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Identification of a butyrophenone analog as a potential atypical antipsychotic agent: 4-[4-(4-Chlorophenyl)-1,4-diazepan-1-yl]-1-(4-fluorophenyl)butan-1-one

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ABSTRACT

The synthesis and exploration of novel butyrophenones have led to the identification of a diazepane analogue of haloperidol, 4-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]-1-(4-fluorophenyl)butan-1-one (compound **13**) with an interesting multireceptor binding profile. Compound **13** was evaluated for its binding affinities at DA subtype receptors, 5HT subtype receptors, H-1, M-1 receptors and at NET, DAT, and SERT transporters. At each of these receptors, compound **13** was equipotent or better than several of the standards currently in use. In in vivo mouse and rat models to evaluate its efficacy and propensity to elicit catalepsy and hence EPS in humans, compound **13** showed similar efficacy as clozapine and did not produce catalepsy at five times its ED_{50} value.

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1. Introduction

The introduction of clozapine[1] (Clozaril, **1**) as a treatment option in the 1990s has opened the door to the use of atypical antipsychotics and the replacement of the prototypic agent, haloperidol (**2**) as a drug of choice for the treatment of schizophrenia. The superior therapeutic profile of clozapine and other atypical antipsychotic drugs and the long-term debilitating side-effects[2] associated with haloperidol treatment have conspired to diminish its use in the clinic. Among several hypotheses put forth to explain the long-term extrapyramidal side-effects of haloperidol including tardive dyskinesia is the fact that haloperidol undergoes biotransformations that lead to the formation of toxic metabolites.[3,4] Specifically, haloperidol has been shown to undergo CYP450-mediated oxidation to form pyridinium metabolites[5] which can potentially damage dopamine receptors in the nigrostriatum of the brain (Chart 1). Based on this hypothesis, we[6–9] proposed a drug-design strategy that replaces the piperidine ring in haloperidol with bioisosteric equivalents, which could not undergo in vivo biotransformation to pyridinium species known to be associated with neuronal toxicity. A similar strategy has more recently appeared in the literature.[10] The outcome of such a strategy was to enhance the pharmacological and side-effect profiles of the resulting agents.

Our laboratory has previously shown that modification in the piperidine ring of haloperidol results in significant changes in pharmacological activity.[6,7] We also identified new bioisosteric groups of the piperidine ring with binding profiles similar or better than those of haloperidol at the D2 dopamine receptor subtype.[7–9] Several of these compounds are shown in Chart 2, with new binding affinity data at selected receptors reported in Table 1.

Although compounds **5** and **6** have high affinity for $5HT_{1A}$ and $5HT_{2A}$ receptors, the demonstration that compound **5** elicits a higher catalepsy than haloperidol dampened our desire to pursue the tropane moiety as a piperidine bioisostere.[9] It is important to note that the alcoholic function in compounds **5** and **6** contributes significantly to affinity not only at the D2-like receptors but also at the $5HT_{1A}$ and $5HT_{2A}$ receptors (cf. compounds **5**–**7**). Interestingly, the OH group does not appear to play a significant role in the binding of the tropane analogs to the $5HT_{2C}$ receptor.

The reaction mechanism by which haloperidol is metabolized in vivo to a pyridinium species or BCPP+ has been suggested to begin

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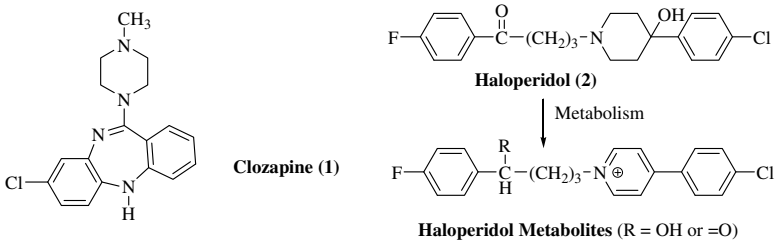


Chart 1.

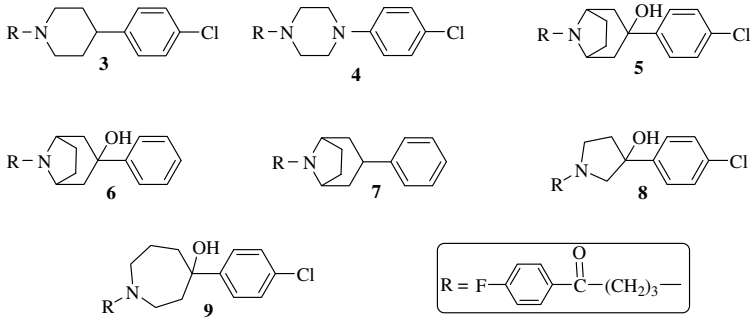


Chart 2.

with dehydration of the tertiary alcoholic function.[5] A drug-design strategy to prevent such a biotransformation is to eliminate the alcoholic function. Compound **3**, a haloperidol analog without its alcoholic function, was previously synthesized and evaluated at D2-like receptors.[7] The results supported the notion that the alcoholic function contributes to affinity but is not an absolute requirement for binding to dopamine receptors. Compound **4** in which the C-OH group was replaced with a nitrogen atom showed a lower binding affinity than haloperidol at the dopamine receptors.[8] Compounds **5** and **6** were designed on the premise that the tropane moiety could not form a pyridinium ring due to the fact that a double bond could not form at the ring junctions adjacent to the N atom.[9] In addition, bridging the ring restricts conformational mobility and holds the alcoholic function in a preferred conformation.[8] Binding evaluation showed that both compounds were as potent or more potent than haloperidol at D2-like receptors. It was further demonstrated that the OH group is in the axial position and this led to the suggestion that haloperidol most likely binds to the dopamine receptors with its OH in the axial position. Comparing **5** and **6** suggests that the chloro group contributes to binding but is also not an absolute requirement. Removal of the OH group from the tropane ring (compound **7**) again decreased affinity but retained sufficient dopamine binding affinity as observed for compound **3**. Contraction of the piperidine ring to a pyrrolidine (**8**) resulted in a decrease in affinity but expansion to a 7-membered homopiperidine ring (**9**) retained affinity as in haloperidol, thus suggesting that homopiperidine ring is bioisosteric to piperidine ring.[7] Separation of the enantiomers of compound **8** and their subsequent evaluation at D2-like receptors revealed that (+)-**8** was the eutomer.[6]

To further explore these changes in the piperidine moiety of haloperidol in our search for new antipsychotic drugs with atypical pharmacological profiles, we have embarked on SAR studies with modifications primarily in the piperidine ring that could lead to the identification of new agents with clozapine-like binding profiles, but without the associated weight gain and new onset type II diabetes.[11] Thus, it was desirable not only to evaluate the binding of the compounds at dopamine receptors but also at serotonergic receptors ($5HT_{1A}$ and $5HT_{2A}$), since binding to these receptors is often associated with therapeutic advantages observed in atypical antipsychotic drugs.[12] In addition, evaluation of the compounds at $5HT_{2C}$ and histamine H-1 receptors will be valuable indicators of whether these compounds have the potential to develop the weight gain side-effect associated with atypical antipsychotic drugs.[13] In line with the multiple receptor-targeting strategy in the development of new antipsychotic agents, we have focused

Table 1
Binding affinity constants of compounds to selected 5-HT and H-1 receptors

Compound	Binding data of compounds, K_i ± SEM (nM)						K_i D_2/K_i D_4 Ratio
	DAD_2	DAD_4	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$	H-1	
Cloz (**1**)[a]	130	54	140	8.9	17	1.8	2.4
Hal (**2**)[a]	0.89	10	3600	120	4700	440	0.09
4[b]	253.5 ± 38.9	17.5 ± 2.0	90.9 ± 21.0	109.6 ± 16.0	3552 ± 943	157.6 ± 36.0	2.8
5[b]	1.6 ± 0.14	5.3 ± 1.0	27.7 ± 8.0	30.9 ± 6.0	872.1 ± 178.0	8780 ± 1625	0.30
6[b]	2.3 ± 0.28	19.2 ± 2.3	37.6 ± 6.0	12.3 ± 3.0	>10,000	635.4 ± 96.0	0.12
7[b]	124.4 ± 16.5	176.8 ± 36.0	414.4 ± 101.0	106.0 ± 21.0	1065 ± 244	973.5 ± 207.0	0.70
(+)-**8**[b]	51.1 ± 6.0	3.6 ± 0.48	772.3 ± 90.0	75.8 ± 12.0	3598 ± 1162	1467 ± 473	14.2
(−)-**8**[b]	489.4 ± 119.4	245.5 ± 29.2	831.5 ± 126.0	241.5 ± 39.0	1252 ± 461	259.6 ± 34.0	2.0

[a] Binding data obtained from Ref. 12b.
[b] The synthesis and/or DA binding data of compounds previously reported in Refs. 7–9.

our design efforts on obtaining agents that have the following receptor binding profiles:

(a) Binding to DA D2 receptor with moderate affinity ($30 < K_i < 150$ nM).
(b) Binding to DA D4 receptor with high affinity ($K_i < 10$ nM).
(c) Binding to $5HT_{1A}$ and $5HT_{2A}$ receptors with high affinity ($K_i < 50$ nM).
(d) Binding to $5HT_{2C}$ and H-1 receptors with very low affinity ($K_i > 500$ nM).

