (1) introduction of two important moiety of ropinirole and BP897; (2) connection of the two moiety with a carbon-chain containing 2-3 carbon atoms in order to adjust the spatial distance of the two fragments; and (3) various substituted phenylpiperazines were also

investigated. Our objective was to determine whether these compounds favor affinity and selectivity for the D3 receptor.

3.2 binding affinity of the target compounds

All the target compounds (**1a**-**2h**) were subjected to competitive binding assays for the human dopamine receptor 3 (D3R) and receptor 2 (D2), and The K_i values of binding assays were evaluated using BP 897 as a positive control. As shown in Table 1, some of the compounds show good binding affinities for the D3 receptor and high D3R selectivities over D2R. We inferred that both of the two fragments could probably make docking with corresponding cavity in the D3 receptor.

By contrast, we found that the affinities of the second series compounds were better than that of the first series, suggesting that it was associated with the length of the carbon-chain between the two fragments. The compounds containing one three-carbon linker are more likely to enter the cavity to dock with the D3 receptor. Moreover, after a close inspection, we also found that compounds **2a**, **2c**, **2e** and **2f-2h** demonstrated good affinities and selectivity for the D3 receptor (K_i < 10 nM). In particular, **2h** has a K_i value of 1.05 nM for its binding affinity to the D3 receptor and is 197-fold more selective for D3R over the D2 receptor.

The binding affinity of the resulting hybrid analogues appeared to be related to the space structure and the electronic effect of the substituents on the phenyl ring on a nitrogen of the piperazine group. It is worth pointing out that compound **2c** without substituent group on the benzene ring had a high binding affinity for the D3 receptor. We propose that the phenyl piperazine moiety might easily enter the binding pocket of the D3 receptor. Moreover, compounds with electron donating groups at 4 position, and, at 3 and 4 positions of the phenyl ring also had high binding affinities for the D3R and high selectivity for the D3R over the D2R. We inferred that the phenyl ring with electron donating groups at the 3 or/and 4 positions could easily enter the binding pocket of the D3R, and the groups on the phenyl ring were able to interact with the corresponding active sites of the D3R, suggesting that the pocket surface is electron-deficient.

4. Conclusion

In our study, adopting a hybrid approach, two series of novel hybrid analogues have been designed and synthesized. The target compounds were assayed for their K_i values against the D3R and D2R. Most tested compounds exhibited evident affinities to the D3R at low nM concentrations while **1a**, **1d** and **2b** manifested affinities to the D3R at a range of a mid to high nM concentrations. The assay results show that compounds could induce good binding affinities to the D3R when the linker is n-propylene. Furthermore, the affinity is affected by the presence of a substituent on the phenyl ring: the electron donating groups at the 3 or/and 4 positions of the phenyl ring lead to a significant improvement in affinity. This study may provide valuable information for further optimization of these two series of compounds for the development of the D3R ligand with an excellent potency and selectivity.

5. Experimental protocols

5.1 Synthesis

All reagents were purchased from commercial sources and used without further purification. Melting points were measured on an RY-1 hot-stage microscope, and the thermometer was uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker-ACF 300/500 spectrometer; chemical shifts (d) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), used as an internal standard. Mass spectra (MS) were obtained from Agilent 1100LC/MS Spectrometry Services. IR spectra were run on FI-IR Spectrometer (PerkineElmer). Elementary analyses were performed on Elementar Vario EL III instrument. All compounds were

routinely checked by TLC with silica gel GF-254 glass plates and viewed under UV light at 254 nm.

*5.1.1 Synthesis of 2-(chloromethyl) phenethyl benzoate (**4**)*

To a stirred solution of compound **3** (65.0 g, 484 mmol) in CH_2Cl_2 (150 mL) was added $ZnCl_2$ (1.95 g, 14.3 mmol). When the resulting mixture was heated to reflux, PhCOCl (71.5 g, 509 mmol) was dropped in slowly. The resulting mixture was refluxed with stirring for 1.5 h and then cooled to room temperature. After that, the mixture was washed with water (3×100 mL), and then dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded the

title compound (132 g, 99%) . ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 3.23 (t, *J* = 7.2 Hz, 2H), 4.58 (t, *J* = 7.2 Hz, 2H), 4.72 (s, 2H), 7.20-7.30 (m, 3H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 8.02 (d, *J* = 7.3 Hz, 2H).

*5.1.2 Synthesis of 2-formyl phenethyl benzoate (**5**)*

To a stirred solution of compound **4** (2.70 g, 9.83 mmol) in 25 mL DMSO was added sodium bicarbonate (1.67 g, 19.9 mmol). The resulting mixture was stirred at 110-120 °C for 1.5 h. Thereafter, the mixture was filtered and distilled under vacuum to remove the solvent. The residue obtained was diluted with water (10 mL) and exacted with dichloromethane (3×10 mL). The organic layers were combined, washed with water (2×10 mL). After drying and filtration, the organic solution was concentrated in vacuo to afford the crude title compound. To a mixture of sodium bisulfite (8.64 g, 83.0 mmol), water (12 mL) and ethanol (7.2 mL) was added the crude product above. The resulting mixture was stirred at 10 °C for 30 min, and a thick white precipitate was produced. The solid was collected with a pump, washed with cold dichloromethane (2×6 mL), and dried. To a mixture of sodium bicarbonate (3.0 g), water (40 mL) and dichloromethane (15 mL) was added the white solid. The resulting mixture was stirred at rt. for 2 h. The aqueous layer was exacted with dichloromethane (2×20 mL). The organic layers were combined, washed with water (2×20 mL) and saturated brine (20 mL), and the organic solution was concentrated in vacuo to afford 1.67 g (67%) of the title compound as virescent oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 3.53 (t, *J* = 6.7 Hz, 2H), 4.57 (t, *J* = 6.7 Hz, 2H), 7.37-7.48 (m, 4H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 2H), 10.26 (s, 1H).

*5.1.3 Synthesis of 2-(2-nitrovinyl) phenethyl benzoate (**6**)*

A mixture of compound **5** (1.78 g, 7.0 mmol), nitromethane (1.35 g, 22.1 mmol), glacial acetic acid (22 mL) and ammonium acetate (1.37 g, 17.8 mmol) was refluxed with stirring for 8-10 h. After that, the mixture was diluted with water (40 mL), and then extracted with dichloromethane (3×40 mL). The combined organic layers were washed with water (3×40 mL) and saturated brine (2×30 mL). After drying (Na_2SO_4) and filtration, the solvent was removed in vacuo to afford 2.04 g (98%) of the title compound as a brown viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 3.26 (t, *J* = 6.7 Hz, 2H), 4.53 (t, *J* = 6.7 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 3H), 7.46 (d, *J* = 4.9 Hz, 1H), 7.53 (m, 3H), 7.97 (m, 2H), 8.45 (d, *J* = 13.5 Hz, 1H).

