Bioorganic & Medicinal Chemistry 20 (2012) 1291–1297

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Multi-receptor drug design: Haloperidol as a scaffold for the design and synthesis of atypical antipsychotic agents

Kwakye Peprah [a], Xue Y. Zhu [a], Suresh V.K. Eyunni [a], Vincent Setola [b], Bryan L. Roth [b], Seth Y. Ablordeppey [a,*]

[a] Division of Basic Pharmaceutical Sciences, Florida A&M University, College of Pharmacy and Pharmaceutical Sciences, Tallahassee, FL 32307, USA
[b] Department of Pharmacology, Medicinal Chemistry and Psychiatry, University of North Carolina at Chapel Hill, School of Medicine, NC 27599, USA

ARTICLE INFO

Article history:
Received 22 October 2011
Revised 6 December 2011
Accepted 13 December 2011
Available online 22 December 2011

Keywords:
Haloperidol
CNS receptor ligands
Antipsychotics
Atypical antipsychotics
Dopaminergic and serotonergic agents

ABSTRACT

Using haloperidol as a scaffold, new agents were designed to investigate the structural contributions of various groups to binding at CNS receptors associated with atypical antipsychotic pharmacology. It is clear that each pharmacophoric group, the butyrophenone, the piperidine and the 4-chlorophenyl moieties contributes to changes in binding to the receptors of interest. This strategy has resulted in the identification of several new agents, compounds **16, 18, 19, 23, 24** and **25,** with binding profiles which satisfy our stated criteria for agents to act as potential atypical antipsychotics. This research demonstrates that haloperidol can serve as a useful lead in the identification and design of new agents that target multiple receptors associated with antipsychotic pharmacology.

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1. Introduction

Until recently, haloperidol (**1**) has been a drug of choice in the treatment of schizophrenia and has represented the typical antipsychotic drugs as a mainstay of treatment from the 1960s until this decade.[1] While its therapeutic effectiveness has been attributed to potent dopamine (DA) D_2 receptor binding affinity (D_2 K_i = 0.89 nM), haloperidol also binds with low to high affinity at several other central nervous system (CNS) receptors, including other DA subtypes, serotonin (5-HT) receptors and alpha (α) adrenoceptors (Tables 1 and 4). Thus, haloperidol can serve as a scaffold for the design of new agents that target multiple receptors associated with antipsychotic pharmacology.

The dwindling interest in haloperidol and other typical antipsychotics is partially related to the induction of severe short- and long-term debilitating movement disorders including Parkinsonism-like symptoms, sometimes referred to as extrapyramidal syndrome (EPS) and tardive dyskinesia (TD).[2,3] Several theories have been proposed to explain haloperidol's long-term side effects including metabolic transformation of the piperidine moiety to quaternary pyridinium (BCPP+) species which have similar but weaker potential as 1-methyl-4-phenyl pyridinium (MPP+) to destroy D_2 receptors in the substantia nigra of the brain.[4,5] More recently, Kim and others have shown that N-dealkylation of the butyrophenone moiety to produce 3-(4-fluorobenzoyl) propionic acid (FBPA) (Fig. 1) may also contribute to haloperidol's EPS problems.[6] These theories have inspired us to begin a search for drugs that could not be transformed in vivo to produce the harmful metabolites.[7] Our laboratory has been interested in the potential of haloperidol as a lead to obtain novel entities without EPS but which display multi-receptor binding profiles similar to those of atypical antipsychotic agents. Towards this end, we have designed and synthesized new agents based on the haloperidol pharmacophore which could not be transformed into the toxic quaternary metabolites, but which possess atypical antipsychotic binding profiles.[7–10] In furtherance of this interest, the current study explores the effect of the replacement of both butyrophenone and piperidine moieties in haloperidol with bioisosteres that could not be bio-transformed into toxic metabolites, that is, BCPP+ and FBPA respectively.

In previous studies, we have proposed a set of binding criteria that would lead to new agents without the known side effects observed with the atypical antipsychotic agents in use.[9] These include: 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.

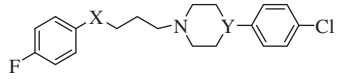
2. Chemistry

Alkylating agent, 1-fluoro-4-(4-iodobutyl)benzene (**2**) was prepared using a literature procedure with modification[11] by

* Corresponding author. Tel.: +1 850 599 3867; fax: +1 850 599 3934.
E-mail address: seth.ablordeppey@famu.edu (S.Y. Ablordeppey).

0968-0896/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.bmc.2011.12.019

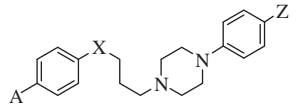
Table 1
Binding of phenyl piperidine analogs at dopamine and serotonin receptors of interest



Compounds			Binding (K_i ± SEM) data of phenyl piperazine analogs at selected receptors (nM)					
#	X	Y	D_2	D_3	D_4	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$
Cloz[a]			130	240	54	140	8.9	17
Hal, 1[a]	C=O	COH	0.89	4.6	10	3600	120	4700
5	CH_2	COH	24 ± 2	666 ± 39	1.5 ± 0.1	658 ± 50	302 ± 23	MP
6	S	COH	8.8 ± 9.5	49.0 ± 1.7	247.8 ± 4.3	317 ± 29	72 ± 7	>10000
7	O	COH	5.3 ± 0.3	182 ± 22	2.4 ± 0.1	74.0 ± 6	93 ± 10	MP
8	S	CH	185 ± 13	130 ± 14	39 ± 3	454 ± 92	112 ± 17	>10000
9	O	CH	41 ± 4	696 ± 50	9.5 ± 0.3	169 ± 15	121 ± 9	>10000
10	S=O	CH	998 ± 68	243 ± 35	35 ± 1	613 ± 216	222 ± 17	>10000

