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Structure–activity relationship studies of SYA 013, a homopiperazine analog of haloperidol

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ABSTRACT

Structure–activity relationship studies on 4-(4-(4-chlorophenyl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl) butan-1-one (SYA 013), a homopiperazine analog of haloperidol has resulted in an understanding of the effect of structural modifications on binding affinity at dopamine and serotonin receptor subtypes. Further exploration, using bioisosteric replacement strategies has led to the identification of several new agents including compounds **7, 8, 11** and **12** which satisfy the initial criteria for further exploration as new antipsychotic agents. In addition, compound **18**, a D_3 selective tropanol, has been identified as having the potential for further optimization into a useful drug which may combat neuropsychiatric diseases.

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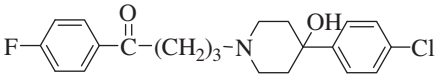
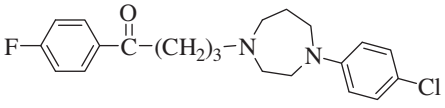
1. Introduction

There is considerable interest in the development of new antipsychotic drugs partially because of the side effects associated with both typical and atypical antipsychotic drugs currently on the market.[1] Atypical antipsychotics were developed to replace typical antipsychotics partially because of the debilitating extrapyramidal side effects. One of the problems in the development of new drugs is the fact that new structural classes of drugs often lead to new types of off-target interactions or side effects when the general population is exposed to the drug. Thus, we hypothesized that there may be advantages in using known drug scaffolds as leads in drug design while attempts are made to eliminate off-target interactions. In this regard, we have focused on the typical antipsychotic drug, haloperidol, taking advantage of the fact that haloperidol binds to several receptors of interest in antipsychotic drug development (D_2K_i = 0.89 nM, $5HT_{1A}$ = 3600 nM; $5HT_{2A}$ = 120 nM; $5HT_{2C}$ = 4700 nM) and thus modifications can be made either to enhance or diminish binding at given receptors.[2–6] In pursuit of this strategy, we have identified several agents[2–6] including a homopiperazine analog of haloperidol, SYA 013 (**2**),[7] with a pharmacological profile similar to those of current atypical antipsychotics but potentially without the EPS associated with haloperidol or the weight gain associated with several atypical antipsychotics.[8–10]



Haloperidol (**1**)



SYA 013 (**2**)

SYA 013 or 4-(4-(4-chlorophenyl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl)butan-1-one is a haloperidol analog with the piperidinol moiety replaced with a homopiperazine. It binds to the DAD_2 receptor (K_i = 43.3 nM), DAD_3 (K_i = 158.8 nM), DAD_4 (K_i = 6.6 nM), $5HT_{1A}$ (K_i = 117.4 nM) and $5HT_{2A}$ (K_i = 23.3 nM) receptor. On the other hand, it has only moderate to weak binding at the $5HT_{2C}$ receptor (K_i = 1425 nM) and Histamine H1 receptor (K_i = 189 nM). This combination of binding affinities inspired in vivo studies that identified SYA 013 as having atypical antipsychotic properties without the associated catalepsy even at five times the ED_{50} dose.[7] In addition, the low binding affinity to $5HT_{2C}$ and H1 receptors compared with clozapine for example, predicts that SYA 013 may not induce weight gain. The current study probes the SYA 013

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scaffold using bioisosteric replacements to design, synthesize, and conduct structure–activity relationships that may serve as a foundation for new lead compounds active at CNS receptors associated with neuropsychiatric drug development. In particular, it is desirable to obtain compounds that meet the following criteria[7]: compounds should bind with moderate affinity at the D_2 receptor (30 nM < K_i < 150 nM), as avid affinity to this receptor may lead to induction of acute EPS; and a weak or no binding affinity to $5HT_{2C}$ and histamine H_1 receptors, as both receptors are reported to be associated with weight gain and subsequently type II diabetes, often observed with some of the atypical antipsychotics.

2. Chemistry

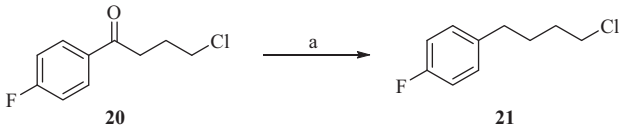
Compounds **2, 3, 4, 5, 6** (Chart 1), analogs of haloperidol **1**, were reported in previous papers from this lab.[6,7] including the synthetic details as well as important intermediates. Alkylating agent 1-(4-chlorobutyl)-4-fluorobenzene **21** was prepared by reductive deoxygenation of 4-chloro-1-(4-fluorophenyl)butan-1-one **20** using Clemmensen's reaction (Scheme 1). Refluxing a mixture of **20** and amalgamated zinc in aqueous acidic toluene for 5 h, afforded **21** after distillation.

Alkylating agents **26** and **27** were prepared from 4-fluorophenol **22** and 4-fluorobenzenethiol **23** (Scheme 2). By refluxing the mixture of 4-fluorophenol **22**, 3-chloropropanol, K_2CO_3, and KI in ^{i}PrOH, 3-(4-fluorophenoxy)propan-1-ol **24**, was obtained. Methanesulfonation was carried out at room temperature with Et_3N as a base afforded 3-(4-fluorophenoxy)propyl methanesulfonate **26**. The same procedure was used to prepare 3-((4-fluorophenyl)thio)propyl methanesulfonate **27**.

Benzothiazole alkylating agents **32**, **33** and **34** were prepared from 2-aminothiophenol with chloroacyl chlorides in toluene at room temperature, as described in Scheme 3.

Alkylating agents 1-(benzo[*d*]thiazol-2-yl)-4-iodobutan-1-one **38** and 1-(benzo[*d*]thiazol-2-yl)-5-iodopentan-1-one **39** were synthesized from benzothiazole **35**, as described in Scheme 4. Deprotonation of benzothiazole **35** with BuLi at −78 °C followed by treatment with lactone **36** or **37**, resulted in the corresponding alcohols. Iodides **38** and **39** were obtained by conversion of the corresponding alcohols into iodides with I_2, imidazole, and Ph_3P in CH_2Cl_2.

Alkylating agent **42** (Scheme 5) was prepared from 4-chloro-1-(4-fluorophenyl)butan-1-one **20** in a three step conversion. 4-Chloro-1-(4-fluorophenyl)-2-methylenebutan-1-one **40** was obtained by the treatment of **20** with Eschenmoser's salt in acetic anhydride at 105 °C for 18 h. The yield was 20–26%. Nazarov related cyclization[11] was carried out in concentrated H_2SO_4 at 60 °C to yield indanone **41** in quantitative yield. Protection of the ketone with ethylene glycol afforded compound **42**.