The above criteria (a–d) will also guide the selection of compounds for evaluation in in vivo animal models for efficacy and the propensity of the compounds to produce catalepsy, a condition associated with extrapyramidal side-effects in humans.[14] To achieve the drug-design objectives, we have utilized observations from previous SAR studies to design compounds **10**–**14** (Chart 3) as probes for the dopamine, serotonin and histamine H-1 receptor subtypes in an attempt to obtain new prototype drugs.

2. Chemistry

Construction of the ethylene-bridged piperazine moiety was initiated using (2*S*,5*R*)-diethyl 2,5-dibromohexanedioate (**16**) as the starting material (Scheme 1) as previously reported.[15,16] Double alkylation of 4-chlorophenyl aniline with **16** yielded *N*-chlorophenyl pyrrolidine (**17**). Amidation of **17** with benzylamine produced the amide, **18**, which underwent a ring closure with the remaining ester function to form the bridged piperazine, **19**. An attempt to reduce the lactam functions of **19** with $LiAlH_4$ also resulted in the removal of the 4-chloro group on the phenyl ring to form the di-substituted 3,8-diaza-bicyclo[3.2.1]octane (**20**). Debenzylation of **20** to form **22** was accomplished by reaction with ethyl chloroformate and the subsequent hydrolytic cleavage of the resulting carbamate, **21**. Compound **10** was obtained by alkylation of the secondary amine function of **22** with 4-chloro-4′-fluorobutyrophenone. Target compounds **11** and **12** were obtained by alkylating the corresponding starting materials, **23** and **24**, respectively (commercially available from Sigma–Aldrich), with 4-chloro-4′-fluorobutyrophenone (Schemes 2 and 3). Scheme 4 describes the synthesis of target compound **13** in five steps. Initial starting material 4-chloroboronic acid (**26**) was synthesized from 4-chlorobromobenzene by lithiation with *n*-butyl lithium and treatment with trimethylborate. The chloroboronic acid was coupled to *N*-Boc protected 1,4-diazepane (**28**) under palladium-catalyzed amination condition to form **29**. Deprotection of **29** in trifluoroacetic acid delivered amine **30**, which was alkylated in the usual way with 4-chloro-4′-fluorobutyrophenone to form **13**. An alternative synthesis of compound **13** was also explored in which the 4-chlorophenyl homopiperazine (**30**) was obtained in one step without the protection and deprotection steps. The reaction involved the coupling of 4-chloroiodobenzene directly with unprotected homopiperazine under CuI catalysis to form compound **30** in excellent yield. The same alkylation step delivered the desired compound **13** in 61% overall yield (Scheme 5).

8-Methyl-8-aza-bicyclo[3.2.1]octa-3-one (**31**) served as the starting material for the synthesis of target compound **14** (Scheme 5). Compound **31** was converted to the cyclic lactam (**32**) by insertion of a nitrogen atom followed by reduction using lithium aluminum hydride to form **33** in very good yield (80%). The free secondary amine in **33** was BOC protected prior to its treatment with ethyl chloroformate to form the carbamate protected amine, **35**. Compound **35** was BOC deprotected and then coupled with 4-chloroboronic acid in the presence of copper acetate to yield **37**. Decarbamylation of **37** was achieved using KOH in ethylene glycol and the resulting secondary amine was alkylated with 4-chloro-4′-fluorobutyrophenone under the usual alkylating condition to produce the desired compound **14** (see Scheme 6).

3. Results and discussion

Our previous observation that bridging the piperidine ring to form the tropane analogs of haloperidol resulted in seven and threefold increases in binding affinity at the D2 and D4 receptors respectively informed the design of target compounds **10** and **14**. The rationale was to investigate bridged analogs to probe the effect of conformational restriction on piperazine and homopiperazine equivalents of haloperidol. Compound **10** can also be viewed as an analog of **7** with the carbon at position 4 of the ring replaced by a nitrogen atom. The ethylene bridge in compound **10** holds the piperazine ring in the chair conformation while in compound **11** the ring is held in the boat conformation by a methylene group. Binding affinity data for compounds **10**–**14** are reported in Table 2.

Both compounds **10** and **11** have only moderate to weak binding affinity at the D2-like receptors and do not meet the proposed criteria. Interestingly, compound **12**, previously reported by Yevich et al.[17] with the 4-chlorophenyl ring in compound **4** replaced by 1,3-diazine moiety, met the four criteria set of interest (Table 3). The authors pharmacologically evaluated compound **12** and its ketone-reduced analog for their binding affinity for DAD2, sigma and cortical α_1 adrenergic receptors, but not at the receptors of interest in this study. Thus, its synthesis provides an opportunity to compare the contributions of 4-chlorophenyl moiety in compound **4** with the 1,3-diazine ring in **12** to the binding affinities at the various receptors.

Compound **13**, which can be viewed as a homopiperazine analog of haloperidol and compound **9**, meets all the criteria except for its binding affinity at the $5HT_{1A}$ receptor. Compound **14**, a bridged analog of compound **13**, also showed low binding affinity for the receptors of interest (Table 2) and failed to meet the other stated criteria. Thus, it would appear that bridging does not necessarily result in favorable attributes for these compounds. Based on these observations, compound **13** was selected for further pharmacological evaluation.

Table 3 shows a head to head comparison of the binding affinities of compound **13** and several atypical antipsychotic drugs currently in use at several receptors known to have implications for the therapeutic value of atypical antipsychotic drugs. Compound **13** has moderate affinity for the DA D2 receptor and high affinity at the D4 receptor. The effect of compound **13** on apormophine-

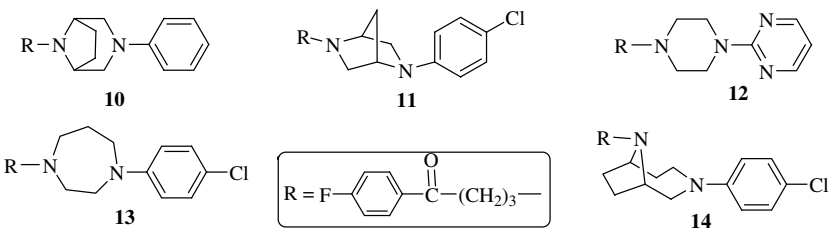
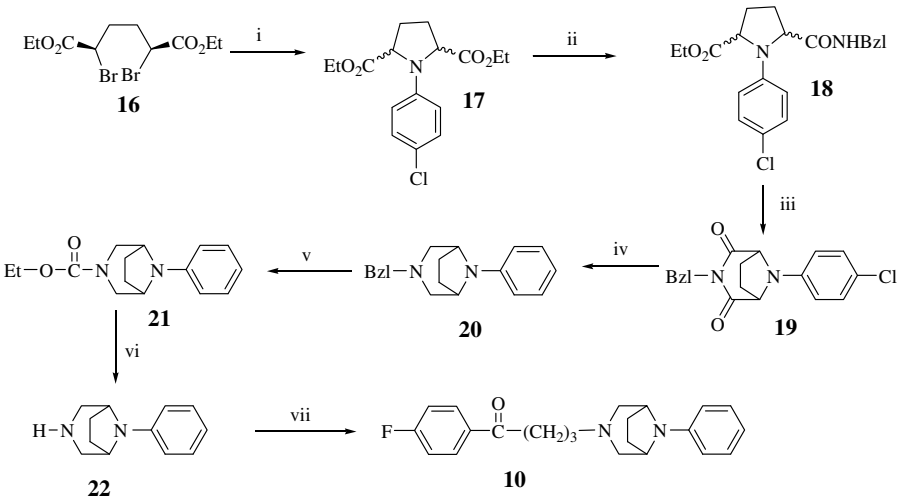
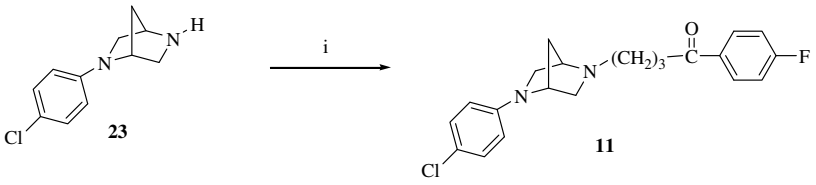


