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Synthesis and functional activity of (2-aryl-1-piperazinyl)-*N*-(3-methylphenyl)acetamides: selective dopamine D_4 receptor agonists

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Abstract—Diaryl piperazine acetamides were identified as potent and selective dopamine D_4 receptor agonists. Our strategy is based on an amide bond reversal of an acid sensitive, dopamine D_4 receptor partial agonist, **PD 168077**. This reversal provided compounds with excellent potency and improved stability. Systematic evaluation of the substitution on the aryl piperazine portion revealed a significant effect on functional activity. The synthesis and biological activity of these new dopamine D_4 agonists is discussed.

1. Introduction

Dopamine receptors are seven transmembrane domain G-coupled protein receptors that have been divided into two subfamilies: D_1-like and D_2-like.[1] The D_1-like family consists of the D_1 and D_5 receptors[2,3] while the D_2-like family includes D_2, D_3, and D_4 receptor subtypes.[4–6] Further characterization of the D_4 subtype has led to the discovery of specific alleles, which differ in the length of the third intracellular loop. The most abundant of these alleles are $D_{4.2}$, $D_{4.4}$, and $D_{4.7}$.[7–9]

The D_4 receptor has long been studied for its role in CNS disorders such as schizophrenia.[10,11] Recently, it has been shown that this receptor could be associated with attention deficit hyperactivity disorder (ADHD),[12–14] mood disorders such as depression,[15] substance abuse,[16,17] and disorders associated with cognitive behavior.[18] Initially, early therapeutic targets were proposed for receptor antagonists. This resulted in a large effort to investigate the structure–activity relationships of dopamine antagonists.[19–23] The expanded role of the D_4 receptor in other indications emphasized the need for selective agonists. Inspection of the literature reveals an emerging effort to identify D_4 receptor agonists (Chart 1). Some examples of selective agonists include benzamide piperazines such as **PD 168077**,[24,25] bicyclic heterocycles such as **CP 226,269**,[26–28] piperidines (**U-101958**),[29,30] and tetrahydropyridines (**RO-10-5824**).[18,31]

In view of the role of a central dopaminergic pathway in the control of male erectile dysfunction (MED), the

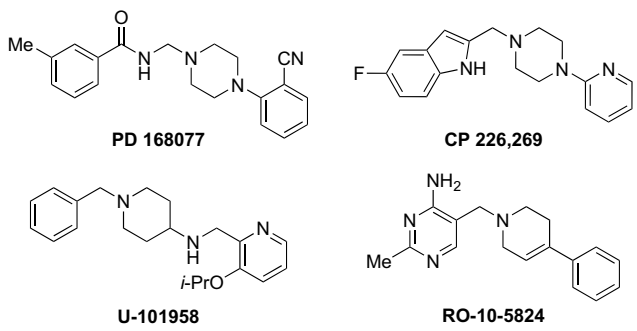

Chart 1. D_4 dopamine agonists.

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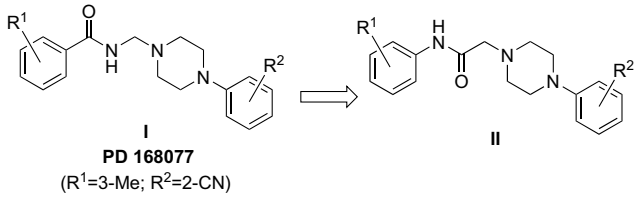


Chart 2. Amide bond transposition of **PD 168077**.

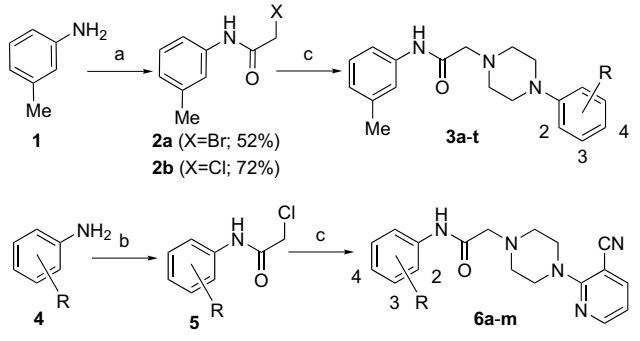
discovery of ABT-724,[32,33] and the potential for dopamine D_4 agonists for the treatment of MED,[34] we were interested in expanding our search for other selective agonists for further characterization of the D_4 receptor.

Glase et al.[24] have described the agonistic activity of substituted benzamide piperazines having structure type **I** (Chart 2). These workers reported, however, that this structural class had limited stability toward acidic hydrolysis. It was believed that one reason for this instability was the acyl aminal bond linkage. A possible solution could be to reverse the atom arrangement in the amide moiety to give acetamides of structure type **II**. The transposition concept of amide to retro amide is known[35–37] and based on previous work[38] with similar heterocyclic bioisoteres, it was anticipated that this small modification would preserve the desired biochemical profile, yet provide analogs with greater chemical stability. We now wish to report, in preliminary form, the biological evaluation of these acetamide analogs as well as some interesting aryl piperazine substituent effects on intrinsic activity.

2. Results

2.1. Chemistry

The synthesis of the required acetamides (**3a**–**t**; **6a**–**m**) is shown in Scheme 1. The bromo acetamide precursor (for **3b**), **2a**, was obtained through a biphasic acylation[39] of 3-methylaniline with chloroacetyl bromide in the presence of a 2 N sodium hydroxide and dichloromethane in 52% yield. The chloro acetamides, **2b** and **5**, were prepared in a similar fashion to **2a**, but substituting with chloroacetyl chloride. In some cases, we found that refluxing toluene was necessary for those aniline starting materials that had either electron withdrawing groups on the ring or *ortho* substitution. Final piperazine coupling was carried out in toluene at elevated temperatures in the presence of *N*,*N*-diisopropylethylamine to give analogs **3a**–**t** and **6a**–**m** in good yields.



Scheme 1. Reagents and conditions: (a) **2a**: $ClC(O)CH_2Br$, 2 N NaOH, CH_2Cl_2, rt; **2b**: $ClC(O)CH_2Cl$, 2 N NaOH, CH_2Cl_2, rt; (b) $ClC(O)CH_2Cl$, 2 N NaOH, CH_2Cl_2, or PhMe, 80 °C; (c) aryl piperazine, *i*-Pr_2EtN, PhMe, 60–80 °C.

2.2. Biology

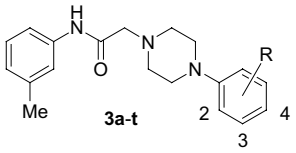
Dopamine D_4 ligands were evaluated both in agonist or antagonist mode using a calcium flux assay and recombinant human $D_{4.4}$ receptor coexpressed with $G\alpha_{qo5}$ in HEK-293 cells as described.[40] Dopamine D_4 ligand binding affinity was determined by radioligand competition against [^{3}H]-spiperone, using similar human dopamine $D_{4.4}$ cells as described for the calcium flux assay.

3. Discussion

As shown (Table 1), the rearrangement of the amide bond linkage in **PD 168077** provided acetamide, **3b**. When this compound was screened in the calcium flux assay (agonist mode), it displayed significantly improved potency and efficacy for the dopamine $D_{4.4}$ receptor over **PD 168077**. In addition, **3b** showed selectivity of >400-fold over D_{2L} and >700-fold over all other dopamine receptor subtypes. A general screen of **3b**, in approximately 70 receptors,[41] showed little activity at other nondopaminergic receptors. There was significant activity at the 5-HT_{1A} receptor but even in that case, the dopamine D_4 selectivity was >350-fold. Furthermore, we observed no degradation of this compound under acidic conditions after 2 days (in 1 M hydrochloric acid). As a result of the biochemical profile and acid stability of **3b**, it was decided to expand the structure–activity relationships in this series.

Table 1 shows acetamide analogs substituted in the aryl piperazine portion (region B). Replacing the *ortho* cyano group in **3b** with other electron withdrawing groups such as nitro (**3j**) and fluoro (**3l**) also generated analogs with good dopamine D_4 potency and efficacy. If the *ortho* position is substituted with an electron donating group such as methyl (**3d**), methoxy (**3g**), or amino (**3q**); observed efficacy decreases slightly compared to **3b**, yet these analogs remain functionally active as partial agonists at the D_4 receptor. A noteworthy effect was observed, however, when we attempted to move the cyano substituent into the *para* position (**3c**). We observed a complete loss of ligand agonist functional activity. This effect was consistent with other analogs substituted in the *para* position. Electron withdrawing groups (**3k**, **3o**, **3p**) or electron donating groups (**3f**, **3i**, **3r**) all display this loss in agonist activity in going from

Table 1. Pharmacologic characterization of **3a**–**t** at the human dopamine $D_{4.4}$ receptor



Compound	R	EC_{50}[a]	$\%E$[b]	K_i[c]	K_b[d]
PD 168077	—	6.9 ± 3.4[e]	60[f]	16.2 ± 2.9[g]	nd[h]
3a	H	10.4 ± 6.0	59	nd	nd
3b	2-CN	7.5 ± 0.8	80	2.7 ± 1.0	nd
3c	4-CN	>10,000	—	nd	nd
3d	2-Me	176 ± 57.5	41	18.0 ± 0.5	nd
3e	3-Me	>10,000	—	nd	0.46 ± 0.06
3f	4-Me	>10,000	—	7.9 ± 0.5	2.4 ± 0.9
3g	2-OMe	26.8 ± 6.7	60	0.7 ± 0.1[i]	nd
3h	3-OMe	>10,000	—	46.8 ± 2.2	nd
3i	4-OMe	>10,000	—	101 ± 12	nd
3j	2-NO_2	13.1 ± 1.2	73	nd	nd
3k	4-NO_2	>10,000	—	3250 ± 1010	nd
3l	2-F	18.0 ± 2.6	71	11.8 ± 0.6	nd
3m	4-F	>10,000	—	61.9 ± 1.6	4.8 ± 1.9
3n	2-Cl	125 ± 21	45	nd	nd
3o	4-Cl	>10,000	—	nd	nd
3p	4-Br	>10,000	—	nd	nd
3q	2-NH_2	86.2 ± 7.7	33	nd	nd
3r	4-NH_2	>10,000	—	7.4 ± 0.3	nd
3s	2-pyr	39.6 ± 22.9	67	56.7 ($n = 1$)[i]	nd
3t	4-pyr	>10,000	—	>10,000	nd
Clozapine	—	—	—	28.4 ± 0.4	2.5 ± 0.3
Haloperidol	—	>10,000	—	1.4 ± 0.04	10.6 ± 0.8