20 21

Scheme 1. Reagents and conditions: (a) Zn, $HgCl_2$, Conc HCl, toluene, reflux, 5 h.

1-(4-Chlorophenyl)-1, 4-diazepane **43** was synthesized[7] according to our previous published method involving the coupling of homopiperazine with 4-iodochlorobenzene in the presence of CuI. 3-(4-Chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol **44** was prepared as previously published by us.[6]

By coupling the alkylating agents **21, 26, 27, 32, 33, 34, 38, 39** and **42** with 1-(4-chlorophenyl)-1,4-diazepane **43**, homopiperazine derived analogs **9**–**17** (Chart 2) were synthesized as shown in Scheme 6. By coupling the alkylating agents **21, 26, 34**, and **39** with 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol **44**, compounds **7, 8, 18** and **19** were obtained (Chart 3) as shown in Scheme 7.

3. Results and discussion

Based on the binding profile of SYA 013 (Table 1), it is clear that replacement of the piperidinol in haloperidol with the homopiperazine moiety has a significant effect on binding to several receptors of interest. Replacement of the seven-membered homopiperazine ring with the six-membered piperazine ring (**3**) or its bridged analog, (1R,5S)-3,6-diazabicyclo[3.1.1]heptane, to form compounds **3** and **4**, respectively, did not result in improved binding at any of the receptors of interest. However, binding to D_2-like receptors was maintained. Bridging the homopiperazine ring with an ethylene group to form compound **5** again failed to improve binding when compared to lead compound **2**. We have previously shown that the tropane analog of haloperidol (**6**) resulted in very potent binding at dopamine receptors.[6] Indeed, compound **6** was found to be more potent than haloperidol at the D_2 receptor and displayed higher potency than SYA 013 at the $5HT_{1A}$ (K_i = 27.7 nM) and $5HT_{2A}$ (K_i = 30.9 nM) receptors as well. Not surprisingly then, it also produced severe catalepsy in animal models. This observation also suggested that binding to $5HT_{1A}$ or $5HT_{2A}$ may not

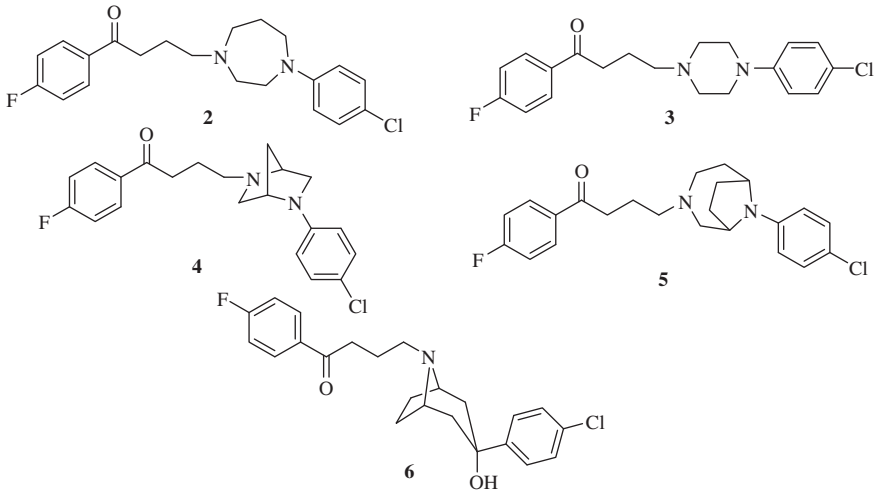
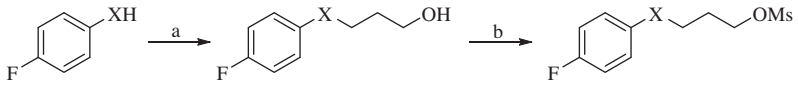


Chart 1. Structures of compounds **2**–**6**.

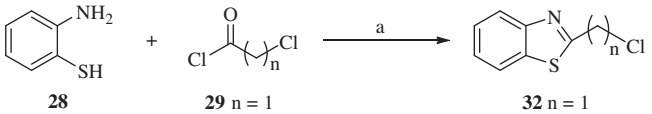


22 X = O
23 X = S

24 X = O
25 X = S

26 X = O
27 X = S

Scheme 2. Reagents and conditions: (a) KI, K_2CO_3, ^{i}PrOH, 3-chloropropanol, 80 °C,12 h; (b) MsCl, Et_3N, CH_2Cl_2, 5 °C–rt.

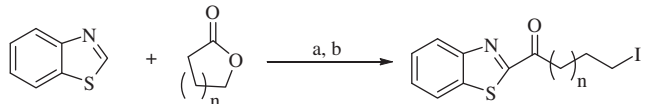


28

29 n = 1
30 n = 3
31 n = 4

32 n = 1
33 n = 3
34 n = 4

Scheme 3. Reagents and conditions: toluene, rt, 16 h.

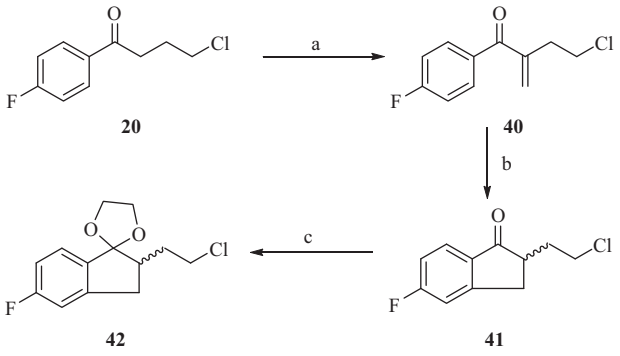


35

36 n = 1
37 n = 2

38 n = 1
39 n = 2

Scheme 4. Reagents and conditions: (a) BuLi, −78 °C, THF; (b) I_2, imidazole, Ph_3P, CH_2Cl_2, 0 °C–rt.



20

40

42

41

Scheme 5. Reagents and conditions: (a) hexamethylenetetramine, Ac_2O, 105 °C, 18 h; (b) H_2SO_4, 60 °C; (c) ethylene glycol, TsOH, toluene, reflux.

necessarily prevent catalepsy in animal models. Based on this profile, we opined that moderating the D_2 binding affinity of **6** might lead to reduction of the catalepsy. Thus, compounds **7** and **8** were synthesized to explore the hypothesis that D_2 binding can be moderated using butyrophenone bioisosteres identified in our laboratory.[12] Both compounds indeed have diminished D_2 binding (K_i = 22.0 and 33 nM, respectively), similar to that of SYA 013 as desired. However, the binding affinity at the $5HT_{1A}$ and $5HT_{2A}$ receptors significantly reduced as well.