MP = Missed primary assay threshold of 50% inhibition, Cloz, Clozapine; Hal, Haloperidol.
[a] The binding data of these compounds were previously reported in Refs. 7,9,10

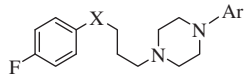
Table 2
Binding of phenyl piperazine analogs at dopamine and serotonin receptors of interest



Compounds			Binding (K_i ± SEM) data of phenyl piperazine analogs at selected receptors (nM)						
#	A	X	Z	D_2	D_3	$^*D_4$	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$
11[a]	F	C=O	4-Cl	254 ± 39	404 ± 66	17.5 ± 2.0	90.9 ± 21.0	110 ± 16	3552 ± 943
12	F	CH_2	4-Cl	284 ± 21	261 ± 23	7.8	112 ± 7	81 ± 5	MP
13	F	S	4-Cl	211 ± 22	422 ± 41	8.7	166 ± 12	53 ± 3	MP
14	F	S	4-CF_3	4753 ± 593	544 ± 58	89	1080 ± 389	1129 ± 114	MP
15	F	O	4-Cl	390 ± 34	885 ± 65	6.9	80 ± 6	60 ± 4	MP
16	F	O	H	37*	207*	7.4	24.0*	57.6 ± 2.8	MP
17	H	O	4-Cl	447*	726*	5.6	154*	19.8 ± 1.0	MP
18	H	O	H	119*	79.3 ± 13.7	4.5	25.0*	46.0 ± 4.2	MP

[a] The synthesis and DA binding data of compound **11** were previously reported in Ref. 9,10; MP = Missed primary assay threshold of 50% inhibition.
* The SEM of the binding data of compounds with asterisk are less than 20%.

Table 3
Binding data for aryl piperazine analogs at dopamine and serotonin receptors of interest



Compounds			Binding (K_i ± SEM) data of aryl piperazine analogs at selected receptors (nM)					
Compd #	X	Ar	D_2	D_3	D_4	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$
19	C=O	2-Pyrimidine	98.0 ± 15.0	244.1 ± 106.0	6.5 ± 0.8	30.5 ± 5	22.0 ± 4.0	4132 ± 1081
20	CH_2	2-Pyrimidine	269 ± 17	262 ± 17	6.2 ± 0.3	8.6 ± 0.7	41.0 ± 2.0	MP
21	S	2-Pyrimidine	424 ± 25	68.0 ± 10.0	21.0 ± 1.0	93.1 ± 29.0	27.0 ± 2.0	8829 ± 2674
22	O	2-Pyrimidine	636 ± 66	778 ± 63	4.2 ± 0.1	23.0 ± 3.0	23.0 ± 1.0	>10000
23	CH_2	2-Pyridine	124 ± 10	86.0 ± 4.0	3.5 ± 0.2	1.1 ± 0.1	50.0 ± 3.0	MP
24	S	2-Pyridine	183 ± 21	160 ± 16	5.7 ± 0.3	6.2 ± 0.5	26.0 ± 1.0	8097 ± 495
25	O	2-Pyridine	186 ± 16	229 ± 20	1.8 ± 0.1	3.6 ± 0.2	18.0 ± 1.0	8277 ± 497

MP = Missed primary assay threshold of 50% inhibition.

coupling 4-fluorophenyl magnesium bromide with 1,4-dibromobutane in the presence of Li_2CuO_4, and followed by halide exchange in acetone under reflux (Scheme 1). Coupling of **2** with selected amines in DME using K_2CO_3 as base provided ligands **5**, **12**, **20**, 23 (Tables 1–3). 3-(4-fluorophenoxy)propan-1-ol, **3a** was obtained by refluxing 4-fluorophenol, 3-chloropropanol, K_2CO_3, and KI in ^{i}PrOH Scheme 2. Mesylation was carried out at room temperature employing Et_3N as a base to afford 3-(4-fluorophenoxy)propyl methane sulfonate, **4a** Scheme 2. Methane sulfonates, **4b** and **4c** were similarly synthesized. Alkylation of selected amines in the presence of K_2CO_3 and KI in DME, with methane sulfonates (**4a**, 4b and **4c**) resulted in the formation of compounds **6**–**9**, **13**–**18**, **21**–**23** and **24**–**26** (Tables 1–3). The syntheses of these compounds are shown in Scheme 3. Sulfoxide **10** was obtained by oxidation of **9** with m-CPBA in MeOH as shown in Scheme 4.

3. Results and discussion

The first strategy was to conduct preliminary SAR studies on haloperidol to observe how changes in the various segments of

Table 4
Binding profile of selected synthetic compounds and their comparison with standard agents

Receptors	Binding (K_i ± SEM) data of compounds at selected receptors (nM)							
	16	**18**	**19**	**23**	**24**	**25**	**Cloz***	**Hal***
D_2	37.0 ± 0.9	119 ± 0.9	98.0 ± 15.3	124 ± 10	183 ± 21	186 ± 16	130	0.89
D_4	7.4 ± 0.9	4.5 ± 0.9	6.5 ± 0.8	3.5 ± 0.2	5.7 ± 0.3	1.8 ± 0.1	54	10
$5HT_{1A}$	24.0 ± 0.9	25.0 ± 0.9	30.5 ± 5.0	1.1 ± 0.1	6.2 ± 0.5	3.6 ± 0.2	140	3600
$5HT_{2A}$	57.6 ± 2.8	46.0 ± 4.2	22.0 ± 4.0	50.0 ± 3.0	26.0 ± 1.0	18.0 ± 1.0	8.9	120
$5HT_{2C}$	MP	MP	4132 ± 1081	MP	8097 ± 495	8277 ± 497	17	4700
$5HT_7$	ND	ND	ND	90.0 ± 4.0	291 ± 36	208 ± 33	ND	ND
H1	62.9 ± 12.7	67.9 ± 9.7	912 ± 152	167 ± 24	212 ± 30	262 ± 23	1.8	440
Alpha 2C	ND	ND	80.0 ± 9.6	308.2 ± 24.4	45.1 ± 8.5	194.5 ± 8.5	ND	ND
M1	MP	MP	MP	MP	MP	MP	1.8	1600

* Cloz, Clozapine; Hal, Haloperidol; ND = Not determined; MP = Missed primary assay threshold of 50% inhibition.