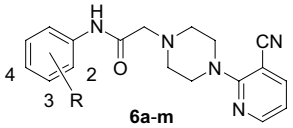
[a] Mean values for agonists (EC_{50} in nM) calculated from at least three determinations ± standard error of the mean (SEM) in the calcium flux assay using HEK-293 cells co-transfected with human $D_{4.4}$ receptor and $G\alpha_{qo5}$.
[b] Efficacy relative to 10 μM dopamine (100%).
[c] Mean values for binding affinity (K_i in nM) calculated from at least three determinations ± SEM versus [^{3}H]-spiperone.
[d] K_b ± SEM (nM) for antagonists calculated from IC_{50} values in the calcium flux assay (at least three determinations) by the method of Cheng and Prusoff.[45]
[e] Reported[24] $EC_{50} = 17$ nM.
[f] Reported[24] $\%E = 80$.
[g] Reported[24] $K_i = 8.7$ nM.
[h] nd = not determined.
[i] In the human dopamine $D_{4.2}$ allele.

the *ortho* position to the *para* position. Small groups such as fluoro, **3m**, and even lone pair of electrons, as represented by 2-pyridyl, **3t**, showed this loss of agonist activity in moving from the *ortho* position to the *para* position. Most of these *para* substituted analogs, however, maintain their binding affinity (e.g., **3f** and **3m**) and have been further characterized and found to be potent antagonists of the $D_{4.4}$ receptor in the calcium flux assay (antagonist mode). Additionally, analogs that are substituted in the *meta* position (e.g., **3e** and **3h**) show the same tendency and exhibit functional antagonism. The noted exception is **3t**. The lone pair of electrons on the pyridine nitrogen could be interfering with some residue on the protein and may be responsible for the poor binding affinity. However, the affinity may be too weak to assess antagonism for this analog.

Table 2 shows the results of substitution on the aryl acetamide portion (region A) of the molecule. Electron donating groups, such as methyl (**6b**–**d**) or methoxy (**6h**–**j**), all retain potency and efficacy as the substituent is moved from the *ortho* to the *para* position. An exception is *para* methoxy (**6j**), which activates the receptor at low concentrations but with significantly less efficacy ($\%E = 33$). Electron withdrawing groups such as trifluoromethyl (**6e**–**g**) and fluoro (**6k**–**m**) show good potency, yet slightly but significantly lowered as compared to the electron donating cases.

At this time, the relationship between substitution on the aromatic ring in region B and its impact on the functional activity is unclear but some trends are clearly indicated. Substitution in this terminal aryl region could selectively stabilize an active conformation of the ligand bound activated protein complex. However, based on the span of substituents in the *ortho* position that produce this effect, it is difficult to correlate this observation to a dissociation constant for a receptor conformation based on enthalpy contributions of the protein–ligand interactions to the ΔG of binding. It may involve a kinetic term relating to a conformation change of the bound receptor.[42]

Table 2. Pharmacologic characterization of **6a–m** at the human dopamine $D_{4.4}$ receptor



6a-m

Compound	R	EC_{50}[a]	%E[b]
6a	H	7.8 ± 3.8	70
6b	2-Me	8.3 ± 3.9	76
6c	3-Me	38.5 ± 12.2	75
6d	4-Me	13.2 ± 1.2	71
6e	2-CF_3	521 ± 41.1	57
6f	3-CF_3	34.6 ± 1.0	74
6g	4-CF_3	205 ± 43.1	72
6h	2-OMe	69.8 ± 4.4	66
6i	3-OMe	18.0 ± 2.8	70
6j	4-OMe	61.3 ± 11.3	33
6k	2-F	80.0 ± 46.1	63
6l	3-F	9.4 ± 1.8	59
6m	4-F	3.8 ± 1.9	72

[a] Mean values for agonists (EC_{50} in nM) calculated from at least three determinations ± SEM in FLIPR assay using HEK-293 cells co-transfected with human $D_{4.4}$ receptor and $G\alpha_{qo5}$.
[b] Efficacy relative to 10 μM dopamine (100%).

4. Conclusion

We have demonstrated that amide bond transposition of a known dopamine D_4 agonist (**PD 168077**) provided novel agonists with excellent potency and selectivity for the human D_4 receptor. Some interesting relationships have been established between regio substitutions in region B and the modulation of ligand functional intrinsic activity as these groups are shifted from *ortho* to *meta* to *para* position on the aromatic ring. This same effect was not observed in region A. Efforts are currently in progress to further elucidate the relationship between affinity and efficacy.

5. Experimental

5.1. General

Melting points were recorded on a Uni-melt apparatus (Arthur H. Thomas Company, Philadelphia, PA) and are uncorrected. Low resolution mass spectra were obtained with a Finnigan SSQ7000 single quad mass spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Inc, Madison, NJ.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz (Varian Mercury 300), 400 MHz (Varian Unity 400) or 500 MHz (Varian Unity 500) as indicated. Chemical shifts are reported in ppm (δ) relative to the residual chloroform resonance (δ 7.24), acetone resonance (δ 2.05), benzene resonance (δ 7.15), or dimethylsulfoxide resonance (δ 2.50) downfield from tetramethylsilane (δ 0.00). Splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). NMR coupling constants (J) are reported in hertz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz (Varian Unity 400) and were assigned using distortionless enhancement by polarization transfer (DEPT) spectra obtained with a phase angle of 135 and 90 and are given the following designations based on their resonance: (s for C) not observed in DEPT 90 and DEPT 135; (d for CH) positive DEPT 90 and DEPT 135; (t for CH_2) not observed in DEPT 90 and negative in DEPT 135; (q for CH_3) not observed in DEPT 90 and positive in DEPT 135. Chemical shifts are reported in ppm (δ) relative to the center resonance of either residual chloroform triplet (δ 77.0) or the residual dimethylsulfoxide heptet (δ 39.5).

Analytical thin layer chromatography (TLC) was carried out on E. Merck TLC plates coated with silica gel 60 F_{254} (0.25 mm layer thickness). TLC visualization was carried out using either a UV lamp and/or charring solution as indicated. Flash chromatography was performed as described[43] on a Biotage Flash 40 chromatography system (Charlottesville, VA) using 40, 90, or 120 g cartridges at 32–63 μm, 60 Å silica gel. Solvent mixtures used for TLC and flash chromatography are reported in v:v total.

Trisorber® tritium manifold was purchased from IN/US Systems, Tampa, Fla. Radiomatic® radioactivity flow detector was purchased from Packard Instrument Co. Radioactivity measurements were performed on a Wallac scintillation counter. Tritium gas was purchased from American Radiolabeled Chemicals.

5.1.1. 2-Bromo-*N*-(3-methylphenyl)acetamide (2a). 3-Methylaniline (15.50 mL, 141.8 mmol) in 2 N aqueous sodium hydroxide (200 mL) at room temperature was treated with bromoacetyl chloride (12.50 mL, 152.0 mmol) as a solution in dichloromethane (200 mL). After 30 min, the layers were separated and the aqueous phase extracted with additional portions of dichloromethane. The organic phases were combined, washed with an aqueous solutions of 1 N HCl, $NaHCO_3$, dried (Na_2SO_4), and concentrated to provide 16.69 g (52% yield) of the desired amide **2a**: white solid; mp 91–92 °C; R_f 0.49 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 4.01 (s, 2H), 6.91 (d, J = 7.5, 1H), 7.20 (dd, J = 7.5, 7.5, 1H), 7.36 (d, J = 8.8, 1H), 7.42 (s, 1H), 10.28 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 30.4 (t), 116.4 (d), 119.7 (d), 124.4 (d), 128.6 (d), 138.0 (s), 138.5 (s), 164.4 (s). MS (DCI/NH_3) m/z 228/230 $(M+H)^+$; 245/247 $(M+NH_4)^+$. Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.44; H, 4.37; N, 6.12.

5.1.2. 2-Chloro-*N*-(3-methylphenyl)acetamide (2b). Compound **2b** was completed using a similar procedure outlined for compound **2a** substituting chloroacetyl chloride for chloroacetyl bromide to provide 18.50 g (72% yield) of the title compound **2b**: white solid; mp 92–93 °C; R_f 0.35 (25% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.20 (s, 2H), 7.00 (s, 1H), 7.22 (m, 1H), 7.35–7.45 (m, 2H), 8.15 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 43.5 (t),

116.5 (d), 119.9 (d), 124.5 (d), 128.6 (d), 138.0 (s), 138.3 (s), 164.5 (s). MS (DCI/NH_3) m/z 184 $(M+H)^+$; 201 $(M+NH_4)^+$. Anal. Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 59.12; H, 5.72; N, 7.59.

