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Synthesis and evaluation of ligands for D_2-like receptors: The role of common pharmacophoric groups

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ABSTRACT

Arylcycloalkylamines, such as phenyl piperidines and piperazines and their arylalkyl substituents, constitute pharmacophoric groups exemplified in several antipsychotic agents. A review of previous reports indicates that arylalkyl substituents can improve the potency and selectivity of the binding affinity at D_2-like receptors. In this paper, we explored the contributions of two key pharmacophoric groups, that is, 4′-fluorobutyrophenones and 3-methyl-7-azaindoles, to the potency and selectivity of synthesized agents at D_2-like receptors. Preliminary observation of binding affinities indicates that there is little predictability of specific effects of the arylalkyl moieties but the composite structure is responsible for selectivity and potency at these receptors.

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1. Introduction

It is now widely accepted based on gene cloning and recombinant DNA techniques that there are at least five major dopamine (DA) receptor subtypes classified as D_1, D_2, D_3, D_4 and D_5. Originally, these receptors were classified into only two groups, D_1-like and D_2-like receptors with D_1 and D_5 falling into the first and D_2, D_3 and D_4 making up the later group.[1] Of the two groups, the D_2-like receptors have been the subject of great therapeutic interest because of their involvement in several psychiatric disorders.[2] The D_2 subtype receptor has been identified as the primary site of action for antipsychotic agents.[3] In addition, they are also implicated in the reinforcing and dependency-producing drugs of abuse.[4] The D_4 receptor subtype mediates functions that include motor activity, initiation and inhibition of behavior and working memory.[5–7] More recently, the D_4 receptor subtype has attracted attention because of its association with the induction of penile erection.[8–10] While the D_2 and D_4 subtypes have become potential targets for drug development for several therapeutic indications, the functions of the D_3 subtype have remained largely uncertain.[2]

Thousands of DA ligands have appeared in the literature over the years.[2] However, a cursory evaluation of the common structural features in D_2 and D_4 receptor subtype ligands reveals the consistent presence of arylcycloalkylamines in the form of alkylated arylpiperidines such as haloperidol (Chart 1) and piperazines such as clozapine. The nature of the alkylated moieties varies and there is little evidence to suggest the role of these alkyl moieties in the selectivity of the ligands for each receptor subtype. In an attempt to understand the structural contributions of the pharmacophoric elements at D_2-like receptors, we have compared the haloperidol analog, **1** with the Merck compound, L745,870 (Chart 1).[11,12] In addition, several other publications have evaluated 3-methyl-7-azaindole and 3-methylindole moieties for D4 receptor selectivities.[13]

The comparison of the binding affinity data at cloned human D_2-like receptors suggests that the presence of the butyrophenone and the 3-methyl-7-azaindole moieties significantly affects binding affinity and selectivity of these compounds at the D_2-like receptors.[11] In particular, a comparison of compound **1** and L745,870 suggests that the presence of the 3-methyl-7-azaindole moiety on 4-chlorophenyl piperazine confers ~40-fold D_4 potency

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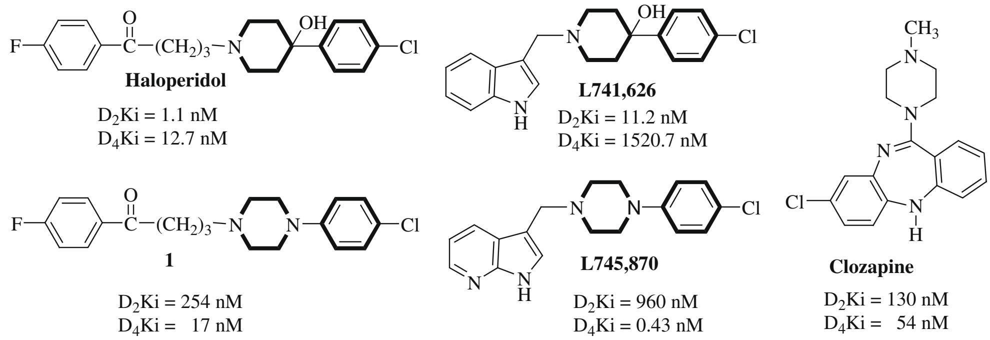


Chart 1.

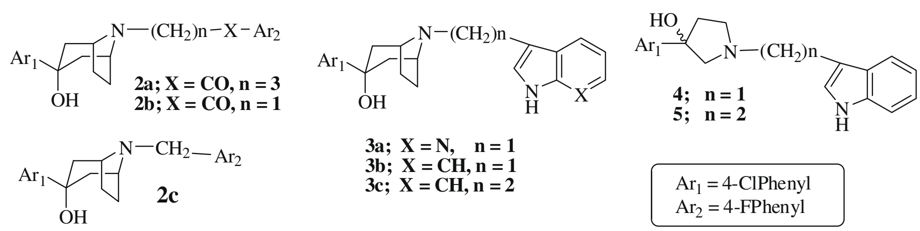


Chart 2.

on L745,870 while the butyrophenone confers less than a 4-fold D_2 potency. In addition, the 3-methyl-7-azaindole moiety appears to have increased D_4 selectively from 15-fold to over 2200-fold. On the other hand, the arylpiperidine and arylpiperazine groups common among CNS drugs appear to have preferences for the D_2 and D_4 subtype receptors, respectively. The aim of this study was to further explore the role of the two alkyl moieties and their impact on D_2/D_4 selectivity and potency (Charts 2 and 3).

