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Synthesis and evaluation of 3-aryl piperidine analogs as potent and efficacious dopamine D_4 receptor agonists

Xueqing Wang,* Pramila A. Bhatia, Jerome F. Daanen, Steve P. Latsaw, Jeffrey Rohde, Teodozyi Kolasa, Ahmed A. Hakeem, Mark A. Matulenko, Masaki Nakane, Marie E. Uchic, Loan N. Miller, Renjie Chang, Robert B. Moreland, Jorge D. Brioni and Andrew O. Stewart

Neuroscience Research, Global Pharmaceutical Research and Development, AP9A/L16, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA

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Abstract—A series of 3-aryl piperidine analogs with 2-piperidinoalkylamino or 2-piperidinoalkyloxy fused bicyclic rings were prepared and found to be potent and efficacious human dopamine D_4 agonists. The synthesis and structure–activity relationship (SAR) studies that led to the identification of these compounds are discussed.

1. Introduction

The dopamine receptor (DA) belongs to a family of G-protein-coupled receptors (GPCRs) with seven transmembrane domains. Several subtypes have been identified and they can be categorized as being D_1- and D_2-like.[1] The D_1-like family consists of subtypes D_1 and D_5 receptors,[2,3] while D_2-like includes D_2, D_3, and D_4 subtypes.[4–6] The fact that clozapine (**1**, Chart 1), a preferential D_4 antagonist, behaves as an atypical antipsy-

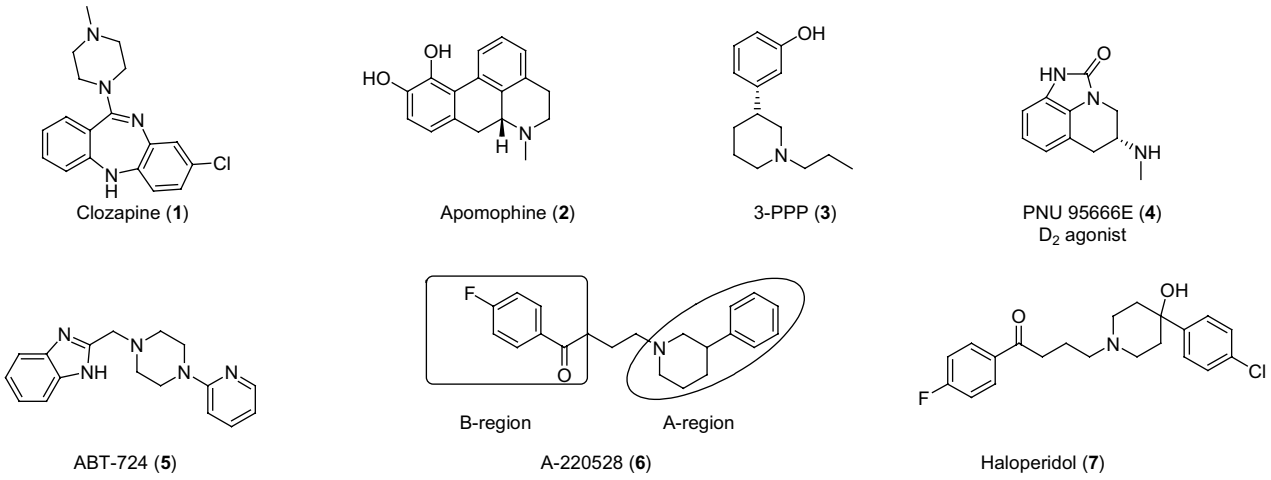

Chart 1. Structures of D_4 ligands.

Keywords: Dopamine D_4 receptor; Agonist potency; Agonist efficacy; 3-Aryl piperidines.
* Corresponding author. Tel.: +1 847 936 0362; fax: +1 847 937 9195; e-mail: xueqing.wang@abbott.com

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chotic that lacks the extrapyramidal side effects normally seen with D_2 antagonists led to the belief that selective D_4 antagonists can be used for the treatment of schizophrenia.[6–8] Many highly selective D_4 antagonists were identified, however, none has shown efficacy in clinical trials.[9–11] It has been reported; that some of these D_4 selective antagonists are in fact D_4 partial agonists, which may help explain their lack of efficacy.[12]

Dopamine agonists such as apomophine (**2**) and (−)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP, **3**) have been associated with the induction of erectile effects in animals and in humans.[13–16] Apomophine is a nonselective dopaminergic agonist used clinically for the treatment of male erectile dysfunction (MED) but it has been reported to have emetic side effects.[17,18] It has been reported recently that the proerectile action of apomorphine in rats is not mimicked by a D_2-selective agonist, PNU 95666E (**4**), but associated with activation of D_4 receptors.[19] Furthermore, studies indicated that PNU 95666E induces emesis,[20] suggesting that D_2 receptor activation may be responsible for the emetic effect of apomophine. With the discovery of ABT-724 (**5**), it has been shown that selective D_4 agonist can be used as a potential treatment for MED and is devoid of emetic side effects.[20–22]

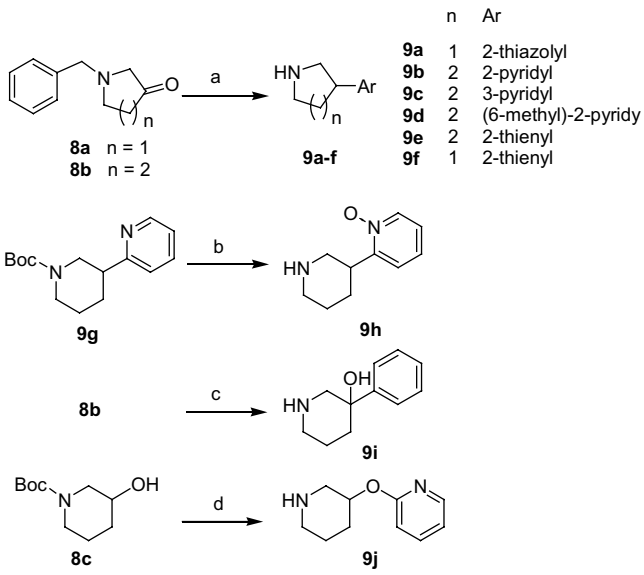
As part of our ongoing dopamine D_4 program with the goal of identifying D_4 agonists for the treatment of D_4-related CNS disorders, a high throughput screen of our internal compound library was conducted. It is noted that the interaction of an agonist ligand with a receptor has two very important but independently measured features: (1) %*E*, the agonist efficacy, also called the intrinsic activity is related to a full agonist (in our study 10 μM dopamine), and (2) EC_{50}, the agonist potency, the concentration at which a compound gives half its maximal D_4 specific efficacy.[23,24] Aryl piperidine analog **6** was identified as a D_4 agonist (EC_{50} = 51 nM, %*E* = 91), and it has a structure similar to that of haloperidol (**7**), a nonselective D_4 antagonist. In this report, we present some of the structure–activity relationship (SAR) studies on **6** and our effort to identify novel and potent efficacious D_4 agonists.

2. Results

2.1. Chemistry

Aryl-substituted piperidines or pyrrolidine **9a–f** were prepared[21] as shown in Scheme 1 starting from **8a** or **8b**. Pyridine *N*-oxide **9h** was prepared by oxidation of **9g** followed by deprotection. The haloperidol-like piperidine **9i** was synthesized by a Grignard reaction followed by debenzylation. Palladium-catalyzed *O*-arylation of 1-Boc-3-hydroxy piperidine with 2-bromopyridine followed by acid deprotection afforded analog **9j**.