5.1.3. 2-[4-(2-Cyanophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3b). 1-(2-Cyanophenyl)piperazine, (1.13 g, 6.04 mmol) in *N*,*N*-diisopropylethylamine (2.0 mL) and toluene (30 mL) was treated with **2a** (1.12 g, 4.90 mmol) and heated at 60 °C for 18 h. The mixture was allowed to cool to room temperature, transferred to a separatory funnel, and washed with saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (elution with 85% hexane–EtOAc then 50% hexane–EtOAc) to provide 1.65 g (92%) of piperazine **3b**: colorless oil; R_f 0.27 (50% EtOAc–hexane; UV). ^1H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.73 (m, 4H), 3.21 (s, 2H), 3.23 (m, 4H), 6.88 (br d, $J = 7.5$, 1H), 7.10 (ddd, $J = 7.5$, 7.5, 0.7, 1H), 7.19 (m, 2H), 7.44 (m, 2H), 7.61 (ddd, $J = 7.5$, 7.5, 1.7, 1H), 7.70 (dd, $J = 7.8$, 1.7 Hz, 1H), 9.68 (br s, 1H). MS (DCI/NH_3) m/z 335 $(M+H)^+$.

Maleate salt: white solid, mp 168–170 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 3.21 (br s, 4H), 3.37 (br s, 4H), 3.82 (br s, 2H), 6.13 (s, 2H), 6.93 (br d, $J = 7.4$, 1H), 7.18 (m, 3H), 7.42 (m, 2H), 7.64 (ddd, $J = 7.5$, 7.5, 1.4, 1H), 7.74 (dd, $J = 7.8$, 1.7, 1H), 10.15 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 49.2 (t), 52.2 (t), 58.5 (t), 105.0 (s), 116.7 (d), 118.0 (s), 119.3 (d), 120.0 (d), 122.6 (d), 124.6 (d), 128.7 (d), 133.6 (d), 134.2 (d), 134.4 (d), 138.0 (s), 138.1 (s), 154.2 (s), 164.8 (s), 167.0 (s). Anal. Calcd for $C_{20}H_{22}N_4O{\cdot}1.0C_4H_4O_4$: C, 63.99; H, 5.82; N, 12.44. Found: C, 63.80; H, 5.80; N, 12.21.

5.1.4. 2-(4-Phenylpiperazin-1-yl)-*N*-(3-methylphenyl)acetamide (3a). Compound **3a** was completed using a similar procedure outlined for compound **3b** substituting 1-phenylpiperazine for 1-(2-cyanophenyl)piperazine to provide 843 mg (86% yield) of the desired compound, **3a**: white solid; mp 120–121 °C; R_f 0.47 (50% EtOAc–hexane; UV). ^1H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.66 (m, 4H), 3.17 (s, 2H), 3.20 (m, 4H), 6.77 (dd, $J = 7.1$, 7.1, 1H), 6.88 (br d, $J = 7.5$, 1H), 6.94 (d, $J = 7.8$, 2H), 7.21 (m, 3H), 7.44 (m, 2H), 9.65 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 48.1 (t), 52.6 (t), 61.6 (t), 115.3 (d), 116.5 (d), 118.7 (d), 119.9 (d), 124.0 (d), 128.4 (d), 128.8 (d), 137.8 (s), 138.4 (s), 150.9 (s), 168.0 (s). MS (DCI/NH_3) m/z 310 $(M+H)^+$. Anal. Calcd for $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58. Found: C, 73.73; H, 7.50; N, 13.64.

5.1.5. 2-[4-(4-Cyanophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3c). 1-(4-Cyanophenyl)piperazine, (900 mg, 4.81 mmol) in *N*,*N*-diisopropylethylamine (3.0 mL) and toluene (20 mL) was treated with **2b** (720 mg, 3.92 mmol) and heated at 90 °C for 18 h. The mixture was allowed to cool to room temperature, transferred to a separatory funnel, and washed with saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (elution with 85% hexane–EtOAc then 50% hexane–EtOAc) to provide 1.10 g (84%) of piperazine **3c**: white solid; mp 161–163 °C; R_f 0.26 (50% EtOAc–hexane; UV). ^1H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.64 (m, 4H), 3.18 (s, 2H), 3.41 (m, 4H), 6.87 (d, $J = 7.5$, 1H), 7.03 (AA′BB′, $J = 9.2$, 2H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.45 (m, 2H), 7.58 (AA′BB′, $J = 9.2$, 2H), 9.67 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 46.3 (t), 52.2 (t), 61.4 (t), 98.2 (s), 114.0 (d), 116.5 (s), 116.6 (d), 119.9 (d), 124.0 (d), 128.4 (d), 133.2 (d), 137.8 (s), 138.4 (s), 153.1 (s), 167.0 (s). MS (DCI/NH_3) m/z 335 $(M+H)^+$. Anal. Calcd for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75. Found: C, 71.50; H, 6.49; N, 16.64.

5.1.6. *N*-(3-Methylphenyl)-2-(4-(2-methylphenyl)piperazin-1-yl)acetamide (3d). Compound **3d** was completed using a similar procedure outlined for compound **3b** substituting 1-(2-methylphenyl)piperazine for 1-(2-cyanophenyl)piperazine to provide 766 mg (75% yield) of the desired compound, **3d**: white solid; mp 104–106 °C; R_f 0.70 (50% EtOAc–hexane; UV). ^1H NMR (300 MHz, DMSO-d_6) δ 2.24 (s, 3H), 2.28 (s, 3H), 2.69 (m, 4H), 2.91 (m, 4H), 3.19 (s, 2H), 6.88 (br d, $J = 7.4$, 1H), 6.95 (dd, $J = 7.1$, 7.1, 1H), 7.05 (m, 1H), 7.17 (m, 3H), 7.45 (m, 2H), 9.64 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.5 (q), 21.1 (q), 51.2 (t), 53.2 (t), 61.7 (t), 116.5 (d), 118.7 (d), 119.9 (d), 122.7 (d), 124.0 (d), 126.4 (d), 128.4 (d), 130.7 (d), 131.7 (s), 137.8 (s), 138.4 (s), 151.2 (s), 168.0 (s). MS (DCI/NH_3) m/z 324 $(M+H)^+$. Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.34; H, 7.85; N, 12.91.

5.1.7. *N*-(3-Methylphenyl)-2-(4-(3-methylphenyl)piperazin-1-yl)acetamide (3e). Compound **3e** was completed using a similar procedure outlined for compound **3b** substituting 1-(3-methylphenyl)piperazine for 1-(2-cyanophenyl)piperazine to provide 694 mg (69% yield) of the desired compound, **3e**: white solid; mp 90–93 °C; R_f 0.52 (50% EtOAc–hexane; UV). ^1H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.27 (s, 3H), 2.65 (m, 4H), 3.17 (s, 2H), 3.18 (m, 4H), 6.60 (br d, $J = 7.5$, 1H), 6.74 (m, 2H), 6.88 (br d, $J = 7.5$, 1H), 7.09 (dd, $J = 7.8$, 7.8, 1H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.45 (m, 2H), 9.65 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 21.4 (q), 48.2 (t), 52.7 (t), 61.7 (t), 112.6 (d), 116.0 (d), 116.5 (d), 119.6 (d), 119.9 (d), 124.0 (d), 128.4 (d), 128.6 (d), 137.8 (s), 137.9 (s), 138.4 (s), 151.0 (s), 168.0 (s). MS (DCI/NH_3) m/z 324 $(M+H)^+$. Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.52; H, 7.82; N, 13.03.

5.1.8. *N*-(3-Methylphenyl)-2-(4-(4-methylphenyl)piperazin-1-yl)acetamide (3f). Compound **3f** was completed using a similar procedure outlined for compound **3b** substituting 1-(4-methylphenyl)piperazine for 1-(2-cyanophenyl)piperazine to provide 768 mg (75% yield) of the

desired compound, **3f**: white solid; mp 118–120 °C; R_f 0.57 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 3H), 2.27 (s, 3H), 2.65 (m, 4H), 3.13 (m, 4H), 3.16 (s, 2H), 6.84 (AA′BB′, $J = 8.8$, 2H), 6.86 (m, 1H), 7.02 (AA′BB′, $J = 8.1$, 2H), 7.18 (dd, $J = 7.6$, 7.6, 1H), 7.44 (m, 2H), 9.64 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.0 (q), 21.1 (q), 48.6 (t), 52.7 (t), 61.7 (t), 115.6 (d), 116.5 (d), 119.9 (d), 124.0 (d), 127.5 (s), 128.4 (d), 129.3 (d), 137.8 (s), 138.41 (s), 148.9 (s), 168.0 (s). MS (DCI/NH_3) m/z 324 $(M+H)^+$. Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.11; H, 7.64; N, 13.02.

5.1.9. 2-[4-(2-Methoxyphenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3g). Compound **3g** was completed using a similar procedure outlined for compound **3b** substituting 1-(2-methoxyphenyl)piperazine for 1-(2-cyanophenyl)piperazine to provide 1.39 g (83% yield) of the desired compound, **3g**: yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.67 (m, 4H), 3.03 (m, 4H), 3.17 (s, 2H), 3.77 (s, 3H), 6.89 (m, 5H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.44 (m, 2H), 9.64 (br s, 1H). MS (DCI/NH_3) m/z 340 $(M+H)^+$.

HCl salt: white solid; mp 80 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 3.11 (br s, 2H), 3.46 (br s, 4H), 3.60 (br s, 2H), 3.80 (s, 3H), 4.25 (br s, 2H), 6.95 (m, 5H), 7.24 (dd, $J = 7.4$, 7.4, 1H), 7.44 (m, 2H), 10.52 (br s, 0.5H), 10.82 (br s, 0.5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 46.7 (t), 51.9 (t), 55.4 (q), 56.5 (t), 112.0 (d), 116.6 (d), 118.2 (d), 119.9 (d), 120.8 (d), 123.4 (d), 124.7 (d), 128.6 (d), 138.0 (s), 139.4 (s), 151.8 (s), 162.6 (s). Anal. Calcd for $C_{20}H_{25}N_3O_2 \cdot 0.90$ HCl: C, 64.53; H, 7.01; N, 11.29. Found: C, 64.38; H, 6.83; N, 11.17.