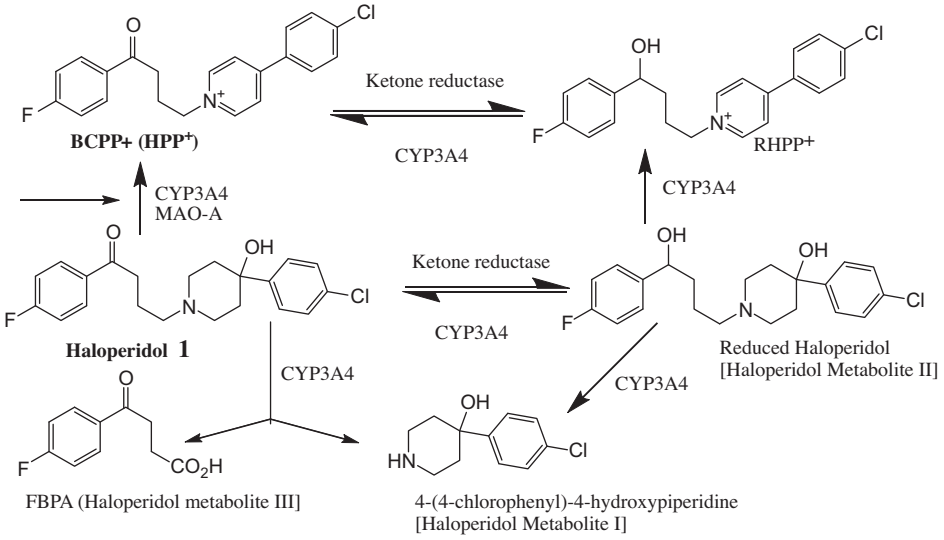
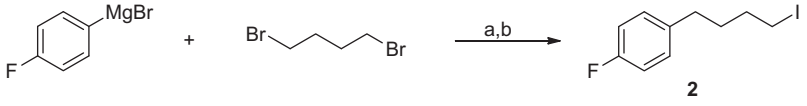
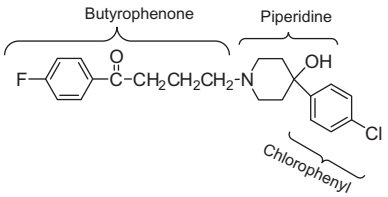


Figure 1. Metabolic transformation of haloperidol.

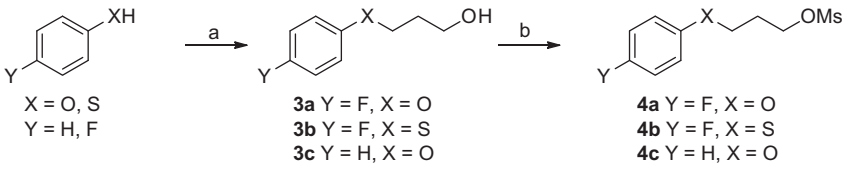


Scheme 1. Reagents and conditions: (a) Li_2CuO_4, THF, N_2, −10 °C, 2 h; (b) KI, acetone, 60 °C, 24 h.

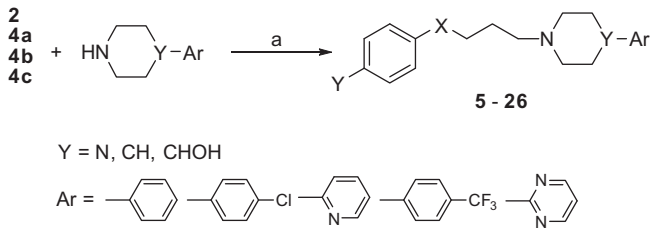
the structure affect binding at DA and 5HT receptor subtypes of interest. The structure was delineated in 3 segments, the butyrophenone moiety, the piperidine and the 4-chlorophenyl moiety as depicted below.



The butyrophenone moiety was the focus of the first modifications and these modifications are referenced to haloperidol. Reduction of the carbonyl to a methylene group **5** (D_2 K_i = 24.0 nM) resulted in a 27-fold decrease in binding to the D_2 receptor compared to haloperidol (Table 1). Replacement of the carbonyl group with sulfur **6** (D_2 K_i = 8.8 nM) and oxygen **7** (D_2 K_i = 5.3 nM) resulted in more moderate decreases in affinity at the D_2 receptor. Overall, with the piperidinol in place, the carbonyl appears to be an important group for binding to D_2 receptors but is not a necessary group since it can be replaced by a methylene group, sulfur, or oxygen to display potent binding at the D_2 receptor. The trend in binding at the D_2 receptor is an increase from the methylene group to sulfur and then to oxygen. Binding to the D_3 receptor for the three compounds shows little or no observable pattern although the sulfur analog displayed the highest potency among them. At the D_4 receptor, the sulfur analog displayed over 24-fold decrease in binding while the oxygen analog displayed over 4-fold increase in binding compared to the methylene analog. A significant observation relates to the binding of two of the compounds to 5HT receptor subtypes. Compound **7**, the oxygen analog, displayed a 49-fold increase in binding (K_i = 74.0 nM) at the $5HT_{1A}$ receptor



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



Scheme 3. Reagents and conditions: (a) KI, K_2CO_3, DME, 90 °C 12 h.