*5.1.4 Synthesis of 2-(3-Chloro-2-oxoindolin-4-yl) ethyl benzoate (**7**)*

A mixture of dichloromethane (50 mL) and ferric chloride (15.9 g, 98.0 mmol) was stirred with ice-salt bath cooling, and acetyl chloride (7.69 g, 98.0 mmol) was slowly dropped into the mixture, keeping the temperature around -5 °C. Thereafter, compound **6** (7.28 g, 24.5 mmol) in 30 mL of dichloromethane was slowly added. The resulting mixture was stirred at -5-0 °C for 2 h, and then water (80 mL) was added. After that, the mixture was stirred at 30 °C for 1 h, and allowed to separate the layers. The aqueous layer was extracted with dichloromethane (2×100 mL). The organic layers were combined, washed with water (2×100 mL) and saturated brine (2×100 mL). After drying and filtration, the solution was concentrated under reduced pressure to a volume of about 70 mL, and petroleum (35 mL) was added. The resulting mixture was cooled to 0-5 °C for 1 h. After that, the product was collected with a pump and washed with a cold mixture (20 mL) of dichloromethane and petroleum (2: 1, v/v), and then dried in vacuo at 65 °C overnight to afford 4.58 g (59%) of the title compound as a off-white solid. mp. 154-155 °C. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H, ppm: 3.15 (m, 2H), 4.56 (t, *J* = 6.7 Hz, 2H), 5.69 (s, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.94 (d, *J* = 7.3 Hz, 2H), 10.76 (s, 1H).

*5.1.5 Synthesis of 4-(2-hydroxyethyl)-1,3-dihydroindol-2-one (**8**)*

A mixture of compound **7** (1.20 g, 3.80 mmol), 10% Pd/C (0.075 g, 0.070 mmol) and 15 mL methanol was stirred and heated to reflux. Thereafter, hydrazine hydrate was slowly dropped into the mixture at a rate to control refluxing, and the mixture was refluxed for 1 h. Sodium hydroxide (8.10 g, 202 mmol) dissolved in water (33 mL) was added, and the mixture was refluxed for additional 1 h. The hot mixture was filtered to remove the catalyst, and the filtrate was concentrated under reduced pressure to remove most of the methanol. After that, the residue was allowed to stand in the refrigerator for 2 h, and the product was collected with a pump, washed with cold water (2×5 mL) and dried in vacuo at 65 °C overnight to afford 0.48 g (71%) of the title compound as a colorless crystal. mp. 146-147 °C. IR (KBr) δ_{max} (cm^{-1}): 3261, 3166, 1682, 1618, 1608; ^{1}H NMR (300 MHz, DMSO-d_6), δ_H, ppm: 2.64 (t, *J* = 7.0 Hz, 2H), 3.41 (s, 2H), 3.59 (t, *J* = 6.9 Hz, 2H), 4.56 (t, *J* = 5.2 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 10.23 (br, s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ: 34.8, 36.3, 61.0, 106.9, 121.9, 124.9, 127.3, 135.7, 143.3, 176.3; Anal. Calcd for $C_{10}H_{11}NO_2$ (%): C, 67.78; H, 6.26; N, 7.90. Found: C 67.73, H 6.35, N, 7.69.

*5.1.6 Synthesis of 2-(2-oxoindolin-4-yl)ethyl 4-methylbenzenesulfonate (**9**)*

To a stirred mixture of compound **8** (2.00 g, 11.29 mmol) and Py (9 mL) was addeda solution of TsCl (3.02 g, 15.84 mmol) in dichloromethane (9 mL) at 5 °C. The resulting mixture was stirred at 5-10 °C for 2 h, and then a mixture of H_2O (10 mL), CH_2Cl_2 (9 mL) and conc. HCl (11 mL) was slowly dropped in. After that, the mixture was stirred for 0.5 h, followed by separating the layers. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL), The organic layers were combined, washed with water (2×30 mL) and saturated brine (2×30 mL). After drying (anhydrous Na_2SO_4) and filtration, the solution was concentrated under reduced pressure to a volume of about 20 mL, and the resulting mixture was cooled to 0-5 °C for 1 h. After that, the precipitate was collected with a pump, and dried to afford light yellow solid (3.22 g, 86%). mp. 128-129 °C. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H, ppm: 2.41 (s, 3 H), 2.86 (t, J = 6.9 Hz, 2 H), 3.30 (s, 2 H), 4.25 (t, J = 6.8 Hz, 2 H), 6.79 (m, 2 H), 7.10-7.29 (m, 3 H), 7.64 (d, J = 7.4 Hz), 9.46 (s, 1 H). MS: 332.1 $[M+H]^+$.

*5.1.7 Synthesis of 4-(2-(propylamino)ethyl)indolin-2-one (**10**)*

Compound **9** (9.08 g, 27.40 mmol) was dissolved in absolute alcohol (85 mL), to this solution was added slowly n-propylamine (85 mL) with ice-water bath under an atmosphere of N_2. The mixture was stirred for 5 min at 0 °C, and then refluxed for 1.5 h. Solvent was evaporated under reduced pressure to get crude product, which was added to water (200 mL) and stirred for 30 min at room temperature. After the pH adjusted to 11 with 20% NaOH at 0 °C , the mixture was extracted with CH_2Cl_2 (150 mL×3). The organic phase was washed with water (150 mL×2) and brine (150 mL×2), and then dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the brown crude product was purified by column chromatography on silica gel. eluting with dichloromethane: methanol: triethylamine (150: 1: 2) to afford brown viscous product (3.59 g, 60 %). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H, ppm: 0.85 (t, *J* = 7.4 Hz, 3H), 1.36-1.43 (m, 2H), 2.45-2.51 (m, 3H), 2.61 (t, *J* = 6.81 Hz, 2H), 2.68-2.74 (m, 2H), 3.43 (s, 2H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 6.81 Hz, 1H), 10.31(br, s, 1H); MS: 219.1 $[M+H]^+$.

*5.1.8 Synthesis of bis(2-chloroethyl)amine hydrochloride (**12**)*

To a stirred mixture of thionyl chloride (128 mL, 1.76 mol) and chloroform (80 mL) was added dropwise a solution of diethanolamine (40 mL, 0.417 mol) in chloroform (68 mL) in 3 h. The resulting mixture was stirred at room temperature for 3 h. After that, the mixture was heated to reflux for 0.5 h, and then cooled to room temperature. The precipitate

obtained was filtered, washed with cold chloroform and dried to yield white solid (66g, 89%). mp: 214-215 °C([33], mp: 207-209 °C). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H, ppm: 3.19-3.34 (m, 4 H), 3.72-3.93 (m, 4 H), 9.84 (s, 1 H). MS: 142.0 $[M+I-HCl]^+$.

*5.1.9 General process for the synthesis of the compounds **13a**-**13k***

To a stirred mixture of compound **12** (30 g, 0.168 mol) and n-BuOH (130 mL) was added slowly a solution of substituted phenylamine (0.153 mol) in n-BuOH (20 mL), and heated at reflux for 24 h, to this solution was added K_2CO_3 (23 g, 0.168 mol), and refluxed for another 48 h. The hot mixture was filtered, and the deep red liquor was allowed to stand in the refrigerator overnight. The precipitate was then collected by filtration, washed with cold n-BuOH and dried to afford **13a-13k**.

Compounds **13a-13k** were characterized as follows.

*5.1.9.1 Synthesis of 1-(m-tolyl)piperazine hydrochloride (**13a**).* Off-white solid, yield: 64%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H, ppm: 2.21 (s, 3 H), 3.16-3.35 (m, 8 H), 6.91-7.19 (m, 4 H), 9.50 (s, 1 H). MS: 177.1 $[M+I-HCl]^+$.

*5.1.9.2 Synthesis of 1-(2,3-dimethylphenyl)piperazine hydrochloride(**13b**).* White solid, yield: 65%, mp: 286-290 °C ([34] Lit. 294 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.18 (s, 3 H), 2.32 (s, 3 H), 2.60-3.37 (m, 8 H), 6.68-7.76 (m, 2 H), 7.13 (m, 1 H), 9.52 (s, 1 H). MS: 191.2 $[M+I-HCl]^+$.