5.1.10. 2-[4-(3-Methoxyphenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3h). Compound **3h** was completed using a similar procedure outlined for compound **3c** substituting 1-(3-methoxyphenyl)piperazine for 1-(4-cyanophenyl)piperazine to provide 1.19 g (91% yield) of the desired compound, **3h**: white solid; mp 104–106 °C; R_f 0.28 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.65 (m, 4H), 3.17 (s, 2H), 3.20 (m, 4H), 3.71 (s, 3H), 6.36 (dd, $J = 7.8$, 2.0, 1H), 6.45 (dd, $J = 2.4$, 2.4, 1H), 6.52 (dd, $J = 8.1$, 2.4, 1H), 6.88 (br d, $J = 7.5$, 1H), 7.10 (dd, $J = 8.1$, 8.1, 1H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.44 (m, 2H), 9.64 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0 (q), 48.0 (t), 52.6 (t), 54.8 (q), 61.6 (t), 101.5 (d), 104.0 (d), 108.0 (d), 116.5 (d), 119.9 (d), 124.0 (d), 128.4 (d), 129.5 (d), 137.8 (s), 138.4 (s), 152.3 (s), 160.1 (s), 168.0 (s). MS (DCI/NH_3) m/z 340 $(M+H)^+$. Anal. Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.73; H, 7.58; N, 12.39.

5.1.11. 2-[4-(4-Methoxyphenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3i). Compound **3i** was completed using a similar procedure outlined for compound **3c** substituting 1-(4-methoxyphenyl)piperazine for 1-(4-cyanophenyl)piperazine to provide 1.17 g (88% yield) of the desired compound, **3i**: white solid; mp 103–105 °C; R_f 0.25 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.66 (m, 4H), 3.08 (m, 4H), 3.16 (s, 2H), 3.68 (s, 3H), 6.82 (AA′BB′, $J = 9.2$, 2H), 6.86 (m, 1H), 6.90 (AA′BB′, $J = 9.0$, 2H), 7.18 (dd, $J = 7.6$, 7.6, 1H), 7.44 (m, 2H), 9.63 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0 (q), 49.5 (t), 52.8 (t), 55.1 (q), 61.7 (t), 114.2 (d), 116.5 (d), 117.3 (d), 119.9 (d), 124.0 (d), 128.4 (d), 137.8 (s), 138.4 (s), 145.3 (s), 152.8 (s), 168.0 (s). MS (DCI/NH_3) m/z 340 $(M+H)^+$. Anal. Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.51; H, 7.44; N, 12.63.

5.1.12. 2-[4-(2-Nitrophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3j). Compound **3j** was completed using a similar procedure outlined for compound **3b** substituting 1-(2-nitrophenyl)piperazine for 1-(2-cyanophenyl)piperazine to provide 1.03 g (91% yield) of the title compound, **3j**: orange oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.66 (m, 4H), 3.07 (m, 4H), 3.18 (s, 2H), 6.88 (br d, $J = 7.8$, 1H), 7.13 (ddd, $J = 8.5$, 7.1, 1.0, 1H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.35 (dd, $J = 8.1$, 1.0, 1H), 7.45 (m, 2H), 7.59 (ddd, $J = 8.1$, 7.1, 1.3, 1H), 7.79 (dd, $J = 8.1$, 1.7, 1H), 9.66 (br s, 1H). MS (DCI/NH_3) m/z 355 $(M+H)^+$.

Maleate salt: yellow solid; mp 172–175 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (s, 3H), 3.22 (m, 8H), 3.88 (s, 2H), 6.13 (s, 2H), 6.91 (br d, $J = 7.4$, 1H), 7.20 (m, 2H), 7.40 (m, 3H), 7.62 (dd, $J = 8.4$, 8.4, 1H), 7.84 (dd, $J = 8.1$, 1.4, 1H), 10.21 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 49.3 (t), 52.3 (t), 58.4 (t), 116.7 (d), 120.0 (d), 122.0 (d), 123.0 (d), 124.7 (d), 125.5 (d), 128.7 (d), 133.8 (d), 134.0 (d), 138.0 (s), 138.1 (s), 143.3 (s), 144.4 (s), 164.6 (s), 167.0 (s). Anal. Calcd for $C_{19}H_{22}N_4O_3 \cdot 1.0C_4H_4O_4$: C, 58.72; H, 5.57; N, 11.91. Found: C, 58.38; H, 5.49; N, 11.64.

5.1.13. 2-[4-(4-Nitrophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3k). Compound **3k** was completed using a similar procedure outlined for compound **3c** substituting 1-(4-nitrophenyl)piperazine for 1-(4-cyanophenyl)piperazine to provide 752 mg (55% yield) of the title compound, **3k**: yellow solid; mp 193–195 °C; R_f 0.11 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.66 (m, 4H), 3.19 (s, 2H), 3.54 (m, 4H), 6.88 (d, $J = 7.5$, 1H), 7.05 (AA′BB′, $J = 9.5$, 2H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.46 (m, 2H), 8.06 (AA′BB′, $J = 9.5$, 2H), 9.68 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 46.3 (t), 52.1 (t), 61.3 (t), 112.6 (d), 116.6 (d), 120.0 (d), 124.1 (d), 125.6 (d), 128.4 (d), 136.8 (s), 137.8 (s), 138.4 (s), 154.7 (s), 167.9 (s). MS (DCI/NH_3) m/z 355 $(M+H)^+$. Anal. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.32; H, 6.27; N, 15.75.

5.1.14. 2-[4-(2-Fluorophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3l). Compound **3l** was completed using a similar procedure outlined for compound **3c** substituting 1-(2-fluorophenyl)piperazine for 1-(4-cyan-

ophenyl)piperazine to provide 1.15 g (84% yield) of the title compound, **3l**: tan solid; mp 100–103 °C; R_f 0.41 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.69 (m, 4H), 3.09 (m, 4H), 3.18 (s, 2H), 6.88 (d, $J = 7.8$, 1H), 7.06 (m, 4H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.45 (m, 2H), 9.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 50.0 (t), 52.7 (t), 61.6 (t), 115.8 (d, $J_{CF} = 20.5$), 116.5 (d), 119.1 (d, $J_{CF} = 3.0$), 119.9 (d), 122.2 (d, $J_{CF} = 7.6$), 124.0 (d), 124.7 (d, $J_{CF} = 3.8$), 128.4 (d), 137.8 (s), 138.4 (s), 139.8 (s, $J_{CF} = 8.3$), 154.9 (s, $J_{CF} = 244.0$), 168.0 (s). MS (DCI/NH_3) m/z 328 $(M+H)^+$. Anal. Calcd for $C_{19}H_{22}FN_3O$: C, 69.70; H, 6.77; N, 12.83. Found: C, 69.52; H, 6.73; N, 12.80.

5.1.15. 2-[4-(4-Fluorophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3m). Compound **3m** was completed using a similar procedure outlined for compound **3c** substituting 1-(4-fluorophenyl)piperazine for 1-(4-cyanophenyl)piperazine to provide 1.01 g (70% yield) of the title compound, **3m**: white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.66 (m, 4H), 3.15 (m, 4H), 3.17 (s, 2H), 6.86–7.08 (m, 5H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.44 (m, 2H), 9.64 (br s, 1H). MS (DCI/NH_3) m/z 328 $(M+H)^+$.

Maleate salt: tan solid; mp 150–153 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (s, 3H), 3.26 (m, 4H), 3.34 (m, 4H), 3.94 (s, 2H), 6.11 (s, 2H), 6.92 (d, $J = 7.4$, 7.4, 1H), 6.99 (m, 2H), 7.08 (AA′BB′, $J = 8.8$, 2H), 7.22 (dd, $J = 7.7$, 7.7, 1H), 7.42 (m, 2H), 10.3 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 46.8 (t), 52.0 (t), 58.0 (t), 115.4 (d, $J_{CF} = 22.0$), 116.7 (d), 117.6 (d, $J_{CF} = 8.3$), 120.0 (d), 124.7 (d), 128.7 (d), 134.2 (d), 138.0 (s, $J_{CF} = 22.7$), 146.8 (s), 155.3 (s), 157.6 (s), 164.2 (s), 167.1 (s). Anal. Calcd for $C_{19}H_{22}FN_3O{\cdot}1.0C_4H_4O_4$: C, 62.29; H, 5.91; N, 9.48. Found: C, 62.05; H, 6.02; N, 9.23.

5.1.16. 2-[4-(2-Chlorophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3n). Compound **3n** was completed using a similar procedure outlined for compound **3c** substituting 1-(2-chlorophenyl)piperazine for 1-(4-cyanophenyl)piperazine to provide 1.22 g (92% yield) of the title compound, **3n**: light tan solid; mp 103–105 °C; R_f 0.48 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.71 (m, 4H), 3.05 (m, 4H), 3.20 (s, 2H), 6.87 (br d, $J = 7.7$, 1H), 7.04 (ddd, $J = 8.0$, 7.4, 1.5, 1H), 7.19 (m, 2H), 7.30 (ddd, $J = 8.0$, 7.4, 1.5, 1H), 7.40 (dd, $J = 8.0$, 1.5, 1H), 7.46 (m, 2H), 9.64 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 50.7 (t), 52.8 (t), 61.6 (t), 116.5 (d), 119.9 (d), 120.8 (d), 123.8 (d), 124.0 (d), 127.6 (s), 127.9 (d), 128.4 (d), 130.3 (d), 137.8 (s), 138.4 (s), 148.9 (s), 168.0 (s). MS (DCI/NH_3) m/z 344 $(M+H)^+$. Anal. Calcd for $C_{19}H_{22}ClN_3O$: C, 66.37; H, 6.45; N, 12.22. Found: C, 66.40; H, 6.50; N, 12.22.