Based on the above observations, it was of interest to explore the butyrophenone moiety in SYA 013 for enhancement in binding affinity at the desired receptors. A published report has suggested that a restricted butyrophenone moiety such as in the indenone analog **9** might increase potency at the $5HT_{2A}$ receptor.[13] Synthesis of compound **9** and its evaluation showed a moderate decrease in $5HT_{1A}$ binding but over 20-fold decrease in $5HT_{2A}$ receptor binding (K_i = 477.5 nM) compared to SYA 013 suggesting that the aryl cycloalkylamine moiety also plays a significant role in binding to the 5HT receptors. In addition, there were similar decreases in binding at the D_2-like receptors. Replacement of the butyrophenone carbonyl group with a sulfur atom (**10**, D_2K_i = 751.1 nM) or with an oxygen atom (**11**, D_2K_i = 172.0 nM) or a methylene group (**12**, D_2K_i = 139.0 nM) have each resulted in lower binding at the D_2 receptor. Despite the reduction in binding affinity, compounds **11** and **12** have similar binding affinity to that of clozapine (D_2K_i = 130 nM). While compound **10** binds with a lower affinity than SYA 013 at the $5HT_{1A}$, both **11** and **12** bind with higher affinity at the $5HT_{1A}$ receptor. All three compounds have only weak to moderate binding at the $5HT_{2A}$ receptor. In a previous evaluation, we discovered that the benzothiazole moiety (unpublished observation) could substitute for the 4-fluorophenyl moiety in butyrophenones. Thus, we synthesized compounds **13**–**15** to explore the effect of the benzothiazole ring on the homopiperazine analog receptor binding. Compound **13** turned out to have a lower binding affinity at all the receptors of interest. Similarly, reducing the chain length between the benzothiazole and the homopiperazine by one, or three methylene groups (compounds **14** and **15**, respectively), led to further reductions in binding at all the receptors evaluated. In fact, compound **15** has no binding affinity at any of the receptors of interest. Insertion of a carbonyl group between the benzothiazole ring and the first methylene group in compound **13** to form **16** and in compound **14** to form **17** also did not result in an increase in binding at any of the receptors of interest. A cursory look at the contribution of each pharmacophoric group suggested that the tropanol moiety contributes significantly to binding at the dopamine receptors. So we hypothesized that replacement of the homopiperazine ring in **16** with the tropanol moiety to form compound **18** should improve binding at the dopamine receptors. Evaluation revealed that compound **18** binds to the D_2 receptor with an affinity of 180 nM, 16 nM at the D_3 and 508 nM at the D_4 receptor. Among the compounds synthesized and evaluated, compound **18** with 180/16 or 11.3 for D_2/D_3 receptor selectivity ratio and 508/16 or 31.8 for D_4/D_3 receptor selectivity ratio is the only compound with selectivity towards the D_3 receptor. It is important to note that there is preclinical evidence that selective antagonism at DAD_3 receptors reduces the reinforcing efficacy of drugs of abuse, reverses cognitive deficits and shows efficacy in animal models of schizophrenia and Parkinson's disease and thus, selective DAD_3 receptor antagonists may hold promise in the treatment of several neuropsychiatric diseases.[14–16] Excision of the carbonyl from compound **18** to form compound **19** produced an increase in binding at the D_2 receptor (D_2K_i = 44 nM) and no significant changes in binding at the D_3 or D_4 receptors. There was also diminished binding at the serotonin receptors of interest for both compounds **18** and **19**. Thus, it would seem that the benzothiazole-linked aryl tropanols may constitute a new scaffold for the development of selective D_3 receptor agents.

Finally, all compounds were evaluated at the histamine H-1 receptors in order to explore their potential to induce weight gain.[10] Apart from compounds **13, 16** and **19**, (Table 1) all compounds bind with lower affinity than SYA 013 and hence can be considered less likely to induce treatment-emergent weight gain.

In conclusion, the SAR studies identified four of the homopiperazine and tropanol analogs, compounds **7, 8, 11** and **12**, satisfy our stated initial criteria for binding to D_2 and $5HT_{1A}$ receptors and compare favorably with clozapine binding at these receptors. In addition, the four compounds have very low binding affinity at

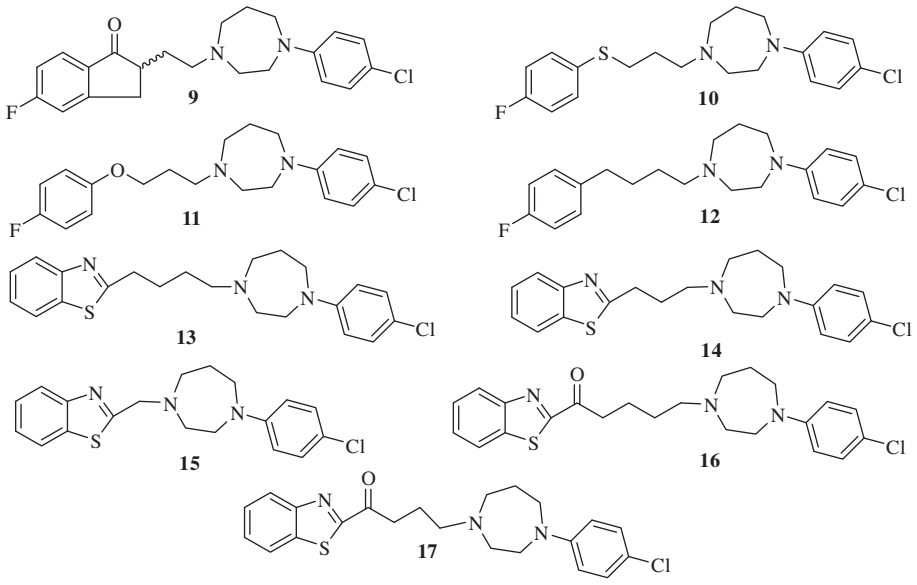
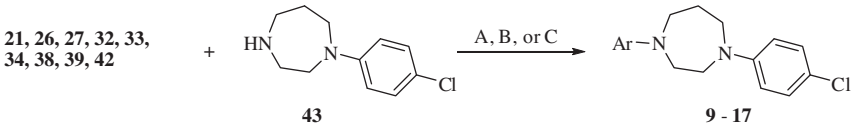


Chart 2. Structures of homopiperazine analogs, 9–17.



Scheme 6. Reagents and conditions: Method A: (1) KI, K_2CO_3, DME, reflux, 16 h; (2) TsOH, MeOH, rt. Method B: KI, K_2CO_3, DME, reflux, 16 h. Method C: K_2CO_3, DME, reflux, 16 h.