2. Chemistry

The binding affinities of compounds **1**, **2a**–**c**, **6**, **8**, **10**, **12** and **14** were previously reported.[11,14] However, the full details of the synthetic procedures for several of them were not provided nor discussed. The key intermediate for the synthesis of compounds **2a**–**c** and **3a**–**c**, 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol, was obtained by treating commercially available carbamate protected tropinone (**16**) with 4-chlorophenyl magnesium bromide under Grignard reaction conditions to form a carbamate protected aminoalcohol (**17**) which was decarbamylated to the aminoalcohol **18**. Compounds **2a**–**c** were obtained by simple alkylation of compound **18** with the appropriate alkylating groups (Scheme 1). Compound **18** was also subjected to treatment with 7-azaindole and formaldehyde under Mannich reaction conditions, to give the desired product, **3a** (Scheme 3). Compound **3b** was similarly prepared using indole instead of 7-azaindole and the synthesis of compound **3c** was accomplished by alkylating compound **18** with 3-(2-bromoethyl)-1H-indole (Scheme 4). Compound **24** (Scheme 2), which was previously reported by our laboratory,[15] served as the key intermediate for the synthesis of compounds **4** and **5**. The first step was to convert the commercially available benzyl-protected pyrrolidinol, **20** to the carbamate-protected pyrrolidinol (**21**) in order to avoid the anticipated dechlorination that often accompanied debenzylation under hydrogenolysis conditions. Oxidation of compound **21** to form ketone **22** and subsequent Grignard reaction with 4-chlorophenyl magnesium bromide produced the carbamate-protected pyrrolidinol **23**. Deprotection with potassium hydroxide produced **24** and subsequent alkylation with the appropriate alkylating agents yielded the desired compounds **4** and **5** (Schemes 3 and 4).

We have previously reported the detailed synthetic procedures for compound **6** including the synthesis of 1-(4-chlorophenyl)-1,4-diazepane, using CuI-catalyzed coupling of 4-chlorophenyl iodide with 1,4-diazepane.[14] Mannich reaction involving 1-(4-chlorophenyl)-1,4-diazepane, formaldehyde and 7-azaindole produced compound **7** in good yield (Scheme 3). The synthesis of compounds **8** and **9** required the previously synthesized 9-methyl-3,9-diazabi-

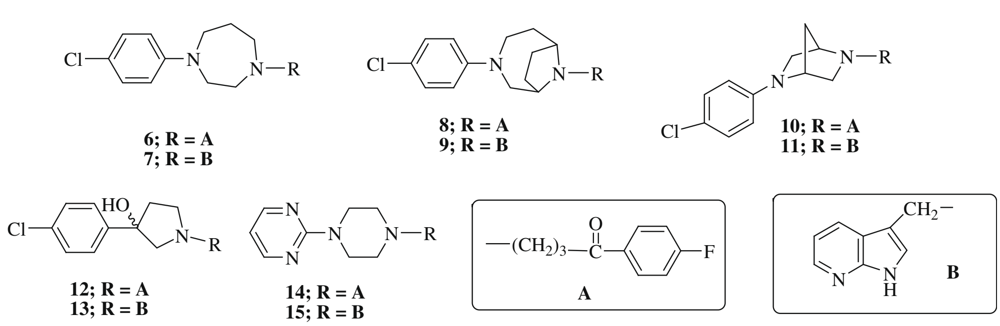
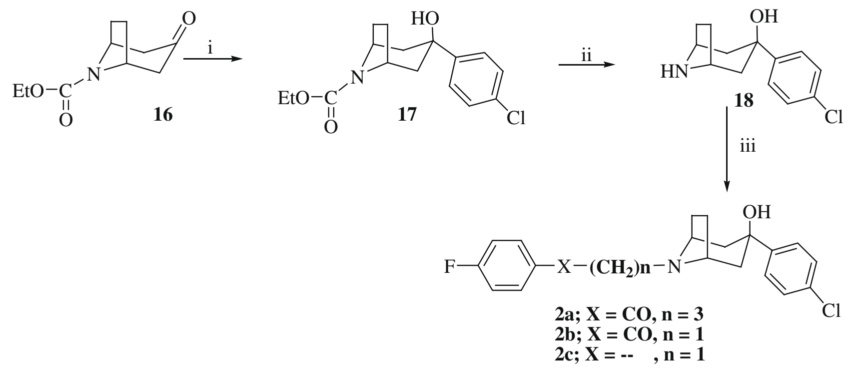
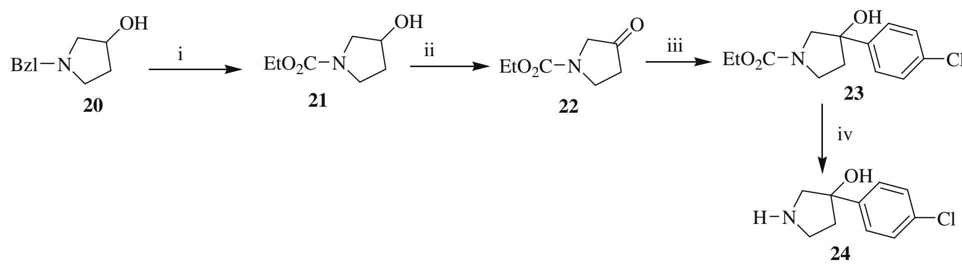