Compounds **10a–q** were obtained by alkylation of **9** shown in Scheme 2, which can be used to prepare either the oxime **10s** or tertiary alcohol **10r**. Intermediates **15** and **17** were prepared by reductive amination of **9** with



Scheme 1. Reagents and conditions: (a) (i) Boc_2O, H_2, Pd/C, MeOH, (ii) $PhNTf_2$, LiHMDS, −78 °C, THF, (iii) Ar–ZnBr, $Pd(Ph_3)_4$, THF, 60 °C, (iv) H_2, Pd/C, MeOH, (v) TFA, CH_2Cl_2; (b) (i) *m*-CPBA, CH_2Cl_2, (ii) HCl, −78 °C, EtOAc; (c) (i) PhMgBr, THF, (ii) H_2, $Pd(OH)_2$/C, MeOH; (d) (i) 2-bromopyridine, Pd_2dba_3, BINAP, NaH, toluene, 75 °C, (ii) TFA.

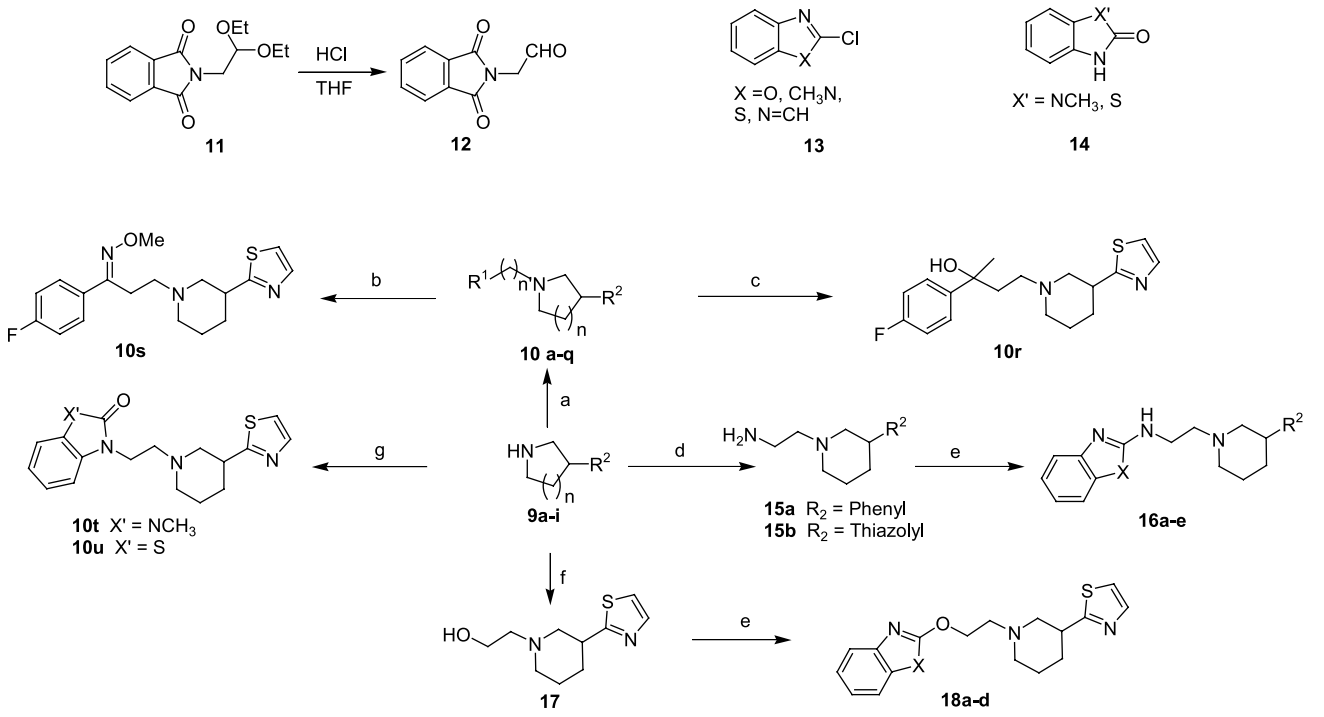
aldehyde **12** followed by hydrazine deprotection and alkylation of **9** with 2-bromoethyl alcohol, respectively. Compounds **16** and **18** were completed by palladium-catalyzed arylations. Analogs with structures **10t** and **10u** were obtained by reductive amination of **9** with chloroacetaldehyde to produce the β-chloroethyl analog followed by alkylation with either 2-hydroxybenzthiazole or 1-methyl-2-benzimidazolinone.

2.2. Biology

Dopamine D_4 ligands were evaluated functionally as agonist or antagonist using a calcium flux assay and recombinant human $D_{4.4}$ receptor coexpressed with $G\alpha_{qo5}$ in HEK-293 cells as described.[25] Dopamine D_4 ligand binding affinity was determined by radioligand competition against 2-[4-(4-[^{3}H]-2-cyanophenyl)piperazinyl]-*N*-(2,4,6-[^{3}H]$_3$-3-methylphenyl)acetamide,[26] using membranes from the human dopamine $D_{4.4}$ cells as described for the calcium flux assay. Dopamine D_2 ligand binding affinity was determined by radioligand competition against [^{125}I]-PIPAT.[25]

3. Results and discussions

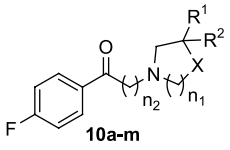
Both enantiomers of **6** were evaluated for their agonist activity and displayed similar potency and efficacy (EC_{50} = 66 nM, %*E* = 85 for (+)-**6** vs EC_{50} = 90 nM, %*E* = 88 for (−)-**6**). Based on this lack of stereospecificity, we evaluated subsequent analogs in this series as the racemates. To help facilitate the SAR studies, the structure of **6** was arbitrarily divided into two parts, region A and region B (Chart 1). Region A represents the 3-aryl piperidine rigid structure, in which the protonated basic amine presumably interacts with the conserved ASP115



Scheme 2. Reagents and conditions: (a) R_1CH_2X, K_2CO_3, NaI, DMF, 70 °C; (b) $CH_3ONH_2{\cdot}HCl$, pyridine; (c) MeMgBr, THF; (d) (i) **12**, HOAc, $Na(OAc)_3BH$, CH_2Cl_2, (ii) $NH_2NH_2{\cdot}H_2O$, MeOH, 70 °C; (e) **13**, $Pd_2(dba)_3$, BINAP, *t*-BuONa, THF, reflux; (f) $BrCH_2CH_2OH$, Na_2CO_3, DME, reflux; (g) (i) chloroacetaldehyde, HOAc, $Na(OAc)_3BH$, CH_2Cl_2, (ii) **14**, KOH, acetone, reflux.