*5.1.9.3 Synthesis of 1-(3-methoxyphenyl)piperazine hydrochloride (**13c**).* White solid, yield: 61%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H, ppm: 3.25-3.49 (m, 8 H), 3.78 (s, 3 H), 6.45-6.57 (m, 2 H), 7.15-7.19 (m, 1 H), 9.58(, 1 H). MS: 193.1 $[M+I-HCl]^+$.

*5.1.9.4 Synthesis of 1-(2-ethylphenyl)piperazine hydrochloride (**13d**).* Off-white solid, yield: 56%, mp: 251-254 °C ([35] Lit. 252 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 1.26 (s, 3 H), 2.50-2.77 (m, 6H), 3.48 (m, 4 H), 6.58-6.73 (m, 2 H), 6.89-7.25 (m, 2 H), 9,62 (s, 1 H). MS: 191.2 $[M+I-HCl]^+$.

*5.1.9.5 Synthesis of 1-(4-chlorophenyl)piperazine hydrochloride (**13e**).* White solid, yield: 72%, mp: 272-276 °C ([36] Lit. 275-278 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 3.18-3.52 (m, 8H), 6.95 (m, 2H), 7.22 (m, 2H), 9.50 (s, 1H). MS: 197.1 $[M+I-HCl]^+$.

*5.1.9.6 Synthesis of 1-(4-(trifluoromethoxy)phenyl)piperazine hydrochloride (**13f**).* Off-white solid, yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 3.09-3.22 (m, 4 H), 3.35-3.44 (m, 4 H), 6.80 (m, 2 H), 7.24 (m, 2 H), 9.46 (s, 1 H). MS: 247.1 $[M+I-HCl]^+$.

*5.1.9.7 Synthesis of 1-phenylpiperazine hydrochloride (**13g**).* Light red solid, yield: 71%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.75-2.81 (m, 4H), 3.46-3.58 (m, 4H), 6.65-7.10 (m, 5H), 9.45 (s, 1H). MS: 163.1 $[M+I-HCl]^+$.

*5.1.9.8 Synthesis of 1-(3,4-dimethylphenyl)piperazine hydrochloride (**13h**).* White solid, yield: 63%, mp: 170-172 °C ([34] Lit. 173 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.18 (s, 3H), 2.36 (s, 3H), 2.98-3.40 (m, 8 H), 6.69 (m, 1 H), 6.86-6.94 (m, 2 H), 9.58 (s, 1 H). MS: 191.2 $[M+I-HCl]^+$.

*5.1.9.9 Synthesis of 1-(p-tolyl)piperazine hydrochloride (**13i**).* White solid, yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.25 (s, 3H), 3.09-3.30 (m, 8H), 6.95-7.13 (m, 4H), 9.50 (s, 1 H). MS: 177.1 $[M+I-HCl]^+$.

*5.1.9.10 Synthesis of 1-(2,6-dimethylphenyl)piperazine hydrochloride (**13j**).* White solid, yield: 68%, mp: 236-239 °C ([34] Lit. 240 °C). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.30 (s, 6 H), 3.16-3.42 (m, 8H), 6.82-6.89 (m, 1 H), 7.05-7.10 (m, 2H), 9.38 (s, 1 H). MS: 191.2 $[M+I-HCl]^+$.

*5.1.9.11 Synthesis of 1-(o-tolyl)piperazine hydrochloride (**13k**).* Off-white solid, yield: 58%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.18 (s, 3 H), 3.14-3.32 (m, 8 H), 6.98-7.16 (m, 4 H), 9.78 (s, 1 H). MS: 177.1 $[M+I-HCl]^+$.

*5.1.10 General process for the synthesis of the compounds **14a**-**14k***

Different substituted phenyl piperazine hydrochloride (0.115 mol) was added into stirred water (200 mL), and the pH value was adjusted to 11-12 with 40% NaOH. The mixture was extracted with ethyl acetate (2×200 mL), and the combined extracts were washed with water (80 mL) and brine (80 mL) respectively. After drying with anhydrous Na_2SO_4, the solvent was removed under vacuum to afford the compounds ***14a*-*14k.***

Compounds **14a**-**14k** were characterized as follows.

*5.1.10.1 Synthesis of 1-(m-tolyl)piperazine (**14a**).* Light yellow oil, yield: 92%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.25 (s, 3 H), 2.95-3.21 (m, 8 H), 6.86 (m, 1 H), 7.12-7.18 (m, 3 H). MS: 177.1 $[M+H]^+$.

*5.1.10.2 Synthesis of 1-(2,3-dimethylphenyl)piperazine (**14b**).* Light yellow oil, yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.10 (s, 3 H), 2.25 (s, 3 H), 2.37 (s, 1 H), 2.52-3.15 (m, 8 H), 6.59-6.72 (m, 2 H), 7.04 (m, 1 H). MS: 191.2 $[M+H]^+$.

*5.1.10.3 Synthesis of 1-(3-methoxyphenyl)piperazine (**14c**).* Light yellow oil, yield: 95%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.32 (s, 1 H), 2.96-3.17 (m, 8 H), 3.74 (s, 3 H), 6.39-6.59 (m, 2 H), 7.11 (m, 1 H). MS: 193.1 $[M+H]^+$.

*5.1.10.4 Synthesis of 1-(2-ethylphenyl)piperazine (**14d**).* Light yellow oil, yield: 95%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 1.18 (s, 3 H), 2.36 (s, 1 H), 2.46-2.71 (m, 6 H), 2.96-3.07 (m, 4 H), 6.48-6.62 (m, 2 H), 6.76-7.16 (m, 2H). MS: 191.2 $[M+H]^+$.

*5.1.10.5 Synthesis of 1-(4-chlorophenyl)piperazine (**14e**).* Light yellow oil, yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.32 (s, 1H), 3.08-3.25 (m, 8H), 6.90 (m, 2H), 7.18 (m, 2H). MS: 197.1 $[M+H]^+$.

*5.1.10.6 Synthesis of 1-(4-(trifluoromethoxy)phenyl)piperazine (**14f**).* Light yellow oil, yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.84-2.90 (m, 4 H), 3.31-3.34 (m, 4 H), 6.68 (s, 2 H), 7.02 (s, 2 H). MS: 247.1 $[M+H]^+$.

*5.1.10.7 Synthesis of 1-phenylpiperazine (**14g**).* Light yellow oil, yield: 95%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H, ppm: 2.25 (s, 1H), 2.88-3.02 (m, 8 H), 6.75 (s, 1H), 6.86-7.23 (m, 4H). MS: 163.1 $[M+H]^+$.

*5.1.10.8 Synthesis of 1-(3,4-dimethylphenyl)piperazine (**14h**).* Light yellow oil, yield: 95%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.12 (s, 6 H), 2.39 (s, 1 H), 2.85-3.34 (m, 8 H), 6.58 (m, 1 H), 6.76-6.82 (m, 2 H). MS: 191.2 $[M+H]^+$.

*5.1.10.9 Synthesis of 1-(p-tolyl)piperazine (**14i**).* Light yellow oil, yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.14 (s, 1 H), 2.30 (s, 3H), 2.85-3.28 (m, 8H), 6.63-7.01 (m, 4H). MS: 177.1 $[M+H]^+$.

*5.1.10.10 Synthesis of 1-(2,6-dimethylphenyl)piperazine (**14j**).* Light yellow oil, yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.10 (s, 6 H), 2.32 (s, 1H), 3.16-3.29 (m, 8H), 6.68-6.96 (m, 3H). MS: 191.2 $[M+H]^+$.

