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Design and Synthesis of Dual 5-HT_{1A} and 5-HT_7 Receptor Ligands

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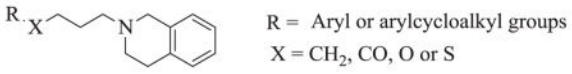
Abstract

5-HT_{1A} and 5-HT_7 receptors have been at the center of discussions recently due in part to their major role in the etiology of major central nervous system diseases such as depression, sleep disorders, and schizophrenia. As part of our search to identify dual targeting ligands for these receptors, we have carried out a systematic modification of a selective $5HT_7$ receptor ligand culminating in the identification of several dual 5-HT_{1A} and 5-HT_7 receptor ligands. Compound **16**, a butyrophenone derivative of tetrahydroisoquinoline (THIQ), was identified as the most potent agent with low nanomolar binding affinities to both receptors. Interestingly, compound **16** also displayed moderate affinity to other clinically relevant dopamine receptors. Thus, it is anticipated that compound **16** may serve as a lead for further exploitation in our quest to identify new ligands with the potential to treat diseases of CNS origin.

Graphical Abstract



Keywords

Dual receptor ligands; multi-receptor targeting; CNS ligands; serotonin receptors; 5-HT_{1A} receptor and 5-HT_7 receptor ligands

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1. Introduction

It is now well established that targeting a single receptor is often inadequate in treating several diseases including diseases originating from the central nervous system. Thus, drugs such as aripiprazole, lurasidone and others derive their superior therapeutic outcomes from their ability to target multiple receptors in the CNS.[1–4]

The neurotransmitters, dopamine (DA) and serotonin (5-HT), are of particular interest because of their involvement in several neurological and psychiatric diseases such as schizophrenia, major depressive disorder (MDD), depression, attention deficit and hyperactivity disorder (ADHD), and addiction.[5–8] Recent research has indicated that the serotonin receptors (5-HTRs) in particular play significant roles in CNS physiological activities, and dysregulation of these receptors often results in several diseases. For example, the serotonin 1A receptor (5-HT_{1A}R) which is found predominantly in the dorsal raphe nuclei, hippocampus, and cortico-limbic regions, controls memory, cognition, and mood, functions which are impaired in anxiety, depression and schizophrenia.[9] Several lines of evidence now support the anti-negative symptoms and cognitive enhancement effects of ligands which activate 5-HT_{1A}R in schizophrenia.[6,10] Similarly, the serotonin 7 receptor (5-HT_7R), the most recent addition to the 5-HT receptor subtypes,[11–13] has been shown to mediate key functions such as sleep, mood, learning, memory, and cognition.[14–17] Interestingly, the 5-HT_7R forms heterodimers with the 5-HT_{1A}R in most brain regions, producing a cross talk which has been implicated in depression and other CNS disorders. Both receptors share over 40% sequence homology which may account for the cross reactivity seen among ligands which interact at both receptors.[18–20] It stands to reason therefore that agents with dual binding affinities to both receptors may be beneficial as treatment options for depression and other cognitive impairment disorders.

Our lab has been engaged in multiple receptor-targeting in order to extend the scope and utility of CNS agents. The purpose of the current research was to investigate the 1,2,3,4-tetrahydroisoquinoline (THIQ) moiety as a pharmacophore for the dual targeting of the 5-HT_{1A} and 5-HT_7 receptors so as to probe their potential utility in CNS diseases. To that end, we have designed and synthesized several arylalkyl substituted THIQs in order to identify new lead agents for further development.

2. Chemistry

In general, the compounds evaluated in this manuscript were obtained by refluxing or carrying out a microwave-assisted reaction of THIQ with various alkylating agents in dimethoxyethane (DME) or acetonitrile (CH_3CN) in the presence of K_2CO_3 as a base and a catalytic amount of KI. The target compounds were prepared by first N-alkylating potassium phthalimide with 1,4-dibromobutane to produce alkyl bromide **1b** which was separately reacted with THIQ, decahydroisoquinoline, and isoindoline to afford compounds **1**, **2** and **3** respectively (Scheme 1). A three-step reaction procedure was used to synthesize compound **4** (Scheme 2). Commercially available 4-(1H-indol-3-yl)butanoic acid, **2a** was reduced using LAH in dry THF to produce the corresponding alcohol which was subsequently converted to the iodo intermediate **2b** via an Appel reaction.[21,22] The obtained alkylating agent was then

coupled to THIQ to afford **4**. Deoxygenation of the previously reported indanone **3a**[23] under Clemmenson reduction conditions yielded **3b** which was then used to alkylate THIQ and afforded compound **5** as shown in Scheme 3. Chloride **4a,** mesylate **4b,** and tosylate **4c** were synthesized by literature procedures and subsequently used to alkylate THIQ to yield compounds **6**, **7**, and **8** respectively (Scheme 4) using the general alkylating conditions described in Scheme 1. Sulfoxide **9** was prepared by oxidation of **8** using the previously reported meta peroxybenzoic acid (*m*-CPBA) mediated oxidative conditions depicted in Scheme 5.[23]

Alkylating agents **6a**, **6b**, and **6e** were obtained commercially and were used to synthesize compounds **10**, **11**, and **16** respectively whereas **6c** and **6d** were prepared following Friedel-Crafts acylation reaction as reported[24] and subsequently used to obtain compounds **12a** and **14** respectively (Scheme 6). Finally, using potassium ferrocyanide ($K_4[Fe(CN)_6].3H_2O$) as the cyanide source, palladium catalyzed cyanation[25] of **12a** afforded compound **12** (Scheme 6). Base-catalyzed hydrolysis of the cyano group[26] in **12** afforded the corresponding amide **13** (Scheme 6). Demethylation of **14** with hydrobromic acid afforded compound **15** (Scheme 6).

3. Results and Discussion

The THIQ moiety has been the subject of several recent publications.[27–33] In a campaign to synthesize new drugs with selective affinity for the 5-HT_7 receptor, we synthesized 2-(4-(3,4-dihydroisoquinolin-2(1H)-yl)butyl)isoindoline-1,3-dione (**1**) and evaluated its affinity for key 5-HTR subtypes including the 5-HT_7R. As shown in Table 1, compound **1** demonstrated a low nanomolar potency at the 5-HT_7R and little affinity to the other key 5-HTR subtypes including 5-HT_{1A}R where it is over 50-fold less potent. Replacement of the THIQ ring in **1** with decahydroisoquinoline to yield **2** resulted in close to a 40-fold decrease in binding affinity to the 5-HT_7R, with binding affinity at 5-HT_{1A}R and 5-HT_{2A}R remaining essentially unchanged. Compound **2** however, displays selectivity towards the 5-HT_{2C}R (*Ki* = 37 nM). Further modification of **1** by replacing the tetrahydroisoquinoline ring with isoindoline ring to obtain **3** resulted in significant loss of activity at all receptor subtypes except the 5-HT_{2C}R where there was moderate affinity (*Ki* = 151 nM). Based on the results of the binding affinities for compounds **1 – 3**, it is clear that the THIQ ring serves as an important pharmacophore for binding affinity to the 5-HT_7R in these compounds. This observation informed the next design strategy to keep the THIQ group and to focus on modifications elsewhere in the molecule, including that of the isoindoline-1,3-dione moiety.