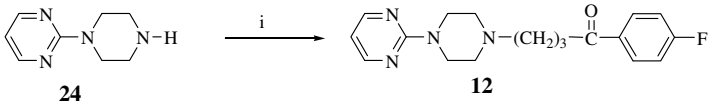
Chart 3.



Scheme 1. Reagents: (i) 4-chloroaniline, DME, KI; (ii) benzylamine, *o*-xylene; (iii) a—NaOH, EtOH; b—Ac_2O, NaOAc; (iv) $LiAlH_4$; (v) $ClCO_2Et$, toluene; (vi) KOH, EtOH, NH_2NH_2; (vii) 4-chloro-4′-fluorobutyrophenone, KI, K_2CO_3, DME.



Scheme 2. Reagents: (i) 4-chloro-4′-fluorobutyrophenone, KI, K_2CO_3, DME.



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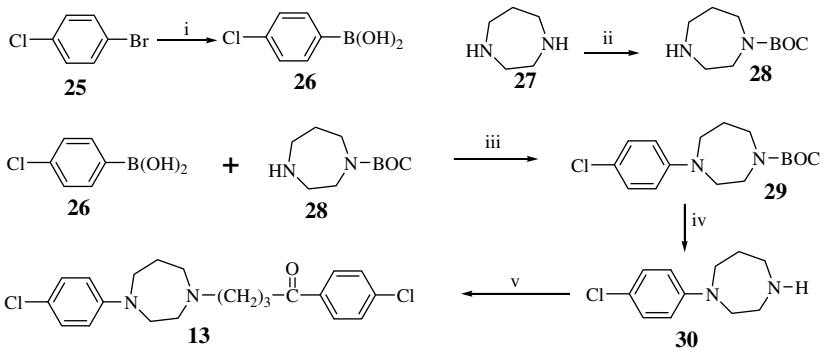
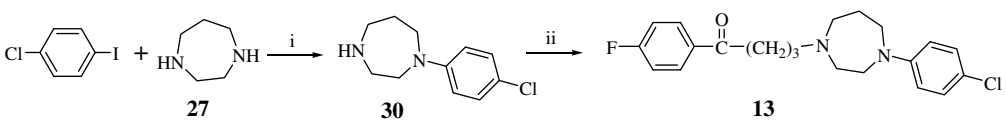
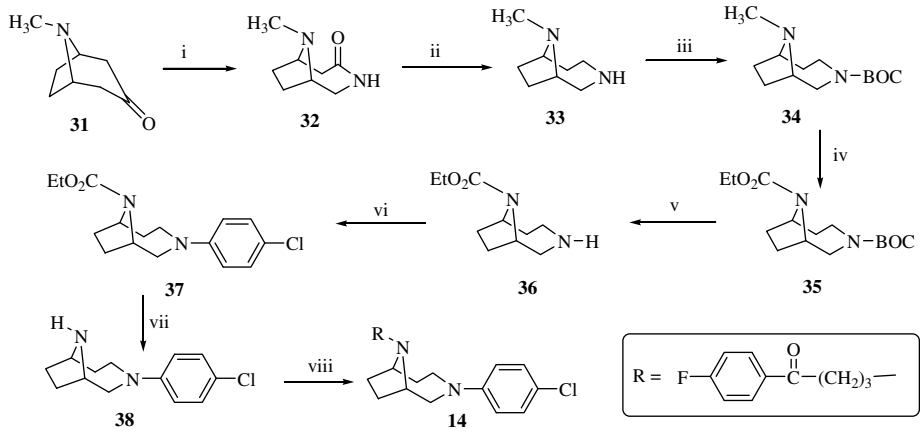


Scheme 4. Reagents: (i) a—*n*-BuLi, −78 °C, THF; b—$B(OMe)_3$; (ii) *t*-BuOH, NaOH, $(t\text{-BuOCO})_2O$; (iii) $Cu(OAc)_2$, NEt_3, Mol sieves (4 Å), rt; (iv) TFA, CH_2Cl_2; (v) 4-chloro-4′-fluorobutyrophenone, KI, K_2CO_3, DME.



Scheme 5. Alternative synthetic scheme for compound **13**. Reagents and conditions: (i) CuI, ethylene glycol, K_2CO_3, *i*-PrOH, 80 °C, reflux, 12 h; (ii) KI, K_2CO_3, DME, 4-chloro-4′-fluorobutyrophenone, reflux, 12 h.



Scheme 6. Reagents: (i) H_2SO_4, NaN_3; (ii) $LiAlH_4$, THF; (iii) *t*-BuOH, $(t\text{-BuOCO})_2O$; (iv) $ClCO_2Et$, toluene; (v) TFA; (vi) 4-chlorophenylboronic acid, $Cu(OAc)_2$, Et_3N, CH_2Cl_2, molecular sieves (4 Å), rt, 24–48 h; (vii) KOH, ethylene glycol; (viii) 4-chloro-4′-fluorobutyrophenone, KI, K_2CO_3, DME.

Table 2
Binding affinity constants of compounds to dopamine, 5HT, and histamine receptors

Compound	Binding (K_i ± SEM) data of synthetic compounds at selected receptors (nM)						
	D2	D3	D4	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$	H1
Cloz(**1**)[a]	130	240	54	140	8.9	17.0	1.8
Hal (**2**)[a]	1.4	2.5	3.3	3600	120	4700	440
10[b]	155	600	2100	ND	ND	ND	ND
11[b]	170	220	520	ND	ND	ND	ND
12	98.0 ± 15.3	244.1 ± 106.0	6.53 ± 0.76	30.5 ± 5.0	22.0 ± 4.0	4132 ± 1081	911.8 ± 152.0
13	43.3 ± 13.3	158.8 ± 35.1	6.6 ± 0.6	117.4 ± 32.6	23.6 ± 2.7	1425 ± 207	188.6 ± 16.0
14	178.4 ± 29.2	548.1 ± 246.0	41.8 ± 9.0	2332 ± 470	194.8 ± 53.0	3513 ± 912	1014 ± 206

ND, not determined; Hal, haloperidol; Cloz, clozapine.
[a] Data for compounds **1** and **2** were obtained from Ref. 12b.
[b] Data from Pfizer Global Research and Development Laboratories by A. W. Schmidt.