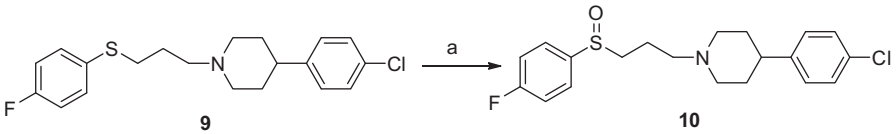
while compound **6** bound with a moderate increase in affinity (K_i = 317.0 nM) compared to haloperidol. At the $5HT_{2A}$ receptor, the methylene substituent had a moderate binding affinity while the sulfur (K_i = 72.0 nM) and oxygen (K_i = 93.0 nM) analogs displayed increased binding over haloperidol.

The next SAR focus was on the piperidine moiety. Removal of the alcohol function from compounds **6** and **7** to form **8** and **9** respectively resulted in significant decreases in binding to the D_2 receptor as observed in previous reports.[7] However, there was an increase in binding for the sulfur analog **8** (K_i = 39.0 nM) and a more moderate decrease in binding at the D_4 receptor for the oxygen analog **9** (K_i = 9.5 nM). At both the $5HT_{1A}$ and $5HT_{2A}$ receptors, the absence of the alcohol group did not result in much change in binding. It is interesting to note that oxidizing the sulfur analog **8** to form the sulfoxide **10** which appears to mimic the carbonyl moiety structurally, resulted in diminished binding at all the receptors examined except at the $5HT_{1A}$ receptor and thus suggests that the sulfoxide may not serve as a bioisostere of the carbonyl group. The next evaluation, replacement of the piperidine with a piperazine resulted in analogs **11–18**. Compound **11,** the piperazine analog of haloperidol, produced a substantial decrease in affinity to the D_2 receptor from 0.89 to 253.5 nM. Binding affinity decreased or changed minimally at essentially all the other receptors evaluated. Reduction of the carbonyl to a methylene group to form compound **12** did not modify binding significantly at these receptors. Likewise, replacement of the carbonyl with sulfur **13** and oxygen **15** did not result in significant changes in binding at dopamine and serotonin receptors of interest. In the eastern hemisphere, replacement of the 4-chloro atom on the phenyl ring with the bigger and more powerful electron withdrawing CF_3 group **14** led to a dramatic decrease in binding affinity at all the receptor subtypes investigated. This may suggest there is a steric obstruction to binding at these receptors. The contributions of the two halogens in the western and eastern hemispheres were also evaluated using compound **15** as the template. Compound **16,** with the chloro atom removed, binds at the D_2 receptor with 37 nM affinity, this being an over 10-fold increase in binding. Removal of the 4′-fluoro atom while retaining the 4-chloro atom **17** did not result in an increase in binding but instead led to significant decreases except for the $5HT_{1A}$ receptor where binding increased by a factor of 3 ($5HT_{1A}$, K_i = 19.8 nM). When both halides were removed to obtain compound **18**, binding improved at all receptors of interest compared to **17** but was mixed compared to compound **16**.

We also investigated replacements of the 4-chlorophenyl ring with heteroaromatic rings associated with increased binding at 5HT receptors. Replacement of the 4-chlorophenyl group in compound **11** with the 2-pyrimidinyl group to obtain compound **19**, led to improvement in binding affinity at all the receptors investigated. Reduction of the carbonyl group to a methylene group **20** did not improve binding at the D_2-like and the $5HT_{2A}$ receptors but did improve binding affinity at the $5HT_{1A}$ receptor (**19** (K_i = 30.5 nM); **20** (K_i = 8.6 nM)). Replacement of the carbonyl group with sulfur **21** or oxygen **22** did not result in any significant modifications of binding affinity at the receptors investigated. Replacing the 2-pyrimidinyl group in compounds **20**, **21** and **22** with a 2-pyridinyl moiety to form **23**, **24** and **25** respectively were also evaluated. Compound **23** binds with increased affinity at the D_2-like receptors and also shows either an increased potency or no changes at the serotonin receptor subtypes investigated. In fact, compound **23** has the highest binding affinity (K_i = 1.1 nM) at the $5HT_{1A}$ receptor in this investigation. Compounds **24** and **25**, the sulfur and oxygen analogs also showed significant D_4 potency and selectivity and high affinity binding to $5HT_{1A}$ and $5HT_{2A}$.

A review of how the current compounds under investigation have satisfied our criteria[9] for obtaining new antipsychotic agents with moderate D_2 binding and high affinity binding (K_i < 50 nM) to $5HT_{1A}$ and $5HT_{2A}$ receptors shows several compounds including **16**, **18**, **19**, **23**, **24**, and **25** meet the stated criteria and were therefore slated for further evaluation.