Replacement of the isoindoline-1,3-dione moiety in **3** with indole to obtain **4** restored nanomolar binding affinity to the 5-HT_7R, while replacement with 5-fluoro-2,3-dihydro-1H-indene to form **5**, led to significant binding affinity to both 5-HT_{1A}R and 5-HT_7R (*Ki* = 193 and 86 nM respectively). Excision of a methylene group from the indene moiety in compound **5** led to ring-opened **6** with improved affinity for both 5-HT_{1A}R and 5-HT_7R. Replacement of the benzylic methylene group in **6** with oxygen **(7**) and sulfur (**8**) did not result in significant changes. However, oxidation of the sulfide to obtain the sulfoxide **9**, increased affinity for both 5-HT_{1A}R (*Ki* = 41 nM) and 5-HT_7R (*Ki* = 22.5 nM).

Next, the sulfoxide group in **9** was replaced by a carbonyl to form 4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-(4-fluorophenyl)butan-1-one (**10**) which resulted in a 3-fold increase in binding affinity at the $HT_{1A}R$ (*Ki* = 12 nM) but a decrease of 16-fold at the 5-HT_7R (*Ki* = 364 nM). Interestingly, affinity at the 5-$HT_{2A}R$ is found to have improved drastically to 14 nM. Similar low nanomolar binding affinities are observed for compounds **11** (the defluorinated analog) and **12** (replacement of the fluoro with the electron withdrawing and hydrophilic cyano substituent) at the 5-$HT_{2A}R$ while significant loss of affinities are noted at the 5-$HT_{1A}R$ and 5-HT_7R. However, changing the *p*-cyano substituent in **12** to the carboxamide **13,** the methoxy group **14,** or its hydroxy analog **15**, produced the desired dual 5-$HT_{1A}R$ and 5-HT_7R binding affinity ligands with low nanomolar affinity constants. Thus, it would appear that various substituents covering at least three quadrants of the Craig plot did not yield a clearly defined structure affinity relationship trend. Finally, we evaluated compound **16**, with the *p*-fluoro atom of compound **10** replaced by a chloro atom which yielded the most potent dual 5-$HT_{1A}R$ (*Ki* = 8.2 nM) and 5-HT_7R (*Ki* = 3.6 nM) binding affinity ligand in the series. Comparing compound **16** and Aripiprazole, both have high affinities at 5-$HT_{1A}R$ (5.6 vrs. 8.2 nM), and 5-HT_7R (3.6 vrs. 10.3 nM), but differ significantly at the other serotonin receptors evaluated, with compound **16** having little or no binding at 5-$HT_{2A}R$ and 5-$HT_{2C}R$ (*Ki* = 2976 nM) and moderate binding at 5-$HT_{2B}R$ (*Ki* = 232 nM), while Aripiprazole has high affinity for 5-$HT_{2A}R$ (*Ki* = 8.7 nM) and 5-$HT_{2B}R$ (Ki = 0.36 nM) and moderate affinity to 5-$HT_{2C}R$ (Ki = 76 nM).

The target compounds were also screened at additional CNS receptors with clinical significance including the D_2R, D_3R, D_4R, H_1R and SERT and the results reported in Table 2. Compounds **1** – **3** showed little if any affinities at the aforementioned receptors/transporter. Compound **4**, the indolealkyl substituted analog of **1**, produced moderate affinities for D_2R, D_4R and SERT while the dihydroindene analog **5** had moderate affinities for D_3R, D_4R and SERT. Opening the dihydroindene ring in **5** with excision of a methylene group (**6**), or replacing the benzylic carbon with oxygen, sulfur, or sulfoxide (**7**-**9**) resulted in significant loss of affinity for SERT with no clear SAR features at the other receptors in Table 2. Replacement of the sulfoxide with a carbonyl (**10**) produced significant increase in binding at the dopamine receptors, suggesting that perhaps the butyrophenone THIQ scaffold could constitute a useful hit for further development as ligands for multiple receptor targeting. However, probing the electron donating or withdrawing nature and/or the hydrophilic/hydrophobic nature of substituents at the *para* position of the phenyl ring (**10**-**16**) according to the Craig plot procedure[34] did not produce an increase in potency at the dopamine receptors and did not reveal any interesting SAR trend. Regarding their histamine binding affinities, only **10** and **11** have affinity constants below 100 nM suggesting that these compounds may have low propensity for interacting at the histamine H1 receptor and hence less sedative effect.

Of the sixteen compounds reported, three, compounds **13**, **14** and **16** (**13**: *Ki* = 13 nM, **14**: *Ki* = 38 nM, **16:** *Ki* = 17 nM respectively) show significant binding affinities to the D_3R. Given their concentration in limbic and cortical regions of the brain, D_3Rs have been hypothesized to be potential targets for the design of new antipsychotics with limited extrapyramidal side effects. However, there have been reports that selective D_3R blockade only resulted in

marginal antipsychotic effects. This has led to the suggestion and indeed demonstration that dual D_2/D_3 receptor blockade produce effective antipsychotic actions.[35–37]

The moderate binding affinities of these compounds for the D_2 receptors (**13**: Ki = 218 nM, **14**: Ki = 249 nM, **16** Ki = 126 nM), combined with their serotonin binding profiles make them potential drug leads for further exploitation. In particular, the preferential and more potent binding of **16** at D_3R (*Ki* = 17 nM) compared to D_2R (7 fold) suggest further evaluation for intrinsic activities and subsequent exploitation in the treatment of CNS conditions including the negative and cognitive symptoms of schizophrenia and bipolar mania.[38–40] Interestingly, the D_3R binding of compound **16** is similar to that of aripiprazole (*Ki* = 17 vrs. 9.7 nM), while the D_2R binding affinity is similar to that of clozapine[41] (*Ki* = 126 nM vrs. *pKi* = 6.87 or *Ki* = 130 nM). Strong binding to the D_3R may also be associated with procognitive effects, as reported.[42]

In conclusion, using compound **1** which showed significant selectivity (>50 fold) for 5-HT_7 receptor compared to the 5-$HT_{1A}R$ as our starting hit, and guided by results from our SAR studies, we were able to obtain very potent dual 5-HT_{1A} and 5-HT_7 receptor affinity ligands. In addition, compound **16** showed moderate binding affinity at D_2R, high affinity at D_3R, and a 7-fold selectivity for D_3R over D_2R, which portends a lead with great potential for further development in treating the negative and cognitive symptoms of schizophrenia, as well as bipolar mania. We opine that butyrophenone derivatives of THIQ such as **16** could serve as important leads to exploit for more potent CNS drugs with multi-receptor affinity features.