Table 3
Comparative binding affinity data for compound **13** and agents currently in use at human receptors and rat transporters

Receptor[a]	Binding (K_i ± SEM) data of compound **13** and standard agents at selected receptors (nM)[b]						
	Comound **13**	Clozapine[b]	Risperidone[b]	Ziprasidone[b]	Olanzapine[b]	Quetiapine[b]	Haldol[b]
DA D1	162.7 ± 33.1	290	580	130	52	1300	120
DA D2	43.3 ± 13.3	130	2.2	3.1	20	180	1.4
DAD3	158.8 ± 35.1	240	9.6	7.2	45	320	2.5
DAD4	6.6 ± 0.6	54	8.5	32	50	2200	3.3
$5HT_{1A}$	117.4 ± 32.6	140	210	2.5	2100	230	3600
$5HT_{2A}$	23.6 ± 2.7	8.9	0.29	0.39	3.3	220	120
$5HT_{2B}$	495.2 ± 94.0	NR	NR	NR	NR	NR	NR
$5HT_{2C}$	1425.0 ± 207	17	10	0.72	10	1400	4700
$5HT_6$	295.9 ± 48.6	11	2000	76	10	1400	6000
Hist H1	188.6 ± 16.0	1.8	19	47	2.8	8.7	440
M1	871.6 ± 75.6	1.8	2800	5100	4.7	100	1600
DAT	1150 ± 133	NR	NR	NR	NR	NR	NR
NET	850.7 ± 175.0	390	28,000	48	2000	680	5500
SERT	56.6 ± 6.0	3900	1400	53	>15,000	>18,000	1800

NR, not reported.
[a] Human cloned receptors were used in all cases except for the NT transporters which are from rats.
[b] Data for standard drugs were obtained from Ref. 12b.

treated mice (see later) suggests D2 receptor antagonism and thus, would be expected to demonstrate antipsychotic properties in humans.[18] $5HT_{1A}$ receptor activation has been suggested to contribute to the improved activity of certain atypical antipsychotic drugs.[12b,19]

Compound **13** has moderate affinity for $5HT_{1A}$ (K_i = 117 nM). This binding affinity is higher than that for risperidone and quetiapine but similar to that of clozapine (K_i = 140 nM). Compound **13** also binds with high affinity at the $5HT_{2A}$ receptor (K_i = 23.6 nM), a receptor implicated in the therapeutic efficacy of atypical antipsychotic drugs in treating the negative symptoms of schizophrenia and preventing motor disturbances associated with antipsychotic treatment.[20] While this affinity is 10-fold better than that of quetiapine, other atypical antipsychotics have higher affinity for this receptor. $5HT_6$ receptors are implicated in the amelioration of the cognitive disturbances in schizophrenia, and both clozapine and olanzapine have high affinity for this receptor.[21] While **13** has weak affinity for the $5HT_6$ receptor (K_i = 295.8 nM),

it is over 13-fold more potent at this receptor than quetiapine and over sixfold better than risperidone.

Treatment of schizophrenia with atypical antipsychotic drugs has been associated with weight gain and the onset of type II diabetes mellitus. Two receptors, histamine H-1 and $5HT_{2C}$, have been suggested to be involved in this adverse event. Several papers[22] have demonstrated that there is significant correlation between affinity for H-1 receptor and weight gain and hence the observation that compound **13** has much lower affinity (K_i = 186 nM) for H1 receptor than risperidone (19 nM), quetiapine (8.7 nM), ziprasidone (47 nM), olanzapine (2.8 nM), and clozapine (1.8 nM) is an indication that compound **13** may have a lower propensity to induce weight gain. In addition, the low affinity of **13** for the $5HT_{2C}$ receptor (K_i = 1425 nM) compared to ziprasidone (K_i = 0.72 nM), risperidone (K_i = 10 nM), and olanzapine (K_i = 10 nM) suggests a possible decrease in the propensity of **13** for treatment-emergent weight gain. The observation that $5\text{-}HT_{2B}$ receptor agonists are associated with increased risk for valvular heart disease[23] will require that antipsychotics that interact with 5HT receptors be evaluated for binding to the $5HT_{2B}$ receptor. Thus, it is encouraging to note that compound **13** does not bind appreciably to $5HT_{2B}$ receptor (K_i = 495). Also encouraging is the observation that compound **13** lacks affinity for the cholinergic muscarinic M_3 receptor (K_i = 3000 nM), a receptor reported to have a contributing role in new-onset diabetes in schizophrenic patients treated with atypical antipsychotics.[12a]

Compound **13** was also evaluated at neurotransmitter uptake transporters. Compound **13** has very weak affinity for both the dopamine (DAT) and norepinephrine (NET) transporters but has similar affinity for the serotonin transporter (SERT) (K_i = 56.6 nM) compared to aripiprazole (K_i = 98 nM).[24] This binding profile at the transporters suggests that while it has potential for antidepressant properties, it has a much lower potential to induce cocaine-like adverse properties since it has a very weak binding affinity for DAT.

Animal behavioral studies were initiated to provide preliminary evidence on efficacy and to evaluate the propensity of compound **13** to induce catalepsy. The ability to block apomorphine-induced stereotypy is an indication of a drug's in vivo capacity to antagonize dopamine D2 receptors, while induction of catalepsy is considered to be an indication of a drug's propensity to produce extrapyramidal symptoms in humans. The ED_{50} values of compound **13**, clozapine, and haloperidol are estimated from the dose–response curves in Figures 1–3. The ED_{50} value of compound **13** in inhibiting apomorphine-induced stereotypy was estimated to be 35.8 μmol/kg compared to clozapine's 42.4 μmol/kg suggesting that compound **13** is slightly more potent at blocking the D2 receptors in vivo than clozapine on a molar basis. This is also consistent with their estimated K_i values at the D2 receptor. The ED_{50} values comparing compound **13**, clozapine, and haloperidol are reported in Table 4. Compound **13** and clozapine have ED_{50}s (μmol/kg) that are about 500 times that of haloperidol. The results of these behavioral studies support the radioligand binding data that compound **13** does not bind to D2 receptors as well as haloperidol, but does bind to D2 receptors with about the same affinity as clozapine.

Figure 4 depicts plots of mean catalepsy scores for compound **13** with clozapine and haloperidol as controls. The vehicle served as a negative control in the study. The ED_{50} value for each compound was used as the basis for the dose used for the first set of comparative evaluations. It is clear that haloperidol showed the highest propensity to induce catalepsy, while clozapine and compound **13** had no significant difference between them. The extent of the absence of catalepsy was evaluated by increasing the dose of compound **13** up to five times the ED_{50} value at which point it was impossible to retain the drug in solution for intraperitoneal delivery. At 5× the ED_{50} value, there was no appreciable cataleptogenic activity observed. Taken together, the combined receptor binding profile and the absence of catalepsy suggest that compound **13**, a butyrophenone analogue, which does not induce catalepsy up to 5× its ED_{50} value, may serve as an atypical antipsychotic agent.

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 CaSO4 and stored over 4Å 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.

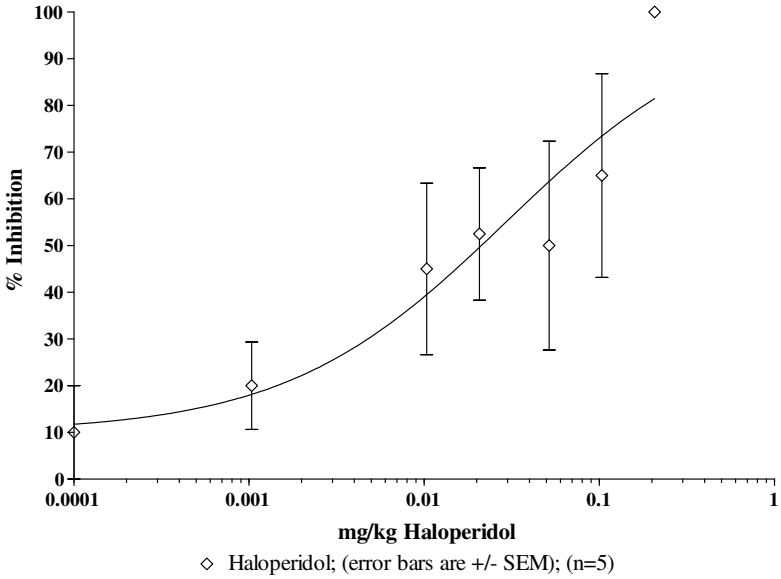


Figure 1. Apomorphine challenge test of haloperidol.