(3.32) in transmembrane–spanning domain 3 (TM3).[27] In analogy to arylpiperazine,[23] region A represents the key feature of the ligand pharmacophore. Region B requires another π-system connected to the basic nitrogen by a linker (Chart 1), which according to CoMFA studies,[28] is another prerequisite for D_4 receptor binding. Table 1 shows mainly changes made to region A. The phenyl group on the piperidine ring can be replaced with a variety of heterocycles. Replacement by 2-pyridyl or 3-pyridyl resulted in loss of agonist potency by almost one order of magnitude (**10d** and **10e**) while maintaining good efficacy. The 2-thiazole (**10j**) and 2-thiophene (**10i**) replacements maintained agonist potency and efficacy with **10j** being more active. Pyridine *N*-oxide **10g**

Table 1. In vitro activity in FLIPR assays at human $D_{4.4}$ receptor



Compound	n_1	n_2	x	R^1	R^2	EC_{50}[a]	%E[b]
6	2	3	CH_2	H	Phenyl	51 ± 5.3	91
10a	2	2	CH_2	H	Phenyl	49 ± 5.3	87
10b	2	2	CH_2	OH	Phenyl	4043 ± 590	38
10c	2	2	S	H	Phenyl	3608 ± 1740	47
10d	2	2	CH_2	H	2-Pyridyl	366 ± 136	78
10e	2	2	CH_2	H	3-Pyridyl	477 ± 74.5	69
10f	2	2	CH_2	H	Piperidin-2-yloxy	134 ± 10.4	27
10g	2	2	CH_2	H	(1-Oxy)-pyridine-2-yl	>10,000	14
10h	2	2	CH_2	H	(6-Methyl)-2-pyridyl	527 ± 89	43
10i	2	2	CH_2	H	2-Thienyl	45 ± 6.3	88
10j	2	2	CH_2	H	2-Thiazolyl	34 ± 13.5	94
10k	2	1	CH_2	H	2-Thiazolyl	1561 ± 842	80
10l	1	2	CH_2	H	Phenyl	>10,000	3
10m	1	2	CH_2	H	2-Thienyl	584 ± 256	36

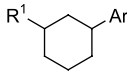
[a] Mean values for agonists (EC_{50} in nM) calculated from at least three determinations ± SEM in FLIPR assay using HEK-293 cells co-transfected with human $D_{4.4}$ receptor and $G\alpha_{qo5}$.
[b] Efficacy relative to 10 μM dopamine (100%).

lost agonist potency completely. Substitutions on the pyridine ring also diminished both potency and efficacy (**10h**). Overall, thiazole (**10j**) is the best R^2 group. The linker length between region A and region B was surveyed. Changing from three to two carbons (**6** vs **10a**) did not result in significant loss of either the potency or efficacy. A significant drop in potency, however, was observed when the linker was shortened from two carbon atoms to one (**10j** and **10k**). A piperidine ring appears to be crucial for agonist activity based on the lack of potency and efficacy found with pyrrolidine analogs, regardless if R^2 was phenyl or thienyl (**10l** and **10m**). Other types of modifications to the 3-aryl piperidine ring, such as substituting one of the ring methylene groups with sulfur (**10c**), adding a hydroxyl at the 3-position (**10b**), or inserting an oxygen between the aryl and piperidine ring (**10f**), all led to significant loss of agonist potency or efficacy or both.

Having identified thiazole-substituted piperidine as the optimum region A group, various region B groups were studied (Table 2). Tertiary alcohol **10r** and oxime **10s** both had lower potency and efficacy than **10j**. Sulfone **10o**, compared to ketone **10n**, lost almost all agonist potency and efficacy.

Bicyclic groups in region B were also investigated. Benzimidazole analogs **10p** and **10q** both displayed reduced agonist potency and efficacy. Compounds that have benzoxazole or benzimidazole as region B with an additional heteroatom linker were all potent, efficacious agonists (**16a**–**b**, **18a**–**b**), while benzothiazole analog (**18c**) was slightly less potent and efficacious. The nitrogen connected to the ring could be replaced by oxygen without losing agonist activity (**18a** vs **16a**, **18b** vs **16b**). When the thiazole ring in region A was switched back to phenyl ring, analogous compounds were less active

Table 2. In vitro activity in FLIPR assays at human $D_{4.4}$ receptor



10j-18d

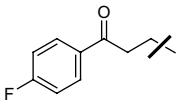
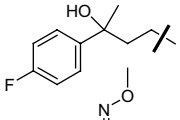
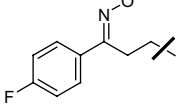
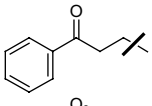
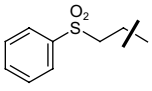
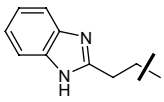
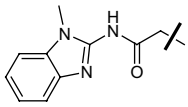
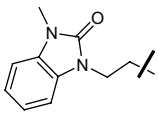
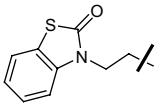
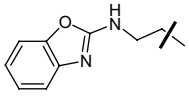
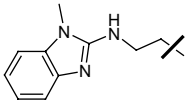
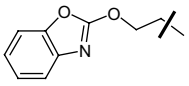
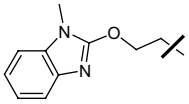
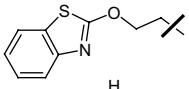
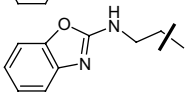
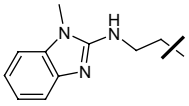
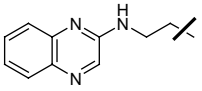
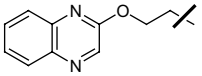
Compound	R^1	Ar	EC_{50}[a]	%E[b]
10j		2-Thiazolyl	34 ± 13.5	94
10r		2-Thiazolyl	289 ± 42	84
10s		2-Thiazolyl	240 ± 13	77
10n		2-Thiazolyl	16 ± 2.0	95
10o		2-Thiazolyl	5290 ± 1660	32
10p		2-Thiazolyl	454 ± 71	70
10q		2-Thiazolyl	148 ± 20	66
10t		2-Thiazolyl	435 ± 51	40
10u		2-Thiazolyl	978 ± 90	55
16a		2-Thiazolyl	15 ± 1.7	86

Table 2 (*continued*)

Compound	R^1	Ar	EC_{50}[a]	%E[b]
16b		2-Thiazolyl	12 ± 2.6	78
18a		2-Thiazolyl	24 ± 6.5	90
18b		2-Thiazolyl	28 ± 4.2	86
18c		2-Thiazolyl	50 ± 8.3	80
16c		Phenyl	82 ± 20	78
16d		Phenyl	167 ± 15	63
16e		2-Thiazolyl	58 ± 8.0	81
18d		2-Thiazolyl	86 ± 16	70

[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%).

(**16c** vs **16a**, **16d** vs **16b**), confirming the superiority of having thiazole in region A. Interestingly, similar analogs with heteroatom-linked benzoazoles as region B and 4-piperazine as region A were reported to be potent D_4 antagonists.[29] Expansion of the 6,5-fused rings to 6,6-fused ring (**16e**, **18d**) also afforded potent, efficacious agonists.

The close structure similarities of region B between analogs **10u** and **18c** and **10t** and **18b** are noted, yet they exhibit dramatically different biochemical profiles. The weaker efficacy, however, could be explained by the proposal that the intrinsic activity (efficacy to activate the receptor) is determined by the interaction of the region B heterocycle unit with the aromatic cluster in TM6 that is in proximity to the conserved serine residue in TM5.[28,30] Consistent with the report, compounds with identical region A but slightly different region B can exhibit very different agonist activity profiles. The weaker EC_{50} of **10u** and **10t** may reflect weaker affinity for the receptor due to the spatial misorientation of region A and region B, which may also be related to the attenuated interaction with TM6 microdomain that constitutes the agonist efficacy (intrinsic activity).[30]

Some of the compounds from this series were also evaluated for their D_4 binding affinity using radioligand competition study against D_4 agonist.[26] As shown in Table 3, all the compounds have high affinity for the D_4 receptor. None of these compounds showed any D_2 agonism, which is believed to cause emesis. D_2 antagonist studies also indicated that they have only weak interaction with the D_2 receptor ($IC_{50} > 2$ μM, data not shown).