*5.1.10.11 Synthesis of 1-(o-tolyl)piperazine (**14k**).* Light yellow oil, yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.28 (s, 3 H), 3.05-3.23 (m, 8 H), 6.80-6.94 (m, 2 H), 7.11-7.24 (m, 2 H). MS: 177.1 $[M+H]^+$.

*5.1.11 General process for the synthesis of the compounds **15a**-**15h** and **16a**-**16h***

K_2CO_3 (2.56 g, 18.5 mmol) was added to the solution of different substituted phenyl piperazine (7.40 mmol) in acetone (25 mL), to this solution was added slowly 1-Bromo-2-chloroethane or 1-Bromo-3-chloropropane (11.1 mmol) by droping at 0 $^\circ$C. The

mixture was stirred for 3 h at 35 °C, and then heated at reflux for 10 h. After cooled to room temperature the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel. eluting with petroleum ether : ethyl acetate (3:1) to afford the compounds **15a-15h** and **16a-16h.**

Compounds **15a-15h** and **16a-16h** were characterized as follows.

*5.1.11.1 Synthesis of 1-(2-chloroethyl)-4-(m-tolyl)piperazine (**15a**).* Light yellow oil, yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.31 (s, 3 H), 2.74 (m, 6 H), 3.20-3.29 (m, 4 H), 3.66-3.71 (m, 2 H), 6.67 (m, 1 H), 6.90-7.31 (m, 3 H). MS: 239.1 $[M+H]^+$.

*5.1.11.2 Synthesis of 1-(2-chloroethyl)-4-(2,3-dimethylphenyl)piperazine (**15b**).* Light yellow oil, yield: 64%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.27 (s, 3 H), 2.33 (s, 3 H), 2.76 (m, 4H), 3.19-3.32 (m, 4 H), 3.61-3.74 (m, 4 H), 6.67-6.74 (m, 2 H), 6.88-7.09 (m, 2 H). MS: 253.1 $[M+H]^+$.

*5.1.11.3 Synthesis of 1-(2-chloroethyl)-4-(3-methoxyphenyl)piperazine (**15c**).* Light yellow oil, yield: 63%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.69 (m, 4 H), 3.16-3.35 (m, 4 H), 3.63-3.80 (m, 7 H), 6.38-5.54 (m, 3 H), 7.20 (m, 1 H). MS: 255,1 $[M+H]^+$.

*5.1.11.4 Synthesis of 1-(2-chloroethyl)-4-(2-ethylphenyl)piperazine (**15d**).* Light yellow oil, yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 1.17 (s, 3 H), 2.58-2.65 (m, 4 H), 3.21-3.42 (m, 4 H), 3.55-3.61 (m, 2 H), 3.66-3.74 (m, 4 H), 6.64-6.79 (m, 2 H), 6.86-7.21 (m, 2 H). MS: 253.1 $[M+H]^+$.

*5.1.11.5 Synthesis of 1-(2-chloroethyl)-4-(4-chlorophenyl)piperazine (**15e**).* Light yellow oil, yield: 63%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.65-2.69 (m, 4 H), 3.17-3.38 (m, 4 H), 3.57-3.71 (m, 4 H), 6.80-6.87 (m, 2 H), 7.03-7.12 (m, 2 H). MS: 259.1 $[M+H]^+$.

*5.1.11.6 Synthesis of 1-(2-chloroethyl)-4-(4-(trifluoromethoxy)phenyl)piperazine (**15f**).* Light yellow oil, yield: 56%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.81 (m, 4 H), 3.19-3.33 (m, 4 H), 3.56-3.68 (m, 4 H), 6.85-7.24 (m, 4 H). MS: 309.1 $[M+H]^+$.

*5.1.11.7 Synthesis of 1-(2-chloroethyl)-4-phenylpiperazine (**15g**).* Light yellow oil, yield: 61%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.72(m, 4 H), 3.21-3.30 (m, 4 H), 3.69-3.77 (m, 4 H), 6.80-7.01 (m, 3 H), 7.27 (m, 2 H). MS: 225.1 $[M+H]^+$.

*5.1.11.8 Synthesis of 1-(2-chloroethyl)-4-(3,4-dimethylphenyl)piperazine (**15h**).* Light yellow oil, yield: 59%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.18 (s, 3 H), 2.21 (s, 3 H), 2.73 (m, 4 H), 3.18-3.34 (m, 4 H), 3.57-3.69 (m, 4 H), 6.72-6.79 (m, 1 H), 6.90-7.14 (m, 2 H). MS: 253.1 $[M+H]^+$.

*5.1.11.9 Synthesis of 1-(3-chloropropyl)-4-(p-tolyl)piperazine (**16a**).* Light yellow oil, yield: 74%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 1.99 (m, 2H), 2.33 (s, 3 H), 2.51-2.58 (m, 4H), 2.67 (m, 4 H), 3.15 (s, 4 H), 3.68 (t, J = 6.6 Hz, 2 H), 6.84-6.91 (m, 2 H), 6.99-7.10 (m, 2 H). MS: 253.1 $[M+H]^+$.

*5.1.11.10 Synthesis of 1-(3-chloropropyl)-4-(2,6-dimethylphenyl)piperazine (**16b**).* Light yellow oil, yield: 69%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.04 (m, 2 H), 2.35 (s, 6 H), 2.57-2.62 (m, 6 H), 3.17-3.21 (m, 4 H), 3.63-3.70 (m, 2 H), 6.95-7.04 (m, 3 H). MS: 267.2 $[M+H]^+$.

*5.1.11.11 Synthesis of 1-(3-chloropropyl)-4-phenylpiperazine (**16c**).* Light yellow oil, yield: 59%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 1.98 (m, 2 H), 2.48-2.63 (m, 6 H), 3.18-3.21 (m, 4 H), 3.59-3.64 (m, 2 H), 6.82-6.91 (m, 3 H), 7.20-7.26 (m, 2 H). MS: 239.1 $[M+H]^+$.

*5.1.11.12 Synthesis of 1-(3-chloropropyl)-4-(2,3-dimethylphenyl)piperazine (**16d**).* Light yellow oil, yield: 63%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 1.98 (m, 2 H), 2.30 (s, 3 H), 2.36 (s, 3 H), 2.54-2.60 (m, 6 H), 3.20-3.25 (m, 4 H), 3.61-3.72 (m, 2 H), 6.88-7.02 (m, 3 H). MS: 267.2 $[M+H]^+$.

*5.1.11.13 Synthesis of 1-(3-chloropropyl)-4-(o-tolyl)piperazine (**16e**).* Light yellow oil, yield: 61%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.01 (m, 2 H), 2.34 (s, 3 H), 2.55-2.76 (m, 6 H), 3.24-3.28 (m, 4 H), 3.64 (t, J = 6.6 Hz, 2 H), 6.67-6.84 (m, 2 H), 6.97-7.16 (m, 2 H). MS: 253.1 $[M+H]^+$.

*5.1.11.14 Synthesis of 1-(3-chloropropyl)-4-(4-(trifluoromethoxy)phenyl)piperazine (**16f**).* Light yellow oil, yield: 61%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 1.96 (m, 2 H), 2.58-2.67 (m, 6 H), 3.15-3.26 (m, 4 H), 3.65 (t, J = 6.7 Hz, 2 H), 6.83-6.91 (m, 2 H), 6.98-7.17 (m, 2 H). MS : 323.1 $[M+H]^+$.