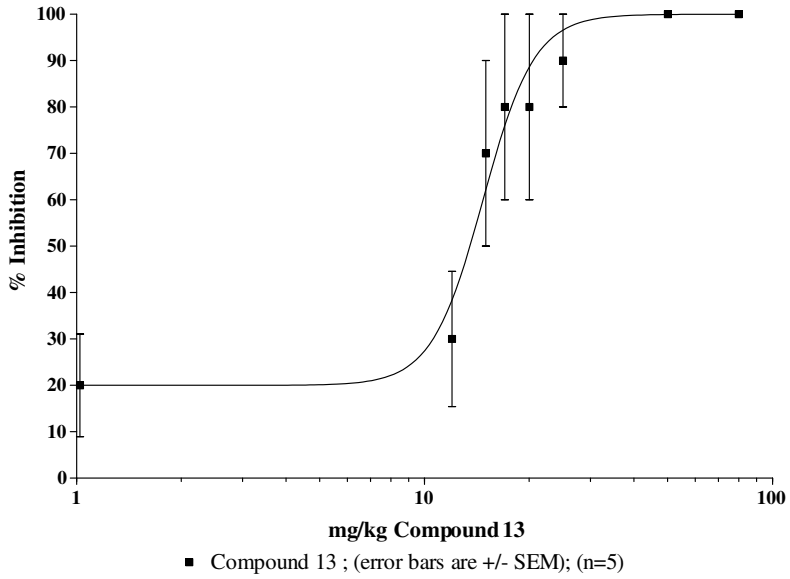


Figure 2. Apomorphine challenge test of compound **13**.

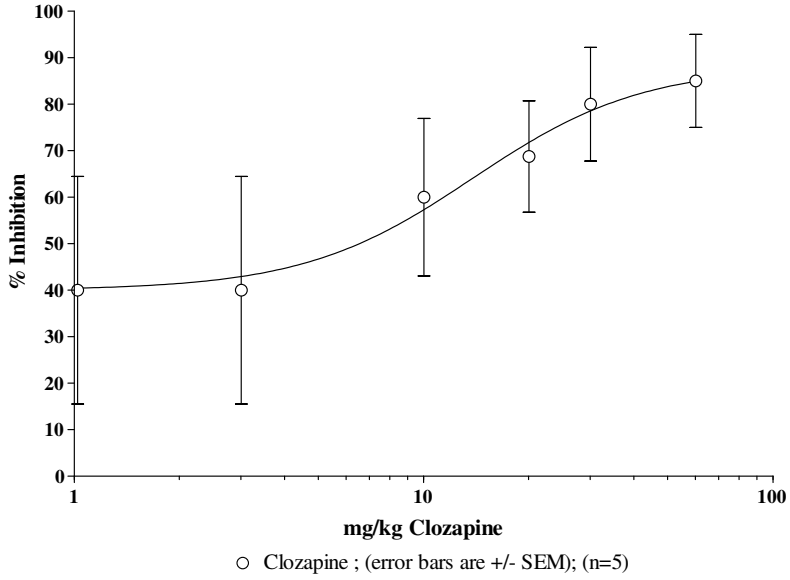


Figure 3. Apomorphine challenge test of clozapine.

Table 4
Comparison of ED_{50} values for apomorphine test

Test compound	FW	ED_{50} (mg/kg)	95% Confidence interval (mg/kg)	ED_{50} (μmol/kg)
Compound **13**	411.3	14.7	13.4–16.1	35.8
Clozapine	326.8	13.8	7.57–25.3	42.4
Haloperidol	375.9	0.0293	0.0112–0.0768	0.0779

4.1. Synthesis of compound 10

The synthesis of compound **10** followed the methods previously reported by Cignarella et al.[15] and Thompson et al.[16] as depicted in Scheme 1.

4.1.1. *cis*-2,5-Dicarboethoxy-1-[4-chlorophenyl]pyrrolidine (17)

To a solution of (2*S*,5*R*)-diethyl 2,5-dibromohexanedioate (**16**) (10 g, 27.8 mmol) in anhydrous DME (80 mL) were added 4-chloroaniline (14.2 g, 111.1 mmol) and KI (1 g, 6.02 mmol). The resulting mixture was refluxed under N_2 with stirring for 16 h. and allowed to cool to room temperature. Excess DME was removed under vacuum and the residue was triturated in Et_2O (100 mL) to yield a solid. The solid obtained was filtered, washed with Et_2O, and the organic phase was treated with 100 mL of ice cold 5 N HCl and H_2O, dried over $MgSO_4$, and solvent removed in vacuo. The crude compound was purified by chromatography on silica gel (hexane/EtOAc, 8:2) to give compound **17** (8.5 g, 93.5%) as a mixture of *trans*-2,5-dicarboethoxy-1-[4-chlorophenyl]pyrrolidine and *cis*-2,5-dicarboethoxy-1-[4-chlorophenyl]pyrrolidine.

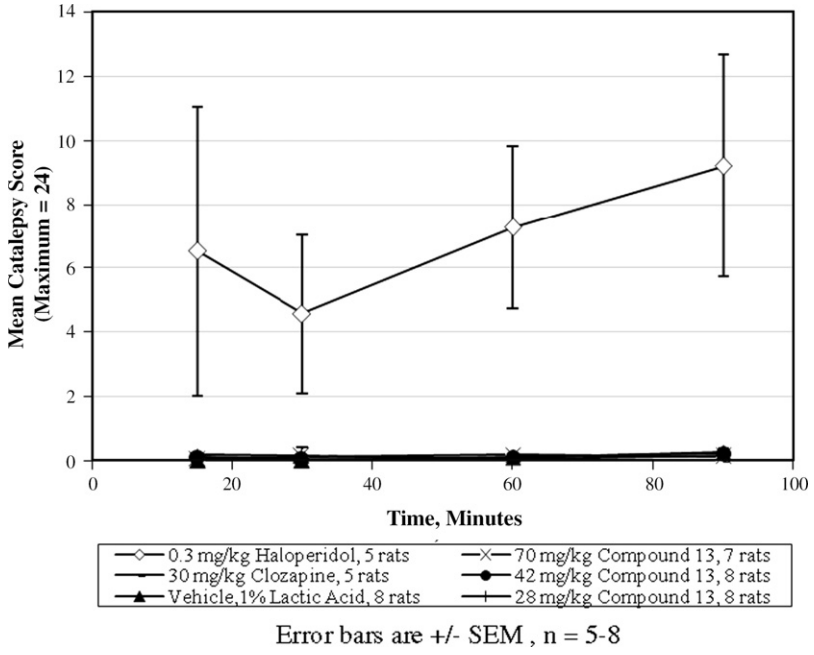


Figure 4. Catelepsy of haloperidol, compound **13**, clozapine and vehicle.

4.1.2. 2-Benzylcarbamyl-5-carboethoxy-1-[4-chlorophenyl]-pyrrolidine (18)

A mixture of *cis*- and *trans*-2,5-dicarboethoxy-1-[4-chlorophenyl]pyrolidine, **17** (8.5 g, 26 mmol), was dissolved in 10 mL of *o*-xylene. Benzylamine (3.61 g, 33.74 mmol) was added to the reaction mixture and refluxed for 18 h under N_2, cooled, and solvent evaporated. The residue was subjected to column chromatography (silica gel) eluting with (1:1) hexane/EtOAc to give compound **18** (4.4 g, 39.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.13 Hz, 3H), 2.01–2.45 (m, 4H), 4.11–4.37 (m, 4H), 4.40–4.46 (dd, J = 6.0, 3.2 Hz, 2H), 6.36–6.44 (m, 2H), 7.09–7.24 (m, 7H), 8.52 (m, 1H).

4.1.3. 3-Benzyl-8-[4-chlorophenyl]-3,8-diazabicyclo[3.2.1]-octane-2,4-dione (19)

The solution of compound **18** (4.0 g, 10.35 mmol) in 30 mL of 1 N NaOH (75% aq ethanol) was stirred at room temperature for 2 h. The reaction mixture was quenched with HCl gas to the end point of phenolphthalein and the solid was filtered. The solvent was removed in vacuo and the solid material was re-dissolved in absolute alcohol. The solution was partially removed in vacuo and the residue was treated with Ac_2O (5 mL) and NaOAc (1 g). After refluxing overnight under N_2, the excess Ac_2O was removed and the reaction mixture was quenched with aq Na_2CO_3, extracted with CH_2Cl_2 (3× 100 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and separated on a silica gel column (hexane/EtOAc, 7:3) to give compound **19** (2.56 g, 56.7%, white solid, mp 163–164 °C). ^{1}H NMR (270 MHz, $CDCl_3$) δ *2.04–2.12* (m, 2H), 2.46–2.55 (m, 2H), 4.63–4.66 (dd, J = 5.1, 2.7 Hz, 2H), 4.70 (s, 2H), 6.70–6.82 (m, 4H), 7.03–7.12 (m, 5H).