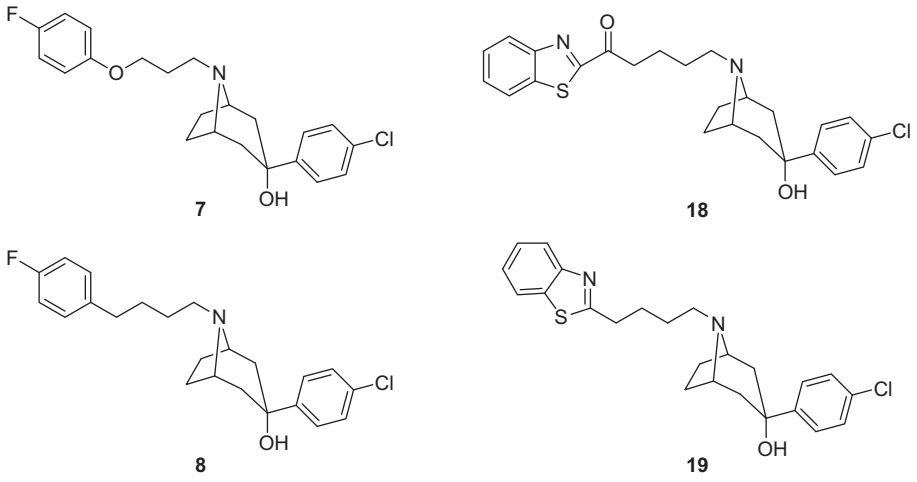
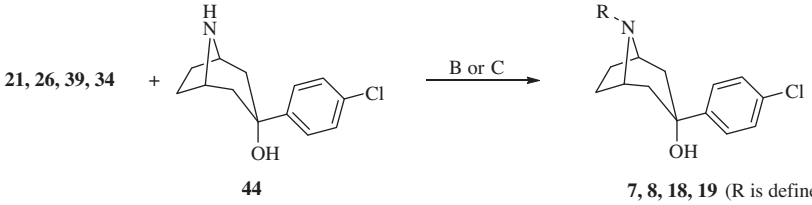


Chart 3. Structures of tropanol analogs **7**, **8**, **18** and **19**.



Scheme 7. Reagents and conditions: Method B: KI, K_2CO_3, DME, reflux, 16 h. Method C: K_2CO_3, DME, reflux, 16 h.

$5HT_{2C}$ and histamine H-1 receptors indicating a low propensity for inducing weight gain. Compounds **18** and **19** show selectivity for the D_3 receptor and thus may constitute a new scaffold for further exploration.

Table 1
Binding affinity constants of compounds at selected DA, 5-HT and H-1 receptors

Compd #	Binding data; K_i ± SEM (nM)						
	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	D_2	D_3	D_4	H_1
Cloz[a]	140	8.9	17.0	130	240	54	1.8
Hal[a]	3600	120	4700	0.89	2.5	3.3	440
2[a]	117.4 ± 32.6	23.6 ± 2.7	1425 ± 207	43.3 ± 13.3	158.8 ± 35.1	6.6 ± 0.6	188.6 ± 16.0
3[a]	90.9 ± 21.0	109.6 ± 16.0	3552± 943	253.5 ± 38.9	ND	17.5 ± 2.0	157.6 ±36.0
4[a]	ND	ND	ND	170	220	520	ND
5[a]	2332 ± 470	194.8 ± 53.0	3513 ± 912	178.4 ± 29.2	548.1± 246.0	41.8 ± 9.0	1014 ± 206
6[a]	27.7 ± 8.0	30.9 ± 6.0	872.1 ± 178.0	1.6 ± 0.1	5.1 ± 3.0	5.3 ± 1.0	8780 ± 1625
7	123.0 ± 12.9	236.0 ± 21.6	MP	22.0 ± 3.1	4.1± 0.6	49.0 ± 9.1	4,149 ± 924
8	102.0 ± 11.8	317.0 ± 29.2	2434 ± 583	33.0 ± 4.6	9.7 ± 1.1	9.4 ± 1.5	1719 ± 368
9	415.0 ± 48.1	411.5 ± 52.5	3775 ± 704	1021 ± 142	590.0 ± 54.3	37.0 ± 4.3	ND
10	168 ± 19	163.0 ± 20.0	2529 ± 223	751.1 ± 92.3	1,020 ± 25	32.1 ± 2.5	800.2 ± 69.9
11	73.0 ± 14.7	566.6 ± 91.9	>10,000	172.0 ± 28.1	208.8 ± 43.4	110.0 ± 12.6	509.0 ± 71.1
12	91.0 ± 10.5	510.3 ±76.9	4097 ± 754	139.0 ± 25.3	3043 ± 176	123.0 ± 19.9	1247 ± 204
13	263.0 ± 36.5	159.0 ± 11.0	1420 ± 295	258.7 ± 48.4	152.0 ± 21.0	28.6 ± 3.4	61.0 ± 8.5
14	216.0 ± 30.0	696.0 ± 51.3	ND	MP	863.0 ± 132.9	431.0 ± 40.7	665.0 ± 47.0
15	MP	MP	MP	MP	MP	MP	MP
16	495.0 ± 91.0	1003 ± 96	5920±769	1983 ± 163	1051 ± 174	1215 ± 67	129.0 ± 12.0
17	MP	1038[b]	MP	MP	777.0 ± 125.7	126.0 ± 20.4	ND
18	MP	MP	MP	180.0 ± 29.5	16.0 ± 2.6	508.0 ± 1.2	ND
19	274.0 ± 52.7	>10,000	4623[b]	44.0 ± 3.1	13.0 ± 1.8	432.0 ± 91.1	187.0 ± 34.5

Abbreviations: MP, Missed primary assay threshold of 50% inhibition; ND, Not determined; Cloz, Clozapine; Hal, Haloperidol.
[a] Results were previously reported in Ref. 7.
[b] Standard Errors are within 20% of the mean.

4. Experimental

4.1. General

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.

4.2. Synthesis

4.2.1. Synthesis of methanesulfonates 26 and 27

A mixture of 4-fluorophenol (1.12 g, 10 mmol), 3-chloropropanol (1.4 g, 15 mmol), KI (50 mg), K_2CO_3 (2.76 g, 20 mmol) in ^{i}PrOH was refluxed under N_2 for 12 h. The resulting mixture was diluted with EtOAc (200 mL), and washed with water (50 mL) then brine (50 mL). The organic layer was dried with Na_2SO_4, filtered and the filtrate was concentrated in vacuo to give 3-(4-fluorophenoxy)propan-1-ol **24** as the product. The product was used for the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 6.96 (2H, t, J = 8.4 Hz), 6.84 (2H, dd, J = 4.5, 9.0 Hz), 4.09 (2H, t, J = 6.0 Hz), 3.85 (2H, m), 2.03 (2H, m).