4. Conclusions

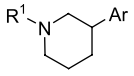
We have demonstrated 3-aryl piperidine analogs as a series of novel D_4 agonists. Thiazole was identified to be the optimum group in region A. When combined with a benzoazole ring in region B with a heteroatom linker, potent D_4 agonists were obtained and were represented by **16a**, **18a**, and **18b**, which exhibited double digit nanomolar potency and full agonism. The spatial orientation between A and B regions is key to providing agonist potency and efficacy. These full agonists can be used as valuable tools to study D_4 agonism related therapeutic indications.

5. Experimental

5.1. Chemistry

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.

Table 3. Binding affinities of selected compounds at human $D_{4.4}$ receptors



16a-c

Compound	EC_{50}[a]	$\%E$[b]	Binding affinity K_i[c] hD_4
16a	15 ± 1.7	86	227 ± 13
16b	12 ± 2.6	78	12.5 ± 3.7
16c	167 ± 15	63	53 ± 1.6

[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%).

[c] Mean values for binding affinity (K_i in nM) calculated from at least three determinations ± SEM versus 2-[4-(4-[^{3}H]-2-cyanophenyl)piperazinyl]-*N*-(2,4,6-[^{3}H]$_3$-3-methylphenyl)acetamide.

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) in hertz are indicated parenthetically.

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 a UV lamp and/or charring solution as indicated. Flash chromatography was performed as described[31] on a Biotage Flash 40 chromatography system (Charlottesville, VA) using 40 g, 90 g, 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.

Preparative HPLC was performed on a Waters Symmetry C8 column (25 mm × 100 mm, 7 μm particle size) using a gradient of 10% to 100%:0.1% aqueous TFA over 8 min (10 min run time) at a flow rate of 40 mL/min.

5.1.1. 3-Thiazol-2-yl-piperidine (9a). A solution of diisopropylamine (13.1 mL, 110 mmol) in dry THF (150 mL) was cooled to −10 °C. To the solution was added *n*-BuLi (2.5 M in hexane, 44 mL, 110 mmol) via syringe. The mixture was stirred for 30 min, cooled to −78 °C, and then to it added a solution of *tert*-butyl 3-oxo-1-piperidinecarboxylate (16 g, 80 mmol) in THF (50 mL). The mixture was stirred for 15 min and then was added a solution of *N*-phenyl-bis-trifluoromethnaesulfonamide (35.0 g, 110 mmol) in THF (60 mL). The reaction mixture was stirred for 15 min and allowed to warm to rt, quenched with saturated $NaHCO_3$ solution (75 mL), and diluted with Et_2O (150 mL). The organic phase was washed with brine, dried with $MgSO_4$, concd in vacuo, and purified by flash chromatography (silica gel, 95:5 hexane/EtOAc) to obtain 5-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester as an oil (7.8 g, 24%): ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.07–7.40 (m, 1H), 3.53 (m, 2H), 2.43 (m, 2H), 1.94 (m, 2H), 1.48 (m, 9H); MS (DCI/NH_3) *m*/*z* 349 $(M+NH_4)^+$. To the mixture of 2-thiazolyl zinc bromide (20 mL, 10 mmol, 0.5 M solution) in dry THF (30 mL) at 0 °C were added the above triflate (3.3 g, 10 mmol) and $Pd(PPh_3)_4$ (10% mol, 1.1 g). The mixture was heated at 50 °C for 2 h, cooled to rt, brine was added, and extracted with EtOAc. The organic layer was dried with $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (silica gel, 75:25 hexane/EtOAc) to obtain the 5-thiazol-2-yl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester as colorless oil (1.4 g, 60%): ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.70 (d, J = 3 Hz, 1H), 7.21 (d, J = 3 Hz, 1H) 7.05 (m, 1H), 3.59 (m, 2H), 2.44 (m, 2H), 1.95 (m, 2H), 1.48 (m, 9H); MS (DCI/NH_3) *m*/*z* 265 $(M+H)^+$. The above tetrahydropyridine was taken up in MeOH (100 mL) and hydrogenated with 20% Pd/C (0.3 g) at rt for 4 days. The solution was filtered and concentrated to give 3-thiazol-2-yl-piperidine-1-carboxylic acid *tert*-butyl ester as yellow oil (1.42 g, 100 %): ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.70 (d, J = 3 Hz, 1H), 7.21 (d, J = 3 Hz, 1H), 4.42 (m, 1H), 4.13 (m, 1H), 3.18 (m, 2H), 2.93 (m, 1H), 2.23 (m, 1H), 1.81 (m, 2H), 1.61 (m, 1H), 1.48 (m, 9H); MS (DCI/NH_3) *m*/*z* 267 $(M+H)^+$. The above piperidine compound (1.2 g, 4.5 mmol) was deprotected in 25% TFA/CH_2Cl_2 (10 mL) for 2 h, concentrated in vacuo, neutralized with saturated $NaHCO_3$ and extracted with $CH_2Cl_2$to obtain the 3-thiazol-2-yl-piperidine (**9a**) as yellow oil (0.53 g, 76%): ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.70 (d, J = 3 Hz, 1H), 7.21 (d, J = 3 Hz, 1H), 3.40 (m, 1H), 3.19 (m, 1H), 3.07 (m, 1H), 2.88 (dd, J = 12 Hz, 9 Hz, 1H), 2.71 (m, 1H), 2.22 (m, 1H), 1.77 (m, 2H), 1.62 (m, 1H); MS (DCI/NH_3) *m*/*z* 169 $(M+H)^+$.

The following compounds were prepared in a manner similar to that of compound **9a**.

5.1.2. 1′,2′,3′,4′,5′,6′-Hexahydro-[2,3′]bipyridinyl (9b). The compound was prepared in 12% overall yield as yellow oil: ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.84 (d, J = 5 Hz, 1H), 8.66 (m, 1H), 8.16 (d, J = 8 Hz, 1H), 8.05 (m, 1H), 3.70 (m, 2H), 3.48 (m, 2H), 3.15 (m, 1H), 2.25 (m, 1H), 2.07 (m, 3H); MS (DCI/NH_3) *m*/*z* 163 $(M+H)^+$.

5.1.3. 1,2,3,4,5,6-Hexahydro-[3,3′]bipyridinyl (9c). The compound was prepared in 8% overall yield as yellow oil and used directly in the next step.

5.1.4. 6-Methyl-1′,2′,3′,4′,5′,6′-Hexahydro-[2,3′]bipyridinyl (9d). The compound was prepared in 12% overall yield as yellow oil and used directly in the next step.

5.1.5. 3-Thiophen-2-yl-piperidine (9e). The compound was prepared in 10% overall yield as HCl salt: white solid; mp 202–204 °C. ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.31 (m, 1H), 6.99 (m, 2H), 3.54 (m, 1H), 3.39

(m, 1H), 3.28 (m, 1H), 3.03 (m, 2H), 2.21 (m, 1H), 2.05 (m, 1H), 1.86 (m, 2H); MS (DCI/NH_3) *m/z* 168 $(M+H)^+$.

5.1.6. 3-Thiophen-2-yl-pyrrolidine (9f). The compound was prepared in 15% overall yield as yellow oil: ^1H NMR (300 MHz, chloroform-*d*) δ 7.14 (d, $J = 5$ Hz, 1.2 Hz, 1H), 6.93 (dd, $J = 5$ Hz, 4 Hz, 1H), 6.83 (m, 1H), 3.51 (m, 1H), 3.33 (m, 1H), 3.14 (m, 1H), 3.05 (m, 1H), 2.91 (m, 1H), 2.28 (m, 1H), 1.91 (m, 1H); MS (DCI/NH_3) *m/z* 154 $(M+H)^+$.