These compounds were thus screened for their binding affinities at $5HT_7$, α_{2c} and M_1 to assess their capacity to improve cognitive properties. They showed only moderate binding affinity at the $5HT_7$ receptor, and similar affinity at the α_{2C} receptor. The 5-HT_7 receptor abounds in the hippocampus, which is involved in learning and memory.[12] Studies have shown that 5-HT_7 receptor antagonists and 5-HT_7 receptor gene knockout have the potential to impair some cognitive functions in mice.[13] The adrenergic α_{2c} receptor has also been implicated as potentially relevant to cognitive function.[14] Evaluation at M_1 receptors showed the compounds to have little or no affinity at the muscarinic M_1 receptor (Table 4). The blockade of this cholinergic receptor has been associated with cognitive deficits, which may be particularly severe in susceptible individuals such as the elderly.[15] The propensity of the compounds to induce metabolic side-effects such as weight gain was investigated by evaluating their binding affinities at H_1 and $5HT_{2C}$ receptors. The results are recorded in Table 4. All the 6 compounds



Scheme 4. Reagents and condition: (a) *m*-CPBA, MeOH, rt, 4 h.

evaluated bind with only moderate affinity at the H_1 receptor and have little or no binding to the $5HT_{2C}$ receptor. Histamine H_1 receptor blockade has been implicated in weight gain associated with atypical antipsychotic therapy[16,17] and so has the $5HT_{2C}$ receptor.[18,19] This suggests that these compounds would have attenuated capacity to induce weight gain.

Overall, the SAR of haloperidol indicates the butyrophenone, the piperidine and the 4-chlorophenyl moieties each play a role in its multi-receptor binding profile. Six compounds (**16, 18, 19, 23, 24** and **25**) have been identified as meeting the general criteria we have proposed as sufficient to be considered for further evaluation. Based on further screening results, there is sufficient data to engender evaluation of these compounds in vivo in order to understand the pharmacology imposed on them as a result of the binding profiles observed. These in vivo evaluations are currently underway.

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. 1-Fluoro-4-(4-iodobutyl)benzene (2)

This iodide was prepared following a literature procedure.[20] The bromide was first obtained, followed by halide exchange to obtain the iodide. Yield 82.1% ^{1}H NMR ($CDCl_3$): δ 7.13 (2H, m), 6.98 (2H, m), 3.20 (2H, t, J = 6.6 Hz), 2.62 (2H, t, J = 7.8 Hz), 1.84 (2H, m), 1.73 (3H, m).

4.1.1. General procedure for the synthesis of methanesulfonates (4a, 4b, 4c)

A mixture of 4-fluorophenol (1.1 g, 10 mmol), 3-chloropropanol (1.4 g, 15 mmol), KI (50 mg), K_2CO_3 (2.8 g, 20 mmol) in ^{i}PrOH was refluxed under N_2 for 1 h. The mixture was diluted with EtOAc (200 mL), and washed with water (50 mL), brine (50 mL). The organic layer was dried with Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and followed by distillation in vacuo to give the desired product 3-(4-fluorophenoxy)propan-1-ol (**3a**). To a solution of **3a** (1.3 g, 7.6 mmol), 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 (**4a**).

4.1.2. 3-(4-Fluorophenoxy)propan-1-ol (3a)

Yield 90%. ^{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).

4.1.3. 3-(4-Fluorophenylthio)propan-1-ol (3b)

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).

4.1.4. 3-Phenoxy-propan-1-ol (3c)

Yield 75%. ^{1}H NMR ($CDCl_3$): δ 7.29 (2H, m), 6.93 (3H, m), 4.13 (2H, t, J = 6.0 Hz), 3.88 (2H, m), 2.06 (2H, m), 1.90 (1H, br s).

4.1.5. 3-(4-Fluorophenoxy)propyl methanesulfonate (4a)

Yield 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).

4.1.6. 3-((4-Fluorophenyl)thio)propyl methanesulfonate (4b)

Yield 94%. ^{1}H NMR1H 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).

4.1.7. 3-Phenoxypropyl methanesulfonate (4c)

Yield 92%. ^{1}H NMR ($CDCl_3$): δ 7.30 (2H, m), 6.97 (1H, m), 6.90 (2H, m), 4.43 (2H, t, J = 6.3 Hz), 4.08 (2H, t, J = 6.0 Hz), 2.97 (3H, s), 2.21 (2H, m).

4.1.8. General procedure for coupling iodides with amines

A mixture of 1-fluoro-4-(4-iodobutyl)benzene (**2**) (1.58 g, 5.7 mmol), 4-(4′-chlorophenyl) piperidin-4-ol (1.0 g, 4.7 mmol), and K_2CO_3 (1.96 g, 17 mmol) in DME (25 mL) was refluxed under N_2 for 12 h with stirring. The mixture was diluted with EtOAc (500 mL) and washed with water (300 mL). The organic phase was collected, dried with sodium sulfate, and filtered. The filtrate was concentrated by evaporation under reduced pressure, followed by purification using column chromatography with hexane:EtOAc (1:4) as eluent to afford 4-(4′-chlorophenyl)-1-(4′-(4-fluorophenyl)butyl)piperidin-4-ol (**5**) (0.83 g) as an off-white solid after crystallization in EtOAc/Et_2O; yield 48.5%, mp 140–141 °C. ^{1}H NMR ($CDCl_3$): δ 7.26 (2H, m), 7.15 (2H, d, J = 4.5 Hz), 6.95 (2H, m), 6.87 (2H, m), 3.98 (2H, t, J = 6.6 Hz), 3.06 (2H, d, J = 5.7 Hz), 2.54 (2H, t, J = 6.9 Hz), 1.98 (4H, m), 1.80 (4H, m). Calcd for $C_{21}H_{25}ClFNO{\cdot}0.2\ H_2O$: C 69.01, H 6.89, N 3.83; *Found*: C 68.82, H 6.86, N 3.82.

4.1.9. 1-(4-Chlorophenyl)-4-(4-(4-fluorophenyl)butyl)piperazine (12)

Using **2** and 1-(4-chlorophenyl) piperazine, produced compound **12**: yield 52.2%, mp 89–90 °C. ^{1}H NMR ($CDCl_3$): δ 7.19 (2H, m), 7.13 (2H, m), 6.95 (2H, m), 6.84 (2H, m), 3.14 (4H, m), 2.56 (6H, m), 2.39 (2H, t, J = 7.5 Hz), 1.59 (4H, m). Calcd for $C_{20}H_{24}ClFN_2$: C 69.97, H 6.97, N 8.08; *Found*: C 69.29, H 7.03, N 7.91.