4.1.4. 3-Benzyl-8-phenyl-3, 8-diazabicyclo[3.2.1]octane (20)

To a solution of compound **19** (0.58 g, 1.70 mmol) in anhydrous THF (3 mL) was added slowly 1 M $LiAlH_4$ (10.24 mL, 10.24 mmol) and refluxed for 2 days under N_2. The reaction mixture was quenched in ice bath with 10% NaOH (20 mL) and extracted with CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$, and removed in vacuo. The residue was subjected to column chromatography (silica gel, hexane/ethyl acetate, 9:1) to give compound **20** (0.4 g, 84.6%, white crystals, mp 115–117 °C). ^{1}H NMR (270 MHz, $CDCl_3$) δ *1.87–2.08* (m, 4H), 2.51–2.52 (d, J = 2.0 Hz, 4H), 3.41 (s, 2H), 4.13–4.15 (m, 2H), 6.65–6.78 (m, 3H), 7.15–7.30 (m, 7H).

4.1.5. 3-Carboethoxy-8-phenyl-3, 8-diazabicyclo[3.2.1]octane (21)

To a solution of compound **20** (0.77 g, 2.8 mmol) in anhydrous toluene (15 mL) was added ethyl chloroformate (1.6 mL, 16.6 mmol) and refluxed for 16 h under N_2. The resulting solution was allowed to cool to RT and excess solvent was removed under vacuum. The resulting residue was subjected to column chromatography (silica gel, hexane/ethyl acetate, 8:2) to give compound **21** (0.65 g, 90.5%) as white crystals, mp 124.4 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.22 (t, J = 8.1 Hz, 3H), 1.79–1.84 (m, 2H), 1.98–2.04 (m, 2H), 3.29 (t, J = 13.5 Hz, 2H), 3.60–3.76 (dd, J = 13.5 Hz, 2H), 4.07–4.18 (m, 4H), 6.70–6.80 (m, 3H), 7.18–7.26 (m, 2H).

4.1.6. 8-Phenyl-3,8-diazabicyclo[3.2.1]octane (22)

To a solution of compound **21** (0.73 g, 2.48 mmol) in EtOH (5 mL), were added KOH [3 g in H_2O (3 mL)], EtOH (25 mL) followed by NH_2NH_2 (3 mL). The resulting mixture was refluxed for 16 h. Excess alcohol was removed and the residue was extracted with EtOAc (4× 50 mL) and H_2O (20 mL) to give compound **22** (0.4 g, 86%). ^{1}H NMR (270 MHz, $CDCl_3$) δ *1.88–2.07* (m, 4H), 2.51–2.57 (dd, J = 13.5, 2.7 Hz, 2H), 3.19–3.24 (d, J = 13.5 Hz, 2H), 4.09 (br s, 2H), 6.67–6.78 (m, 3H), 7.17–7.24 (m, 2H).

4.1.7. 8-Phenyl-3,8-diazabicyclo[3.2.1]octan-1-yl-1-(4-fluorophenyl)butan-1-one (10)

To a mixture of compound **22** (0.56 g, 2.96 mmol), K_2CO_3 (1.4 g, 10 mmol), and KI (0.3 g) in DME (10 mL) was added 4-chloro-4-fluorobutyrophenone (2.0 g, 10.01 mmol) and stirred. The mixture was refluxed for 16 h under N_2 atmosphere and the reaction mixture was allowed to cool to room temperature. Excess DME was removed in vacuo and the residue was extracted with CH_2Cl_2 (3× 50 mL) followed by brine (50 mL). The organic phase was collected and dried over anhydrous $MgSO_4$ and the solvent evaporated. The resulting crude product was subjected to column chromatography (silica gel, EtOAc/MeOH, 8:2) to give an oily residue (1.21 g, 68.2%) and subsequently converted to an oxalate salt as a

white solid, mp 194.7–195.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ *1.89–1.99* (m, 6H), 2.39 (t, *J* = 6.8, 2H), 2.47–2.65 (m, 4H), 3.06 (t, *J* = 7.3, 2H), 4.21 (m, 2H), 6.73–6.85 (m, 3H), 7.17–7.33 (m, 4H), 8.05–8.10 (m, 2H). Anal. Calcd for $C_{24}H_{26}CFN_2O_5 \cdot H_2O$: C, 64.62; H, 6.19; N, 6.28. Found: C, 64.66; H, 6.11; N, 6.14.

4.1.8. 4-[5-(4-Chloro-phenyl)-2,5-diaza-bicyclo[2.2.1]hept-2-yl]-1-(4-fluoro-phenyl)-butan-1-one (11)

A mixture of compound **23** (0.5 g, 2.4 mmol), 4-chloro-4-fluorobutyrophenone (1.9 g, 9.6 mmol), KI (50 mg), and K_2CO_3 (138 mg) in DME (10 mL) was refluxed in an atmosphere of N_2 for 60 h. Excess DME was removed under vacuum and residue was partitioned between CH_2Cl_2 (3× 75 mL) and brine (50 mL). The organic phase was pooled, dried over anhydrous Na_2SO_4, and the solvent removed in vacuo to afford a residue as the crude product. The crude product was purified by column chromatography using 0–20% MeOH in EtOAc to yield compound **11** (755 mg, 84.5%), which was subsequently converted to the oxalic acid salt as a white crystal, mp 116.4–116.8 °C. ^{1}H NMR (300 MHz, DMSOd_6) δ *1.86–1.93* (m, 4H), 2.09–2.21 (AB system, *J* = 10.7, 2H), 3.00–3.37 (m, 6H), 3.11 (t, *J* = 6.7, 2H), 3.37–3.58 (AB system, *J* = 9.3, 2H). 4.42 (m, 1H), 4.60 (m, 1H), 6.65–6.68 (Part of AAXX, 2H), 7.32–7.38 (Part of AAXX, 2H), 8.00–8.04 (Part of AAXX, 2H). Anal. Calcd for $C_{21}H_{22}ClFN_2O \cdot 1.5C_2H_2O_4$: C, 56.73; H, 4.96; N, 5.52; Found: C, 56.49; H, 4.91; N, 5.42.

4.1.9. 4-[4-(2-Pyrimidine)piperazin-1-yl]-1-(4-fluorophenyl)-butan-1-one (12)

A mixture of 2-(piperazin-1-yl)pyrimidine dihydrochloride (0.5 g, 2.1 mmol), 4-chloro-4′-fluorobutyrophenone (1.3 g, 6.3 mmol), KI (25 mg), and K_2CO_3 (1.5 g, 10.9 mmol) in DME (10 mL) was refluxed with stirring under N_2 for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc (200 mL) and washed with H_2O. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to dryness and the residue was purified by chromatography on silica gel to give compound **12** (563 mg, 78%), mp 109–110 °C. ^{1}H NMR ($CDCl_3$): 8.29 (2H, d, *J* = 4.5 Hz), 8.02 (2H, dd, *J* = 5.1, 8.7 Hz), 7.13 (2H, t, *J* = 8.7 Hz), 6.47 (1H, t, *J* = 4.5 Hz), 3.76 (4H, m), 3.01 (2H, t, *J* = 7.5 Hz), 2.46 (6H, m), 1.99 (2H, m). Anal. Calcd for $C_{18}H_{21}FN_4O$: C, 65.84; H, 6.45; N, 17.06. Found: C, 65.91; H, 6.51; N 16.86.