5.1.7. 3′,4′,5′,6′-Tetrahydro-2′H-[2,3′]bipyridinyl-1′-carboxylic acid *tert*-butyl ester (9g). The title compound was prepared as an intermediate to **9b** in 21% yield as yellow oil: ^1H NMR (300 MHz, chloroform-*d*) δ 8.54 (d, $J = 4$ Hz, 1H), 7.61 (m, 1H), 7.14 (m, 2H), 4.15 (m, 2H), 3.01 (m, 1H), 2.83 (m, 2H), 2.04 (m, 1H), 1.78 (m, 2H), 1.61 (m, 1H), 1.45 (m, 9H); MS (DCI/NH_3) *m/z* 263 $(M+H)^+$.

5.1.8. 1′,2′,3′,4′,5′,6′-Hexahydro-[2,3′]bipyridinyl 1-oxide (9h). To a solution of **9g** (980 mg, 3.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added dropwise a solution of *m*-CPBA (1.21 g, 7.0 mmol) in CH_2Cl_2 (10 mL). The solution was warmed to room temperature and stirring was continued for 2 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30:1 CH_2Cl_2/MeOH) to provide 0.90 g (87%) of the desired *N*-oxide as yellow oil: ^1H NMR (300 MHz, chloroform-*d*) δ 8.29 (d, $J = 9$ Hz, 1H), 7.24 (d, $J = 6$ Hz, 1H), 7.16 (m, 2H), 4.19 (m, 1H), 3.97 (m, 1H), 3.65 (m, 1H), 3.02 (m, 2H), 2.18 (m, 1H), 1.67 (m, 3H), 1.47 (m, 9H); MS (APCI) *m/z* 279 $(M+H)^+$. The above *N*-oxide (870 mg, 3.2 mmol) was dissolved in EtOAc and HCl gas was bubbled through for 15 min. The resulting solution was warmed to rt and the solvent was removed in vacuo to afford an amorphous solid (680 mg, 97%): ^1H NMR (300 MHz, MeOD-d_4) δ 7.96 (m, 2H), 7.60 (m, 1H), 7.47 (d, $J = 8$ Hz, 1H), 3.98 (m, 1H), 3.71 (m, 1H), 3.49 (m, 1H), 3.11 (m, 2H), 2.16 (m, 2H), 1.99 (m, 2H); MS (APCI) *m/z* 179 $(M+H)^+$.

5.1.9. 3-Phenyl-piperidin-3-ol (9i). To a solution of 1-benzyl-3-piperidone (2.32 g, 12,3 mmol) in anhydrous THF at 0 °C was added phenylmagnesium bromide (3 M in Et_2O, 5 mL, 15 mmol) dropwise. The reaction was quenched with H_2O after 18 h. Saturated $NaHCO_3$ was added to the reaction mixture and it was extracted with EtOAc (3×50 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, concentrated in vacuo, and purified by flash chromatography (silica gel, 4:1 CH_2Cl_2/EtOAc) to give the product as yellow oil (2.3 g, 71%): ^1H NMR (300 MHz, chloroform-*d*) δ 7.49 (m, 2H), 7.32 (m, 6H), 7.23 (m, 2H), 3.58 (d, $J = 2.0$ Hz, 2H), 2.93 (m, 1H), 2.75 (m, 1H), 2.32 (d, $J = 11$ Hz, 1H), 2.00 (m, 2H), 1.70 (m, 3H); MS (DCI/NH_3) *m/z* 268 $(M+H)^+$. To a solution of the above compound (1.33 g, 5 mmol) in MeOH (10 mL) was added $Pd(OH)_2$/C (20% wt, 0.27 g). The reaction was hydrogenated on a Parr shaker under 60 psi of H_2 for 17 h. The catalyst was removed by filtration and the solvent was removed to give the product (0.45 g, 52%) as colorless oil: ^1H NMR (300 MHz, chloroform-*d*) δ 7.51 (m, 2H), 7.31 (m, 3H), 3.64 (m, 1H), 3.47 (m, 1H), 3.28 (m, 2H), 2.10 (m, 4H), 2.00 (m, 2H), 1.70 (m, 3H); MS (DCI/NH_3) *m/z* 178.1 $(M+H)^+$.

5.1.10. 2-(Piperidin-3-yloxy)-pyridine (9j). To a solution of 3-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (2.02 g, 10 mmol) and 2-bromopyridine (1.66 g, 10.5 mmol) in toluene (10 mL) was added NaH (60% in mineral oil, 570 mg, 14.2 mmol) portionwise and heated to 75 °C for 15 min then cooled to rt. To this were added $Pd_2(dba)_3$ (275 mg, 0.3 mmol), racemic BINAP (250 mg, 0.4 mmol) in toluene and the reaction mixture heated to 75 °C for 2 h. The reaction mixture was concentrated and purified by flash chromatography (silica gel, 13:1 hexane/EtOAc) to obtain 3-(pyridin-2-yloxy)-piperidine-1-carboxylic acid *tert*-butyl ester as yellow oil (2.52 g, 90%): ^1H NMR (300 MHz, chloroform -*d*) δ 8.12 (m, 1H), 7.55 (m, 1H), 6.84 (m, 1H), 6.69 (d, $J = 8$ Hz, 1H), 5.05 (m, 1H), 3.24–3.73 (m, 4H), 1.85 (m, 3H), 1.54 (m, 1H), 1.37 (s, 9H); MS (DCI/NH_3) *m/z* 328 $(M+H)^+$. The above compound (2.1 g, 7.5 mmol) was deprotected in neat TFA (7 mL) for 2 h, concentrated in vacuo, neutralized with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were combined, dried, and concentrated. The residue was purified by flash chromatography (silica gel, 10:1 CH_2Cl_2/MeOH) to obtain 2-(piperidin-3-yloxy)-pyridine as yellow oil (1.18 g, 87%): ^1H NMR (300 MHz, chloroform-*d*) δ 8.10 (m, 1H), 7.57 (m, 1H), 6.85 (m, 2H), 5.32 (m, 1H), 3.18 (m, 3H), 2.99 (m, 1H), 2.05 (m, 1H), 1.95 (m, 2H), 1.74 (m, 1H); MS (DCI/NH_3) *m/z* 179 $(M+H)^+$.

5.1.11. 1-(4-Fluoro-phenyl)-3-(3-phenyl-piperidin-1-yl)-propan-1-one (10a). A mixture of 3-chloro-4′-fluoropropiophenone (63 mg, 0.34 mmol), 3-phenylpiperidine (67 mg, 0.34 mmol), K_2CO_3 (118 mg, 0.85 mmol), NaI (51 mg, 0.34 mmol), and DMF (5 mL) was stirred at 70 °C for 2 h. The mixture was diluted with EtOAc (30 mL), washed with brine. After extractive work-up, the reaction mixture was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to obtain the product as yellow oil: ^1H NMR (300 MHz, chloroform-*d*) δ 7.98 (dd, $J = 9$ Hz, 6 Hz, 1H), 7.25 (m, 5H), 7.12 (t, $J = 9$ Hz, 1H), 3.17 (t, $J = 7$ Hz, 2H), 3.02 (m, 2H), 2.84 (m, 3H), 2.08 (m, 2H), 1.93 (m, 1H), 1.75 (m, 2H), 1.47 (m, 1H); MS (DCI/NH_3) *m/z* 312 $(M+H)^+$.

The following compounds were prepared in a manner similar to that of compound **10a**.