4.1.10. 2-(4-(4-(4-Fluorophenyl)butyl)piperazin-1-yl)pyrimidine (20)

Using **2** and 2-(piperazin-1-yl)pyrimidine, produced compound **20**; yield 51.7%, mp 54–55 °C. ^{1}H NMR ($CDCl_3$): δ 8.31 (2H, m), 7.12 (2H, m), 6.95 (2H, m), 6.47 (1H, m), 3.82 (4H, m), 2.61 (2H, t, J = 6.9 Hz), 2.48 (4H, m), 2.38 (2H, m), 1.62 (4H, m). Calcd for $C_{18}H_{23}FN_4$: C 68.76, H 7.37, N 17.82; *Found*: C 68.47, H 7.45, N 17.64.

4.1.11. 1-(4-(4-Fluorophenyl)butyl)-4-(pyridin-2-yl)piperazine (23)

Using **2** and 1-(pyridin-2-yl)piperazine, produced compound **23**; yield 44%, mp 58–59 °C. ^{1}H NMR ($CDCl_3$): δ 8.19 (1H, m), 7.47 (1H, m), 7.13 (2H, m), 6.96 (2H, m), 6.62 (2H, m), 3.54 (4H, t, J = 4.8 Hz), 2.61 (2H, t, J = 7.2 Hz), 2.53 (4H, t, J = 5.1 Hz), 2.39 (2H, t, J = 7.8 Hz), 1.60 (2H, m). Calcd for $C_{19}H_{24}FN_3{\cdot}0.1H_2O$: C 72.40, H 7.67, N 13.33; Found: C 72.39, H 7.81, N 13.14.

4.1.12. General procedure for the coupling reaction of methane sulfonates with amines

A mixture of 3-(4-fluorophenylthio)propyl methanesulfonate (**4b**) (1.0 g, 3.79 mmol), 4-(4-chloro-phenyl)-piperidin-4-ol (0.8 g, 3.79 mmol), KI (120 mg), K_2CO_3 (1.2 g, 8.7 mmol) in DME (10 mL) was heated to reflux under N_2 for 12 h. The cooled mixture was then diluted with EtOAc (400 mL) and washed with H_2O (200 mL). The

organic layers were pooled, dried with Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, then followed by purification through column chromatography on silica gel, to afford 4-(4-chlorophenyl)-1-(3-((4-fluorophenyl)thio)propyl)piperidin-4-ol (**6**); yield 74%, mp 121–122 °C. ^{1}H NMR ($CDCl_3$): δ 7.43 (2H, d, J = 8.4 Hz), 7.35 (2H, dd, J = 4.8, 8.7 Hz), 7.31 (2H, d, J = 8.4 Hz), 6.99 (2H, t, J = 8.4 Hz), 2.92 (2H, t, J = 7.5 Hz), 2.75 (2H, m), 2.51 (2H, t, J = 7.8 Hz), 2.41 (2H, m), 2.08 (2H, m), 1.82 (2H, m), 1.70 (2H, m). Calcd for $C_{20}H_{23}ClFNOS$: C 63.23, H 6.10, N 3.69; Found: C 63.08, H 6.12, N 3.71.

4.1.13. 4-(4-Chloro-phenyl)-1-[3-(4-fluoro-phenoxy)-propyl]-piperidin-4-ol (7)

Using 3-(4-fluorophenoxy)propyl methanesulfonate (**4a**) and 4-(4-chlorophenyl) piperidin-4-ol, produced compound **7**; yield 43.8%, mp 140.0–141.4 °C. ^{1}H NMR ($CDCl_3$): δ 7.45 (2H, d, J = 9.0 Hz), 7.32 (2H, d, J = 9.0 Hz), 6.96 (2H, t, J = 9.0 Hz), 6.84 (2H, dd, J = 4.5, 9.0 Hz), 4.00 (2H, t, J = 6.0 Hz), 2.85 (2H, m), 2.61 (2H, t, J = 7.5 Hz), 2.49 (2H, t, J = 9.0 Hz), 2.13 (2H, m), 2.10 (2H, m), 1.74 (2H, m). Calcd for $C_{20}H_{23}ClFNO_2$: C 66.02, H 6.37, N 3.85; Found: C 66.01, H 6.34, N 3.86

4.1.14. 4-(4-Chlorophenyl)-1-(3-((4-fluorophenyl)thio)propyl)piperidine hydrochloride (8)

Using **4b** and 4-(4-chlorophenyl)-piperidine produced the free base of **9** which was converted into the HCl salt; yield 82%, mp 172–173 °C. ^{1}H NMR (DMSO-d_6): δ 10.37 (1H, br s), 7.45 (2H, dd, J = 5.1, 8.7 Hz), 7.38 (2H, d, J = 9.0 Hz), 7.22 (2H, t, J = 8.7 Hz), 7.18 (2H, d, J = 9.0 Hz), 3.49 (2H, m), 3.13 (2H, m), 3.20 (4H, m), 2.80 (1H, m), 1.96 (4H, m). Calcd for $C_{20}H_{24}Cl_2FNS$: C 60.00, H 6.04, N 3.50; Found: C 60.32, H 5.99, N 3.54.