4. EXPERIMENTAL

Melting points were determined on a Gallenkamp (UK) apparatus and are uncorrected. All NMR spectra were obtained on a Varian 300 MHz Mercury Spectrometer and the free induction decay (FID) data were processed using Mestrelab's Mnova NMR software (version 8.1) to obtain the reported NMR data. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA, and are within 0.4% of theory unless otherwise noted. Flash chromatography was performed using CombiFlash® with Davisil grade 634 silica gel. Starting materials were obtained from Sigma–Aldrich and were used without further purification. All microwave assisted syntheses (MW) were carried out using a Biotage Initiator®.

4.1. Synthesis of 2-(4-Bromobutyl)isoindoline-1,3-dione, 1b

A mixture of potassium phthalimide **1a** (0.93 g, 5 mmol) and 1,4-dibromobutane (5.4 g, 25 mmol) was stirred in dry DMF (10 mL) at 100 °C for 12 h. The condenser was then set for distillation, and the excess of 1,4-dibromobutane and DMF was removed under reduced pressure. The crude product obtained was purified by column chromatography (silica gel, ethyl acetate/light petroleum 1:50) to afford intermediate **1b** as a colorless solid. ^1H NMR ($CDCl_3$): δ 7.87-7.84 (2H, m), 7.74-7.71 (2H, m), 3.73 (2H, t, *J* = 6.9 Hz), 3.45 (2H, t, *J* = 6.3 Hz), 1.90-1.88 (4H, m).

4.2. General alkylation procedure for compounds 1-3

A mixture of **1b** (1 equiv), an appropriate amine (1.2 equiv), KI (100 mg), and K_2CO_3 (10 equiv), in CH_3CN (15 mL) or DME was refluxed for 12–24 h. The reaction progress was monitored by TLC and at completion, the mixture was cooled to room temperature, solvent removed, the resulting residue loaded onto a cartridge and purified by flash chromatography using an EtOAc/hexane gradient up to 80% EtOAc) to give the pure desired products.

4.2.1. 2-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)butyl)isoindoline-1,3-dione, 1— Following the general alkylation procedure described in section 4.2 and using THIQ as the amine, compound **1** was obtained as the free base. Yield: 22%, mp: 68–69 °C. ^{1}H NMR (DMSO-d_6): δ 7.86-7.79 (4H, m), 7.07-6.98 (4H, m), 3.58 (2H, t, J = 6.9 Hz), 3.47 (2H, s), 2.75 (2H, t, J = 5.4 Hz), 2.58 (2H, t, J = 6.0 Hz), 2.43 (2H, t, J = 6.9 Hz), 1.68-1.48 (4H, m). Calcd for $C_{21}H_{22}N_2O_2 \cdot 0.2H_2O$; C 74.62, H 6.68, N 8.29; Found: C 74.55, H 6.55, N 8.25.

4.2.2. 2-(4-(Octahydroisoquinolin-2(1H)-yl)butyl)isoindoline-1,3-dione, 2—Using decahydroisoquinoline as the amine, compound **2** was prepared similarly to **1** above. Yield: 12%, mp: 64–65°C. ^{1}H NMR ($CDCl_3$): δ 7.84-7.82 (2H, dd, J = 3.0, 8.7 Hz), 7.70 (2H, dd, J = 3.0, 9.0 Hz), 3.70 (2H, t, J = 7.2 Hz), 2.91 (1H, d, J = 8.1 Hz), 2.75 (1H, d, J = 9.0 Hz), 2.31 (2H, s), 1.77 (1H, t, J = 7.2 Hz), 1.71-1.48 (1H, m), 1.26-1.19 (4H, m), 0.98-0.87 (2H, m). Calcd for $C_{21}H_{28}N_2O_2$; C 74.08, H 8.29, N 8.23; Found: C; 73.82, H; 8.09, N; 8.19.

4.2.3. 2-(4-(Isoindolin-2-yl)butyl)isoindoline-1,3-dione, 3—Following the general alkylation procedure in section 4.2 and using isoindoline as the amine, compound **3** was obtained as the free base. Yield: 21%, mp: 95–96°C. ^{1}H NMR (DMSO-d_6): δ 7.88-7.78 (m, 4H), 7.20-7.12 (m, 4H), 3.76 (s, 4H), 3.59 (t, 2H, J = 5.7 Hz), 2.63 (t, 2H, J = 7.2 Hz), 1.70-1.44 (m, 4H). Calcd for $C_{20}H_{20}N_2O_2 \cdot 0.11\ H_2O$; C 72.78, H 6.11, N 8.49; Found: C 72.75, H 6.16, N 8.12.

4.3. Synthesis of 3-(4-iodobutyl)-1H-indole, 2b

To a solution of indole-3-butyric acid **2a** (2 g, 9.8 mmol) dissolved in dry THF (30 mL) and cooled to 0 °C was added portionwise $LiAlH_4$ (2.2 g, 59 mmol, 6 eq) in dry THF. The mixture was allowed to warm to room temperature (rt) with stirring for 18h. The reaction mixture was cooled to 0 °C and a saturated solution of Na_2SO_4 (20 mL) was added in a dropwise manner over the period of 30 min. The resulting white precipitate was filtered, the filtrate washed with EtOAc (2 × 100 mL), the pooled organic phase washed with water (50 mL) and saturated brine solution (50 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to obtain the crude product. The crude 3-(4-hydroxybutyl)-1H-indole was used for the next step without further purification.

The crude obtained was converted to compound **2b** following a procedure reported in literature.[21] Briefly, to a stirred solution of PPh_3 (4.46 g, 17.0 mmol) and imidazole (1.58 g, 17.0 mmol) in DCM (45 mL) at 0 °C, was added I_2 (4.32 g, 17.0 mmol) and the reaction mixture was stirred at this temperature for 30 min. Thereafter, a solution of crude 3-(4-hydroxybutyl)-1H-indole (2.30 g, 12.2 mmol) in DCM (5 mL) was added, the reaction mixture was allowed to warm to rt and stirred for 12 h. The crude product was directly

purified using silica gel on CombiFlash with gradient up to 40% EtOAc in hexanes to afford compound **2b** (2.40 g) as an oily liquid. Yield: 66%. ^{1}H NMR ($CDCl_3$): δ 7.91 (1H, s). 7.59 (1H, d, *J* = 8.1Hz), 7.35 (1H, d, *J* = 8.1 Hz), 7.22-/7.17 (1H, t, *J* = 6.9 Hz), 7.12 (1H, m), 6.97 (1H, d, *J* = 2.1 Hz), 3.22 (2H, t, *J* = 6.9 Hz), 2.84 (2H, t, *J* = 6.9 Hz), 1.96-1.76 (4H, m).