5.1.17. 2-[4-(4-Chlorophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3o). Compound **3o** was completed using a similar procedure outlined for compound **3c** substituting 1-(4-chlorophenyl)piperazine for 1-(4-cyanophenyl)piperazine to provide 1.11 g (83% yield) of the title compound, **3o**: light tan solid; mp 103–105 °C; R_f 0.30 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.65 (m, 4H), 3.17 (s, 2H), 3.20 (m, 4H), 6.88 (d, $J = 7.5$, 1H), 6.95 (AA′BB′, $J = 9.2$, 2H), 7.18 (dd, $J = 7.8$, 1H), 7.23 (AA′BB′, $J = 9.2$, 2H), 7.44 (m, 2H), 9.64 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 47.9 (t), 52.4 (t), 61.6 (t), 116.5 (d), 116.8 (d), 119.9 (d), 122.3 (s), 124.0 (d), 128.4 (d), 128.5 (d), 137.8 (s), 138.4 (s), 149.7 (s), 168.0 (s). MS (DCI/NH_3) m/z 344 $(M+H)^+$. Anal. Calcd for $C_{19}H_{22}ClN_3O$: C, 66.37; H, 6.45; N, 12.22. Found: C, 66.28; H, 6.53; N, 12.29.

5.1.18. 2-[4-(4-Bromophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3p). Compound **3p** was completed using a similar procedure outlined for compound **3b** substituting 1-(4-bromophenyl)piperazine for 1-(2-cyanophenyl)piperazine to provide 745 mg (61% yield) of the title compound, **3p**: white solid; mp 129–131 °C; R_f 0.34 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.65 (m, 4H), 3.17 (s, 2H), 3.20 (m, 4H), 6.89 (m, 3H), 7.18 (dd, $J = 7.6$, 1H), 7.34 (AA′BB′, $J = 9.2$, 2H), 7.44 (m, 2H), 9.65 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 47.8 (t), 52.4 (t), 61.6 (t), 109.9 (s), 116.6 (d), 117.2 (d), 119.9 (d), 124.0 (d), 128.4 (d), 131.4 (d), 137.8 (s), 138.4 (s), 150.1 (s), 167.9 (s). MS (DCI/NH_3) m/z 388/390 $(M+H)^+$. Anal. Calcd for $C_{19}H_{22}BrN_3O$: C, 58.77; H, 5.71; N, 10.82. Found: C, 58.62; H, 5.76; N, 10.59.

5.1.19. 2-[4-(2-Aminophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3q). A solution of **3j** (299 mg, 0.636 mmol) in methanol (20 mL) was treated with 10% palladium on carbon and placed under 60 psi of hydrogen at room temperature for 80 min. The heterogeneous mixture was filtered, concentrated under reduced pressure, and the residue portioned between 2 N sodium hydroxide and dichloromethane. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to provide 160 mg (78% yield) of the title compound, **3q**: light tan solid; mp 170–172 °C; R_f 0.21 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.69 (m, 4H), 2.87 (m, 4H), 3.17 (s, 2H), 4.69 (s, 2H), 6.55 (ddd, $J = 7.5$, 7.5 1.7, 1H), 6.66 (dd, $J = 7.8$, 1.4, 1H), 6.80 (ddd, $J = 7.5$, 7.5, 1.4, 1H), 6.88 (m, 1H), 6.92 (dd, $J = 7.8$, 1.4, 1H), 7.19 (dd, $J = 7.8$, 7.8, 1H), 7.46 (m, 2H), 9.63 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 50.3 (t), 53.3 (t), 61.8 (t), 114.3 (d), 116.5 (d, overlapped), 119.0 (d), 119.9 (d), 123.9 (d), 124.0 (d), 128.4 (d), 137.8 (s), 138.0 (s), 138.4 (s), 142.2 (s), 168.1 (s). MS (DCI/NH_3) m/z 325 $(M+H)^+$. Anal. Calcd for $C_{19}H_{24}N_4O{\cdot}0.05CH_2Cl_2$: C, 69.62; H, 7.39; N, 17.05. Found: C, 69.52; H, 7.32; N, 17.13.

5.1.20. 2-[4-(4-Aminophenyl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (3r). Compound **3r** was completed

using a similar procedure outlined for compound **3q** substituting compound **3k** for compound **3j** to provide 260 mg (90% yield) of the title compound, **3r**: tan solid; mp 110–113 °C; R_f 0.43 (5% MeOH–CH_2Cl_2; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.63 (m, 4H), 2.98 (m, 4H), 3.15 (s, 2H), 4.55 (br s, 2H), 6.49 (AA′BB′, $J = 8.8$, 2H), 6.70 (AA′BB′, $J = 8.8$, 2H), 6.87 (br d, $J = 7.5$, 1H), 7.17 (dd, $J = 7.6$, 1H), 7.44 (m, 2H), 9.62 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 50.2 (t), 53.0 (t), 61.7 (t), 114.7 (d), 116.5 (d), 117.9 (d), 119.9 (d), 124.0 (d), 128.4 (d), 137.8 (s), 138.4 (s), 142.0 (s), 142.3 (s), 168.0 (s). MS (DCI/NH_3) m/z 325 $(M+H)^+$. Anal. Calcd for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.46; N, 17.27. Found: C, 70.37; H, 7.55; N, 16.96.

5.1.21. 2-(4-Pyridin-2-yl-piperazin-1-yl)-*N*-(3-methylphenyl)acetamide (3s). Compound **3s** was completed using a similar procedure outlined for compound **3b** substituting 1-(2-pyridinyl)piperazine for 1-(2-cyanophenyl)piperazine to provide 745 mg (61% yield) of the title compound, **3s**: white solid; mp 126–127 °C; R_f 0.19 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.60 (m, 4H), 3.17 (s, 2H), 3.55 (m, 4H), 6.63 (ddd, $J = 6.7$, 4.7, 0.6, 1H), 6.82 (d, $J = 8.8$, 1H), 6.88 (br d, $J = 7.8$, 1H), 7.18 (dd, $J = 6.7$, 4.7, 0.6, 1H), 7.46 (m, 2H), 7.52 (ddd, $J = 8.8$, 7.1, 2.0, 1H), 8.11 (m, 1H), 9.67 (br s, 1H); MS (DCI/NH_3) m/z 311 $(M+H)^+$. ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 44.5 (t), 52.4 (t), 61.7 (t), 107.0 (d), 112.9 (d), 116.6 (d), 119.9 (d), 124.0 (d), 128.4 (d), 137.4 (d), 137.8 (s), 138.4 (s), 147.5 (d), 159.0 (s), 168.0 (s). Anal. Calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.72; H, 7.09; N, 18.22.

5.1.22. 2-(4-Pyridin-4-yl-piperazin-1-yl)-*N*-(3-methylphenyl)acetamide (3t). Compound **3t** was completed using a similar procedure outlined for compound **3b** substituting 1-(4-pyridinyl)piperazine for 1-(2-cyanophenyl)piperazine to provide 190 mg (8% yield) of the title compound, **3t**: light tan solid; mp 166–169 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.63 (m, 4H), 3.18 (s, 2H), 3.38 (m, 4H), 6.82 (m, 2H), 6.88 (br d, $J = 7.8$, 1H), 7.18 (dd, $J = 7.8$, 7.8, 1H), 7.44 (m, 2H), 8.16 (m, 2H), 9.67 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1 (q), 45.3 (t), 52.1 (t), 61.4 (t), 108.3 (d), 116.6 (d), 119.9 (d), 124.1 (d), 128.4 (d), 137.8 (s), 138.4 (s), 149.7 (d), 154.4 (s), 167.9 (s). MS (DCI/NH_3) m/z 311 $(M+H)^+$. Anal. Calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.47; H, 7.20; N, 17.69.

5.1.23. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-phenylacetamide (6a). 2-Piperazin-1-ylnicotinonitrile, (Chess, 770 mg, 4.09 mmol) in *N*,*N*-diisopropylethylamine (3.0 mL) and toluene (20 mL) was treated with 2-chloro-*N*-phenylacetamide (620 mg, 3.66 mmol) and heated at 80 °C for 18 h. The mixture was allowed to cool to room temperature, transferred to a separatory funnel, and washed with saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (elution with 85% hexane–EtOAc then 50% hexane–EtOAc) to provide 610 g (52%) of piperazine **6a**: white solid; mp 110–112 °C; R_f 0.18 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (m, 4H), 3.21 (s, 2H), 3.68 (m, 4H), 6.93 (dd, $J = 7.8$, 4.7, 1H), 7.06 (dd, $J = 7.8$, 7.8, 1H), 7.31 (dd, $J = 7.8$, 7.8, 2H), 7.64 (dd, $J = 8.8$, 1.4, 2H), 8.07 (dd, $J = 7.8$, 2.0, 1H), 8.42 (dd, $J = 4.8$, 1.7, 1H), 9.76 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.7 (t), 52.3 (t), 61.4 (t), 94.3 (s), 114.6 (d), 117.8 (s), 119.5 (d), 123.3 (d), 128.5 (d), 138.5 (s), 144.2 (d), 152.0 (d), 160.2 (s), 168.0 (s). MS (DCI/NH_3) m/z 322 $(M+H)^+$. Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.21; H, 5.77; N, 21.59.