4.1.15. 4-(4-Chlorophenyl)-1-(3-(4-fluorophenoxy)propyl)piperidine (9)

Using **4a** and 4-(4-chlorophenyl) piperidine, produced compound **8**; yield 35.1%, mp 63–65 °C. ^{1}H NMR ($CDCl_3$): δ 7.26 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.4 Hz), 6.96 (2H, t, J = 9.0 Hz), 6.84 (2H, dd, J = 9.0, 4.5 Hz), 3.99 (2H, t, J = 6.6 Hz), 3.06 (2H, m), 2.54 (2H, t, J = 6.9 Hz); 2.06 (2H, m), 1.98 (2H, m), 1.77 (4H, m). Calcd for $C_{20}H_{23}ClFNO$: C 69.09, H 6.66, N 4.03; Found: C 69.49, H 6.80, N 4.04.

4.1.16. 1-(4-Chlorophenyl)-4-(3-((4-fluorophenyl)thio)propyl)piperazine (13)

Using **4b** and 1-(4-chlorophenyl) piperazine dihydrochloride, produced **13**; yield 70.3%, mp 85–86 °C. ^{1}H NMR ($CDCl_3$): δ 7.36 (2H, dd, J = 5.1, 8.7 Hz), 7.21 (2H, d, J = 8.7 Hz), 7.01 (2H, t, J = 8.7 Hz), 6.82 (2H, d, J = 8.7 Hz), 3.36 (4H, br s), 2.96 (4H, m), 2.90 (4H, m), 2.03 (2H, m). Calcd for $C_{19}H_{22}ClFN_2S$: C 62.54, H 6.08, N 7.68; Found: C 62.21, H 5.96, N 7.61.

4.1.17. 1-(3-((4-Fluorophenyl)thio)propyl)-4-(4-(trifluoromethyl)phenyl)piperazine HCl (14)

Using **4b** and 1-(4-(trifluoromethyl)phenyl)piperazine produced the free base of **14** which was converted to the HCl salt immediately, **14**; yield 78%, mp 213–214 °C. ^{1}H NMR (DMSO-d_6): δ 10.44 (1H, br s), 7.55 (2H, d, J = 9.0 Hz), 7.45 (2H, dd, J = 5.1, 8.7 Hz), 7.20 (2H, t, J = 8.7 Hz), 7.11 (2H, d, J = 9.0 Hz), 3.97 (2H, d, J = 12 Hz), 3.53 (2H, d, J = 12 Hz), 3.21 (4H, m), 3.10 (2H, m), 3.00 (2H, m), 1.96 (2H, m). Calcd for $C_{20}H_{23}ClF_4N_2S$: C 55.23, H 5.33, N 6.44; Found: C 55.04, H 5.29, N 6.44.

4.1.18. 1-(4-Chlorophenyl)-4-(3-(4-fluorophenoxy)propyl)piperazine (15)

Using **4a** and 1-(4-chlorophenyl) piperazine dihydrochloride, produced **15**; yield 75.9%, mp 97–98 °C. ^{1}H NMR ($CDCl_3$): δ 7.20 (2H, d, J = 6.0 Hz), 6.96 (2H, t, J = 8.4 Hz), 6.83 (4H, m), 4.00 (2H, t, J = 6.3 Hz), 3.17 (2H, t, J = 5.1 Hz), 2.60 (6H, m), 2.00 (2H, m). Calcd for $C_{19}H_{22}ClFN_2O$: C 65.42, H 6.36, N 8.03; Found: C 65.22, H 6.40, N 8.01.

4.1.19. 1-(3-(4-Fluorophenoxy)propyl)-4-phenylpiperazine (16)

Using **4a** and 1-phenylpiperazine, produced **16**; yield 48.9%, mp 63.1–64.9 °C. ^{1}H NMR ($CDCl_3$): δ 7.26 (m, 2H), 6.95 (m, 4H), 6.84 (3H, m), 4.0 (2H, t, J = 6.3 Hz), 3.22 (4H, m), 2.61 (6H, m), 2.00 (2H, m). Calcd for $C_{19}H_{23}FN_2O$: C 72.58, H 7.37, N 8.91; Found: C 72.59, H 7.37, N 8.73.

4.1.20. 1-(4-Chlorophenyl)-4-(3-phenoxypropyl)piperazine HCl (17)

Using 3-phenoxypropyl methanesulfonate **4c** and 1-(4-chlorophenyl)piperazine produced **17** which was converted into the HCl salt, followed by re-crystallization from MeOH using EtOAc; yield of 39%, mp 208–209 °C. ^{1}H NMR (DMSO-d_6): δ 11.07 (1H, br s), 7.28 (4H, m), 7.02 (2H, d, J = 9.0 Hz), 6.92 (3H, m), 4.04 (2H, t, J = 6.0 Hz), 3.79 (2H, m), 3.58 (2H, m), 3.27 (2H, m), 3.14 (4H, m), 2.21 (2H, m). Calcd for $C_{19}H_{24}Cl_2N_2O$: C 62.13, H 6.59, N 7.63; Found: C 62.29, H 6.67, N 7.60.

4.1.21. 1-(3-Phenoxypropyl)-4-phenylpiperazine (18)

Using **4c** and 1-phenylpiperazine produced **18** which was converted into the HCl salt followed by re-crystallization from MeOH/EtOAc; yield 48%, mp 195–196 °C. ^{1}H NMR (DMSO-d6): 11.07 (1H, br s), 7.26 (4H, m), 6.96 (5H, m), 6.84 (1H, m), 4.05 (2H, t, J = 6.0 Hz), 3.80 (2H, m), 3.59 (2H, m), 3.28 (2H, m), 3.13 (4H, m), 2.22 (2H, m). Calcd for $C_{19}H_{25}ClN_2O$: C 68.56, H 7.57, N 8.42; Found: C 68.30, H 7.56, N 8.26.