*5.1.11.15 Synthesis of 1-(3-chloropropyl)-4-(3-methoxyphenyl)piperazine (**16g**).* Light yellow oil, yield: 66%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 1.99 (m, 2 H), 2.48-2.61 (m, 4 H), 3.17 (s, 4 H), 3.67 (t, J = 6.7 Hz, 2 H), 3.79 (s, 3 H), 6.83-7.06 (m, 4 H). MS: 269.1 $[M+H]^+$.

*5.1.11.16 Synthesis of 1-(3-chloropropyl)-4-(3,4-dimethylphenyl)piperazine (**16h**).* Light yellow oil, yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 2.01 (m, 2 H), 2.48 (s, 6 H), 2.51-2.61 (m, 6 H), 3.10-3.15 (m, 4 H), 3.66 (t, J = 6.7 Hz, 2 H), 6.84-7.10 (m, 3 H). MS: 267.2 $[M+H]^+$.

*5.1.12 General process for the synthesis of the compounds **1a-1h** and **2a-2h***

Compound **10** (0.70 g, 3.21 mmol) and compound **15a-15h** or **16a-16h** (3.21 mmol) were dissolved in acetonitrile (22 mL), to this solution was added K_2CO_3 (0.89 g, 6.44 mmol) and KI (0.54 g, 3.25 mmol). The mixture was stirred for 8 h at 45 °C. The hot precipitate was filtered

and the filtrate was evaporated under reduced pressure to get crude product, which was purified by column chromatography on silica gel. eluting with dichloromethane: methanol: three ethylamine (200: 0.1: 1) to afford the final product.

Compounds **1a**-**1h** and **2a**-**2h** were characterized as follows.

*5.1.12.1 Synthesis of 4-(2-(propyl(2-(4-(m-tolyl)piperazin-1-yl)ethyl)amino)ethyl) indol-in-2-one (**1a**).* Brown sticky product, yield: 72%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.3 Hz, 3H), 1.43-1.58 (m, 2H), 2.30 (s, 3H), 2.54-2.82 (m, 10H), 3.17-3.41 (m, 8H), 3.49 (s, 2H), 6.66 (d, *J* = 7.3 Hz, 1H), 6.71-6.73 (m, 3H), 6.84 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 2H), 9.08 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.8, 20.2, 21.7, 30.8, 34.9, 51.4, 53.3, 53.7, 54.7, 56.5, 57.0, 113.1, 116.8, 120.5, 120.6, 122.7, 128.0, 128.1, 128.9, 135.3, 135.4, 135.4, 136.8, 138.7, 142.5, 142.7, 151.2, 151.3, 156.1, 177.4, 177.5; MS: 421.3 $[M+H]^+$; Anal. calcd. for $C_{26}H_{36}N_4O$ (%): C 74.25, H 8.63, N 13.32; found: C 74.12, H 8.60, N 13.41.

*5.1.12.2 Synthesis of 4-(2-((2-(4-(2,3-dimethylphenyl)piperazin-1-yl)ethyl)(propyl) amin-o)ethyl)indolin-2-one (**1b**).* Grey solid, yield: 69%, mp: 116-118 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.3 Hz, 3H), 1.43-1.55 (m, 2H), 2.21 (s, 3H), 2.25 (s, 3H), 2.50 (t, *J* = 7.7 Hz, 2H), 2.54-2.71 (m, 12H), 2.91 (t, *J* = 4.2 Hz, 4H), 3.49 (s, 2H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.84-6.92 (m, 3H), 7.06 (t, *J* = 7.7 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 9.32 (br, s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 13.9, 20.3, 20.5, 31.0, 35.2, 51.5, 52.0, 54.2, 54.8, 56.6, 56.8, 107.5, 116.6, 122.7, 124.0, 124.9, 125.7, 127.9, 131.2, 137.0, 137.8, 142.5, 151.5, 177.7, 177.8; IR (KBr, cm^{-1}): 3283, 3060, 2948, 2813, 1687, 1616, 1580, 1512, 1459, 1378, 1241, 1142, 1061, 777, 724, 648; MS: 435.3 $[M+H]^+$; Anal. calcd. for $C_{27}H_{38}N_4O$ (%): C 74.61, H 8.81, N 12.89; found: C 74.51, H 8.74, N 12.96.

*5.1.12.3 Synthesis of 4-(2-((2-(4-(3-methoxyphenyl)piperazin-1-yl)ethyl)(propyl) amino)ethyl)indolin-2-one (**1c**).* Brown sticky product, yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.3 Hz, 3H), 1.43-1.52 (m, 2H), 2.47-2.53 (m, 4H), 2.62 (t, *J* = 4.7 Hz, 4H), 2.68-2.70 (m, 6H), 3.19 (t, *J* = 4.7 Hz, 4H), 3.48 (s, 2H), 3.78 (s, 3H), 6.41 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 7.11-7.18 (q, *J* = 7.3 Hz, 2H), 9.15 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 20.3, 30.9, 35.1, 48.9, 51.5, 53.6, 54.7, 55.1, 56.5, 56.6, 102.4, 104.4, 107.5, 108.8, 122.7, 124.0, 128.0, 129.7, 137.0,

142.5, 152.6, 160.5, 177.6; IR (KBr, cm^{-1}): 3200, 3083, 2950, 2873, 2822, 1701, 1604, 1580, 1497, 1453, 1299, 1248, 1204, 1171, 1055, 774, 759, 719, 687, 650; MS: 437.2 $[M+H]^+$; Anal. calcd. for $C_{26}H_{36}N_4O_2$ (%): C 71.53, H 8.31, N 12.83; found: C 71.64, H 8.30, N 12.88.

*5.1.12.4 Synthesis of 4-(2-((2-(4-(2-ethylphenyl)piperazin-1-yl)ethyl)(propyl)amino) ethyl)indolin-2-one (**1d**).* Brown sticky product, yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.3 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H), 1.43-1.55 (m, 2H), 2.48-2.57 (m, 4H), 2.64-2.71 (m, 12H), 2.92 (t, *J* = 4.4 Hz, 4H), 3.50 (s, 2H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 7.01-7.09 (m, 2H), 7.13-7.17 (m, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 9.19 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 14.8, 20.3, 23.3, 31.0, 35.2, 51.5, 52.5, 54.3, 54.8, 56.6, 56.8, 107.5, 119.9, 122.8, 123.8, 124.0, 126.4, 128.0, 128.8, 137.0, 139.2, 142.5, 151.2, 177.7; IR (KBr, cm^{-1}): 3193, 3099, 3062, 3027, 2958, 2872, 1704, 1605, 1491, 1457, 1376, 1302, 1247, 1223, 1124, 762, 720, 651; MS m/z: 435.3$[M+H]^+$; Anal. calcd. for $C_{27}H_{38}N_4O$ (%): C 74.61, H 8.81, N 12.89; found: C 74.66, H 8.67, N 12.86.

*5.1.12.5 Synthesis of 4-(2-((2-(4-(4-chlorophenyl)piperazin-1-yl)ethyl)(propyl)amino) ethyl)indolin-2-one (**1e**).* Grey solid, yield: 68%, mp: 136-137 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.88 (t, *J* = 7.2 Hz, 3H), 1.44-1.52 (m, 2H), 2.50-2.70 (m, 14H), 3.15 (s, 4H), 3.49 (s, 2H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* = 8.3 Hz, 3H), 7.11-7.19 (m, 3H), 9.19 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 20.3, 31.0, 35.2, 49.0, 51.6, 53.5, 54.7, 56.5, 56.6, 107.5, 117.1, 122.8, 124.0, 124.4, 128.0, 128.9, 137.0, 142.5, 149.8, 177.6; IR (KBr, cm^{-1}): 3211, 3066, 3039, 3019, 2948, 2873, 1669, 1603, 1498, 1451, 1299, 1245, 1128, 1082, 813, 769, 696, 658; MS: 441.2$[M+H]^+$; Anal. calcd. for $C_{25}H_{33}ClN_4O$ (%): C 68.09, H 7.54, N 12.70; found: C 68.03, H 7.52, 12.76.