To a solution of 3-(4-fluorophenoxy)propan-1-ol **24** (1.3 g, 7.6 mmol) and Et_3N (3 mL) in CH_2Cl_2 (10 mL) was added at room temperature MsCl (0.8 mL, 10.3 mmol). The mixture was stirred at room temperature for 12 h followed by direct purification through column chromatography on silica gel to provide 3-(4-fluorophenoxy)propyl methanesulfonate **26**, with a yield of 95%. ^{1}H NMR ($CDCl_3$): δ 6.97 (2H, t, J = 8.1 Hz), 6.83 (2H, dd, J = 4.5, 9.0 Hz), 4.44 (2H, t, J = 6.0 Hz), 4.05 (2H, t, J = 6.0 Hz), 2.21 (2H, m).

4.2.2. 3-(4-Fluorophenylthio)propan-1-ol (25)

Yield 72%. ^{1}H NMR ($CDCl_3$): δ 7.35 (2H, dd, J = 5.4, 8.4 Hz), 6.99 (2H, t, J = 8.4 Hz), 3.76 (2H, t, J = 6.0 Hz), 2.98 (2H, t, J = 7.2 Hz), 1.85 (2H, m).

4.2.3. 3-((4-Fluorophenyl)thio)propyl methanesulfonate (27)

Yield 94%. ^{1}H NMR ($CDCl_3$): δ 7.37 (2H, dd, J = 9.0, 4.8 Hz), 7.00 (2H, t, J = 9.0 Hz), 4.30 (2H, t, J = 8.0 Hz), 3.00 (3H, s), 2.78 (2H, t, J = 7.2 Hz), 2.02 (2H, m).

4.3. General procedure for the synthesis of 32, 33 and 34

4.3.1. 2-(4-Chlorobutyl)benzo[d]thiazole (34)

A solution of 2-aminothiophenol **28** (5 g, 39.93 mmol) in toluene (50 ml) and 5-chloropentanoyl chloride (**18**) (6.81 g, 44 mmol) was added dropwise with cotinuous stirring over a 15 min period resulting in the formation of an off-white precipitate. The mixture was allowed to continue stirring at rt overnight and then partitioned between H_2O (100 mL) and EtOAc (200 mL) and the organic layer separated. The organic layer was washed with a saturated solution of NaCl (100 mL), H_2O (100 mL) dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (Combiflash) using EtOAc/Hexanes (1:9) to produce 2-(4-chlorobutyl)benzo[*d*]thiazole **34** as an oily liquid (5 g, 55.5%). ^{1}H NMR ($CDCl_3$): δ 7.95 (1H, d, J = 6.2 Hz), 7.8 (1H, d, J = 8.7 Hz), 7.46–7.40 (1H, m), 7.35–7.30 (1H, m), 3.52 (2H, t, J = 6.6 Hz), 3.10 (2H, t, J = 7.8 Hz), 1.95–1.77 (2H, m), 1.62–1.54 (2H, m).

4.3.2. 2-(3-Chloropropyl)benzo[*d*]thiazole, 33

Using 4-chlorobutanoyl chloride, compound **33** was obtained in 72% yield. ^{1}H NMR (CD_3OD): δ 8.14 (1H, d, J = 4.1 Hz), 8.02 (1H, d, J = 4.1 Hz), 7.72–7.59 (2H, m), 3.64–3.57 (2H, m), 3.38–3.28 (2H, m), 1.95–1.86 (2H, m).

4.3.3. 2-(Chloromethyl)benzo[*d*]thiazole (32)

Using 2-chloroacetyl chloride, compound **32** was obtained in 76% yield. ^{1}H NMR ($CCCl_3$): δ 7.96 (1H, d, J = 7.5 Hz), 7.70 (1H, dd,

J = 7.8, 09 Hz), 7.48–7.43 (1H, m), 7.39–7.33 (1H, m), 3.32 (2H, t, *J* = 6.0 Hz).

4.4. General procedure for the synthesis of 38 and 39

4.4.1. 1-(Benzo[*d*]thiazol-2-yl)-5-iodopentan-1-one, 39

To a stirred solution of benzothiazole **35** (10 g, 74.0 mmol) in dry THF (37 mL) was added drop wise *n*-BuLi (37 mL 1 M solution in THF) at −78 °C under N_2. A clear orange solution was obtained. To this resulting solution was added a solution of lactone **37** (8.14 g, 94.7 mmol) in dry THF (37 mL) at −78 °C and the mixture continuously stirred at −78 °C for 1 h. After removal of the cold bath, the reaction mixture was continuously stirred for 30 min and then quenched with large excess of (0.1 M) HCl (300 mL). The aqueous mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic extract was washed with H_2O (2 × 100 mL), saturated NaCl, and dried over Na_2SO_4. The solution was concentrated in vacuo and the crude product was dissolved in EtOAc (50 mL), and hexane (200 mL) was added. An orange precipitate resulted, was collected, washed with 10% EtOAc in Hexane (200 mL), and dried in vacuo to give the pure product 1-(benzo[*d*]thiazol-2-yl)-5-hydroxypentan-1-one (6.5 g). The product was used directly without further purification in subsequent reactions. ^{1}H NMR ($CDCl_3$): δ 8.20–8.16 (1H, dd, *J* = 1.8, 6.9 Hz), 7.99–7.96 (1H, dd, *J* = 1.5, 7.2 Hz), 7.62–7.52 (2H, m), 3.74–3.72 (2H, t, *J* = 6.3 Hz), 3.51–3.30 (2H, t, *J* = 7.2 Hz), 2.00–1.88 (2H, m), 1.76–1.67 (2H, m).

To a solution of triphenylphosphine (TPP) (3.12 g, 11.9 mmol) and imidazole (810 mg) in dichloromethane (30 mL) was added iodine (3.02 g, 11.9 mmol) at 0–5 °C. The reaction mixture was stirred at 0–5 °C for 30 min. A solution of 1-(benzo[*d*]thiazol-2-yl)-5-hydroxypentan-1-one (2.0 g, 8.5 mmol) in dichloromethane (15 mL) was added drop wise in 5 min. The reaction mixture was stirred at 0–5 °C for another 30 min, and then the ice bath was removed and continuously stirred at room temperature for 12 h. When TLC showed that the reaction was completed, the reaction mixture was treated with water (100 mL). The two layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water (2 × 100 mL), 10% sodium thiosulfate (50 mL), water (100 mL) and saturated NaCl aqueous solution (75 mL), then dried over Na_2SO_4 and concentrated in vacuo. The crude product was further purified by flash chromatography (Combiflash) using EtOAc/Hexane (1:9) to obtain the pure product 1-(benzo[*d*]thiazol-2-yl)-5-iodopentan-1-one (**39**) 1.8 g, in a yield of 61%. ^{1}H NMR ($CDCl_3$): δ 8.20–8.17 (1H, m), 8.00–7.97 (1H, m), 7.61–7.51 (2H, m), 3.34–3.29 (2H, t, *J* = 6.6 Hz), 3.27–3.23 (2H, t, *J* = 6.9 Hz), 1.98–1.92 (4H, m).