4.1.10. 4-Chlorophenylboronic acid (26)

To a solution of 4-bromochlorobenzene, **25** (4 g, 20.9 mmol), in THF (80 mL) was added *n*-BuLi (22 mL, 1.6 M) at −78 °C under N_2 and stirred for 1 h at the same temperature. The reaction mixture was treated with $B(OMe)_3$ (398.8 mL, 78.3 mmol) at −78 °C, allowed to warm up to room temperature, and then stirred overnight. The pH of the mixture was then adjusted with a solution of $NaHCO_3$ to pH 6.5 and extracted with CH_2Cl_2 (3× 150 mL). The pooled organic phase was dried ($MgSO_4$), the solvent was removed in vacuo, and the crude product was column chromatographed (silica gel, hexane/EtOAc, 7:3) to yield compound **26** (4-chlorophenyl-boronic acid) (2 g, 61%) as a white solid. ^{1}H NMR (270 MHz, CD_3OD) δ *7.30–7.77* (m, 4H).

4.1.11. 1-*t*-Butyl homopiperazine carboxylate (28)

To a solution of homopiperazine, **27** (10 g, 0.1 mol) in H_2O (104 mL) and *t*-BuOH (119 mL) containing 2.5 N NaOH (16 mL) was added di-*tert*-butyl dicarbonate (8.55 g, 0.039 mol) at 0 °C for 40 min. The resulting mixture was stirred for 1 h at room temperature and the solution was concentrated in vacuo. The crude material was extracted with CH_2Cl_2 (3× 100 mL), dried over $MgSO_4$, and the solvent evaporated. The crude product was subjected to column chromatography (silica gel, MeOH/CH_2Cl_2/NH_4OH, 9:1:1) to give 1-*t*-Butyl homopiperazine carboxylate, **28** (5 g, 64%). ^{1}H NMR (270 MHz, CD_3OD) δ 1.46 (s, 9H), 1.79 (q, *J* = 5.9, 2H), 2.78–2.87 (m, 4H), 3.41–3.49 (m, 4H).

4.1.12. 1-*t*-Butyl-4-(4-chlorophenyl)homopiperazine carboxylate (29)

The mixture of 4-chlorophenyl-boronic Acid, 26 (1.65 g, 10.54 mmol), 28 (1.05 g, 5.27 mmol), $Cu(OAc)_2$ (1.43 g, 7.87 mmol), triethylamine (0.726 mL), and molecular sieves (4 g) in CH_2Cl_2 (50 mL) was stirred at room temperature under air. The reaction mixture was quenched with a 4 mL of NH_4OH in 4 mL of MeOH. The mixture was filtered through Celite and purified by column chromatography using hexane/EtOAc (7:3) as eluent on silica gel to give compound 29 (1.2 g, 73%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 4H), 1.42 (s, 5H), 1.91–1.98 (m, 2H), 3.18 (t, 1H, *J* = 6.2 Hz), 3.29 (t, 1H, *J* = 6 Hz), 3.48–3.7 (m, 6H), 6.58 (d, 2H, *J* = 8.7 Hz), 7.12 (m, 2H, *J* = 9 Hz).

4.1.13. 1-(4-Chlorophenyl)homopiperazine (30)

Trifluoroacetic acid (5 mL) was slowly added in a drop-wise manner to a solution of compound **29** in CH_2Cl_2 (5 mL) at ambient temperature and the resulting mixture was allowed to stir overnight. The reaction mixture was quenched with aq NaOH and extracted with EtOAc (3× 100 mL), washed with $NaHCO_3$ solution (50 mL) and brine (50 mL). The organic phase was collected and dried over $MgSO_4$ and evaporated in vacuo. The crude product was subjected to column chromatography (silica gel, MeOH/CH_2Cl_2/NH_4OH, 9:1:1) to yield 1-(4-chlorophenyl)homopiperazine, **30** (0.720 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ *1.92–1.98* (m, 2H), 2.86 (t, 2H, *J* = 5.7 Hz), 3.04 (t, *J* = 5.4 Hz), 3.53 (q, 4H, *J* = 6.4 Hz), 5.50 (br s, 1H), 6.58 (d, 2H, *J* = 9), 7.14 (d, 2H, *J* = 9.2 Hz).

4.1.14. 4-[4-(4-Chlorophenyl)-1,4-diazepan-1-yl]-1-(4-fluorophenyl)butan-1-one (13)

A mixture of compound **30** (709 mg, 3.4 mmol) in dry DME (15 mL) and K_2CO_3 (1.9 g, 13.9 mmol) was heated for 20 min after which 4-chloro-4-flourobutyrophenone (2.8 g, 13.9 mmol) was added followed by KI (0.3 g). The reaction mixture was refluxed for 18 h under an atmosphere of N_2. Excess DME was removed in vacuo and the residue was extracted with CH_2Cl_2 (3× 100 mL) and brine (50 mL). The organic phase was collected and dried over $MgSO_4$ and solvent removed under vacuum. The crude product was subjected to column chromatography (silica gel, EtOAc/MeOH, 9:1) to yield compound **13** (1.19 g, 87%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ *1.84–1.95* (m, 4H), 2.53–2.62 (m, 4H), 2.75 (t, 2H, *J* = 5.1 Hz), 2.93 (t, 2H, *J* = 7.2 Hz) 3.39–3.48 (m, 4H), 6.58 (d, 2H, *J* = 9.6 Hz), 7.05–7.13 (m, 4H), 7.96–7.92 (dd, 2H, *J* = 9, 5.1 Hz). Subsequently, compound **13** was converted to the oxalate salt, crystallized from MeOH/Et_2O as a white solid, mp 146.6–146.4 °C. Anal. Calcd for $C_{23}H_{26}ClFN_2O_2$: C, 59.42; H, 5.64; N, 6.03. Found: C, 59.27; H, 5.70; N, 6.05.

4.1.15. Alternative method for compound (13)

A mixture of homopiperazine (2 g, 20 mmol), CuI (380 mg, 2 mmol), K_2CO_3 (5.5 g, 40 mmol), ethylene glycol (2.4 g, 40 mmol), and 1-chloro-4-iodobenzene (4.76 g, 20 mmol) in *i-PrOH* (50 mL) was refluxed for 12 h under N_2. The mixture was diluted with EtOAc (500 mL) and washed with water. The organic phase was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to dryness followed by chromatography on silica gel (EtOAc then MeOH/EtOAc, 10:90) to afford 1-(4-chlorophenyl)-1,4-diazepane (3.8 g, 90%).

A mixture of 1-(4-chlorophenyl)-1,4-diazepane (**30**) (540 mg, 2.57 mmol), 4-chloro-4-fluorobutyrophenone (2 g, 10.28 mmol), KI (25 mg), and K_2CO_3 (880 mg, 6.38 mmol) in DME (20 mL) was refluxed under N_2 for 12 h. The mixture was diluted with EtOAc (500 mL) and washed with H_2O. The organic phase was dried

(Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to dryness followed by column chromatography on silica gel (pure EtOAc) to afford 4-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]-1-(4-fluorophenyl)butan-1-one, **13**. The product was converted to the salt form using ethereal HCl and then crystallized from MeOH/Et_2O to give the pure HCl salt (715 mg, 68%) mp 165–166 °C, ^{1}H NMR (DMSO): δ 10.48 (1H, br s), 8.04 (2H, dd, J = 5.7, 9.3 Hz), 7.35 (2H, t, J = 8.7 Hz), 7.19 (2H, d, J = 9.3 Hz), 7.76 (2H, d, J = 9.3 Hz), 3.78 (2H, m), 3.42 (4H, m), 3.15 (6H, m), 2.38 (1H, m), 2.15 (1H, m), 2.03 (2H, m). Anal. Calcd for $C_{21}H_{25}Cl_2FN_2O$: C, 61.32; H, 6.13; N, 6.81. Found: C, 61.20; H, 5.98; N, 6.78.

4.1.16. 9-Methyl-3,9-diazabicyclo[4.2.1]nonan-4-one (32)

Using the method reported by Michaels and Zaugg,[25] concd H_2SO_4 (37.5 mL) was added dropwise at −20 °C to a mixture of tropinone, **31** (16.7 g, 32 mmol), in anhydrous $CHCl_3$ (120 mL). This was followed by a slow addition of sodium azide (15.6 g) for 30 min while maintaining the temperature below −5 °C. After completing the addition, the reaction mixture was stirred at room temperature for 15 min, and then heated at 50 °C overnight under nitrogen. The reaction mixture was then neutralized with $NaHCO_3$, extracted with CH_2Cl_2, and the organic layer was collected, dried over Na_2SO_4, and evaporated in vacuo to afford a light yellowish substance as **32** (13.8 g, 78%); MS: 155 $(M+1)^+$, IR (KBr): 3190 (–NH), 1620 (C=O).