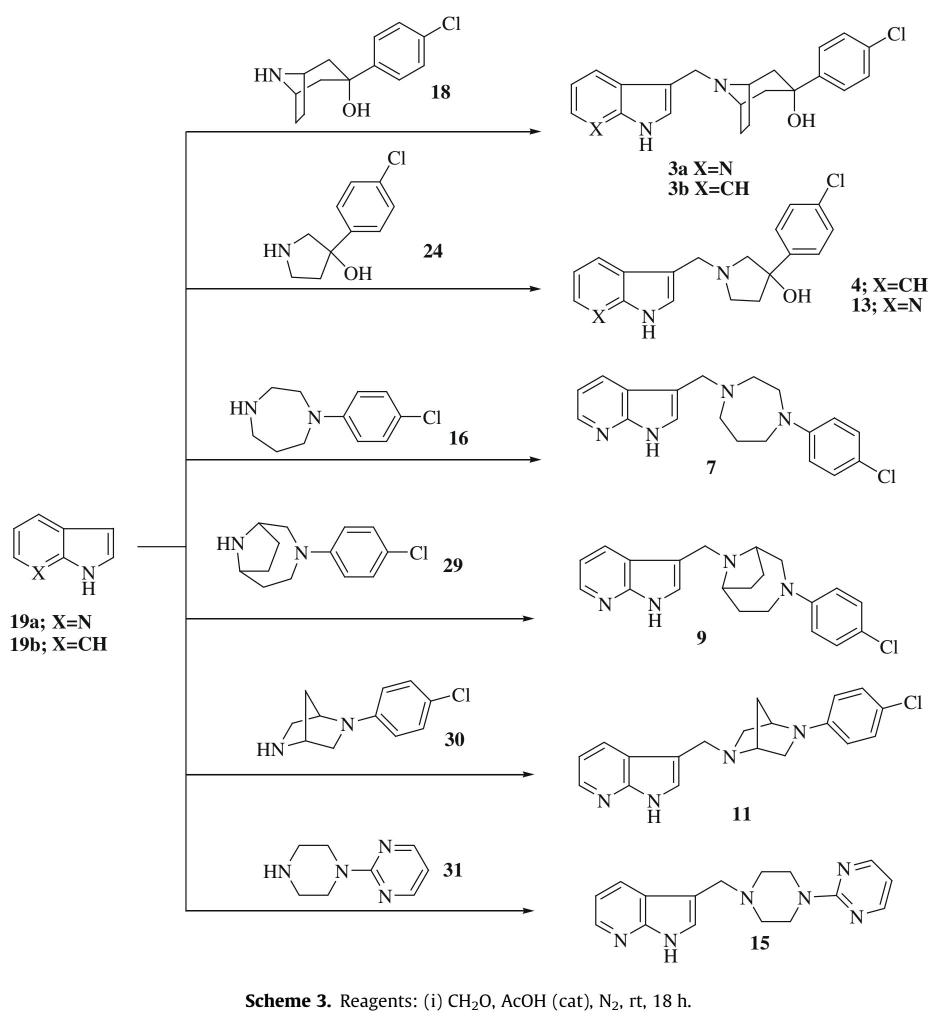
Chart 3.



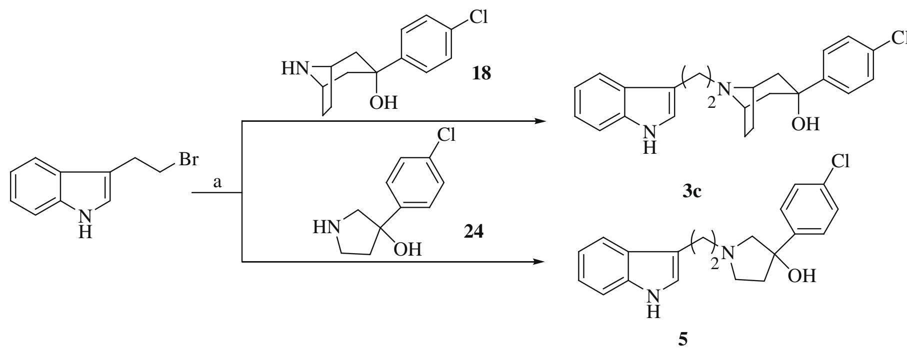
Scheme 1. Reagents and conditions: (i) 4-Cl–Ph MgBr, (ii) KOH/ethylene glycol, (iii) 4′-fluoro-4-chlorobutyrophenone/DME/KI/K_2CO_3 (**2a**); 4′-fluoro-2-chloroacetophenone/DME/KI/K_2CO_3 (**2b**); 4-fluorobenzyl bromide/DME/KI/K_2CO_3 (**2c**).



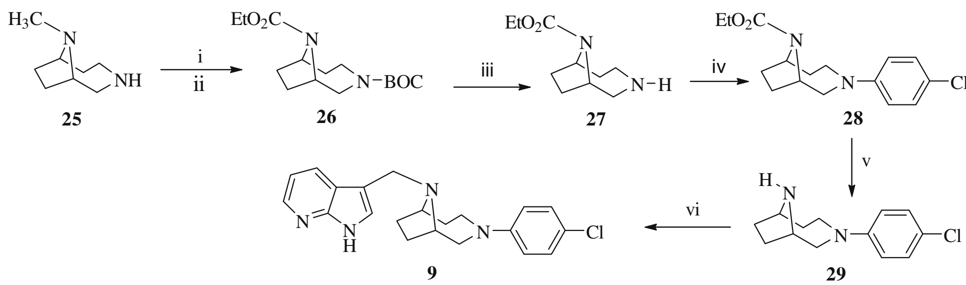
Scheme 2. Reagents: (i) ClCOOEt, (ii) chromic acid, (iii) 4-Cl-PhMgBr, (iv) alcoholic KOH.



Scheme 3. Reagents: (i) CH_2O, AcOH (cat), N_2, rt, 18 h.



Scheme 4. Reagents and conditions: (a) $NaHCO_3$, CH_3CN, reflux, 4 h.



Scheme 5. Reagents: (i) t-BuOH, BOC; (ii) $ClCO_2Et$, Toluene; (iii) TFA (iv) 4-Chlorophenylboronic Acid, $Cu(OAc)_2$, TEA, CH_2Cl_2, Molecular sieves, rt, 24 – 48 hr; (v) KOH, Ethylene glycol; (vi) 7-azaindole, CH_2O, AcOH (cat), BuOH, N_2, rt, 18h.

cyclo[4.2.1]nonane (**25**) as a key intermediate.[14] To obtain compound **8**, intermediate **25** was BOC protected and carbamylated using ethyl chloroformate (**26**). N-Arylation of **27** with 4-chlorophenylboronic acid produced compound **28** which underwent deprotection to now produce the secondary amine of the other nitrogen (**29**) (Scheme 5). Alkylation of compound **29** with 4-chloro-4′-fluorobutyrophenone delivered the target compound **8** as desired. Compound **9** was obtained by reacting 9-(4-chlorophenyl)-3,9-diazabicyclo[4.2.1]nonane (**29**) with 7-azaindole under Mannich reaction condition (Method A) (Scheme 3). The synthesis of compound **10** was previously reported[14] while compound **11** was synthesized using the commercially available 5-(4-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane (**30**) as the starting material. Compound **30** was treated with 7-azaindole and formaldehyde under Mannich reaction condition as before to form compound **11** (Scheme 3). The synthesis of compounds **12** and **14** were also previously reported[14] and compounds **13** and **15** were synthesized using the same procedure for the synthesis of compound **11** (Scheme 3). 3-(4-Chlorophenyl)-3-hydroxypyrrolidine **24**, previously reported,[15] (Scheme 2) and the commercially available 1-(2-pyrimidyl)piperazine **31** served as starting materials for the Mannich reaction mediated conversion to target compounds **13** and **15**, respectively (Scheme 3).