4.4.2. 1-(Benzo[*d*]thiazol-2-yl)-4-iodobutan-1-one, 38

Using benzothiazole **35** and lactone **36**, compound **38** was obtained (as described for compound **39** above) in 37% yield. ^{1}H NMR ($CDCl_3$): δ 8.21–8.18 (1H, m), 8.00–7.97 (1H, m), 7.62–7.52 (2H, m), 3.47–3.42 (2H, t, *J* = 6.9 Hz), 3.37–3.32 (2H, t, *J* = 6.6 Hz), 2.39–2.30 (2H, q, *J* = 6.9 Hz).

4.4.3. Synthesis of 2′-(2-chloroethyl)-5′-fluoro-2′,3′-dihydrospiro[[1,3]dioxolane-2,1′-indene], 42

A mixture of **20** (10 g, 50 mmol), hexamethylenetetraamine (10.5 g, 75 mmol) in Ac_2O (25 mL) was refluxed under N_2 for 16 h and allowed to cool to room temperature. The mixture was then diluted with $CHCl_3$ (500 mL), washed with 10% HCl solution (2 × 300 mL), H_2O (300 mL) and saturated $NaHCO_3$ (300 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 affording the pure product as 4-chloro-1-(4-fluorophenyl)-2-methylenebutan-1-one **40**, (2.8 g, 26.4% yield). ^{1}H NMR ($CDCl_3$): δ 7.82 (2H, dd, *J* = 5.7, 9.0 Hz), 7.13 (2H, t, *J* = 9.0 Hz), 5.99 (1H, s), 5.73 (1H, s), 3.72 (2H, t, *J* = 6.6 Hz), 2.94 (2H, t, *J* = 6.0 Hz).

Compound **40** (1.2 g, 5.64 mmol) was dissolved in concentrated H_2SO_4 (4 mL) and heated at 60 °C for 1 h. After cooling to room temperature, the mixture was diluted with EtOAc (200 mL) and washed with saturated $NaHCO_3$ (2 × 200 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 affording 2-(2-chloroethyl)-5-fluoro-2,3-dihydro-1*H*-inden-1-one **41**. ^{1}H NMR ($CDCl_3$): δ 7.76 (1H, dd, *J* = 5.4, 8.4 Hz), 7.08 (2H, m), 3.83 (1H, m), 3.76 (1H, m), 3.42 (1H, dd, *J* = 7.8, 17.1 Hz), 2.93 (1H, m), 2.83 (1H, dd, *J* = 4.2, 17.1 Hz), 2.44 (1H, m), 1.91 (1H, m).

A solution of compound **41** (5 g, 23.5 mmol), ethylene glycol (5 mL), and TsOH (100 mg) in toluene (50 mL) was refluxed under N_2 for 48 h. Water was removed by azeotropic distillation and the reaction was monitored by ^{1}H NMR. The reaction was quenched by addition of Et_3N (1 mL), diluted with EtOAc (250 mL), washed with saturated $NaHCO_3$ (25 mL) followed by water (25 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to obtain a mixture of 2-(2-chloro-ethyl)-5-fluoro-inden-1-one **41** and its ethylene acetal **42** in a ratio of 1:4. 2-(2-chloroethyl)-5-fluoro-indan-1-one **41** was removed by reducing it to its 2-(2-chloroethyl)-5-fluoro-indan-1-ol with $NaBH_4$ in MeOH followed by column chromatography on silica gel affording 2-(2-chloro-ethyl)-5-fluoro-indan-1-one ethylene acetal **42** (4.5 g, 75% yield). ^{1}H NMR ($CDCl_3$): δ 7.26 (1H, m), 6.92 (2H, m), 4.26 (1H, m), 4.12 (3H, m), 3.71 (1H, m), 3.60 (1H, m), 3.07 (1H, m), 2.72 (1H, m), 2.64 (1H, m), 2.16 (1H, m), 1.94 (1H, m), 1.94 (1H, m).

4.5. Synthesis of compound 9

4.5.1. Method A: 2-(2-(4-(4-chlorophenyl)-1,4-diazepan-1-yl)ethyl)-5-fluoro-2,3-dihydro-1*H*-inden-1-one, 9

A mixture of **42** (1.2 g, 4.67 mmol), **43** (1.3 g, 5.6 mmol), KI (100 mg, 0.5 mmol), and K_2CO_3 (1.2 g, 8.75 mmol) in DME (10 mL) was heated to reflux under N_2 for 16 h. The mixture was directly purified through column chromatography on silica gel affording 2-{2-[4-(4-chlorophenyl)-[1,4]diazepan-1-yl]-ethyl}-5-fluoro-indan-1-one ethylene acetal. This product was dissolved in wet MeOH, and TsOH added with stirring at rt. After stirring at rt for 12 h, the solution was diluted with EtOAc (450 mL), followed by washing with saturated $NaHCO_3$ (40 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to dry and followed by column chromatography on silica gel affording 2-(2-(4-(4-chlorophenyl)-1,4-diazepan-1-yl)ethyl)-5-fluoro-2,3-dihydro-1*H*-inden-1-one. The product was converted to its hydrochloride salt, and recrystallized from MeOH–Et_2O affording the HCl salt of **9**, in a yield of 25%, mp 176–177 °C. ^{1}H NMR (DMSO-*d*6): δ 11.16 (1H, br s), 7.71 (1H, dd, *J* = 5.4, 8.7 Hz), 7.43 (1H, d, *J* = 8.7 Hz), 7.27 (1H, t, *J* = 8.7 Hz), 7.19 (2H, d, *J* = 8.7 Hz), 6.75 (2H, d, *J* = 8.7 Hz), 3.77 (2H, m), 3.47 (2H, m), 3.34 (3H, m), 3.12 (4H, m), 2.83 (2H, m), 2.37 (1H, m), 2.23 (1H, m), 2.11 (1H, m), 1.86 (1H, m). Calcd for $C_{22}H_{26}Cl_3FN_2O$:C 57.47, H 5.70 N 6.09; Found: C 57.94, H 6.04, N 6.02.