*5.1.12.6 Synthesis of 4-(2-(propyl(2-(4-(4-(trifluoromethoxy)phenyl)piperazin-1-yl) ethyl)amino)ethyl)indolin-2-one (**1f**).* Brown sticky product, yield: 59%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.3 Hz, 3H), 1.45-1.52 (m, 2H), 2.47-2.53 (m, 4H), 2.63 (t, *J* = 4.7 Hz, 4H), 2.68-2.71 (m, 6H), 3.17 (t, *J* = 4.6 Hz, 4H), 3.49 (s, 2H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.83-6.88 (m, 3H), 7.08-7.16 (m, 3H), 9.39 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 20.4, 31.0, 35.2, 49.1, 51.6, 53.6, 54.8, 56.6, 56.7, 107.5, 116.5, 121.9, 122.3, 122.8, 124.0, 128.0, 137.1, 141.9, 142.4, 150.0, 177.5; IR (KBr, cm^{-1}): 3166, 3019, 2955, 2871, 2819, 1684, 1605, 1515, 1458, 1268, 1238, 1159, 1003, 832, 718, 646; MS: 491.2 $[M+H]^+$; Anal. calcd. for $C_{26}H_{33}F_3N_4O_2$ (%): C 63.66 H 6.78 N 11.42; found: C 63.64, H 6.71, N 11.51.

*5.1.12.7 Synthesis of 4-(2-((2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino)ethyl) indolin-2-one (**1g**).* Grey solid, yield: 71%, mp: 113-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.2 Hz, 3H), 1.44-1.56 (m, 2H), 2.47-2.53 (m, 4H), 2.64 (t, *J* = 4.6 Hz, 4H), 2.67-2.80 (m, 6H), 3.12-3.27 (m, 4H), 3.50 (s, 2H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.83-6.88 (m, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 2H), 8.12 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 20.4, 31.0, 35.1, 49.0, 51.6, 53.7, 54.8, 56.6, 56.7, 107.5, 116.0, 119.6, 122.8, 124.0, 128.0, 129.0, 137.1, 142.4, 151.2, 177.5; IR (KBr, cm^{-1}): 3183, 3058, 3039, 3021, 2957, 2867, 1664, 1606, 1577, 1505, 1456, 1321, 1301, 1249, 1140, 1084, 753, 690, 656; MS: 407.3 $[M+H]^+$; Anal. calcd. for $C_{25}H_{34}N_4O$ (%): C 73.85, H 8.43, N 13.78; found: C 73.78, H 8.48 N 13.77.

*5.1.12.8 Synthesis of 4-(2-((2-(4-(3,4-dimethylphenyl)piperazin-1-yl)ethyl)(propyl) amino)ethyl)indolin-2-one (**1h**).* Brown sticky product, yield: 70%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.88 (t, *J* = 7.2 Hz, 3H), 1.44-1.52 (m, 2H), 2.17 (s, 3H), 2.22 (s, 3H), 2.47-2.53 (m, 4H), 2.63-2.70 (m, 10H), 3.14 (s, 4H), 3.48 (s, 2H), 6.66-6.74 (m, 3H), 6.84 (d, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 9.22 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 18.7, 20.1, 20.4, 31.0, 35.1, 49.6, 51.6, 53.7, 54.8, 56.6, 56.7, 107.5, 113.7, 118.0, 122.7, 124.0, 127.9, 128.0, 130.1, 137.0, 137.0, 142.5, 149.5, 177.6; IR (KBr, cm^{-1}): 3186, 3080, 3025, 2948, 2856, 1702, 1605, 1569, 1505, 1455, 1307, 1242, 1140, 1091, 886, 804, 704, 660; MS: 435.3 $[M+H]^+$; Anal. calcd. for $C_{27}H_{38}N_4O$ (%): C 74.61, H 8.81, N 12.89; found: C 74.74 H 8.79, 12.94.

*5.1.12.9 Synthesis of 4-(2-(propyl(3-(4-(p-tolyl)piperazin-1-yl)propyl)amino)ethyl) indolin-2-one (**2a**).* Brown sticky product, yield: 67%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.88 (t, *J* = 7.2 Hz, 3H), 1.41-1.53 (m, 2H), 1.63-1.73 (m, 2H), 2.26 (s, 3H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.60 (s, 4H), 2.67 (s, 4H), 3.15 (s, 4H), 3.47 (s, 2H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 7.7 Hz, 1H), 9.28 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 20.3, 20.3, 24.5, 30.9, 35.1, 49.6, 52.1, 53.2, 54.3, 56.1, 56.6, 107.5, 116.3, 122.7, 124.0, 127.9, 129.1, 129.5, 137.1, 142.5, 149.2, 177.6; IR (KBr, cm^{-1}): 3368, 2954, 2815, 1687, 1610, 1577, 1511, 1459, 1451, 1237, 811, 720, 651; MS: 435.3 $[M+H]^+$; Anal. calcd. for $C_{27}H_{38}N_4O$ (%): C 74.61, H 8.81, N 12.89; found: 74.55, H 8.83, N 12.89.

*5.1.12.10 Synthesis of 4-(2-((3-(4-(2,6-dimethylphenyl)piperazin-1-yl)propyl)(propyl) amino)ethyl)indolin-2-one (**2b**).* Brown sticky product, yield: 71%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.90 (t, *J* = 7.2 Hz, 3H), 1.45-1.55 (m, 2H), 1.69-1.79 (m, 2H), 2.32 (s, 6H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.61 (s, 4H), 2.72 (s, 4H), 3.16 (s, 4H), 3.48 (s, 2H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.94-6.97 (m, 3H), 7.15 (t, *J* = 7.7 Hz, 1H), 8.34 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), *δ*: 11.7, 19.5, 19.9, 24.0, 30.5, 35.0, 49.2, 51.9, 52.8, 54.3, 55.8, 56.8, 107.7, 122.4, 123.9, 124.9, 127.8, 128.7, 136.5, 136.7, 142.8, 148.0, 177.3; IR (KBr, cm^{-1}): 3423, 3060, 2944, 1678, 1606, 1550, 1476, 1460, 1248, 769, 721, 651; MS: 449.3 $[M+H]^+$; Anal. calcd. for $C_{28}H_{40}N_4O$ (%): C 74.96, H 8.99, N 12.49; found: C 75.08, H 8.93, N 12.44.

*5.1.12.11 Synthesis of 4-(2-((3-(4-phenylpiperazin-1-yl)propyl)(propyl)amino)ethyl) indolin-2-one (**2c**).* Brown sticky product, yield: 64%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.92 (t, *J* = 7.2 Hz, 3H), 1.54-1.59 (m,2H), 1.75-1.85 (m, 2H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.63-2.81 (m, 12H), 3.22 (s, 4H), 3.46 (s, 2H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.91-6.94 (m, 3H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.23-7.30 (m, 2H), 9.71 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), *δ*: 11.7, 19.5, 24.2, 30.6, 35.5, 48.6, 51.4, 52.9, 53.3, 53.9, 55.1, 56.7, 107.9, 115.8, 120.4, 122.9, 124.2, 128.02, 129.1, 136.5, 142.8, 149.6, 177.1; MS: 421.3 $[M+H]^+$; Anal. calcd. for $C_{26}H_{36}N_4O$ (%): C 74.25, H 8.63, N 13.32; found: C 74.32, H 8.60, N 13.37.