3. Results and discussion

We have previously shown that replacing the piperidine ring in haloperidol with a tropane moiety enhanced binding affinity to dopamine D_2 receptors.[15,16] Later, we compared the effect of a 4′-fluorobutyrophenone and 3-methyl-7-azaindole moieties on 4-(4-chlorophenyl)piperazine and observed that the 3-methyl-7-azaindole moiety conferred both potency and D_4 selectivity.[11] At the time, we were drawn to the possibility that the distance between the aromatic ring and the N atom in the piperazine ring might be important. That hypothesis was tested using the potent tropane analog of haloperidol (**2a**) and the shorter arylalkyl groups (**2b** and **2c**) but we failed to achieve either increased potency or D_4 selectivity.[11] To further explore other physicochemical aspects of the azaindole ring, we synthesized compounds **3a**–**c** and evaluated their binding affinities for the D_2-like receptors. Compounds **3a** [Ki (nM), D_2 = 588; D_4 = 7873] and **3b** [Ki (nM), D_2 = 160; D_4 = 3007] are analogs of L745,870 and L741,626 with the piperazine and piperidinol moieties replaced with the tropanol moiety respectively. Surprisingly, both compounds had significantly reduced affinity for the D_2 receptor. In addition, one would have expected **3b** to at least retain its binding affinity at the D_2 receptor (Ki of L741,626 at D_2 = 11.2 nM) since replacement of the piperidine ring with tropane (**2a**) in haloperidol enhanced potency at the D_2 subtype. Addition of a methylene group to extend the chain of **3b** to **3c** [Ki (nM) at D_2 = 53.0; D_4 = 277.5] improved affinity somewhat at all DA subtypes. In particular, affinity was significantly improved at the D_3 subtype with moderate selectivity when compared to the D_2 and D_4. Comparison of compounds **3a** and **3b** also suggests that the presence of the pyridine nitrogen in the azaindole analog detracts somewhat from binding affinity to the D_2-like receptors. Further attempts to improve binding affinity by synthesizing pyrrolidinol analogs of **3b** and **3c** (compounds **4** and **5**, respectively) were also unsuccessful. These surprising observations led us to synthesize and evaluate the 3-methyl-7-azaindole and 4′-fluorobutyrophenone moieties on several aryl cycloalkylamine structures shown in Chart 3.

We recently reported that compound **6**, a diazepane analog of haloperidol, has a favorable atypical antipsychotic profile.[14] Replacement of the butyrophenone moiety with the 3-methyl-7-azaindole moiety led to the formation of compound **7**. Evaluation of the binding affinities of the two compounds shows **7** has a 7- and 3-fold lower affinity for the D_2 and D_4 receptors, respectively, when determined using the same assay procedure in the same laboratory (Table 2). The Ki values in parenthesis for compound **6** are obtained in a different laboratory. This observation demonstrates that the 3-methyl-7-azaindole moiety does not necessarily confer D_4 receptor potency on its own but is dependent on the amine to which it is attached. A similar observation was made when the bridged analog of compounds **6** and **7**, that is, 8 [Ki (nM); D_2 = 178.4; D_4 = 41.8) and **9** [Ki (nM); D_2 > 10,000; D_4 = 583.7] were evaluated. Compound **8** did meet our initial criterion for further evaluation. At 5-HT receptors, **8** has weak binding affinity for 5-HT_{1A} and 5-HT_{2C} receptors but a moderate affinity for 5-HT_{2A} receptors [Ki (nM); 5-HT_{1A} = 2332; 5-HT_{2A} = 194.8; 5-HT_{2C} = 3513)]. Compared to its un-bridged counterpart, compound **6**, 8 has an 8-fold lower affinity for the 5-HT_{2A} receptor. These differences can be exploited to investigate the correlation of D_2/D_4 affinity ligands without substantial 5-HT binding affinity and the absence of extrapyramidal activity associated with typical antipsychotic agents. Compound **10** is the boat-constrained analog of **1** and **11** is an analog of **10** with the butyrophenone replaced with the 3-methyl-7-azaindole moiety. Compound **10** has moderate affinity for the D_2 and D_3 receptors and a weak affinity for the D_4 receptor. However, unlike the previous two pairs of compounds, **11** has a significantly higher affinity for all the D_2-like receptors. Indeed, compound **11** has the highest D_3 receptor affinity of all the compounds tested [Ki (nM); D_2 = 62.0; D_3 = 11.0; D_4 = 69.0] in this paper.

We have also previously shown that replacement of the piperidine in haloperidol with the pyrrolidine ring (**12**) results in an analog with reduced binding affinity at the D_2 subtype.[15] Separation and evaluation of the enantiomers indicated that the (+)-enantiomer is the eutomer and its behavioral profile was desirable.[17] Thus, we opined that replacement of the 4′-fluorobutyrophenone moiety in **12** with the 3-methyl-7-azaindole moiety might be useful. The results indicate that there was little or no affinity for both D_2 and D_3 receptor subtypes and over 100-fold lower affinity for the D_4 receptor subtype. Synthesis and evaluation of compound 15 [Ki (nM); D_2 = 1170; D_3 = 1500; D_4 = 56.0), a 7-azaindole counterpart of the previously reported compound **14**, also resulted in diminished binding affinity for the D_2-like receptors. It is important to note however that the binding affinities were determined in different laboratories and hence inter-laboratory differences (see the results for the determination of haloperidol, compound **2a** and **6**) may play a role as well.