5.1.12. 1-(4-Fluoro-phenyl)-3-(3-hydroxy-3-phenyl-piperidin-1-yl)-propan-1-one (10b). The compound was prepared in 40% yield, purified by HPLC, and isolated as TFA salt as yellow oil: ^1H NMR (300 MHz, MeOD-d_4) δ 8.11 (m, 2H), 7.57 (m, 2H), 7.41 (m, 2H), 7.28 (m, 3H), 3.59 (m, 5H), 3.41 (s, 2H), 3.15 (m, 1H), 2.37 (m, 1H), 2.16 (m, 1H), 1.96 (m, 2H); MS (DCI/NH_3) *m/z* 328 $(M+H)^+$. Anal. Calcd for $C_{20}H_{22}FNO_2 \cdot 1.6$ TFA: C, 54.66; H, 4.67; N, 2.75; Found: C, 54.94; H, 4.78; N, 2.79.

5.1.13. 1-(4-Fluoro-phenyl)-3-(2-phenyl-thiomorpholin-4-yl)-propan-1-one (10c). The compound was prepared in 70% yield as yellow oil: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.97 (m, 2H), 7.32 (m, 5H), 7.13 (m, 1H), 4.01 (m, 1H), 3.19 (m, 4H), 2.96 (m, 3H), 2.57 (m, 3H); MS (DCI/NH_3) m/z 330 $(M+H)^+$.

5.1.14. 1-(4-Fluoro-phenyl)-3-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,3′]bipyridinyl-1′-yl)-propan-1-one (10d). The compound was prepared in 26% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.56 (d, J = 6 Hz, 1H), 7.96 (dd, J = 9 Hz, 6 Hz, 2H), 7.63 (td, J = 8 Hz, 3 Hz, 1H), 7.14 (m, 4H), 3.22 (m, 3H), 2.97 (m, 4H), 2.33 (m, 1H), 2.18 (m, 1H), 2.01 (m, 1H), 1.81 (m, 2H), 1.63 (m, 1H); MS (DCI/NH_3) m/z 313 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}FN_2O$: C, 73.05; H, 6.78; N, 8.97; Found: C, 73.51; H, 7.03; N, 9.11.

5.1.15. 1-(4-Fluoro-phenyl)-3-(3,4,5,6-tetrahydro-2*H*-[3,3′]-bipyridinyl-1-yl)-propan-1-one (10e). The compound was prepared in 5% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.26 (m, 1H), 7.91 (m, 2H), 7.56 (m, 2H), 7.43 (m, 2H), 7.08 (m, 1H), 3.96 (m, 1H), 3.11 (m, 2H), 2.85 (m, 3H), 2.59 (m, 1H), 2.23 (m, 2H), 2.06 (m, 1H), 1.83 (m, 1H), 1.65 (m, 1H), 1.52 (m, 1H); MS (DCI/NH_3) m/z 313 $(M+H)^+$.

5.1.16. 1-(4-Fluoro-phenyl)-3-[3-(pyridin-2-yloxy)-piperidin-1-yl]-propan-1-one (10f). The compound was prepared in 68% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.12 (dd, J = 5 Hz, 2 Hz, 1H), 7.98 (m, 2H), 7.54 (m, 2H), 7.54 (m, 1H), 7.12 (m, 2H), 6.83 (m, 1H), 6.72 (d, J = 9 Hz, 1H), 5.17 (m, 1H), 3.16 (m, 2H), 2.98 (dd, J = 10 Hz, 3 Hz, 1H), 2.87 (t, J = 7 Hz, 2H), 2.65 (m, 1H), 2.38 (m, 2H), 1.99 (m, 1H), 1.85 (m, 1H), 1.65 (m, 2H); MS (DCI/NH_3) m/z 329 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}FN_2O_2{\cdot}0.1\ H_2O$: C, 69.11; H, 6.47; N, 8.48; Found: C, 68.93; H, 6.46; N, 8.56.

5.1.17. 1-(4-Fluoro-phenyl)-3-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,3′]bipyridinyl-1′-yl)-propan-1-one (10g). The compound was prepared in 37% yield as maleic acid salt as amorphous solid: ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.34 (d, J = 5.5 Hz, 1H), 8.03 (m, 2H), 7.53 (m, 2H), 7.40 (m, 1H), 7.22 (m, 2H), 3.79 (m, 1H), 3.28–3.20 (m, 3H), 2.97–2.77 (m, 3H), 2.31–2.13 (m, 2H), 1.99 (m, 1H), 1.85–1.53 (m, 3H); MS (APCI) m/z 329 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}FN_2O_2{\cdot}1.0\ C_4H_4O_4$: C, 62.15; H, 5.67; N, 6.30; Found: C, 62.02; H, 5.27; N, 6.24.

5.1.18. 1-(4-Fluoro-phenyl)-3-(6-methyl-3′,4′,5′,6′-tetrahydro-2′*H*-[2,3′]bipyridinyl-1′-yl)-propan-1-one (10h). The compound was prepared in 3% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.99 (m, 2H), 7.45 (t, J = 9 Hz, 1H), 7.14 (t, J = 9 Hz, 2H), 6.96 (d, J = 9 Hz, 2H), 3.11 (m, 3H), 2.85 (m, 4H), 2.52 (s, 3H), 2.39 (m, 1H), 2.18 (m, 1H), 1.96 (m, 1H), 1.79 (m, 1H), 1.61 (m, 1H), 1.52 (m, 1H); MS (DCI/NH_3) m/z 327 $(M+H)^+$. Anal. Calcd for $C_{20}H_{23}FN_2O$: C, 73.59; H, 7.10; N, 5.82; Found: C, 73.81; H, 7.03; N, 5.97.

5.1.19. 1-(4-Fluoro-phenyl)-3-(3-thiophen-2-yl-piperidin-1-yl)-propan-1-one (10i). The compound was prepared in 47% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.00 (m, 2H), 7.13 (m, 3H), 6.94 (dd, J = 4.5 Hz, 3.9 Hz, 1H), 6.83 (d, J = 4.5 Hz, 1H), 3.16 (m, 2H), 3.11 (m, 2H), 2.87 (m, 3H), 2.13 (m, 1H), 2.08 (m, 2H), 1.72 (m, 2H), 1.45 (m, 1H); MS (DCI/NH_3) m/z 318 $(M+H)^+$.

5.1.20. 1-(4-Fluoro-phenyl)-3-(3-thiazol-2-yl-piperidin-1-yl)-propan-1-one (10j). The compound was prepared in 66% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.95 (dd, J = 6 Hz, 3 Hz, 2H), 7.69 (d, J = 3 Hz, 1H), 7.21 (d, J = 3 Hz, 1H), 7.14 (t, J = 9 Hz, 2H), 3.33 (m, 1H), 3.22 (m, 2H), 2.93 (m, 4H), 2.18 (m, 1H), 2.10 (m, 2H), 1.83 (m, 1H), 1.63 (m, 2H); MS (DCI/NH_3) m/z 319 $(M+H)^+$. Anal. Calcd for $C_{17}H_{19}FN_2OS$: C, 64.13; H, 6.01; N, 8.80; Found: C, 64.21; H, 6.32; N, 8.41.

5.1.21. 1-(4-Fluoro-phenyl)-2-(3-thiazol-2-yl-piperidin-1-yl)-ethanone (10k). The compound was prepared in 4% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.06 (dd, J = 9 Hz, 3 Hz, 2H), 7.68 (d, J = 3 Hz, 1H), 7.21 (d, J = 3 Hz, 1H), 7.14 (t, J = 9 Hz, 2H), 3.85 (d, J = 6 Hz, 2H), 3.43 (m, 1H), 3.31 (m, 1H), 2.96 (m, 1H), 2.58 (t, J = 9 Hz, 1H), 2.33 (m, 1H), 2.18 (m, 1H), 1.81 (m, 2H), 1.68 (m, 1H); MS (DCI/NH_3) m/z 305 $(M+H)^+$. Anal. Calcd for $C_{16}H_{17}FN_2OS{\cdot}0.25\ H_2O$: C, 62.14; H, 5.73; N, 9.07; Found: C, 61.90; H, 5.34; N, 9.18.