*5.1.12.12 Synthesis of 4-(2-((3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propyl)(propyl) amino)ethyl)indolin-2-one (**2d**).* Brown sticky product, yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.3 Hz, 3H), 1.43-1.55 (m, 2H), 1.65-1.75 (m, 2H), 2.22 (s, 3H), 2.27 (s, 3H), 2.39-2.49 (m, 4H), 2.53-2.69 (m, 10H), 2.91-2.94 (m, 4H), 3.48 (s, 2H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.83-6.93 (m, 3H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 9.08 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), *δ*: 11.9, 13.9, 20.2, 20.5, 24.5, 30.8, 35.1, 52.0, 52.1, 53.7, 54.2, 56.0, 56.7, 107.5, 116.6, 122.7, 124.0, 124.8, 125.7, 127.9, 131.1, 137.1, 137.8, 142.5, 151.5, 177.6; IR (KBr, cm^{-1}): 3440, 3067, 3025, 2952, 2872, 1679, 1619, 1606, 1581, 1475, 1460, 1452, 1376, 1243, 1145, 1082, 779, 721, 651; MS: 449.4$[M+H]^+$; Anal. calcd. for $C_{28}H_{40}N_4O$ (%): C 74.96, H 8.99, N 12.49; found: C 74.85, H 8.98, N 12.52.

*5.1.12.13 Synthesis of 4-(2-(propyl(3-(4-(o-tolyl)piperazin-1-yl)propyl)amino)ethyl) indolin-2-one (**2e**).* Brown sticky product, yield: 66%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.2 Hz, 3H), 1.44-1.51 (m, 2H), 1.64-1.74 (m, 2H), 2.30 (s, 3H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 2.54 (t, *J* = 7.4 Hz, 2H), 2.60 (s, 4H), 2.68 (s, 4H), 2.94 (s, 4H), 3.48 (s, 2H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 7.15-7.17 (m, 3H), 9.31 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), *δ*: 11.9, 17.8, 20.3, 24.6, 30.9, 35.1, 51.6, 52.1, 53.7, 54.3, 56.0, 56.7, 107.5, 118.9, 122.7, 123.0, 124.0, 126.5, 127.9, 130.9, 132.5, 137.1, 142.5, 151.4, 177.7; IR (KBr, cm^{-1}): 3199, 3066, 3021, 2954, 2872, 1687, 1618, 1607, 1492, 1458, 1375, 1266, 1146, 1084, 777, 722, 650; MS: 435.2 $[M+H]^+$; Anal. calcd. for $C_{27}H_{38}N_4O$ (%): C 74.61, H 8.81, N 12.89; found: C 74.65, H 8.79, N 12.84.

*5.1.12.14 Synthesis of 4-(2-(propyl(3-(4-(4-(trifluoromethoxy)phenyl)piperazin-1-yl) propyl)amino)ethyl)indolin-2-one (**2f**).* Brown sticky product, yield: 70%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.2 Hz, 3H), 1.43-1.54 (m, 2H), 1.65-1.75 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.58-2.71 (m, 10H), 3.18 (t, *J* = 4.5 Hz, 4H), 3.45 (s, 2H), 6.81-6.89 (m, 4H), 7.08-7.14 (m, 3H), 9.64 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), *δ*: 11.7, 19.7, 23.9, 29.6,, 30.3, 35.1, 49.0, 51.8, 52.8, 53.0, 54.0, 55.7, 56.2, 108.0, 116.4, 121.8, 122.4, 124.0, 127.9, 136.1, 141.8, 142.9, 149.9, 177.1; IR (KBr, cm^{-1}): 3392, 3079, 2955, 2874, 2818, 1697, 1618, 1607, 1512, 1457, 1380, 1264, 1159, 1085, 1008, 834, 807, 710, 647; MS: 505.2 $[M+H]^+$; Anal. calcd. for $C_{27}H_{35}F_3N_4O_2$ (%): C 64.27, H 6.99, N 11.10; found: C 64.16, H 6.99, N 11.14.

*5.1.12.15 Synthesis of 4-(2-((3-(4-(3-methoxyphenyl)piperazin-1-yl)propyl)(propyl) amino)ethyl)indolin-2-one (**2g**).* Brown sticky product, yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.89 (t, *J* = 7.0 Hz, 3H), 1.43-1.55 (m, 2H), 1.66-1.76 (m, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 2.51 (t, *J* = 7.4 Hz, 2H), 2.59-2.72 (m, 10H), 3.20 (s, 4H), 3.44 (s, 2H), 3.78 (s, 3H), 6.40 (d, *J* = 7.9 Hz, 1H), 6.46 (s, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 6.9 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 9.71 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), *δ*: 11.8, 19.9, 24.1, 30.5, 35.1, 48.8, 51.8, 52.9, 54.1, 55.1, 55.8, 56.3, 102.3, 104.3, 108.0, 108.7, 122.3, 123.9, 127.9, 129.6, 136.3, 142.9, 152.5, 160.4, 177.0; IR (KBr, cm^{-1}): 3392, 3079, 2954, 2871, 2816, 1683, 1605, 1576, 1533, 1496, 1456, 1255, 1171, 1050, 1011, 801, 776, 689, 650; MS: 451.3 $[M+H]^+$; Anal. calcd. for $C_{27}H_{38}N_4O_2$ (%): C 71.97, H 8.50, N 12.43; found: C 71.99, H 8.52, N 12.36.

*5.1.12.16 Synthesis of 4-(2-((3-(4-(3,4-dimethylphenyl)piperazin-1-yl)propyl)(propyl) amino)ethyl)indolin-2-one (**2h**).* Brown sticky product, yield: 63%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H, ppm: 0.88 (t, J = 7.3 Hz, 3H), 1.41-1.53 (m, 2H), 1.62-1.72 (m, 2H), 2.17 (s, 3H), 2.22 (s, 3H), 2.39 (t, J = 7.5 Hz, 2H), 2.45 (t, J = 7.5 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 2.59 (t, J = 4.6 Hz, 4H), 2.67 (s, 4H), 3.15 (t, J = 4.5 Hz, 4H), 3.47 (s, 2H), 6.67-6.74 (m, 3H), 6.83 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 9.15 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.9, 18.7, 20.1, 20.3, 24.6, 30.9, 35.1, 49.7, 52.1, 53.3, 54.3, 56.1, 56.6, 107.4, 113.7, 118.0, 122.7, 124.0, 127.9, 130.1, 137.0, 137.2, 142.5, 149.6, 177.6; IR(KBr, cm^{-1}): 3195, 3021, 2954, 2872, 1695, 1614, 1572, 1505, 1455, 1379, 1149, 1085, 880, 803, 719, 651; MS: 449.3 $[M+H]^+$; Anal. calcd. for $C_{28}H_{40}N_4O$ (%): C 74.96, H 8.99, N 12.49; found: C 74.87, H 8.95, N 12.50.