4.6. Synthesis of compounds 7, 8, 10–15, 19: General procedure: Method B

4.6.1. 3-(4-Chlorophenyl)-8-(3-(4-fluorophenoxy)propyl)-8-azabicyclo[3.2.1]octan-3-ol (7)

A mixture of 3-(4-fluorophenoxy)propylmethanesulfonate **26** (0.73 g, 3.1 mmol), 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol **44** (1.0 g, 2.56 mmol), KI (0.2 g), and K_2CO_3 (1.10 g, 7.69 mmol) in DME (25 ml) was heated to reflux under N_2 for 16 h. The mixture was diluted with EtOAc (450 mL), followed by washing with saturated $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4

and filtered. The filtrate was concentrated in vacuo to dry followed by column chromatography on silica gel affording 3-(4-chlorophenyl)-8-(3-(4-fluorophenoxy)propyl)-8-azabicyclo[3.2.1]octan-3-ol **7** in an off white semi-solid form. The product was converted to the HCl salt, followed by recrystallization in EtOAc–Et_2O to give its HCl salt (722 mg), in a yield of 72.3%, mp 218.4–219.2 °C. ^{1}H NMR (CD_3OD): δ 7.40 (2H, m), 7.15 (2H, m), 7.88 (2H, m), 6.77 (2H, m), 3.89 (2H, t, J = 6.3 Hz), 3.21 (3H, m), 2.53 (2H, m), 2.20 (4H, m), 1.88 (4H, m), 1.69 (2H, m). Calcd for $C_{22}H_{26}Cl_2FNO_2$:C 61.98, H 6.15, N 3.26; Found: C 61.48, H 6.13, N 3.23.

4.6.2. 3-(4-Chlorophenyl)-8-(4-(4-fluorophenyl)butyl)-8-azabicyclo[3.2.1]octan-3-ol HCl, 8

The product of alkyl chloride **21** and amine **44** was converted into its HCl salt and recrystallized from EtOAc to give the HCl salt of **8** in a yield of 79.5%, mp 223.2–224.9 °C. ^{1}H NMR ($CDCl_3$): δ 7.56 (2H, m), 7.35 (2H, m), 7.23 (2H, m), 7.00 (2H, m), 4.11 (2H, m), 3.32 (2H, m), 3.07 (2H, t, J = 16.5 Hz), 2.67 (4H, m), 2.54 (2H, m), 2.20 (4H, m), 1.79 (4H, m). Calcd for $C_{23}H_{28}Cl_2FNO$:C 65.09, H 6.65, N 3.30; Found: C 64.95, H 6.66, N 3.31.

4.6.3. 1-(4-Chlorophenyl)-4-(3-((4-fluorophenyl)thio)propyl)-1,4-diazepane, 10

The product of the reaction of methanesulfonate **27** and amine **43** was converted to the HCl salt and recrystallized from MeOH–Et_2O. Yield 69%, mp 172–173 °C. ^{1}H NMR (DMSO-*d*6): δ 11.2 (1H, s), 7.63 (1H, s), 7.42 (2H, dd, J = 5.4, 9.0 Hz), 7.17 (4H, m), 6.75 (2H, d, J = 9.0 Hz), 3.75 (2H, m), 3.41 (4H, m), 3.16 (2H, m), 3.08 (2H, m), 2.99 (2H, t, J = 7.2 Hz), 2.38 (2H, m), 2.10 (2H, m), 1.98 (2H, m). Calcd for $C_{20}H_{26}Cl_3FN_2S$:C53.16, H 5.80, N 6.20; Found: C 53.39, H 5.98, N 6.22.

4.6.4. 1-(4-Chlorophenyl)-4-(3-(4-fluorophenoxy)propyl)-1,4-diazepane, 11

The product of the methanesulfonate **26** and amine **43** was converted to the HCl salt after crystallization from MeOH–Et_2O, in a yield of 53.9%, mp 207–208 °C. ^{1}H NMR ($CDCl_3$): δ 7.23 (4H, m), 6.98 (4H, m), 4.89 (2H, s), 4.432 (2H, s), 3.66 (2H, m), 3.30 (3H, m), 3.19 (2H, t, J = 6.6 Hz), 2.710(2H, t, J = 7.8 Hz), 1.79 (4H, m). Calcd for $C_{20}H_{26}Cl_3FN_2O{\cdot}0.25H_2O$:C 54.56, H 6.07, N 6.36; Found: C 54.58, H 5.902, N 6.00.

4.6.5. 1-(4-Chlorophenyl)-4-(4-(4-fluorophenyl)butyl)-1,4-diazepane, 12

The product of alkyl chloride **21** and amine **43** was converted to the HCl salt after crystallization from MeOH–Et_2O, in a yield of 83.2%, mp 206–207 °C. ^{1}H NMR ($CDCl_3$): δ 7.21 (4H, m), 7.07 (2H, m), 6.75 (2H, m), 4.23 (1H, m), 3.60 (6H, m), 3.00 (6H, m), 2.60 (2H, m), 2.31 (1H, m), 1.95 (2H, m), 1.65 (2H, m). Calcd for $C_{21}H_{27}Cl_2FN_2{\cdot}0.75H_2O$: C 61.39, H 6.99, N 6.82; Found: C 61.22, H 6.89, N 6.80.

4.6.6. 2-(4-(4-(4-Chlorophenyl)-1,4-diazepan-1-yl)butyl) benzo[*d*]thiazole, 13

The product of benzothiazole **34** and amine **43** was converted into the tosylate salt, and re-crystallized from MeOH–Et_2O, in a yield of 15%, mp 146–147 °C. ^{1}H NMR (DMSO-*d*6): δ 9.29 (1H, br s), 8.24 (2H, m), 7.64 (2H, m), 7.45 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 9.0 Hz), 7.08 (2H, d, J = 8.1 Hz), 6.76 (2H, d, J = 9.0 Hz), 3.77 (1H, m), 3.61 (2H, m), 3.40 (8H, m), 3.23 (3H, m), 2.26 (3H, s), 2.15 (2H, m), 2.07 (2H, m). Calcd for $C_{29}H_{34}ClN_3O_3S_2$:C 60.87, H 5.99, N 7.34; Found: C 60.82, H 5.78, N 7.35.