5.1.24. 2-Chloro-*N*-(2-methylphenyl)acetamide (5b). 2-Methylaniline (8.50 mL, 79.6 mmol) in 2 N aqueous sodium hydroxide (200 mL) at room temperature was treated with chloroacetyl chloride (10.00 mL, 125.7 mmol) as a solution in dichloromethane (200 mL). After 30 min, the layers were separated and the aqueous phase extracted with additional portions of dichloromethane. The organic phases were combined, washed with an aqueous solutions of 1 N HCl, saturated sodium bicarbonate, dried (Na_2SO_4), and concentrated to provide 13.15 g (90% yield) of the desired amide **5b**: white solid; mp 110–112 °C; R_f 0.57 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 3H), 4.30 (s, 2H), 7.16 (m, 3H), 7.38 (d, $J = 7.8$, 1H), 9.63 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.6 (q), 43.1 (t), 125.0 (d), 125.6 (d), 126.0 (d), 130.3 (d), 131.9 (s), 135.5 (s), 164.8 (s). MS (DCI/NH_3) m/z 184 $(M+H)^+$. Anal. Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.74; H, 5.62; N, 7.54.

5.1.25. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(2-methylphenyl)acetamide (6b). Compound **6b** was completed using a similar procedure outlined for compound **6a** substituting compound **5b** for 2-chloro-*N*-phenylacetamide to provide 751 mg (58% yield) of the title compound, **6b**: light tan solid; mp 123–125 °C; R_f 0.23 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.73 (m, 4H), 3.22 (s, 2H), 3.69 (m, 4H), 6.94 (dd, $J = 7.8$, 4.8, 1H), 7.06 (ddd, $J = 7.4$, 7.4, 1.0, 1H), 7.17 (d, $J = 7.8$, 1H), 7.21 (dd, $J = 8.5$, 8.5, 1H), 7.75 (d, $J = 7.8$, 1H), 8.08 (dd, $J = 7.8$, 1.7, 1H), 8.42 (dd, $J = 5.0$, 1.7, 1H), 9.42 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.5 (q), 48.0 (t), 52.5 (t), 61.2 (t), 94.5 (s), 114.7 (d), 117.7 (s), 122.3 (d), 124.4 (d), 126.1 (d), 129.1 (s), 130.2 (d), 136.0 (s), 144.2 (d), 151.9 (d), 160.2 (s), 167.7 (s). MS (DCI/NH_3) m/z 336 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_5O{\cdot}0.2H_2O$: C, 67.32; H, 6.36; N, 20.66. Found: C, 67.29; H, 6.23; N, 20.66.

5.1.26. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(3-methylphenyl)acetamide (6c). Compound **6c** was completed using a similar procedure outlined for compound **3b** substituting compound 2-piperazin-1-ylnicotinonitrile for 1-(2-cyanophenyl)piperazine to provide 1.46 g

(64% yield) of the title compound, **6c**: white solid; mp 99–101 °C; R_f 0.23 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.68 (m, 4H), 3.19 (s, 2H), 3.68 (m, 4H), 6.88 (br d, $J = 7.8$, 1H), 6.93 (dd, $J = 7.8$, 4.8, 1H), 7.18 (dd, $J = 7.5$, 7.5, 1H), 7.44 (br d, $J = 8.2$, 1H), 7.47 (br s, 1H), 8.07 (dd, $J = 7.8$, 2.0, 1H), 8.42 (dd, $J = 5.1$, 2.0, 1H), 9.68 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0 (q), 47.7 (t), 52.3 (t), 61.4 (t), 94.3 (s), 114.6 (d), 116.6 (d), 117.8 (s), 120.0 (d), 124.0 (d), 128.4 (d), 137.8 (s), 138.4 (s), 144.2 (d), 151.9 (d), 160.2 (s), 167.9 (s). MS (DCI/NH_3) m/z 336 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_5O$: C, 68.04; H, 6.31; N, 20.88. Found: C, 68.19; H, 6.36; N, 21.15.

5.1.27. 2-Chloro-*N*-(4-methylphenyl)acetamide (5d). Compound **5d** was completed using a similar procedure outlined for compound **5b** substituting 4-methylaniline for 2-methylaniline to provide 697 mg (70% yield) of the title compound, **5d**: white solid; mp 162–165 °C; R_f 0.60 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.18 (s, 2H), 7.16 (AA′BB′, $J = 8.1$, 2H), 7.42 (AA′BB′, $J = 8.5$, 2H), 8.16 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.4 (q), 43.5 (t), 119.3 (d), 129.1 (d), 132.8 (s), 135.9 (s), 164.3 (s). MS (DCI/NH_3) m/z 201 $(M+NH_4)^+$. Anal. Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.82; H, 5.33; N, 7.56.

5.1.28. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(4-methylphenyl)acetamide (6d). Compound **6d** was completed using a similar procedure outlined for compound **6a** substituting compound **5d** for 2-chloro-*N*-phenylacetamide to provide 514 mg (70% yield) of the title compound, **6d**: yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.84 (m, 4H), 3.26 (s, 2H), 3.82 (m, 4H), 6.82 (dd, $J = 7.6$, 4.9, 1H), 7.14 (AA′BB′, $J = 8.1$, 2H), 7.47 (AA′BB′, $J = 8.5$, 2H), 7.80 (dd, $J = 7.6$, 1.9, 1H), 8.37 (dd, $J = 4.9$, 1.9, 1H), 9.10 (br s, 1H). MS (DCI/NH_3) m/z 336 $(M+H)^+$.

Maleate salt: light tan solid; mp 156–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H), 3.20 (m, 4H), 3.82 (m, 4H), 3.84 (s, 2H), 6.12 (s, 2H), 6.99 (dd, $J = 7.5$, 4.8, 1H), 7.13 (AA′BB′, $J = 8.0$, 2H), 7.49 (AA′BB′, $J = 8.3$, 2H), 8.10 (dd, $J = 7.7$, 1.8, 1H), 8.44 (dd, $J = 4.8$, 1.7, 1H), 10.20 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.4 (q), 45.9 (t), 51.8 (t), 58.5 (t), 95.3 (s), 115.6 (d), 117.5 (s), 119.6 (d), 129.2 (d), 133.0 (s), 133.7 (d), 135.5 (s), 144.3 (d), 152.0 (d), 160.0 (s), 164.4 (s), 167.0 (s). Anal. Calcd for $C_{19}H_{21}N_5O{\cdot}1.0C_4H_4O_4{\cdot}0.20\ H_2O$: C, 60.70; H, 5.63; N, 15.39. Found: C, 60.33; H, 5.55; N, 15.10.

5.1.29. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(2-trifluoromethylphenyl)acetamide (6e). Compound **6e** was completed using a similar procedure outlined for compound **6a** substituting *N*-chloroacetyl-2-(trifluoromethyl)aniline (Apollo) for 2-chloro-*N*-phenylacetamide to provide the title compound, **6e**: colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.74 (m, 4H), 3.27 (s, 2H), 3.65 (m, 4H), 6.97 (dd, $J = 7.5$, 4.8, 1H), 7.36 (dd, $J = 7.8$, 7.8, 1H), 7.69 (d, $J = 7.5$, 1H), 7.73 (dd, $J = 8.1$, 8.1, 1H), 8.10 (dd, $J = 8.1$, 2.0, 1H), 8.21 (d, $J = 8.5$, 1H), 8.44 (dd, $J = 4.7$, 2.3, 1H), 9.89 (br s, 1H). MS (DCI/NH_3) m/z 390 $(M+H)^+$.

Maleate salt: 622 mg (47% yield); white solid, mp 143–145 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.99 (m, 4H), 3.61 (s, 2H), 3.73 (m, 4H), 6.18 (s, 2H), 6.98 (dd, $J = 7.7$, 4.9, 1H), 7.40 (dd, $J = 7.7$, 7.7, 1H), 7.70 (dd, $J = 7.8$, 7.8, 1H), 7.74 (d, $J = 7.7$, 1H), 8.00 (br d, $J = 8.0$, 1H), 8.09 (dd, $J = 7.7$, 1.8, 1H), 8.44 (dd, $J = 4.8$, 2.0, 1H), 10.05 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.9 (t), 52.1 (t), 59.4 (t), 95.3 (s), 115.4 (d), 117.5 (s), 123.8 (s, $J_{CF} = 272.8$), 125.7 (d), 126.0 (s, obscured J_{CF} ; overlapped d), 126.3 (d, $J_{CF} = 5.3$), 132.1 (d), 133.4 (d), 134.7 (s), 144.2 (d), 152.0 (d), 160.1 (s), 166.8 (s), 167.2 (s). Anal. Calcd for $C_{19}H_{18}F_3N_5O{\cdot}1.0C_4H_4O_4$: C, 54.65; H, 4.39; N, 13.86. Found: C, 54.61; H, 4.32; N, 13.83.

5.1.30. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(3-trifluoromethylphenyl)acetamide (6f). Compound **6f** was completed using a similar procedure outlined for compound **6a** substituting *N*-chloroacetyl-3-(trifluoromethyl)aniline for 2-chloro-*N*-phenylacetamide to provide the title compound, **6f**: yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.69 (m, 4H), 3.25 (s, 2H), 3.69 (m, 4H), 6.93 (dd, $J = 7.8$, 4.7, 1H), 7.41 (br d, $J = 7.8$, 1H), 7.56 (dd, $J = 7.8$, 7.8, 1H), 7.90 (br d, $J = 8.4$, 1H), 8.07 (dd, $J = 7.8$, 2.1, 1H), 8.15 (br s, 1H), 8.42 (dd, $J = 4.7$, 1.7, 1H), 10.11 (br s, 1H). MS (DCI/NH_3) m/z 390 $(M+H)^+$.