5.1.22. 1-(4-Fluoro-phenyl)-3-(3-phenyl-pyrrolidin-1-yl)-propan-1-one (10l). The compound was prepared in 92% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.85 (m, 2H), 7.24 (m, 5H), 7.06 (m, 2H), 3.27 (m, 2H), 3.00 (m, 3H), 2.57 (m, 1H), 2.31 (q, J = 8 Hz, 1H), 2.16 (m, 1H), 1.82 (m, 3H); MS (DCI/NH_3) m/z 298 $(M+H)^+$.

5.1.23. 1-(4-Fluoro-phenyl)-3-(3-thiophen-2-yl-pyrrolidin-1-yl)-propan-1-one (10m). The compound was prepared in 25% yield, purified by HPLC, and isolated as TFA salt as yellow oil: ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.12 (m, 1H), 7.35 (m, 1H), 7.27 (m, 2H), 7.02 (m, 2H), 4.07 (m, 1H), 3.87 (m, 2H), 3.71 (m, 2H), 3.59 (m, 3H), 2.57 (m, 1H), 2.22 (m, 2H); MS (DCI/NH_3) m/z 304 $(M+H)^+$.

5.1.24. 1-Phenyl-3-(3-thiazol-2-yl-piperidin-1-yl)-propan-1-one (10n). The compound was prepared in 51% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.96 (m, 2H), 7.67 (d, J = 3 Hz, 1H), 7.58 (m, 1H), 7.45 (m, 2H), 7.18 (d, J = 3 Hz, 1H), 3.21 (m, 3H), 2.91 (m, 3H), 2.36 (m, 1H), 2.21 (m, 2H), 1.81 (m, 1H), 1.63 (m, 3H); MS (DCI/NH_3) m/z 301 $(M+H)^+$. Anal. Calcd for $C_{17}H_{20}N_2OS{\cdot}0.25\ H_2O$: C, 66.96; H, 6.89; N, 9.20; Found: C, 66.63; H, 6.69; N, 8.94.

5.1.25. 1-(2-Benzenesulfonyl-ethyl)-3-thiazol-2-yl-piperidine (10o). The compound was prepared in 49% yield as yellow oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.93 (m, 2H), 7.65 (m, 2H), 7.56 (m, 2H), 7.20 (d, J = 3 Hz, 1H), 3.34 (m, 2H), 3.04 (m, 2H), 2.85 (m, 2H), 2.72 (d, J = 10.2 Hz, 1H), 2.24 (t, J = 10.2 Hz,

1H), 2.09 (m, 2H), 1.71 (m, 1H), 1.52 (m, 2H); MS (DCI/NH_3) *m/z* 337 $(M+H)^+$.

5.1.26. 2-[2-(3-Thiazol-2-yl-piperidin-1-yl)-ethyl]-1*H*-benzoimidazole (10p). The compound was prepared in 48% yield, purified by HPLC, and isolated as TFA salt as amorphous solid: ^1H NMR (300 MHz, MeOD-d_4) δ 7.76 (m, 2H), 7.66 (d, $J = 3$ Hz, 1H), 7.56 (d, $J = 3$ Hz, 1H), 7.54 (m, 2H), 3.87 (m, 1H), 3.75 (m, 6H), 3.58 (m, 2H), 2.28 (m, 1H), 1.99 (m, 3H); MS (DCI/NH_3) *m/z* 313 $(M+H)^+$. Anal. Calcd for $C_{17}H_{20}N_4S \cdot 2.5$ TFA: C, 44.22; H, 3.80; N, 9.38; Found: C, 44.52; H, 3.56; N, 9.39.

5.1.27. *N*-(1-Methyl-1*H*-benzoimidazol-2-yl)-2-(3-thiazol-2-yl-piperidin-1-yl)-acetamide (10q). To a round bottomed flask containing THF (300 mL) was added 2-amino-1-methylbenzimidazole (20 g, 136 mmol) and the mixture was cooled to 0 °C. To the flask were added TEA (34.42 g, 340 mmol, 2.5 equiv) followed by chloroacetychloride (17.27 g, 136 mmol) and the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was poured into EtOAc (300 mL) and washed with HCl (1 N), saturated with $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo to yield yellow oil: ^1H NMR (300 MHz, MeOD-d_4) δ 7.25–7.50 (m, 4H), 4.70 (s, 2H), 3.30 (s, 3H); MS (DCI/NH_3) *m/z* 224 $(M+H)^+$. To a round bottomed flask containing dry toluene (20 mL) were added the above α-chloro acetamide (1.13 g, 6.7 mmol), compound **9a** and diisopropylethylamine (1.73 mg, 13.50 mmol, 2.0 equiv) and the reaction mixture was heated at 80 °C for 24 h. The reaction mixture was washed with H_2O, concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, 10:1 CH_2Cl_2/MeOH) to yield the product (0.52 g, 22% yield): ^1H NMR (300 MHz, MeOD-d_4) δ 7.67 (d, $J = 3.4$ Hz, 1H), 7.54 (m, 1H), 7.46 (m, 2H), 7.28 (m, 2H), 3.61 (s, 3H), 3.46 (m, 1H), 3.36 (m, 4H), 3.02 (m, 1H), 2.41 (m, 1H), 2.22 (m, 1H), 1.84 (m, 2H), 1.66 (m, 1H); MS (DCI/NH_3) *m/z* 356 $(M+H)^+$. Anal. Calcd for $C_{18}H_{21}N_5OS \cdot 0.10$ H_2O: C, 58.79; H, 5.57; N, 12.10; Found: C, 58.64; H, 5.51; N, 12.06.

5.1.28. 2-(4-Fluoro-phenyl)-4-(3-thiazol-2-yl-piperidin-1-yl)-butan-2-ol (10r). To a solution of **10j** in dry THF (5 mL) at 0 °C was added methylmagnesium bromide (3.0 M in THF, 0.2 mL, 0.6 mmol). The reaction mixture was allowed to warm to rt and stirred under N_2 for 16 h before it was quenched with saturated NH_4Cl (10 mL), and extracted with EtOAc (3×30 mL). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica gel, 95:5 CH_2Cl_2/MeOH) to give the desired alcohol as an oil (0.0580 g, 58%): ^1H NMR (300 MHz, chloroform-*d*) δ 7.68 (d, $J = 3$ Hz, 1H), 7.45 (dd, $J = 6$ Hz, 3 Hz, 2H), 7.21 (d, $J = 3$ Hz, 1H), 7.04 (t, $J = 9$ Hz, 2H), 3.43 (m, 1H), 3.22 (m, 3H), 2.93 (m, 1H), 2.18 (m, 2H), 2.08 (m, 2H), 1.83 (m, 2H), 1.58 (m, 2H), 1.51 (s, 3H); MS (DCI/NH_3) *m/z* 335 $(M+H)^+$. Anal. Calcd for $C_{18}H_{23}FN_2OS \cdot 0.1$ CH_2Cl_2: C, 63.39; H, 6.82; N, 8.17; Found: C, 63.50; H, 6.51; N, 8.09.