4.6.7. 2-(3-(4-(4-Chlorophenyl)-1,4-diazepan-1-yl)propyl)benzo[d]thiazole, 14

The product of benzothiazole **33** and amine **43** was converted to the hydrochloride salt after crystallization from MeOH–Et_2O. Yield 48%, mp 97–100 °C. ^{1}H NMR (CD_3OD): δ 8.16 (1H, d, J = 4.1 Hz), 8.02 (1H, d, J = 4.1 Hz), 7.72–7.59 (2H, m), 7.21 (2H, d, J = 9.0 Hz), 6.98 (2H, d, J = 4.5 Hz), 3.92 (3H, m), 3.60 (3H, d, J = 5.7 Hz), 2.51–3.41 (7H, m), 2.52–2.34 (5H, m), 1.28–1.25 (1H, m). Calcd for $C_{21}H_{27}Cl_4N_3S{\cdot}1.5H_2O$:C 48.29, H 5.21, N 8.04; Found: C 48.26, H 5.64, N 8.09.

4.6.8. 2-((4-(4-Chlorophenyl)-1,4-diazepan-1-yl)methyl)benzo[*d*]thiazole, 15

The product of the benzothiazole **32** and amine **43** was converted to the HCl salt after recrystallization from MeOH–Et_2O in a yield of 53%, 197–199 °C. ^{1}H NMR ($CDCl_3$): δ 8.08 (2H, t, J = 7.8 Hz), 7.62–7.49 (2H, m), 7.29 (2H, d, J = 4.5 Hz), 7.05 (2H, d, J = 5.1 Hz), 5.02 (2H, s), 4.99 (4H, s), 3.98–3.63 (7H, m). Calcd for $C_{19}H_{21}Cl_2N_3S$:C 57.87, H 5.37, N 10.66; Found: C 57.69, H 5.26, N 10.99.

4.6.9. 8-(4-(Benzo[*d*]thiazol-2-yl)butyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol, 19

The product of the benzothiazole **34** and amine **44** was converted to the HCl salt after recrystallization from MeOH–Et_2O in a yield of 37%, mp 198–200 °C. ^{1}H NMR (DMSO-*d*6): δ 10.92 (1H, br s), 8.04 (1H, d, J = 8.1 Hz), 7.92 (1H, d, J = 8.1 Hz), 7.77 (2H, d, J = 8.4 Hz), 7.47 (1H, m), 7.40 (1H, m), 7.34 (2H, d, J = 8.4 Hz), 3.98 (2H, m), 3.15 (2H, m), 3.00 (2H, m), 2.63 (2H, m), 2.46 (4H, m), 2.08 (2H, m), 1.93 (6H, m). Calcd for $C_{24}H_{28}Cl_2N_2OS{\cdot}0.4H_2O$:C 61.24, H 6.00, N 5.95; Found: C 61.29, H 6.05, N 5.85.

4.7. Synthesis of compounds 16–18: Method C General procedure:

4.7.1. 1-(Benzo[*d*]thiazol-2-yl)-5-(3-(4-chlorophenyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)pentan-1-one, 18

A mixture of 1-(benzo[*d*]thiazol-2-yl)-5-iodopentan-1-one **39** (0.635 g, 2.5 mmol), 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol **44** (680 mg, 2.85 mmol), K_2CO_3 (700 mg, 5.07 mmol) in DME (10 mL) was heated to reflux under N_2 for 16 h. The mixture was diluted with EtOAc (400 mL) and washed with brine (50 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to dry followed by column chromatography on silica gel affording 1-benzothiazol-2-yl-5-(4-phenyl-piperidin-1-yl)-pentan-1-one. The product was converted into the HCl salt followed by crystallization from MeOH–Et_2O (520 mg) in a yield of 43%, mp 202–204 °C. ^{1}H NMR (DMSO-*d*6): δ 10.46 (1H, br s), 8.24 (2H, m), 7.73 (2H, d, J = 8.7 Hz), 7.64 (2H, m), 7.36 (2H, d, J = 9.0 Hz), 5.47 (1H, s), 4.30 (2H, m), 3.35 (4H, m), 3.14 (2H, m), 3.00 (2H, m), 2.57 (2H, m), 2.09 (2H, m), 1.88 (4H, m), 1.75 (2H, m). Calcd for $C_{25}H_{28}Cl_2N_2O_2S{\cdot}0.8H_2O$: C 59.36, H 5.58, N 5.54; Found: C 59.46, H 5.82, N 5.57.

4.7.2. 1-(Benzo[*d*]thiazol-2-yl)-5-(4-(4-chlorophenyl)-1,4-diazepan-1-yl)pentan-1-one, 16

Using 1-(benzo[*d*]thiazol-2-yl)-5-iodopentan-1-one **39** and amine **43**, the free base of compound **16** was obtained and converted to HCl salt followed by crystallization from MeOH–Et_2O in a yield of 32%. ^{1}H NMR ($CDCl_3$) δ 8.18–8.15 (2H, d, J = 8.7 Hz), 7.97–7.94 (2H, d, J = 8.7 Hz), 7.59–7.50 (2H, m), 7.13–7.09 (2H, d,

J = 9.3 Hz), 6.57–6.54 (2H, d, *J* = 9 Hz), 3.49–3.39 (4H, m), 3.28 (2H, t, *J* = 7.2 Hz), 2.74–2.71 (2H, m), 2.59–2.5 (4H, m), 1.96–1.8 (4H, m), 1.64–1.56 (2H, m).

The free base was converted to the HCl salt, mp 242 °C. ^{1}H NMR (CD_3OD): δ 8.14–8.05 (2H, m), 7.61–7.51 (2H, m), 7.16 (2H, br s), 6.79 (2H, br s), 3.85–3.45 (13H, m), 2.30 (2H, m), 1.90 (3H, m). Calcd for $C_{23}H_{28}Cl_3N_3OS$.$3H_2O$:C 49.78, H 5.09, N 7.57; Found:C 49.68, H 5.28, N 7.43.

4.7.3. 1-(Benzo[*d*]thiazol-2-yl)-4-(4-(4-chlorophenyl)-1,4-diazepan-1-yl)butan-1-one, 17

The product of 1-(benzo[*d*]thiazol-2-yl)-4-iodobutan-1-one **38** and amine **43** was converted to the hydrochloride salt followed by crystallization from MeOH–Et_2O. Yield 22%, mp 194–195 °C. ^{1}H NMR (DMSO-*d*6): δ 10.83 (1H, br s), 8.23 (2H, m), 7.64 (2H, m), 7.19 (2H, d, *J* = 9.0 Hz), 6.76 (2H, d, *J* = 9.0 Hz), 3.78 (2H, m), 3.50 (2H, m), 3.40 (4H, m), 3.16 (4H, m), 2.35(1H, m), 2.11 (3H, m). Calcd for $C_{22}H_{26}Cl_3N_3OS$: C 54.27, H 5.38, N 8.63; Found:C 54.71, H 5.33, N 8.64.

4.8. Receptor binding studies

Binding affinities reported in Table 1 were conducted by the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP). Details of the methods and radioligands used for the binding assays were previously reported.[17]

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