Maleate salt: tan solid; mp 157–158 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.07 (br s, 4H), 3.73 (br s, 2H), 3.79 (br s, 4H), 6.15 (s, 2H), 7.00 (dd, $J = 7.4$, 4.7, 1H), 7.46 (br d, $J = 7.8$, 1H), 7.59 (dd, $J = 7.8$, 7.8, 1H), 7.85 (br d, $J = 8.2$, 1H), 8.13 (m, 2H), 8.45 (dd, $J = 4.7$, 2.0, 1H), 10.48 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.2 (t), 51.9 (t), 59.1 (t), 95.1 (s), 115.4 (d), 115.7 (d, $J_{CF} = 3.8$), 117.5 (s), 120.2 (d, $J_{CF} = 3.8$), 123.1 (d), 124.0 (s, $J_{CF} = 272.0$), 129.5 (s, $J_{CF} = 31.8$), 130.1 (d), 133.0 (d), 138.9 (s), 144.3 (d), 152.0 (s), 159.9 (s), 166.1 (s), 166.9 (s). Anal. Calcd for $C_{19}H_{18}F_3N_5O{\cdot}1.0C_4H_4O_4$: C, 54.56; H, 4.39; N, 13.86. Found: C, 54.30; H, 4.42; N, 13.42.

5.1.31. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(4-trifluoromethylphenyl)acetamide (6g). Compound **6g** was completed using a similar procedure outlined for compound **6a** substituting *N*-chloroacetyl-4-(trifluoromethyl)aniline (Maybridge) for 2-chloro-*N*-phenylacetamide to provide 1.05 g (78% yield) of the title compound, **6g**: white solid; mp 147–150 °C; R_f 0.24 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.69 (m, 4H), 3.26 (s, 2H), 3.68 (m, 4H), 6.93 (dd, $J = 7.5$, 4.7, 1H), 7.68 (AA′BB′, $J = 8.8$, 2H), 7.88 (AA′BB′, $J = 8.5$, 2H), 8.07 (dd, $J = 7.8$, 2.0, 1H), 8.42 (dd, $J = 4.7$, 2.0, 1H), 10.14 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.7 (t), 52.3 (t), 61.4 (t), 94.3

(s), 114.6 (d), 117.8 (s), 119.3 (d), 123.4 (s, $J_{CF} = 31.8$), 124.3 (s, $J_{CF} = 271.3$), 125.8 (d, $J_{CF} = 3.8$), 142.1 (s), 144.2 (d), 151.9 (d), 160.2 (s), 168.8 (s). MS (DCI/NH_3) m/z 390 $(M+H)^+$. Anal. Calcd for $C_{19}H_{18}F_3N_5O$: C, 58.61; H, 4.66; N, 17.99. Found: C, 58.35; H, 4.45; N, 18.02.

5.1.32. 2-Chloro-*N*-(2-methoxyphenyl)acetamide (5h). To a slurry of 2-methoxyaniline (5.46 g, 44.3 mmol) in toluene (50 mL) was added chloroacetylchloride (5.40 mL, 67.9 mmol) and the mixture heated to 100 °C for 16 h. The solvent and excess acid chloride was removed under reduced pressure. The residue was evaporated from toluene (×2) and the residue purified by column chromatography (10% EtOAc–hexane) to provide 7.35 g (83% yield) of the title compound, **5h**: white solid; mp 40–43 °C; R_f 0.23 (25% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.85 (s, 3H), 4.38 (s, 2H), 6.92 (m, 1H), 7.08 (m, 2H), 7.91 (d, $J = 7.8$, 1H), 9.48 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.4 (t), 55.7 (q), 111.2 (d), 120.3 (d), 121.4 (d), 124.9 (d), 126.6 (s), 149.4 (s), 164.7 (s). MS (DCI/NH_3) m/z 200 $(M+H)^+$. Anal. Calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 53.99; H, 4.81; N, 6.90.

5.1.33. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(2-methoxyphenyl)acetamide (6h). Compound **6h** was completed using a similar procedure outlined for compound **6a** substituting **5h** for 2-chloro-*N*-phenylacetamide to provide 481 mg (34% yield) of the title compound, **6h**: white solid; mp 174–175 °C; R_f 0.31 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.71 (m, 4H), 3.22 (s, 2H), 3.70 (m, 4H), 3.88 (s, 3H), 6.96 (m, 2H), 7.07 (m, 2H), 8.10 (dd, $J = 7.8$, 2.1, 1H), 8.21 (d, $J = 7.8$, 1H), 8.44 (dd, 4.7, 1.7, 1H), 9.73 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.1 (t), 52.4 (t), 56.0 (q), 61.2 (t), 94.6 (s), 110.9 (d), 114.8 (d), 117.7 (s), 118.9 (d), 120.5 (d), 123.7 (d), 127.0 (s), 144.3 (d), 148.2 (s), 152.0 (d), 160.2 (s), 167.6 (s). MS (DCI/NH_3) m/z 352 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_5O_2$: C, 64.94; H, 6.02; N, 19.93. Found: C, 64.70; H, 5.95; N, 19.71.

5.1.34. 2-Chloro-*N*-(3-methoxyphenyl)acetamide (5i). Compound **5i** was completed using a similar procedure outlined for compound **5b** substituting 3-methoxyaniline for 2-methylaniline to provide 430 mg (26% yield) of the title compound, **5i**: white solid; mp 92–94 °C; R_f 0.24 (25% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.73 (s, 3H), 4.24 (s, 2H), 6.68 (dd, $J = 8.1$, 2.7, 1H), 7.13 (br d, $J = 7.8$, 1H), 7.24 (dd, $J = 8.1$, 8.1, 1H), 7.27 (dd, $J = 2.4$, 2.4, 1H), 10.26 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.6 (t), 54.9 (q), 105.2 (d), 109.2 (d), 111.6 (d), 129.6 (d), 139.6 (s), 159.5 (s), 164.6 (s). MS (DCI/NH_3) m/z 200 $(M+H)^+$; 217 $(M+H)^+$. Anal. Calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.09; H, 4.94; N, 7.00.

5.1.35. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(3-methoxyphenyl)acetamide (6i). Compound **6i** was completed using a similar procedure outlined for compound **6a** substituting **5i** for 2-chloro-*N*-phenylacetamide to provide 1.07 g (75% yield) of the title compound, **6i**: colorless oil; R_f 0.20 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (m, 4H), 3.20 (s, 2H), 3.68 (m, 4H), 3.73 (s, 3H), 6.64 (m, 1H), 6.93 (dd, $J = 7.6$, 4.9, 1H), 7.21 (d, $J = 5.1$, 2H), 7.34 (s, 1H), 8.07 (dd, $J = 7.6$, 1.9, 1H), 8.41 (dd, $J = 4.8$, 2.0, 1H), 9.75 (br s, 1H). MS (DCI/NH_3) m/z 352 $(M+H)^+$.

Maleate salt: white solid; mp 154–156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.19 (m, 4H), 3.73 (s, 3H), 3.84 (m, 6H), 6.12 (s, 2H), 6.67 (dd, $J = 8.0$, 1.8, 1H), 6.99 (dd, $J = 7.4$, 4.6, 1H), 7.15 (br d, $J = 8.0$, 1H), 7.23 (dd, $J = 8.3$, 8.3, 1H), 7.30 (br s, 1H), 8.10 (dd, $J = 7.8$, 1.8, 1H), 8.44 (dd, $J = 4.6$, 1.8, 1H), 10.26 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.0 (t), 51.9 (t), 55.0 (q), 58.7 (t), 95.3 (s), 105.4 (d), 109.3 (d), 111.8 (d), 115.5 (d), 117.5 (d), 129.7 (d), 133.7 (d), 139.3 (s), 144.3 (d), 152.0 (d), 159.5 (s), 159.9 (s), 164.9 (s), 167.0 (s). Anal. Calcd for $C_{19}H_{21}N_5O_2 \cdot 1.0C_4H_4O_4$: C, 59.09; H, 5.39; N, 14.98. Found: C, 59.22; H, 5.54; N, 15.03.

5.1.36. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(4-methoxyphenyl)acetamide (6j). Compound **6j** was completed using a similar procedure outlined for compound **6a** substituting 2-chloro-*N*-(4-methoxyphenyl)acetamide (Buttpark) for 2-chloro-*N*-phenylacetamide to provide 1.33 g (90% yield) of the title compound, **6j**: white solid; mp 102–104 °C; R_f 0.15 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.67 (m, 4H), 3.17 (s, 2H), 3.68 (m, 4H), 3.72 (s, 3H), 6.88 (AA′BB′, $J = 9.2$, 2H), 6.93 (dd, $J = 7.5$, 4.8, 1H), 7.54 (AA′BB′, $J = 9.2$, 2H), 8.07 (dd, $J = 7.5$, 2.0, 1H), 8.41 (dd, $J = 4.8$, 2.0, 1H), 9.63 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.7 (t), 52.4 (t), 55.1 (q), 61.4 (t), 94.3 (s), 113.7 (d), 114.5 (d), 117.8 (s), 121.1 (d), 131.7 (s), 144.2 (d), 151.9 (d), 155.3 (s), 160.1 (s), 167.5 (s). MS (DCI/NH_3) m/z 352 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_5O_2$: C, 64.94; H, 6.02; N, 19.93. Found: C, 64.73; H, 6.22; N, 19.95.