4.4. 2-(4-(1H-indol-3-yl)butyl)-1,2,3,4-tetrahydroisoquinoline, 4

Following the general alkylation procedure described above (section 4.2.) and using the obtained **2b** as the alkylating agent, compound **4** was obtained. Yield: 52%, mp: 139–140 °C. ^{1}H NMR ($CDCl_3$): δ 7.96 (1H, s), 7.62-7.60 (1H, d, *J* = 8.4 Hz), 7.35 (1H, d, *J* = 7.8 Hz), 7.21-7.15 (1H, m), 7.13-7.07 (4H, m), 7.01-6.98 (2H, m), 2.90 (2H, t, *J* = 5.7 Hz), 2.81 (2H, t, *J* = 6.9 Hz), 2.73 (2H, t, J = 6.0 Hz), 2.56 (2H, t, *J* = 7.2 Hz), 1.80-1.69 (6H, m,). Calcd for $C_{21}H_{24}N_2$; C 82.85, H 7.97, N 9.20; Found: C 82.65, H 7.97, N 8.97.

4.5. Synthesis of 2-(2-chloroethyl)-5-fluoro-2,3-dihydro-1H-indene, 3b

Amalgamated zinc was prepared by stirring a mixture of zinc (1.2 g), $HgCl_2$ (0.12 g) in 5 mL water with conc. HCl (0.1 mL) at room temperature. After stirring for 5 min, the mixture was decanted and followed by adding in order water (1 mL), conc HCl (1.75 mL), toluene (10 mL), and then 2-(2-Chloro-ethyl)-5-fluoro-indan-1-one **3a** (2 g, 9.43 mmol), synthesis of which was previously reported by us.[23] The mixture was refluxed with stirring for 12 h. The solid was filtered off, aqueous layer was diluted with EtOAc (200 mL), washed with water, and then saturated $NaHCO_3$ (50 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* followed by column chromatography on silica gel to afford **3b**, 1.68 g, Yield 90%. ^{1}H NMR ($CDCl_3$): δ 7.09 (1H, dd, *J* = 4.8, 7.8 Hz), 6.85 (2H, m), 3.60 (2H, t, *J* = 7.2 Hz), 3.04 (2H, m), 2.70 (1H, m), 2.56 (2H, m), 1.98 (2H, m).

4.6. 2-(2-(5-Fluoro-2,3-dihydro-1H-inden-2-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride, 5

Alkylating agent **3b** was reacted with THIQ following the general alkylation procedure described in section 4.2 to obtain compound **5** as its HCl salt. Yield: 42%, mp: 211–212 °C. ^{1}H NMR (DMSO-d_6): 10.85 (1H, s), 7.19 (5H, m), 7.02 (1H, d, *J* = 9.0 Hz), 6.92 (1H, t, *J* = 9.0 Hz), 4.51 (1H, m), 4.27 (1H, m), 3.67 (1H, m), 3.40 (1H, m), 3.23 (4H, m), 3.02 (4H, m), 2.60 (1H, m), 1.98 (2H, m). Calcd for $C_{20}H_{23}ClFN$: C 72.00, H 6.95, N 4.20; Found: C 71.89, H 6.97, N 4.28.

4.7. General alkylation procedure for compounds 6-8, 10-12a, 14, and 16

A mixture of alkylating agent (1 equiv), THIQ (1.1 equiv) K_2CO_3 (1.1 equiv), and KI (catalytic) in DME (10 mL) was placed in a 20 mL microwave vial with a stirrer and tightly sealed. The mixture was subjected to microwave heating at 120°C for 60 mins. The mixture was directly purified on silica by flash chromatography (gradient up to 70% EtOAc in hexanes) to afford compound **7**. The free base where necessary, was converted to the HCl salt and crystallized out of a MeOH-Et_2O solvent mixture.

4.7.1. 2-(4-(4-Fluorophenyl)butyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride, 6—

The synthesis of 1-(4-chlorobutyl)-4-fluorobenzene **4a** was previously reported by us[23]

and following the procedure described in section 4.7., **4a** was reacted with THIQ to afford compound **6** as its HCl salt form. Yield: 75%, mp: 205–206 °C. ^{1}H NMR (DMSO-d_6): δ 7.30-7.06 (6H, m); 6.99-6.92 (2H, m); 4.60-4.55 (1H, m); 4.01-3.94 (1H, m), 3.65-3.59 (1H, m), 3.51-3.42 (1H, m), 3.27-3.17 (1H, m), 3.07-2.93 (4H, m), 2.66 (2H, t, *J* = 7.5); 2.08-1.96 (2H, m), 1.75-1.63 (2H, m). Calcd for $C_{19}H_{23}ClFN{\cdot}0.2H_2O$: C 70.55, H 7.17, N 4.33; Found: C 70.73, H 7.36, N 4.45.

4.7.2. 2-(3-(4-Fluorophenoxy)propyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride, 7—Following the general alkylation procedure described above (section 4.7.), previously reported alkylating agent 3-(4-fluorophenoxy)propyl methanesulfonate **4b**[23] was reacted with THIQ to give compound **7** as a white crystalline HCl salt. Yield: 30%, mp: 196–197 °C. ^{1}H NMR (DMSO-d_6): δ 11.23 (1H, brs), 7.25 (4H, m), 7.15 (2H, m), 6.95 (2H, m), 4,54 (1H, d, *J* = 15.6 Hz), 4.28 (1H, dd, *J* = 8.4, 15.6 Hz), 4.06 (2H, t, *J* = 6.0 Hz), 3.69 (1H, m), 3.24 (2H, m), 3.34 (2H, m), 3.00 (1H, m), 2.28 (2H, m). Calcd for $C_{18}H_{21}ClFNO$: C 67.18, H 6.58, N 4.35; Found: C 67.10, H 6.55, N 4.38.

4.7.3. 3-((4-Fluorophenyl)thio)propyl 4-methylbenzenesulfonate, 4c—To a solution of 3-(4-fluorophenylthio)propan-1-ol[23] (1 g, 5.4 mmol), Et_3N (2 mL) in CH_2Cl_2 (10 mL) was added at room temperature TsCl (1.54 g, 8.1 mmol). The mixture was stirred at room temperature for 12 h, followed by direct purification using column chromatography on silica gel to provide **4c**, 1.72 g, Yield 94%. ^{1}H NMR ($CDCl_3$): δ 7.77 (2H, *J* = 8.4 Hz), 7.34 (2H, *J* = 8.4 Hz), 7.30 (2H, dd, *J* = 5.4, 8.4 Hz), 6.97 (2H, *J* = 8.7 Hz), 4.13 (2H, t, *J* = 8.0 Hz), 2.86 (2H, *J* = 7.2 Hz), 1.89 (2H, m).

4.7.4. 2-(3-((4-Fluorophenyl)thio)propyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride, 8—Reacting alkylating agent **4c** and THIQ under the general alkylation conditions (section 4.7.) produced compound **8** as an HCl salt. Yield: 29%, mp: 172–173 °C. ^{1}H NMR (DMSO-d_6): δ 11.31 (1H, m), 7.44 (2H, m), 7.22 (6H, m), 4.46 (1H, d, *J* = 15.3 Hz), 4.22 (1H, dd, *J* = 7.5, 15.3 Hz), 3.61 (1H, m), 3.27 (4H, m), 3.04 (2H, t, *J* = 6.0 Hz), 2.95 (1H, m), 2.08 (2H, m). Calcd for $C_{18}H_{21}ClFNS$: C 63.98, H 6.26, N 4.15; Found: C 63.77, H 6.27, N 4.18.