Overall, these results suggest that the *N*-arylalkyl substituents on aryl cycloalkylamines can modify significantly the binding affinities of the resulting compounds at the dopamine receptor subtypes. There does not appear to be a specific and predictable effect of the nature of the arylalkyl moiety and the binding affinity appears to be due to a combination of effects involving the two component parts. These observations are consistent with the fact that the pharmacophoric elements of both typical and atypical antipsychotic drugs are found in both the cycloalkylamine and the arylalkyl moieties of these compounds.

4. Experimental

Melting points were determined on a Gallenkamp (UK) apparatus and are uncorrected. NMR spectra were obtained on a Varian 300 MHz Mercury Spectrometer. 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 with Davisil grade 634 silica gel. *N*,*N*-Dimethylformamide was distilled from $CaSO_4$ and stored over 4 Å molecular sieves. 4-Chloro-4′-fluorobutyrophenone was obtained from Sigma–Aldrich but was purified by distillation under reduced pressure to a colorless liquid prior to use. Other starting materials were used without further purification.

4.1. Preparation of 3-(4-chlorophenyl)-8-azabicyclo [3.2.1]octan-3-ol (18)

A Grignard reagent, *p*-chlorophenyl magnesium bromide,[18] was generated in situ by reacting 4-bromochlorobenzene (5.82 g, 30.40 mmol), Mg (0.8 g, 32.90 mmol) and I_2 (ca. 1 mg) in anhydrous Et_2O (20 mL), and refluxing the mixture for 4 h. A solution of *N*-carbethoxy tropinone (**16**) (2 g or 10.1 mmol) in anhydrous THF (10 mL) was slowly added to the reaction mixture and further refluxing continued for 18 h. The resulting mixture was allowed to cool to room temperature, saturated NH_4Cl solution (50 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with H_2O (50 mL) followed by brine (50 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. Column chromatography (gradient solvent of 8:2 to 7:3 hexane/EtAOc) on silica gel afforded ethyl-3-(4-chlorophenyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (**17**) as a yellowish oil which solidified on standing at room temperature for one day, 1.3 g, 41.5%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, t, J = 7.1 Hz), 1.55 (2H, d, J = 9.2 Hz), 1.81 (2H, d, J = 14.5 Hz), 1.96 (2H, m), 2.27 (4H, d, J = 6.8 Hz), 4.15 (2H, q, J = 7.1, J = 7.3 Hz), 7.28 (4H, d, J = 4.0 Hz). A mixture of KOH (3.2 g, 56.5 mmol) in ethylene glycol (20 mL) was added to a solution of **17** (2.5 g or 8.1 mmol) in MeOH (10 mL) and the resulting mixture was heated at 150 °C, with constant stirring, for 4 h and then allowed to cool to room temperature. Water (200 mL) was added, and the mixture was extracted with EtOAc (2 × 100 mL) followed by CH_2Cl_2 (3 × 100 mL). The organic phases were combined, washed with H_2O (400 mL), brine (100 mL) and dried (Na_2SO_4). The organic phase was filtered, and the filtrate was concentrated in vacuo and the residue was column chromatographed on silica gel (4:2 CH_2Cl_2/MeOH) to give white yellowish crystals of 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (**18**) (1.40 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (4H, m), 2.17 (2H, dd, J = 3.7, J = 3.7 Hz), 2.34 (2H d, J = 7.5 Hz), 3.56 (2H, br s), 7.27 (2H, d, J = 8.7 Hz), 7.48 (2H, d, J = 8.7 Hz).

4.2. 4-[3-(4-Chlorophenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]-1-(4-fluorophenyl)butan-1-one (2a)

A mixture of **18** (0.46 g, 1.94 mmol), 4-chloro-4′-fluorobutyrophenone (0.60 g, 3 mmol), KI (0.5 g, 3 mmol), K_2CO_3 (0.70 g, 5.1 mmol) in DME (10 mL) was refluxed under N_2 for 18 h. The reaction mixture was allowed to cool to room temperature, H_2O (20 mL) was added, and the mixture was extracted with EtOAc (4 × 50 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography was carried out using CH_2Cl_2 followed by 2:3 EtOAc/MeOH to afford a yellowish oil of **2a** (0.18 g, 23%) which was then converted to its HCl salt, mp 237.2–238.3 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.24 (m, 6H), 2.57 (m, 2H,) 2.72 (d, J = 9.0 Hz, 2H), 3.17 (m, 2H), 3.27 (t, J = 6.6 Hz, 2H), 4.19 (br s, 2H), 7.26 (dd, J_{H-F} = 8.7 Hz, J_{H-H} = 8.8 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7, 2H), 8.11 (dd, J_{H-F} = 5.4 Hz, J_{H-H} = 8.8 Hz, 2H). Anal. Calcd for $C_{23}H_{26}Cl_2FN_2O\cdot0.5H_2O$: C, 61.75; H, 6.08; N, 3.13. Found: C, 61.93; H, 6.03; N, 3.20.

4.3. 2-[3-(4-Chlorophenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]-1-(4-fluorophenyl)ethanone (2b)

A mixture of **18** (0.700 g, 2.94 mmol), 2-chloro-4′-fluoroacetophenone (0.83 g, 3.83 mmol), KI (0.800 g, 2.94 mmol), and K_2CO_3 (2.44 g, 17.6 mmol) in DME (10 mL) was refluxed for 18 h. The reaction was cooled to rt, H_2O (20 mL) was added, and the mixture was extracted with EtAOc (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. Column chromatography (7:3 hexane/EtAOc) resulted in a yellowish oil of **2b** (0.480 g, 44%) which was converted into an HCl salt; mp 256.8–257.5 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.28 (7H, m), 2.71 (4H, m), 4.19

(2H, br s), 7.34 (2H, t, J_{H-F} = 8.8, J_{H-H} = 8.8 Hz), 7.38 (2H, d, J = 8.8, J_{H-H} = 8.8 Hz) 7.59 (2H, d, J = 8.8), 8.18 (2H, dd, J_{H-F} = 5.5, J_{H-H} = 8.8 Hz). Anal. Calcd for $C_{21}H_{22}Cl_2FNO_2{\cdot}0.2H_2O$: C, 60.94; H, 5.45; N, 3.38. Found: C, 60.96; H, 5.34; N, 3.40.