5.1.37. 2-Chloro-*N*-(2-fluorophenyl)acetamide (5k). Compound **5k** was completed using a similar procedure outlined for compound **5h** substituting 2-fluoroaniline for 2-methoxyaniline to provide 4.45 g (88% yield) of the title compound, **5k**: white solid; mp 88–90 °C; R_f 0.37 (25% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.35 (s, 2H), 7.23 (m, 3H), 7.87 (m, 1H), 10.17 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.1 (t), 115.5 (d, $J_{CF} = 18.9$), 124.1 (d), 124.4 (d, $J_{CF} = 3.0$), 125.5 (s, $J_{CF} = 11.4$), 125.8 (d, $J_{CF} = 7.6$), 153.7 (s, $J_{CF} = 245.5$), 165.2 (s). MS (DCI/NH_3) m/z 188 $(M+H)^+$. Anal. Calcd for C_8H_7ClFNO: C, 51.22; H, 3.76; N, 7.47. Found: C, 51.16; H, 3.61; N, 7.41.

5.1.38. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(2-fluorophenyl)acetamide (6k). Compound **6k** was completed using a similar procedure outlined for compound **6a** substituting **5k** for 2-chloro-*N*-phenylacetamide to provide 615 mg (42% yield) of the title compound, **6k**:

white solid; mp 78–79 °C; R_f 0.37 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.71 (m, 4H), 3.27 (s, 2H), 3.67 (m, 4H), 6.94 (dd, $J = 7.8$, 4.8, 1H), 7.18 (m, 2H), 7.26 (m, 1H), 7.98 (m, 1H), 8.08 (dd, $J = 7.8$, 2.0, 1H), 8.42 (dd, $J = 5.1$, 2.1, 1H), 9.65 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.9 (t), 52.3 (t), 60.9 (t), 94.5 (s), 114.7 (d), 115.2 (d, $J_{CF} = 19.7$), 117.7 (d), 123.1 (d), 124.4 (d, $J_{CF} = 3.0$), 125.1 (d, $J_{CF} = 7.6$), 125.8 (d, $J_{CF} = 11.4$), 144.2 (d), 152.0 (d), 153.3 (d, $J_{CF} = 244.0$), 160.2 (s), 168.2 (s). MS (DCI/NH_3) m/z 340 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}FN_5O$: C, 63.70; H, 5.35; N, 20.64. Found: C, 63.48; H, 5.32; N, 20.54.

5.1.39. 2-Chloro-*N*-(3-fluorophenyl)acetamide (5l). Compound **5l** was completed using a similar procedure outlined for compound **5b** substituting 3-fluoroaniline for 2-methylaniline to provide 1.25 g (74% yield) of the title compound, **5l**: white solid; mp 121–123 °C; R_f 0.24 (25% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (s, 2H), 6.88 (dddd, $J = 8.1$, 8.1, 2.7, 1.0, 1H), 7.19 (ddd, $J = 8.1$, 2.0, 1.0, 1H), 7.31 (ddd, $J = 8.1$, 8.1, 6.4, 1H), 7.52 (ddd, $J = 10.6$, 2.3, 2.3, 1H), 8.26 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.5 (t), 106.2 (d, $J_{CF} = 26.5$), 110.2 (d, $J_{CF} = 21.2$), 115.1 (d, $J_{CF} = 2.3$), 130.4 (d, $J_{CF} = 9.1$), 140.1 (s, $J_{CF} = 10.6$), 162.1 (s, $J_{CF} = 241.7$), 164.9 (s). Anal. Calcd for C_8H_7ClFNO: C, 51.22; H, 3.76; N, 7.47. Found: C, 51.16; H, 3.61; N, 7.41. MS (DCI/NH_3) m/z 187 $(M+H)^+$; 205 $(M+NH_4)^+$.

5.1.40. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(3-fluorophenyl)acetamide (6l). Compound **6l** was completed using a similar procedure outlined for compound **6a** substituting **5l** for 2-chloro-*N*-phenylacetamide to provide 1.13 g (81% yield) of the title compound, **6l**: tan solid; mp 128–130 °C; R_f 0.23 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (m, 4H), 3.23 (s, 2H), 3.68 (m, 4H), 6.89 (m, 1H), 6.93 (dd, $J = 7.8$, 4.8, 1H), 7.34 (ddd, $J = 8.0$, 8.0, 6.6, 1H), 7.42 (ddd, $J = 8.1$, 1.5, 1.5, 1H), 7.65 (ddd, $J = 11.7$, 2.4, 2.4, 1H), 8.07 (dd, $J = 7.5$, 2.0, 1H), 8.42 (dd, $J = 4.8$, 2.0, 1H), 9.98 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.6 (t), 52.3 (t), 61.4 (t), 94.3 (s), 106.3 (d, $J_{CF} = 26.5$) 109.7 (d, $J_{CF} = 20.5$), 114.5 (d), 115.2 (d, $J_{CF} = 2.3$), 117.8 (s), 130.1 (d, $J_{CF} = 9.1$), 140.3 (s, $J_{CF} = 11.4$), 144.2 (d), 151.9 (d), 160.1 (s), 162.1 (s, $J_{CF} = 241.0$), 168.4 (s). MS (DCI/NH_3) m/z 340 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}FN_5O$: C, 63.71; H, 5.35; N, 20.64. Found: C, 63.59; H, 5.11; N, 20.56.

5.1.41. 2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]-*N*-(4-fluorophenyl)acetamide (6m). Compound **6m** was completed using a similar procedure outlined for compound **6a** substituting 2-chloro-*N*-(4-fluorophenyl)acetamide (Avacado) for 2-chloro-*N*-phenylacetamide to provide 1.32 g (91% yield) of the title compound, **6m**: white solid; mp 98–100 °C; R_f 0.23 (50% EtOAc–hexane; UV). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (m, 4H), 3.20 (s, 2H), 3.68 (m, 4H), 6.92 (dd, $J = 7.5$, 4.8, 1H), 7.15 (m, 2H), 7.67 (m, 2H), 8.07 (dd, $J = 7.8$, 2.0, 1H), 8.41 (dd, $J = 4.8$, 1.7, 1H), 9.83 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.7 (t), 52.4 (t), 61.4 (t), 94.3 (s), 114.5 (d), 115.1 (d, $J_{CF} = 22.7$), 117.8 (s), 121.3 (d, $J_{CF} = 8.3$), 134.9 (s), 144.2 (d), 151.9 (d), 158.1 (d, $J_{CF} = 240.2$), 160.1 (s), 168.0 (s). MS (DCI/NH_3) m/z 340 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}FN_5O$: C, 63.71; H, 5.35; N, 20.64. Found: C, 63.57; H, 5.32; N, 20.79.

6. Biological procedures

6.1. $D_{4.4}$ calcium flux assay (agonist mode)

Human $D_{4.4}$ was coexpressed with $G\alpha_{qo5}$ in HEK-293 cells as described.[40] Cells were plated into 96-well, black-wall/clear-bottom microplates (Biocoat, Becton Dickinson, Boston, MA) at 20,000 cells per well. After 2 days of culture, the culture medium was removed by aspiration and replaced by 0.1 mL of DPBS (Dulbecco's Phosphate Buffered Saline with D-glucose and sodium pyruvate) containing 0.04% Pluronic F-127 and 4 μM Fluo-4, fluorescent calcium indicator dye. After incubation for 1 h at room temperature, the cells were washed four times with DPBS in a plate washer (Molecular Devices). After the final wash, 150 μL of DPBS was added to each well. Fluorometric imaging plate reader (FLIPR384, Molecular Devices) transferred 50 μL from the compound plate to the cells and made fluorescence reading for 3 min (every second for the first minute and every 5 s for the next 2 min). The instrument software normalizes the fluorescent reading to give equivalent initial readings at time zero and all the data were normalized with the response of 10 μM dopamine.

6.2. $D_{4.4}$ calcium flux assay (antagonist mode)

Procedure as described above with the following addition. After the final fluorescence reading in agonist mode, another 50 μL from the dopamine plate was added to the cells to make the final concentration of 1 μM. Fluorescence readings were continued for an additional 3 min. The data were normalized with the response of 1 μM dopamine alone.

6.3. Radioligand binding assay

Human dopamine $D_{4.4}$ receptor-transfected HEK-293 cells as described above ($hD_{4.4}$-$G\alpha_{qo5}$ HEK-293) were cultured in DMEM supplemented with 10% fetal calf serum, 1 mM glutamine, 100 U/mL penicillin and 100 μg/mL streptomycin (Invitrogen, Rockville, MD). For membrane preparation, the cells were seeded into a Cell Factory (VWR, Plainfield, NJ) and the confluent cells were rinsed with DPBS and detached with cell dissociation buffer (Invitrogen). The resulting cell suspension was centrifuged the pellet was homogenized by Polytron for 10 s in 50 mM Tris–HCl, pH 7.4. Membrane aliquots were stored at −80 °C until use.[40,44] Binding assays were initiated by addition 250 μL of membrane to 200 μL of [^{3}H]-spiperone (119 Ci/mmol)

and were incubated at room temperature for 2 h. Nonspecific binding was determined in the presence of 10 μM haloperidol (RBI-Sigma). The incubation buffer consisted of 50 mM Tris–HCl, pH 7.4, 5 mM KCl, 120 mM NaCl, 5 mM $MgCl_2$, and 1 mM EDTA. In competition binding studies, agonists or antagonists were prepared with 0.1% ascorbic acid and 0.5% IBMX (3-isobutyl-1-methylxanthine) in the buffer. The final concentration for [^{3}H]-spiperone was 0.2 nM. The reaction was terminated by rapid filtration through UniFilter-96 GF/B filers, pre-soaked in 0.5% PEI (poly(ethyleneimine)), using a Filtermate Harvester (Packard, Meriden, CT). Filters were washed three times with 1 mL of ice cold 50 mM Tris–HCl, pH 7.4. Radioactivity was measured by TopCount Microplate Scintillation Counter (Packard, Meriden, CT). Proteins were determined by BCA Protein Assay Kit (Pierce, Rockford, IL) using BSA as a standard.

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