4.7.5. 2-(3-((4-Fluorophenyl)sulfinyl)propyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride, 9—To a solution of **8** (0.2g, 0.59 mmol) in MeOH (5 mL) was added with stirring *m*-CPBA (0.2 g) at 0 °C. After stirring for 1 h. at room temperature, the mixture was diluted with Et_2O (10 mL). A solid precipitate was collected by filtration. Further crystallization from MeOH-Et_2O gave 0.15g of **9** as an HCl salt. 73% Yield: 73%, mp: 177–178 °C. ^{1}H NMR (DMSO-d_6): δ 10.53 (1H, brs), 7.74 (2H, dd, *J* = 4.8, 8.4 Hz), 7.45 (2H, t, *J* = 8.7 Hz), 7.22 (4H, m), 4.50 (1H, d, *J* = 15.3 Hz), 4.25 (1H, dd, *J* = 7.5, 15.3 Hz), 3.63 (1H, m), 3.27 (3H, m), 3.14 (2H, m), 3.98 (1H, m), 2.88 (1H, m), 2.15 (1H, m), 2.00 (1H, m). Calcd for $C_{18}H_{21}ClFNOS{\cdot}0.3H_2O$: C 60.17, H 5.89, N 3.90; Found: C 60.09, H 5.82, H 3.94.

4.7.6. 4-(3,4-Dihydroisoquinolin-2(1H)-yl)-1-(4-fluorophenyl)butan-1-one, 10—Using 4-chloro-1-(4-fluorophenyl)butan-1-one **6a** as the alkylating agent, compound **10** was

obtained as a white solid (free base) following the general alkylation method (section 4.7.). Yield: 38%, mp: 104–105 °C. ^{1}H NMR ($CDCl_3$): 7.96 (2H, dd, *J* = 5.4, 9.0 Hz), 6.98–7.11 (6H, m), 3.61 (2H, m), 3.03 (2H, t, *J* = 7.2 Hz), 2.86 (2H, t, *J* = 6.0 Hz), 2.72 (2H, t, *J* = 6.0 Hz), 2.58 (2H, t, *J* = 6.9 Hz), 2.03 (2H, q, *J* = 6.9 Hz). Calcd for $C_{19}H_{20}FNO$: C 76.74, H 6.78, N 4.71; Found: C 76.51, H 6.83, N 4.69.

4.7.7. 4-(3,4-Dihydroisoquinolin-2(1H)-yl)-1-phenylbutan-1-one, 11—Following the general alkylation procedure (section 4.7.), 4-chloro-1-phenylbutan-1-one **6b** was reacted with THIQ to produce compound **11** as its HCl salt to afford a white crystalline solid (1.2g). Yield: 69%, mp: 185–187 °C. ^{1}H NMR (DMSO-d_6) δ 11.39 (s, 1H), 7.98 (2H, d, *J* = 7.6 Hz), 7.63 (1H, d, *J* = 7.3 Hz), 7.53 (2H, dd, *J* = 7.5 Hz), 7.28 - 7.17 (4H, m), 4.53 (1H, dd, *J* = 3.1, 15.4 Hz), 4.27 (1H, dd, *J* = 7.7, 15.6 Hz), 3.68 (1H, s), 3.35 - 3.17 (6H, m), 2.98 (1H, dd, *J* = 3.3, 12.6 Hz), 2.24 - 2.07 (2H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ 199.18, 136.82, 133.77, 131.96, 129.19, 129.01, 128.95, 128.36, 127.95, 127.09, 127.00, 54.97, 51.91, 48.93, 35.68, 25.19, 18.40. Calcd for $C_{19}H_{22}ClNO$: C 72.25, H 7.02, N 4.43; Found: C 71.97, H 7.01, N 4.30.

4.7.8. 1-(4-Bromophenyl)-4-(3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one hydrochloride, 12a—Following the procedure in section 4.7., the alkylating agent 1-(4-bromophenyl)-4-chlorobutan-1-one **6c** was reacted with THIQ to obtain **12a** as its HCl salt. Yield: 54%, mp: 211–212°C. ^{1}H NMR (DMSO-d_6) δ 11.44 (1H, s), 7.90 (2H, dd, *J* = 8.5, 1.9 Hz), 7.73 (2H, dd, *J* = 8.5, 1.9 Hz), 7.29 - 7.16 (4H, m), 4.51 (1H, d, *J* = 15.5 Hz), 4.34-4.19 (1H, m), 3.69 - 3.62 (1H, m), 3.36 - 3.19 (6H, m), 2.97 (1H, d, *J* = 13.1 Hz), 2.13 (2H, q, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 198.43, 135.84, 132.23, 131.96, 130.38, 128.99, 128.93, 127.94, 127.81, 127.07, 126.99, 54.90, 51.90, 48.92, 35.74, 25.17, 18.32. Calcd for $C_{19}H_{21}BrClNO$: C 57.81, H 5.36, N 3.55; Found: C 57.67, H 5.29, N 3.65.

4.8. 4-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)butanoyl)benzonitrile, 12

To a 25 mL flask equipped with a stirrer was added **12a** (0.79 g, 2.6 mmol) in its free base form, dimethylacetamide (DMAC) (15 mL), $K_4[Fe(CN)_6].3H_2O$ (0.93 g, 2.2 mmol), Na_2CO_3 (0.23 g, 2.2 mmol), KI (73.0 mg, 20 mol%), and $Pd(OAc)_2$ (0.4 mol%). The flask was evacuated and filled with N_2 and heated to 120 °C for 12 hours. Reaction conversion was monitored by TLC. Upon completion, the reaction mixture was cooled to rt, 5% NH_4OH (20 mL) was added, extracted with 20 mL x 3 of EtOAc, the pooled organic layers was washed with brine (20 mL), dried over Na_2SO_4 and the filtrate was concentrated *in-vacuo*. The crude was purified on silica by flash chromatography (Hexanes: EtOAc gradient up to 80% EtOAc) to afford **12** which was converted to the HCl salt (0.508 g) as white crystals. Yield: 68%, mp: 199–200 °C. ^{1}H NMR (DMSO-d_6) δ 11.11 (1H, s), 8.12 (2H, dd, *J* = 1.8, 8.5 Hz), 8.03 (2H, dd, *J* = 2.1, 8.5 Hz), 7.31-7.16 (4H, m,), 4.55 (1H, dd, *J* = 3.2, 14.7 Hz), 4.28 (1H, dd, *J* = 7.7, 15.5 Hz), 3.70 (1H, d, *J* = 9.7 Hz), 3.36 - 3.21 (6H, m), 3.02 (1H, d, *J* = 3.6 Hz), 2.15 (2H, q, *J* = 6.9, 7.9 Hz).^{13}C NMR (75MHz, DMSO-d_6) δ 198.70, 140.17, 134.68, 134.28, 132.29, 128.58, 128.38,126.52, 126.13, 125.56, 118.10, 115.77, 57.15, 55.93, 50.81, 36.51, 28.96, 22.03. Calcd for $C_{20}H_{21}ClN_2O$: C 70.48; H 6.21; N 8.22. Found: C 70.30, H 6.36, N 8.15.