4.1.22. 2-(4-(3-((4-Fluorophenyl)thio)propyl)piperazin-1-yl)pyrimidine (21)

Using **4b** and 2-(piperazin-1-yl)pyrimidine, produced **21;** yield 87%. The free base was converted to the HCl salt; mp 150–151 °C. ^{1}H NMR (DMSO-d_6): δ 8.42 (2H, d, J = 4.8 Hz), 7.44 (2H, dd, J = 5.4, 9.0 Hz), 7.19 (2H, t, J = 9.0 Hz), 6.75 (1H, d, J = 4.8 Hz), 4.66 (2H, d, J = 12 Hz), 3.50 (2H, d, J = 12 Hz), 3.31 (2H, m), 3.18 (2H, m), 3.00 (4H, m), 1.95 (2H, m). Calcd for $C_{17}H_{22}ClFN_4S$: C, 55.35; H, 6.01; N, 15.19; Found: C 55.35; H 5.86; N 15.19.

4.1.23. 2-(4-(3-(4-Fluorophenoxy)propyl)piperazin-1-yl)pyrimidine (22)

Using **4a** and 2-(piperazin-1-yl)pyrimidine hydrochloride, produced **22**; yield 54.8%, mp 82–83 °C. ^{1}H NMR ($CDCl_3$): δ 8.34 (2H, d, J = 4.5 Hz), 6.96 (2H, t, J = 8.4 Hz), 6.84 (2H, dd, J = 4.5, 9.0 Hz), 6.47 (1H, t, J = 4.5 Hz), 4.01 (2H, t, J = 6.0 Hz); 3.83 (4H, t, J = 5.4 Hz), 2.55 (6H, *m*); 2.00 (2H, m). Calcd for $C_{17}H_{21}FN_4O{\cdot}0.2H_2O$: C 63.81, H 6.62, N 17.51; Found: C 64.03, H 6.65, N 17.63.

4.1.24. 1-(3-((4-Fluorophenyl)thio)propyl)-4-(pyridin-2-yl)piperazine (24)

Using **4b** and 1-(pyridin-2-yl)piperazine produced **24**; yield 48.1%, mp 81–82 °C. ^{1}H NMR ($CDCl_3$): δ 8.18 (1H, m), 7.46 (1H, m), 7.36 (2H, m), 7.00 (2H, m), 6.62 (2H, m), 3.523 (4H, t, J = 5.4 Hz), 2.94 (2H, t, J = 7.2 Hz), 2.51 (6H, m), 1.82 (2H, m). *Calcd for* $C_{18}H_{22}FN_3S$: C 65.23, H 6.69, N 12.68; Found: C 64.97, H 6.58, N 12.53.

4.1.25. 1-(3-(4-Fluorophenoxy)propyl)-4-(pyridin-2-yl)piperazine (25)

Using **4a** and 1-(pyridin-2-yl)piperazine, produced **25**; yield 51.2%, mp 73–74 °C. ^{1}H NMR ($CDCl_3$): δ 8.20 (1H, m), 7.47 (1H, m); 6.95 (2H, m), 6.85 (2H, m), 6.63 (2H, m), 4.000 (2H, t, J = 6.3 Hz), 3.55 (4H, t, J = 4.8 Hz), 2.58 (6H, m), 2.00 (2H, m). Calcd for $C_{18}H_{22}FN_3O$: C 68.55, H 7.03, N 13.32; Found: C 68.44, H 7.18, N 13.14.

4.1.26. 1-(4-Chlorophenyl)-4-(3-((4-fluorophenyl)thio)propyl)-1,4-diazepane (26)

Using **4b** and 1-(4-chlorophenyl)-1,4-diazepane produced **26** which 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 $C_{20}H_{26}Cl_3FN_2S$: C 53.16, H 5.80, N 6.20; Found: C 53.39, H 5.98, N 6.22.

4.1.27. 4-(4-Chlorophenyl)-1-(3-((4-fluorophenyl)sulfinyl)propyl) piperidine HCl (10)

To a solution of 1-(3-(4-fluorophenylthio)propyl)-4-(4-chlorophenyl)piperidine (**9**) (200 mg, 0.549 mmol) in MeOH was added with stirring *m*-CPBA (200 mg) at room temperature. After stirring for 4 h at room temperature, the mixture was diluted with EtOAc (200 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the residue subjected to column chromatography on silica gel to afford 4-(4-chlorophenyl)-1-(3-((4-fluorophenyl)sulfinyl)propyl)piperidine. The product was converted to the HCl salt immediately and then recrystallized from MeOH–Et_2O to yield (178 mg, 78%), mp 196–197 °C. ^{1}H NMR (DMSO-d_6): δ 7.75 (2H, dd, J = 5.4, 9.0 Hz), 7.46 (2H, t, J = 9.0 Hz), 7.39 (2H, d, J = 8.4 Hz), 7.24 (2H, d, J = 8.4 Hz), 3.50 (2H, m), 3.13 (2H, m), 3.00 (2H, m), 2.85 (2H, m), 2.06 (1H, m), 1.94 (6H, m). Calcd for $C_{20}H_{24}Cl_2FNOS$: C 57.69, H 5.81, N 3.36; *Found*: C 57.54, H 5.84, N 3.40.

4.2. Receptor binding studies

Binding affinities reported in Tables 1–4 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.[21]

Acknowledgments

We gratefully acknowledge the financial support of the National Institute of General Medical Studies (NIGMS) for MBRS Grant No. 1SC1GM088451-01, NIMH Psychoactive Drug Screening Program, and a Title III Grant to Florida A&M University. This work was supported in part by the Pharmaceutical Research Center NIH/NCRR 1 C06-RR12512-01 Grant. The authors would like to thank Mrs Barbara Bricker for her editorial assistance during the writing of this manuscript.

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