4.4. 3-(4-Chlorophenyl)-8-(4-fluorobenzyl)-8-azabicyclo[3.2.1]octan-3-ol (2c)

A mixture of **18** (0.50 g, 2.10 mmol), 4-fluorobenzyl bromide (0.517 g, 2.70 mmol), KI (0.350 g, 2.10 mmol), and K_2CO_3 (1.74 g, 12.6 mmol) was refluxed in DME (6 mL) for 18 h. After cooling to room temperature, H_2O (20 mL) was added and the mixture was extracted with EtAOc (4 × 50 mL). Organic phases were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. Column chromatography on silica gel (starting with 100% hexane and then 7:3 hexane/EtAOc) yielded a yellowish oil of **2c** (0.425 g, 59%), which was then converted into an HCl salt, mp 110.4–111.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (2H, d, J = 14 Hz), 2.18 (2H, m), 2.80 (2H, m), 3.10 (2H, d, J = 14 Hz), 3.70 (2H, br s), 4.07 (2H, d, J = 6.0 Hz), 7.12 (2H, t, J_{H-F} = 8.5, J_{H-H} = 8.5 Hz), 7.26 (2H, d, J = 8.5), 7.78 (2H, d, J = 8.6 Hz), 7.87 (2H, dd, J_{H-F} = 5.3, J_{H-H} = 8.5 Hz). Anal. Calcd for $C_{20}H_{22}Cl_2FNO{\cdot}0.25H_2O$: C, 62.10; H, 5.86; N, 3.62. Found: C, 62.05; H, 6.01; N, 3.60.

4.5. 3-(4-Chlorophenyl)-8-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-8-azabicyclo[3.2.1]octan-3-ol (3a)

Method A: A mixture of **18** (0.60 g, 2.50 mmol), 7-azaindole (0.400 g, 3.40 mmol), AcOH (6 drops, 17 M), and CH_2O (0.203 g, 2.50 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 18 h. The reaction mixture was basified with NaOH (10% aqueous solution) and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. Purification by preparatory TLC (4:2 CH_2Cl_2/MeOH) yielded flaky white crystals of **3a** (0.46 g, 50%), mp 94.2–94.5 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 1.84 (2H, d, J = 14 Hz), 2.30 (6H, m), 3.45 (2H, br s), 3.84 (2H, br s), 7.14 (1H, dd, J = 5.0, J = 7.8 Hz), 7.27 (2H, d, J = 8.6 Hz), 7.46 (1H, s) 7.50 (2H, d, J = 8.6 Hz), 8.20 (2H, m). Anal. Calcd for $C_{21}H_{22}ClN_3O{\cdot}0.75H_2O$: C, 66.13; H, 6.21; N, 11.02. Found: C, 66.12; H, 6.04; N, 10.87.

4.6. 3-(4-Chlorophenyl)-8-(1*H*-indol-3-ylmethyl)-8-azabicyclo[3.2.1]octan-3-ol (3b)

A mixture of **18** (0.50 g, 2.10 mmol), indole (0.250 g, 2.1 mmol), AcOH (6 drops, 17 M), and CH_2O (0.065 g, 2.10 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 18 h. The reaction mixture was basified (10% aq NaOH solution), extracted with CH_2Cl_2 (4 × 25 mL), the pooled organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4 and the filtrate was concentrated in vacuo. Purification by preparatory TLC (4.5:0.5 CH_2Cl_2/2 M NH_3 in MeOH) yielded yellowish crystals of **3b** (0.39 g, 51%). Mp 72.4–73.1 °C, ^{1}H NMR (300 MHz, CD_3OD): δ 1.83 (2H, d, J = 14 Hz), 2.26 (5H, m), 2.37 (2H, d, J = 6.1 Hz), 2.40 (1H, d, J = 7.2 Hz), 3.35 (1H, s), 3.84 (2H d, J = 11.0 Hz), 7.04 (1H, m), 7.11 (1H, m), 7.26 (2H, d, J = 8.6 Hz), 7.36 (1H, m), 7.52 (2H, d, J = 8.6 Hz), 7.70 (1H, m). Anal. Calcd for $C_{22}H_{23}ClN_2O{\cdot}1.0H_2O$: C, 68.65; H, 6.55; N, 7.28. Found: C, 68.43; H, 6.29; N, 7.04.

4.7. 3-(4-Chlorophenyl)-8-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylethyl)-8-azabicyclo[3.2.1]octan-3-ol (3c)

A mixture of **18** (0.200 g, 0.84 mmol), 3-(2-bromoethyl)-1H-indole (0.094 g, 0.42 mmol), and $NaHCO_3$ (0.14 g, 1.68 mmol) in anhydrous CH_3CN (5 mL) was refluxed for 4 h under N_2. The reaction mixture was allowed to cool to rt and H_2O (15 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 25 mL) and the combined organic layers was washed with brine (20 mL), dried over Na_2SO_4 and the filtrate was concentrated in vacuo. White crystals of **3c** (0.18 g, quantitative) were obtained after preparatory TLC purification (4:1 CH_2Cl_2/MeOH), mp 186.5–187.1 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 1.83 (2H, d, J = 14 Hz), 2.00 (2H, m), 2.32 (5H, m), 2.82 (2H, m), 3.03 (2H, m), 3.50 (2H, br s), 7.08 (1H, s), 7.10 (1H, dt, J = 1.2, J = 8.0 Hz), 7.28 (2H, d, J = 8.7 Hz), 7.32 (2H, m), 7.54 (2H, d, J = 8.7Hz), 7.56 (2H, m). Anal. Calcd for $C_{23}H_{25}ClN_2O{\cdot}0.75H_2O$: C, 70.04; H, 6.77; N, 7.10. Found: C, 69.86; H, 6.56; N, 7.00.