4.9. 4-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)butanoyl)benzamide, 13

A mixture of **12** (0.3 g, 1 mmol) and KOH (0.22 g, 4 mmol) in t-BuOH (10 mL) was refluxed for 12 h. The reaction was allowed to cool to room temperature and extracted with EtOAc (15 mLx2). The organic layers were pooled and washed with brine (20 mL), dried over Na_2SO_4, filtered, and the filtrate reduced *in-vacuo*. The crude was purified by flash chromatography (Hexanes: EtOAc gradient up to 80% EtOAc) to obtain **13** (0.40 g) as white crystals. Yield: 46%, mp: 177–178°C. ^{1}H NMR (DMSO-d_6) δ 8.11 (1H, s), 7.97 (2H, dd, *J* = 2.5, 8.8 Hz), 7.92 (2H, dd, J = 2.5, 8.8 Hz), 7.54 (1H, s), 7.10 - 6.95 (4H, m), 3.48 (2H, s), 3.06 (2H, t, *J* = 7.0 Hz), 2.71 (2H, t, *J* = 5.8 Hz), 2.59 (2H, t, *J* = 5.8 Hz), 2.48 (2H, t, *J* = 7.1 Hz), 1.86 (2H, q, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 200.07, 167.50, 139.17, 138.25, 135.30, 134.61, 128.75, 128.17, 128.15, 126.80, 126.28, 125.80, 57.32, 55.86, 50.85, 36.46, 29.06, 21.79. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.59; H, 6.70; N, 8.58.

4.10. 4-(3,4-Dihydroisoquinolin-2(1H)-yl)-1-(4-methoxyphenyl)butan-1-one hydrochloride, 14

Following the alkylation procedure described in section 4.7. above and using 4-chloro-1-(4-methoxyphenyl)butan-1-one **6d** as the alkylating agent, compound **14** was obtained as the HCl salt. Yield: 60%, mp: 194–195°C. ^{1}H NMR (DMSO-d_6) δ 11.57 (1H, s), 7.97 (2H, dd, *J* = 2.1, 8.8 Hz), 7.31 - 7.19 (4H, m), 7.05 (2H, dd, *J* = 2.0, 8.7 Hz), 4.53 (1H, d, *J* = 15.5 Hz), 4.29 (1H, d, *J* = 11.1 Hz), 3.84 (3H, s), 3.67 (1H, s), 3.35 - 3.11 (6H, m), 2.99 (1H, d, *J* = 12.7 Hz), 2.16 (2H, q, *J* = 7.9 Hz,).^{13}CNMR (75 MHz, DMSO-d_6) δ 197.55, 163.63, 132.01, 130.69, 129.83, 129.03, 128.94, 127.95, 127.10, 127.00,114.35, 56.04, 55.06, 51.89, 48.89, 35.32, 25.19, 18.56. Calcd for $C_{20}H_{24}ClNO_2$: C 69.45, H 6.99, N 4.05. Found: C 69.28; H 6.87, N 4.09.

4.11. 4-(3,4-Dihydroisoquinolin-2(1H)-yl)-1-(4-hydroxyphenyl)butan-1-one hydrochloride, 15

To a dry microwave vial equipped with a stirrer and charged with NaI (0.17 g, 1.10 mmol) in HBr solution (48% aq., 10 mL) was added compound **14** in its free base form (0.31 g, 1.0 mmol). The mixture was subjected to microwave heating at 110 °C for 30 mins. The reaction vial was allowed to cool to room temperature (rt) and the mixture directly purified using flash column chromatography (gradient elution up to 80% EtOAc in hexane). The product obtained was converted to its HCl salt to obtain compound **15** as a white flaky solid (0.21g). Yield: 63%, mp: 218–219°C. ^{1}H NMR (DMSO-d_6) δ 11.13 (1H, s), 10.51 (1H, s), 7.84 (2H, d, *J* = 8.0 Hz), 7.33 - 7.15 (4H, m), 6.87 (2H, d, *J* = 7.9 Hz), 4.48 (1H, s), 4.28 (1H, s), 3.66 (1H, s), 3.35 - 2.93 (7H, m), 2.11 (2H, t, *J* = 7.8 Hz).^{13}C NMR (75 MHz, DMSO-d_6) δ 197.24, 162.69, 131.95, 130.85, 128.94, 128.40, 127.98, 127.09, 127.01, 115.69, 55.20, 52.14, 49.06, 35.00, 25.28, 18.74. Calcd. for $C_{19}H_{22}ClNO_2 \cdot 0.75H_2O$; C 66.08, H 6.86, N 4.06; Found: C 66.17, H 6.49, N 4.03.

4.12. 1-(4-Chlorophenyl)-4-(3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one hydrochloride, 16

THIQ was alkylated with 4-chloro-1-(4-chlorophenyl)butan-1-one **6e** and the product converted to its HCl salt to afford compound **16** as its HCl salt. Yield: 61%, mp: 209–210 °C. ^{1}H NMR (DMSO-d_6): δ 11.00 (brs, 1H), 7.97 (2H, d, *J* = 9.0 Hz), 7.62 (2H, d, *J* = 9.0 Hz), 7.27-7.18 (4H, m), 5.4 (1H, d, *J* = 14.4 Hz), 4.31-4.23 (1H, m), 3.74-3.64 (1H, m),

3.50-3.38 (2H, m), 3.36-3.25 (4H, m), 3.08-2.90 (1H, m), 2.17-2.10 (2H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ 198.25, 138.62, 135.55, 131.96, 130.29, 129.29, 128.97, 128.94, 127.97, 127.08, 127.08, 127.01, 54.93, 51.94, 48.95, 35.75, 25.17, 18.34. Calcd. $C_{19}H_{21}Cl_2NO$; C 65.15, H 6.04, N 4.00; Found: C 65.03, H 6.16, N 3.99.