5.2. Binding assays (K_i values)

All the target compounds were subjected to competitive binding assays for the human dopamine receptor 3 and receptor 2, using membrane protein obtained from HEK-293 cells stably transfected respective receptor, and [^{3}H]-spiperone was used as standard radiolabeled ligand. Duplicated tubes were incubated at 30 °C for 50 min with increasing concentrations (1 nM-100 μM) of respective compound and with 0.7 nM [^{3}H] spiperone in a final volume of 200 μL binding buffer containing 50 mM Tris, 4 mM $MgCl_2$ and pH value of 7.4. Non-specific binding was determined by parallel incubations with 10 μM spiperone for D2 and D3 receptors respectively. Binding was terminated by the condition of ice bath and filtration over a glass-fiber filter (Schleicher and Schuell No.32). Filters were washed with cold buffer (50 mM Tris-HCl, PH 7.5) (3 mL×3)and the radioactivity were measured using a Packard Cobra gamma counter. Estimates of the equilibrium dissociation constant and maximum number of binding sites were obtained using non-linear regression analysis[37]. Data from competitive inhibition experiments were modeled using non-linear regression analysis to determine the concentration of inhibitor that inhibits 50% of the specific binding of the radioligand. Competition curves were modeled for a single site, and the IC 50 values will be converted to equilibrium dissociation constants (K_i values) (GraphPad, San Diego, CA, USA).

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1	**Fig 1**.	Chemical structure of ropinirole.
2	**Fig. 2**.	A design for hybrid analogues.
3	**Scheme 1**.	Synthetic route for the preparation of the compound **10**. Reagents and conditions: (a) $ZnCl_2$, PhCOCl, CH_2Cl_2, reflux, 1.5 h, 99%; (b) DMSO, $NaHCO_3$, 110-120 °C, 1.5 h, 67%; (c) $MeNO_2$, NH_4OAc, AcOH, reflux, 8-10 h, 98%; (d) $FeCl_3$, AcCl, CH_2Cl_2, -5-0 °C, 2 h, 59%; (e) $N_2H_4 \cdot H_2O$, MeOH, 10%Pd/C, reflux, 1 h, NaOH, H_2O, reflux, 1 h, 71%; (f) TsCl, Py, CH_2Cl_2, 5-10 °C, 2 h, 86%; (g) n-$PrNH_2$, EtOH, reflux, 1.5 h, 60%.
4	**Scheme 2**.	Synthetic route for the preparation of the compounds **1a**-**1h** and **2a**-**2h**. Reagents and conditions: (a) $SOCl_2$, $CHCl_3$, rt, 3 h, reflux, 0.5 h, 89%; (b) substituted phenylamine, n-BuOH, K_2CO_3, reflux, 48 h, 56-72%; (c) NaOH, rt. 0.5 h, 92-96%; (d) 1-Bromo-2-chloroethane or 1-Bromo-3-chloropropane, K_2CO_3, acetone, 35 °C, 3 h, reflux, 10 h, 56-74%; (e) **10**, K_2CO_3, KI, CH_3CN, 45 °C, 8 h, 59-72%.
5	**Table 1**	Binding affinities of target compounds for D2R and D3R (K_i values)
6	Supporting Information	

I have stated that my co-authors and I have no conflict of interest.

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Table 1

Binding affinities of target compounds for D2R and D3R (K_i values)

Compd	n	R	K_i ± SEM (nM)		
			D_3R	D_2R	D_2R/D_3R
1a	2	3-Me	49.3±3.1	433±28	8.8
1b	2	2,3-di-Me	24.7±0.43	107±4.1	4.3
1c	2	3-OMe	13.5±0.76	118±2.6	8.7
1d	2	2-Et	168±13	2108±360	13
1e	2	4-Cl	18.7±0.62	82.3±12	4.4
1f	2	4-OCF_3	22.6±0.55	69.3±0.79	3.1
1g	2	H	12.8±0.61	397±51	31
1h	2	3,4-di-Me	15.7±0.72	98.3±2.6	6.3
2a	3	4-Me	2.13±0.37	195±3.1	92
2b	3	2,6-di-Me	48.5±3.6	202±14	4.2
2c	3	H	3.61±0.40	258±9.6	71
2d	3	2,3-di-Me	12.7±1.4	169±5.8	13
2e	3	2-Me	7.28±0.36	209±11	29
2f	3	4-OCF_3	9.04±0.25	367±13	41
2g	3	3-OMe	7.71±0.38	344±16	45
2h	3	3,4-di-Me	1.05±0.23	207±15	197
BP 897			1.27±0.25	69±4.81	54

Fig 1. Chemical structure of ropinirole.

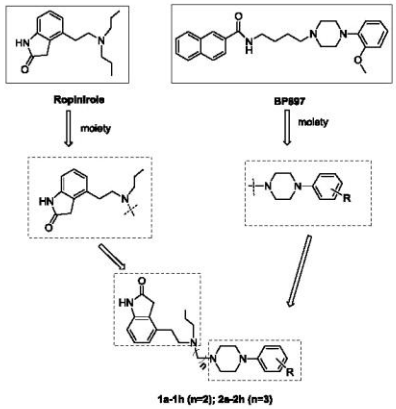
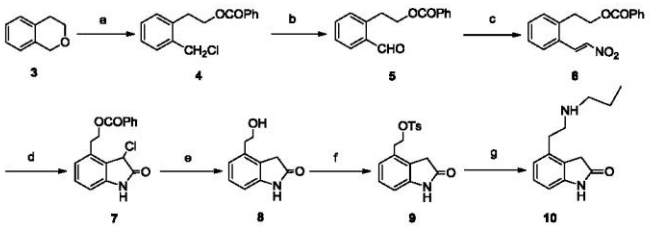
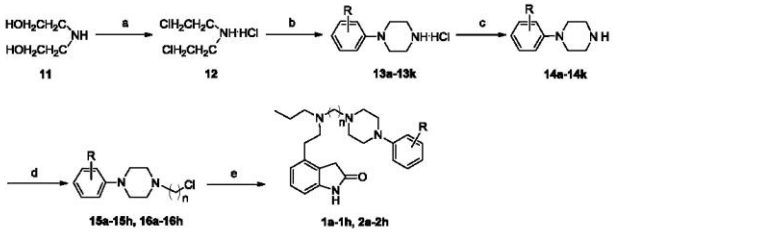


Fig. 2. A design for hybrid analogues.



Scheme 1. Synthetic route for the preparation of the compound **10**. Reagents and conditions: (a) $ZnCl_2$, PhCOCl, CH_2Cl_2, reflux, 1.5 h, 99%; (b) DMSO, $NaHCO_3$, 110-120 °C, 1.5 h, 67%; (c) $MeNO_2$, NH_4OAc, AcOH, reflux, 8-10 h, 98%; (d) $FeCl_3$, AcCl, CH_2Cl_2, -5-0 °C, 2 h, 59%; (e) $N_2H_4H_2O$, MeOH, 10%Pd/C, reflux, 1 h, NaOH, H_2O, reflux, 1 h, 71%; (f) TsCl, Py, CH_2Cl_2, 5-10 °C, 2 h, 86%; (g) n-$PrNH_2$, EtOH, reflux, 1.5 h, 60%.



Scheme 2. Synthetic route for the preparation of the compounds **1a-1h** and **2a-2h**. Reagents and conditions: (a) $SOCl_2$, $CHCl_3$, rt, 3 h, reflux, 0.5 h, 89%; (b) substituted phenylamine, n-BuOH, K_2CO_3, reflux, 48 h, 56-72%; (c) NaOH, rt. 0.5 h, 92-96%; (d) 1-Bromo-2-chloroethane or 1-Bromo-3-chloropropane, K_2CO_3, acetone, 35 °C, 3 h, reflux, 10 h, 56-74%; (e) **10**, K_2CO_3, KI, CH_3CN, 45 °C, 8 h, 59-72%.