4.8. 3-(4-Chlorophenyl)-1-(1*H*-indol-3-ylmethyl)pyrrolidin-3-ol (4)

A solution of 3-(4-chlorophenyl)pyrrolidin-3-ol (0.60 g, 3.04 mmol), indole (0.46 g, 3.95 mmol), AcOH (6 drops, 17 M), and CH_2O (0.08 mL, 3.04 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 18 h. The mixture was basified (10% NaOH solution), extracted with CH_2Cl_2 (4 × 25 mL), the combined organic layers was washed with brine (20 mL), dried over Na_2SO_4 and the filtrate was concentrated in vacuo. Purification using preparatory TLC (4.5:0.5: CH_2Cl_2/2 M NH_3 in MeOH) gave yellowish crystals of **4** (0.49 g, 49%), mp 56.9–57.2 °C, ^{1}H NMR (300 MHz, CD_3OD): δ 2.13 (1H, m), 2.25 (1H, m), 2.94 (1H, m), 2.98 (2H, m), 3.08 (1H, m), 3.96 (2H, s), 7.03 (1H, m), 7.10 (1H, m), 7.24 (1H, s), 7.28 (2 H, d, J = 8.7 Hz), 7.35 (1H, m), 7.45 (2H, d, J = 8.7 Hz), 7.66 (1H, m). Anal. Calcd for $C_{19}H_{19}ClN_2O{\cdot}0.4H_2O$: C, 68.32; H, 5.97; N, 8.39. Found: C, 68.40; H, 5.86; N, 8.28.

4.9. 3-(4-Chlorophenyl)-1-[2-(1*H*-indol-3-yl)ethyl]pyrrolidin-3-ol (5)

A mixture of 3-(4-chlorophenyl)pyrrolidin-3-ol (0.40 g, 2.02 mmol), 3-(2-bromoethyl)indole (0.23 g, 1.01 mmol), and $NaHCO_3$ (0.68 g, 8.08 mmol) in anhydrous CH_3CN (5 mL) was refluxed for 4 h under N_2. The reaction mixture was allowed to cool to room temperature and H_2O (15 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 25 mL), the pooled organic layers was washed with brine (20 mL), dried over Na_2SO_4 and the filtrate was concentrated in vacuo. Purification by column chromatography (4:1 CH_2Cl_2/MeOH) afforded white crystals of **5** (0.15 g, 22%), mp 54.1–55.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (1H, m), 2.28 (1H, m), 2.60 (2H, m), 2.92 (4H, m), 3.06 (1H, d, J = 9.7 Hz), 3.25 (1H, m), 6.98 (1H, s), 7.09 (2H, m), 7.26 (2H, m), 7.38 (2H, d, J = 8.6 Hz), 7.55 (1H, d, J = 7.8 Hz), 7.93 (1H, br s). Anal. Calcd for $C_{20}H_{21}ClN_2O{\cdot}0.5MeOH$: C, 68.99; H, 6.50; N, 7.85. Found: C, 68.80; H, 6.27; N, 7.49.

4.10. 3-{[4-(4-Chlorophenyl)-1,4-diazepan-1-yl]methyl}-1*H*-pyrrolo[2,3-*b*]pyridine, HCl (7)

Using Method A and 1-(4-chlorophenyl)-1,4-diazepane and 7-azaindole as starting materials, compound **7** was obtained as the HCl salt, mp 158.0–159.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.30 (1H, br s), 8.28 (1H, d, J = 4.5 Hz), 7.96 (1H, dd, J = 1.5, 7.5 Hz), 7.19 (1H, s), 7.12 (2H, d, J = 9.0 Hz), 7.03 (1H, dd, J = 4.8, 8.1 Hz), 6.58 (2H, d, J = 9.0 Hz), 3.79 (2H, s), 3.51 (2H, t, J = 4.8 Hz), 3.47 (2H, t, J = 6.3 Hz), 2.78 (2H, t, J = 4.8 Hz), 2.65 (2H, t, J = 4.8 Hz), 1.90 (2H, m). Anal. Calcd for $C_{19}H_{21}ClN_4{\cdot}HCl{\cdot}0.35H_2O$: C, 59.49; H, 5.78; N, 14.60. Found: C, 59.40; H, 5.54; N, 14.59.

4.11. 9-[(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methyl]-3-(4-chlorophenyl)-3,9-diazabicyclo[4.2.1]nonane (9)

The method of Michaels and Zaugg was followed.[19] to deliver intermediate **29** as previously reported in Ref. 14. A mixture of 3-(4-chlorophenyl)-3,9-diazabicyclo[4.2.1]nonane, **29** (0.130 g, 0.55 mmol), 7-azaindole (0.130 g, 1.1 mmol), AcOH (6 drops, 17 M) CH_2O (0.016 g, 0.53 mmol) in butanol (8 mL) was refluxed overnight under N_2. The excess butanol was removed in vacuo and residue was extracted with methylene chloride (3 × 60 mL). The organic phase was dried (Na_2SO_4) and removed. The crude product was purified on silica gel column with 1:1 CH_2Cl_2 and EtOAc to yield compound **9** (80 mg, 62.2%) as a white hygroscopic crystalline solid. Mp 194–196 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (m, 1H), 8.05 (m, 1H), 7.04 (m, 4H), 6.56 (d, *J* = 6.5 Hz, 2H), 3.58 (d, *J* = 6.5 Hz, 2H), 3.50 (m, 6H), 3.12 (m, 1H), 2.20–1.10 (m, 6H). Anal. Calcd. for $C_{21}H_{23}N_4Cl{\cdot}0.125H_2O$: C, 68.33; H, 6.35; N, 15.18. Found: C, 68.17; H, 6.30, N, 14.92.