Receptor Binding studies

Binding affinities reported in Tables 1 and 2 were conducted by the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP) unless otherwise stated. Details of the methods and radioligands used for the binding assays were previously reported.[3]

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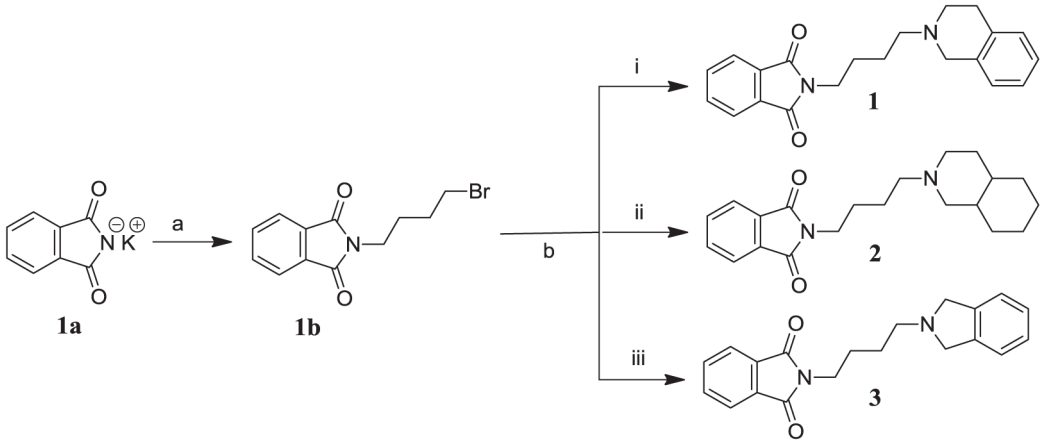
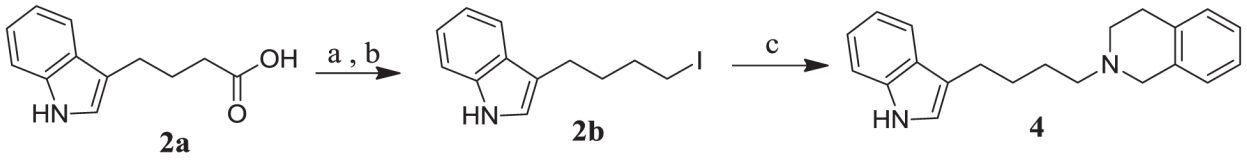


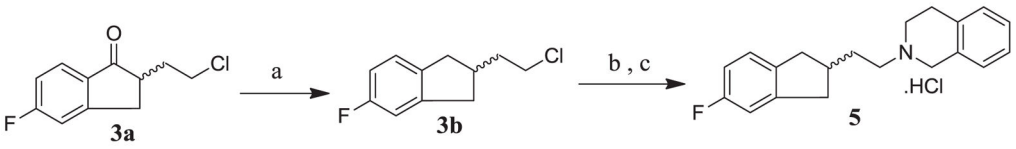
Scheme 1.

Synthesis of isoindoline-1,3-dione analogs. Reagents and conditions: a) 1,4-dibromobutane, DMF, 100 °C; b) K_2CO_3/KI, CH_3CN, reflux, 12–24 h. I = THIQ; ii = decahydroisoquinoline; iii = isoindoline.



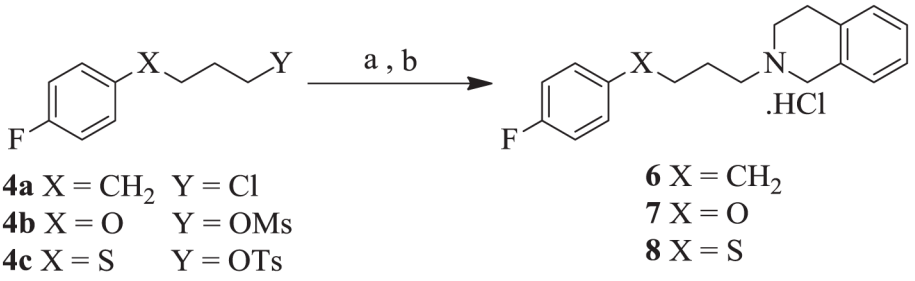
Scheme 2.

Synthesis of 3-substituted-1H-indole analog. Reagents and condition: a) $LiAlH_4$ in dry THF, rt,12 h; b) I_2/PPh_3, imidazole; c) THIQ, K_2CO_3/KI, DME, reflux,12 h.



Scheme 3.

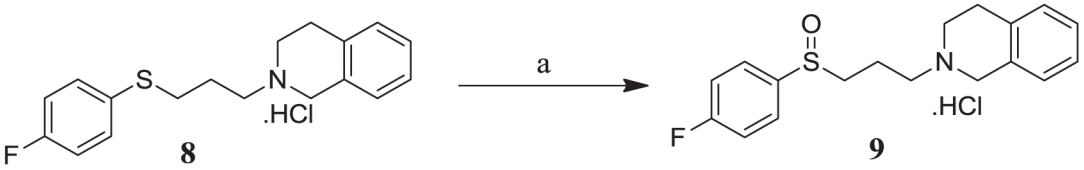
Synthesis of 5-fluoro-2,3-dihydro-1H-indene analog. Reagents and conditions: a) Zn Amalgam, Conc. HCl, toluene, reflux; b) THIQ, K_2CO_3/KI, DME, reflux, 12 h; c) ethereal HCl.



4a X = CH_2 Y = Cl
4b X = O Y = OMs
4c X = S Y = OTs

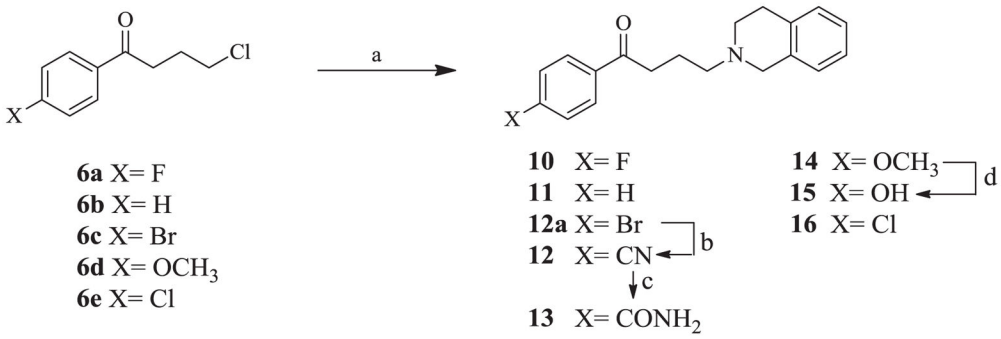
6 X = CH_2
7 X = O
8 X = S

Scheme 4.
Synthesis of 4-fluorobutyrophenone analogs. Reagents and conditions: a) THIQ, K_2CO_3/KI, DME, MW; b) ethereal HCl.



Scheme 5.

Synthesis of sulfoxide analog. Reagents and conditions: a) m-CPBA, MeOH, 0 °C to rt



Scheme 6.

Synthesis of 4-subtituted-butyrophenone analogs. Reagents and conditions: a. THIQ, K_2CO_3/KI, DME, 120 °C, MW; (b) $K_4[Fe(CN)_6].3H_2O$, $Pd(OAc)_2$, KI, Na_2CO_3, N_2, DMA, 120 °C, 12 h; (c) KOH, *t*-butyl alcohol, reflux, 12 h; d) aq. HBr 48%, NaI, 110°C, MW.