4.1.17. 3,9-Diazabicyclo[4.2.1]nonane-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-ethyl ester (35)

To a solution of compound **32** (15.2 g, 30 mmol) in anhydrous THF (100 mL) was added very slowly under nitrogen powdered LAH (14.1 g, 8 equiv). The mixture was allowed to stir at room temperature overnight before being quenched with MeOH, followed by H_2O, filtered, washed twice with CH_2Cl_2, extracted, dried over Na_2SO_4, and evaporated to yield 9-Methyl-3,9-diazabicyclo[4.2.1]nonane, compound **33** (11 g, 80%). TLC analysis showed a single spot and was used as such without characterization. Compound **33** (12.0 g, 24 mmol) was dissolved in 15 mL of *t*-BuOH and added a solution of Boc-anhydride (5.8 g, 28 mmol) in *t*-BuOH (10 mL) for 5 min and the reaction mixture was stirred overnight. The reaction mixture was then neutralized with $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated in vacuo to yield 9-methyl-3,9-diazabicyclo[4.2.1]nonane-3-carboxylic acid *tert*-butyl ester, **34** (13.8 g, 67%). Compound **34** (5.8 g, 32 mmol) was dissolved in anhydrous toluene (20 mL) and ethyl chloroformate (3.6 g, 33.3 mmol) was slowly added in a drop-wise manner. The reaction mixture was refluxed overnight and the solvent was evaporated as an azeotrope with alcohol. The resulting product, 3,9-diazabicyclo[4.2.1]nonane-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-ethyl ester, **35** was dried and used as such without further purification for the next reaction.

4.1.18. 3-(4-Chlorophenyl)-3,9-diazabicyclo[4.2.1]nonane-9-dicarboxylic acid ethyl ester (37)

Compound **35** (5.5 g, 18.4 mmol) was dissolved in CF_3COOH (3 mL) and stirred for 4 h at room temperature. The reaction mixture was then neutralized with $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated to get a light yellowish oil, 3,9-diazabicyclo[4.2.1]nonane-9-carboxylic acid ethyl ester, **36** (2.85 g, 78%). Compound **36** (5 g, 25.6 mmol), 4-chlorophenylboronic acid (5.6 g, 35.8 mmol), $Cu(OAc)_2$ (5.7 g, 31.4 mmol), and Et_3N (2 mL) in CH_2Cl_2 (50 mL) with molecular sieves (2 g) were stirred in open air for 48 h. The reaction mixture was then quenched with methanolic NH_3 solution, filtered over Celite, extracted with CH_2Cl_2 (100 mL), dried, and solvent evaporated under vacuum. The crude residue was subjected to column chromatography (silica gel, CH_2Cl_2/MeOH, 4:1) to give a yellowish compound **37** (4.5 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ *1.20–1.26* (m, 3H), 1.39–1.6 (m, 2H), 1.75–1.95 (m, 2H), 2.0–2.29 (m, 2H), 3.0–3.30 (m, 2H), 3.54–3.68 (m, 1H), 3.70–3.8 (m, 1H), 4.05–4.20 (m, 2H), 426–4.43 (m, 2H), 6.62–6.66 (dd, 2H, J = 7.8, 3.3 Hz), 7.06–7.12 (m, 2H).

4.1.19. 3-(4-Chlorophenyl)-3,9-diazabicyclo[4.2.1]nonane (38)

Compound **37** (2.2 g, 7.12 mmol) and 50% aq KOH (2 mL) in ethylene glycol (2 mL) was heated at 90 °C overnight. The reaction mixture were then extracted with CH_2Cl_2 (2× 80 mL), dried over Na_2SO_4, and evaporated under vacuum. The crude product was subjected to column chromatography (silica gel, CH_2Cl_2/MeOH, 4:2) to yield compound **38** (0.99 g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ *1.32–1.76* (m, 4H), 1.90–2.25 (m, 4H), 3.15–3.35 (m, 4H), 6.63 (d, 2H, J = 9 Hz), 7.09 (d, 2H, J = 9 Hz).

4.1.20. 4-[3-(4-Chlorophenyl)-3,9-diazabicyclo[4.2.1]non-9-yl]-1-(4-fluorophenyl)butan-1-one (14)

A mixture of compound **38** (0.45 g, 1.9 mmol) and K_2CO_3 (1 g, 7.6 mmol) in dry DME (15 mL) was heated at 80 °C for 20 minutes and 4-chloro-4-fluorobutyrophenone (2.2 mL, 7.6 mmol) was added in a dropwise manner and refluxed overnight under nitrogen. Excess DME was removed in vacuo and the residue was extracted with CH_2Cl_2 (3× 60 mL). The pooled organic phase was collected and dried over Na_2SO_4 and evaporated under vacuum. The crude product was subjected to column chromatography (silica gel, CH_2Cl_2/EtOAc, 4:1) to yield compound **4** (0.55 g, 68.2%) as an oil which was converted into the oxalate salt (white crystalline solid, mp 182–184 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ *1.20–1.66* (m, 4H), 1.80–2.00 (m, 4H), 2.50–2.75 (m, 2H), 2.90–3.05 (m, 2H), 3.35–3.60 (m, 6H), 6.58 (m, 2H), 7.05–7.15 (m, 4H), 7.91–7.97 (m, 2H), Anal. Calcd for $C_{25}H_{26}N_2O_5ClF{\cdot}0.25H_2O$: C, 60.61; H, 5.80; N, 5.65. Found: C, 60.53; H, 5.75, N, 5.53.

4.2. Biology

4.2.1. Receptor binding studies

Binding affinities reported in Tables 1–3 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.[26]

4.2.2. Apomorphine-induced climbing stereotypy

A modified climbing test by Needham et al. was used[27] and provides the extent a potential antipsychotic agent inhibits the effect of apomorphine-induced stereotypy. Swiss Webster male mice (~30 g) in groups of five were administered an intraperitoneal (IP) injection of 0.3 mL of vehicle (filtered 1% lactic acid) or increasing doses of the dopamine antagonists haloperidol (0.001, 0.01, 0.02, 0.05, 0.1, and 0.2 mg/kg), compound **13** (12, 15, 17, 20, 25, 50, and 80 mg/kg), and clozapine (3, 10, 20, 30, and 60 mg/kg). Animals were then challenged at 30 minutes post-injection with 1.5–1.6 mg/kg of the agonist apomorphine in 0.9% NaCl + 0.1% ascorbic acid, placed in cylindrical wire cages (12 cm in diameter, 14 cm in height), and observed for climbing behavior at 10 and 20 min post-dose. Climbing behavior was assessed as follows: 3–4 paws on the cage floor = 0 score; 2 and 3 paws on the cage = 1 score; 4 paws on the cage = 2 score. Scores were expressed as mean percentage climbing inhibition, and plotted in Figures 1–3. ED_{50}s in Table 4 were calculated using Graph Pad Prism non-linear regression software with sigmoidal dose–response, variable slope curve-fitting.

4.2.3. Bar test for catalepsy

The bar test used by Hoffman and Donovan[28] was modified for our use. Male Sprague–Dawley rats (88–207 g) in groups of 5–8

were dosed by IP injection with 1–23 mL/kg of vehicle (filtered 1% lactic acid), haloperidol (0.3 mg/kg), compound **13** (28, 42, and 70 mg/kg), or clozapine (30 mg/kg). Catalepsy severity was assessed at time points (15, 30, 45, 60, and 90 min) post-injection, by scoring how long the rat maintained both forepaws motionless on a horizontal metal bar (1.1 cm in diameter, 10 cm above the bench top in a box) up to a maximum of 120 s. This was repeated two more times and the average ($n = 3$ tries) seconds recorded for each rat. The mean of all the average seconds for one dose for one time point ($n = 5$–8 rats) was divided by 5 and a mean catalepsy score assigned and plotted in Figure 4 with a maximum possible score of 24.

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