4.12. 2-{(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)methyl}-5-(4-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane (11)

Using method A and 5-(4-chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane and 7-azaindole as starting materials, compound **11** was obtained as the free base, mp 176–178 °C. ^{1}H NMR ($CDCl_3$): δ 10.03 (1H, br s), 8.29 (1H, d, *J* = 4.5 Hz), 8.01 (1H, d, *J* = 8.1 Hz), 7.22 (1H, s), 7.13 (2H, d, *J* = 9.0 Hz), 7.05 (1H, dd, *J* = 4.8, 7.8 Hz), 6.47 (2H, d, *J* = 9.0 Hz), 4.18 (1H, s), 3.85 (2H, s), 3.60 (1H, s), 3.36 (1H, d, *J* = 9.0 Hz), 3.29 (1H, d, *J* = 9.0 Hz), 2.93 (1H, d, *J* = 9.6 Hz), 2.73 (1H, d, *J* = 9.6 Hz), 2.00 (1H, d, *J* = 9.3 Hz), 1.86 (1H, d, *J* = 9.3 Hz). Anal. Calcd for $C_{19}H_{19}ClN_4$: C, 67.35; H, 5.65; N, 16.54. Found: C, 67.10; H, 5.74; N, 16.25.

4.13. 3-(4-Chlorophenyl)-1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)pyrrolidin-3-ol (13)

Using Method A and 3-(4-chlorophenyl)pyrrolidin-3-ol, **24** and 7-azaindole as starting materials, compound **13** was obtained in 37% yield, mp 62.9–63.2 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.15 (1H, m), 2.90 (1H, m), 2.95 (2H, m), 3.05 (1H, m), 3.93 (2H, s), 7.12 (1H, dd, *J* = 5.0, *J* = 7.8 Hz), 7.29 (2H, d, *J* = 8.6 Hz), 7.39 (1H, s), 7.47 (2H, d, *J* = 8.6 Hz), 8.16 (2H, m). Anal. Calcd for $C_{18}H_{18}ClN_3O{\cdot}0.4H_2O$: C, 64.53; H, 5.66; N, 12.54. Found: C, 64.48; H, 5.57; N, 12.39.

4.14. 3-{(4-(Pyrimidin-2-yl)piperazin-1-yl)methyl}-1*H*-pyrrolo[2,3-b]pyridine (15)

Using method A and 1-(2-pyrimidyl)piperazine and 7-azaindole, produced compound **15** as a solid, mp 185–187 °C. ^{1}H NMR ($CDCl_3$): 9.00 (1H, br s), 8.31 (1H, dd, *J* = 1.5, 5.1 Hz), 8.28 (2H, d, *J* = 4.8 Hz), 8.09 (1H, dd, *J* = 1.5, 7.8 Hz), 7.24 (1H, s), 7.08 (1H, dd, *J* = 4.8, 8.4 Hz), 6.45 (1H, t, *J* = 4.8 Hz), 3.83 (4H, t, *J* = 5.4Hz), 3.73 (2H, s), 2.54 (4H, t, *J* = 5.4 Hz). Anal. Calcd for $C_{16}H_{18}N_6$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.02; H, 6.20; N, 28.26.

5. Biology

5.1. 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.[20]

Table 1
Binding affinity constants of synthetic compounds to D_2-like receptors

Compound	Binding data of compounds,[a] Ki ± SEM (nM)			
	D_2	D_3	D_4	D_2/D_4
Haloperidol	1.1 ± 0.07 [0.89]	5.5 ± 3.0 [4.6]	12.7 ± 7.2 [10.0]	0.10 [0.09]
2a	1.6 ± 0.14 [0.31]	5.1 ± 3.0 [0.71]	5.3 ± 0.99 [12.1]	0.30 [0.03]
2b	1231 ± 145	>10,000	789 ± 363	1.60
2c	1050 ± 209	172 ± 33	1015 ± 179	1.03
3a	588 ± 57.6	128 ± 13	7873 ± 1437	0.07
3b	160.3 ± 11.8	25.0 ± 1.7	3007 ± 561	0.05
3c	53.0 ± 6.4	18.0 ± 1.6	277.5 ± 26.5	0.19
4	MPA	2874 ± 584	816.5 ± 194.4	—
5	MPA	3074 ± 553	MPA	—

[a] Data obtained from the NIMH-PDSP and those in square brackets are from Ref. 15. Ki is the mean value obtained on triplicate or quadruplicate determinations unless otherwise indicated. MPA = Missed primary assay threshold of 50% inhibition.

Table 2
Binding affinity constants of synthetic compounds to D_2-like receptors

Compound	Binding data of synthetic compounds,[a] Ki ± SEM (*n*) in nM			
	D_2	D_3	D_4	D_2/D_4
Clozapine[b]	130	240	54	2.4
6[b]	43.3 ± 13.3 (130)	158.8 ± 35.1 (567)	6.6 ± 0.6 (56)	6.6 (2.3)
7[c]	970 (*n* = 2)	370 (219–631)	18.6 (14.5–24.0)	5.1
8[b]	178.4 ± 29.2	548.1 ± 246.0	41.8 ± 9.0	4.3
9	>10,000	335.5 ± 178.0	583.7 ± 114.9	>17
10[c]	170.0 (123–234)	220.0 (148–339)	513.0 (447–589)	0.33
11[c]	62.0 (38.0–100)	11.0 (7.94–15.1)	69.0 (56.2–85.1)	0.90
12[c]	33.0 (21.9–50.1)	200.0 (144.5–275.4)	11.0 (8.9–12.3)	3.0
13	MPA	MPA	1213 ± 260	—
14[b]	98.0 ± 15.3	244.1 ± 106.0	6.5 ± 0.8	15
15[c]	1170 (*n* = 2)	1500 (912–2399)	56.0 (45.7–69.2)	21

[a] Data obtained from the NIMH-PDSP. Data for compounds **6** (parenthesis) **7**, **10**, **11**, **12**, and **15** were provided by A. W. Schmidt, at Pfizer laboratories as described in Ref. 15. Ki is the mean value obtained on triplicate or quadruplicate determinations unless otherwise indicated. MPA = Missed primary assay threshold of 50% inhibition.
[b] Binding data were previously reported (Ref. 14).
[c] The data in brackets is the range of the mean relative to the SEM.

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