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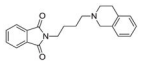
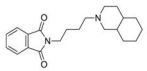
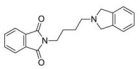
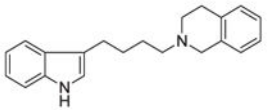
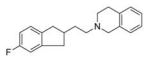
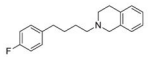
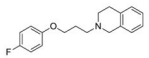
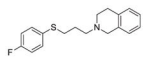
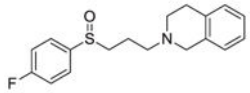
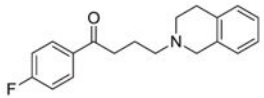
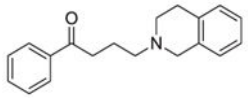
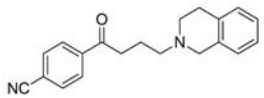
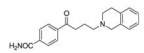
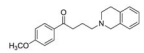
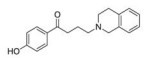
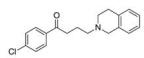
Table 1

Binding affinity of analogs at selected serotonin receptors

Compound	Structure	*Ki nM (p*Ki*) 5-HT$_{1A}$	5-HT$_{2A}$	5-HT$_{7}$	5-HT$_{2B}$	5-HT$_{2C}$
1		499 (6.3 ± 0.05)	MTA	8.6 (8.07 ± 0.05)	MTA	MTA
2		533 (6.27 ± 0.07)	>10,000	330 (6.48 ± 0.07)	400 (6.4 ± 0.08)	37 (7.43 ± 0.07)
3		MTA	MTA	MTA	MTA	151 (6.82 ± 0.07)
4		1689 (5.77 ± 0.06)	926 (6.03 ± 0.08)	52 (7.29 ± 0.07)	MTA	MTA
5		193 (6.72 ± 0.04)	522.5	86.0	1247 (5.9±0.09)	MTA
6		141 (6.85 ± 0.06)	726±117	27 (7.57 ± 0.08)	1713 (5.77 ± 0.08)	4440 (5.4 ± 0.1)
7		244 (6.61 ± 0.05)	322 ± 61.9	100 (7.00 ± 0.06)	561 (6.25 ±0.09)	MTA
8		217 (6.66±0.06)	317 (6.43±0.07)	49 (7.31±0.05)	204 (6.69± 0.07)	2623 (5.58 ± 0.09)

Compound	Structure	*Ki nM (p*Ki*) 5-HT$_{1A}$	5-HT$_{2A}$	5-HT$_{7}$	5-HT$_{2B}$	5-HT$_{2C}$
9		41 (7.39 ± 0.05)	1779 (5.75 ± 0.09)	22.5 (7.64 ± 0.07)	1166 (5.93 ± 0.08)	MTA
10*		12 ± 1.0	14 ± 1.0	364 ± 12	614 ± 36	>10,000
11		710 (6.15 ± 0.08)	3.9 (8.41 ± 0.05)	358 (6.45 ± 0.05)	273 (6.56 ± 0.06)	603 (6.22 ± 0.05)
12		295 (6.53 ± 0.06)	23 (7.64 ± 0.05)	755 (6.12 ± 0.06)	152 (6.82 ± 0.08)	443 (6.12 ± 0.06)
13		38 (7.42 ± 0.07)	404 (6.39 ± 0.04)	12 (7.91 ± 0.08)	587 (6.23 ± 0,07)	1892 (5.72 ± 0.05)
14		23 (7.54 ± 0.07)	2993 (5.67 ± 0.05)	17 (7.77 ± 0.08)	723 (6.14 ± 0.05)	1404 (5.85 ± 0.07)
15		33.50 (7.46 ± 0.07)	851 (6.14 ± 0.05)	10 (7.99 ± 0.08)	358 (6.45 ± 0.05)	MTA
16		8.2 (8.09 ± 0.07)	MTA	3.6 (8.45 ± 0.07)	232 (6.63 ± 0.07)	2976 (5.53 ± 0.06)
	Aripiprazole**	5.6 ± 0.8	8.7 ± 2.0	10.3 ± 3.7	0.36 ± 0.11	76 ± 8.0

MTA = Missed 50% of threshold inhibition.

*Ki values without the associated SEM, are within 20% of the mean value.

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** Binding affinity data from reference 3.

Table 2

Binding affinity of analogs at dopamine subtype receptors, histamine H1 receptor, and SERT

	Ki nM (p*Ki*)				
Compound	**D_2**	**D_3**	**D_4**	**H1**	**SERT**
1	MTA	491 (6.3 ± 0.10)	240 (6.62 ± 0.08)	MTA	MTA
2	>10,000	630 (6.2±010)	>10,000 (<5.0)	3632 (5.44 ± 0.06)	>10,000 (<5.0)
3	MTA	MTA	1,361 (5.87 ± 0.09)	MTA	MTA
4	170 (6.8 ± 0.10)	469 (6.33 ± 0.09)	35 (7.46 ± 0.06)	836 (6.08 ± 0.08)	113.0
5 *	1150	162	123	NA	163.0
6	319 (6.5 ± 0.07)	6007 ± 1491 NA	160 (6.8±0.05)	738 (6.13±0.06)	4284
7	166 (6.78±0.05)	769±161 NA	83 (7.08±0.05)	382 (6.42±0.08)	MTA
8	123 (6.91±0.04)	118 (6.93±0.04)	146 (6.84±0.06)	NA	MTA
9	422 (6.37 ± 0.08)	161 (6.79 ± 0.04)	460 (6.39 ± 0.06)	NA	MTA
10 *	49 ± 3	72 ± 5	2.3 ± 0.2	86.3 ± 7.26	MTA
11	646 (6.19 ± 0.06)	161 (6.79 ± 0.04)	MTA	68 (7.2±0.20)	1534
12	1456 (5.84 ± 0.09)	336 (6.47 ± 0.04)	345 (6.46 ± 0.04)	177 (6.8 ± 0.10)	895
13	218 (6.66 ± 0.05)	18 (7.75 ± 0.06)	205 (6.69 ± 0.04)	1427 (5.8 ± 0.10)	MTA
14	249 (6.6 ± 0.07)	38 (7.42 ± 0.05)	210 (6.68 ± 0.05)	216 (6.7 ± 0.10)	2442
15	366 (6.44 ± 0.08)	143 (6.84 ± 0.05)	773 (6.11 ± 0.04)	MTA	MTA
16	126 (6.9 ± 0.06)	17 (7.77 ± 0.04)	86 8.09 ± 0.07	597 (6.22 ± 0.05)	MTA
Aripiprazole	3.3 ± 1.1	9.7 ± 5.4	510 ± 93	25.1 ± 2.6	1080 ± 180

MTA = Missed 50% of threshold inhibition.

* Only *Ki* values reported. NA = Not available. *Ki* values without the associated SEM, are within 20% of the mean value.