5.1.29. 1-(4-Fluoro-phenyl)-3-(3-thiazol-2-yl-piperidin-1-yl)-propan-1-one *O*-methyl-oxime (10s). A mixture of **10j** (190 mg, 0.6 mol) and *O*-methylhydroxylamine hydrochloride (50.1 mg, 0.6 mmol) were placed in a round bottomed flask under a condenser. Pyridine (5 mL) was added at room temperature from the top of the condenser and the resulting mixture was stirred at ambient temperature for 12 h. The pyridine was concentrated under reduced pressure, saturated $NaHCO_3$ was added and the mixture was extracted with EtOAc. The extract was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give yellow oil (137 mg, 63%): ^1H NMR (300 MHz, DMSO-d_6) δ 7.69 (m, 3H), 7.58 (m, 1H), 7.22 (m, 2H), 3.90 (s, 3H), 3.13 (m, 2H), 2.90 (m, 2H), 2.71 (m, 1H), 2.50 (m, 2H), 2.22 (m, 1H), 2.03 (m, 2H), 1.66 (m, 1H), 1.51 (m, 2H); MS (DCI/NH_3) *m/z* 348 $(M+H)^+$.

5.1.30. 1-Methyl-3-[2-(3-thiazol-2-yl-piperidin-1-yl)-ethyl]-1,3-dihydro-benzoimidazol-2-one (10t). To a solution of **9a** (113 mg, 0.67 mmol) in CH_2Cl_2 (10 mL) were added $Na(OAc)_3BH$ (148 mg. 0.67 mmol), HOAc (40 mg, 0.67 mmol) followed by addition of chloroacetaldehyde (50% aqueous solution, 105 mg, 0.67 mmol). The reaction mixture was stirred for 20 min before quenched with saturated $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried, and concentrated to give a yellowish residue. In a separate vial was charged with 2-hydroxybenzothiazole (101 mg, 0.67 mmol) with KOH (38 mg, 0.67 mmol) in acetone/H_2O (1:1, 3 mL). To this suspension was added the above yellowish residue and the reaction temperature was raised to 80 °C for 1 h. The product was purified by flash chromatography (silica gel, 30:1 CH_2Cl_2/MeOH) to give the desired compound as yellow oil (127 mg, 55%): ^1H NMR (300 MHz, chloroform-*d*) δ 7.66 (d, $J = 3$ Hz, 1H), 7.52 (dd, $J = 7.5$ Hz, 1 Hz, 1H), 7.40 (m, 1H), 7.36 (dd, $J = 7.5$ Hz, 1 Hz, 1H), 7.30 (m, 1H), 7.20 (m, 1H), 4.20 (m, 2H), 3.26 (m, 1H), 2.90 (m, 1H), 2.85 (m, 2H), 2.52 (m, 2H), 2.06 (m, 2H), 1.78 (m, 1H), 1.65 (m, 2H); MS (DCI/NH_3) *m/z* 346 $(M+H)^+$. Anal. Calcd for $C_{17}H_{19}N_3OS_2 \cdot 0.10$ H_2O: C, 58.79; H, 5.57; N, 12.10; Found: C, 58.64; H, 5.51; N, 12.06.

5.1.31. 3-[2-(3-Thiazol-2-yl-piperidin-1-yl)-ethyl]-3*H*-benzothiazol-2-one (10u). The title compound was prepared using a similar procedure as outlined for compound **10t** substituting 1-methyl-2-benzimidazolinone for 2-hydroxybenzothiazole in step 2 and purified by HPLC in 35% yield as TFA salt as yellow oil: ^1H NMR (300 MHz, MeOD-d_4) δ 7.56 (d, $J = 3$ Hz, 1H), 7.21 (m, 5H), 4.41 (t, $J = 6$ Hz, 2H), 4.17 (m, 1H), 3.92 (m, 1H), 3.63 (m, 3H), 3.45 (s, 3H), 3.11 (m, 1H), 2.26 (m, 2H), 1.94 (m, 3H); MS (DCI/NH_3) *m/z* 343 $(M+H)^+$. Anal. Calcd for $C_{18}H_{22}N_4OS \cdot 1.60$ TFA: C, 48.51; H, 4.53; N, 10.67; Found: C, 48.34; H, 4.43; N, 10.62.

5.1.32. (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetaldehyde (12). To a solution of 2-phthalimidoacetaldehyde diethylacetal (4.86 g, 18.5 mmol) in THF (25 mL) was added HCl (6 N, 90 mL) and stirred at rt overnight. The

solution was concentrated and treated with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3×50 mL). The organic layers were combined, washed with brine, dried with $MgSO_4$, and concentrated to give the desired product (2.80 g, 80%): white solid; mp 98–100 °C. ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.66 (s, 1H), 7.90 (m, 2H), 7.76 (d, J = 5.4 Hz, 3.0 Hz, 2H), 4.56 (s, 2H); MS (DCI/NH_3) *m/z* 189 $(M+H)^+$, 207 $(M+NH_4)^+$.

5.1.33. 2-(3-Phenyl-piperidin-1-yl)-ethylamine (15a). To a solution of 3-phenyl piperidine hydrochloride (358 mg, 1.81 mmol) in CH_2Cl_2 (10 mL) was added $Na(OAc)_3BH$ (444 mg, 2.0 mmol) followed by portionwise addition of the compound **12** (378 mg, 2.0 mmol). The reaction mixture was quenched after 4 h with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, 30:1 CH_2Cl_2/MeOH) to give the product as yellow oil (380 mg, 63%): ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.23 (m, 5H), 3.84 (t, J = 8 Hz, 2H), 3.07 (m, 1H), 3.01 (m, 1H), 2.73 (tt, J = 12 Hz, 3 Hz, 1H), 2.65 (td, J = 8 Hz, 3 Hz, 2H), 2.07 (t, 10 Hz, 2H), 1.88 (m, 1H), 1.95 (m, 1H), 1.61 (m, 1H), 1.46 (m, 1H); MS (DCI/NH_3) *m/z* 335 $(M+H)^+$. To a solution of the above compound (372 mg, 1.1 mmol) in MeOH (5 mL) was added hydrazine monohydrate (83 mg, 1.67 mmol) and the reaction mixture was heated at 80 °C for 2 h. A solid came out upon cooling. Et_2O was added to the mixture and the solid was filtered out. The solid was washed with Et_2O (1×10 mL). The filtrate was washed with NaOH solution (5 mL, 2 N), dried with Na_2SO_4, concentrated, and used directly in the next step (153 mg, 68%): ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.26 (m, 5H), 2.97 (m, 2H), 2.81 (m, 3H), 2.44 (t, J = 6 Hz, 2H), 2.03 (m, 1H), 1.95 (m, 2H), 1.71 (m, 2H), 1.46 (m, 1H); MS (DCI/NH_3) *m/z* 205 $(M+H)^+$.

5.1.34. 2-(3-Thiazol-2-yl-piperidin-1-yl)-ethylamine (15b). The title compound was prepared using a procedure similar to that outlined for compound **15a** substituting compound **9a** for 3-phenylpiperidine: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.69 (d, J = 3 Hz, 1H), 7.47 (d, J = 3 Hz, 1H), 3.35 (m, 1H), 3.11 (m, 1H), 2.84 (m, 1H), 2.77 (t, J = 6 Hz, 2H), 2.50 (t, J = 6 Hz, 2H), 2.34 (m, 1H), 2.21 (m, 1H), 2.11 (m, 1H), 1.73 (m, 3H); MS (DCI/NH_3) *m/z* 212 $(M+H)^+$.

5.1.35. Benzooxazol-2-yl-[2-(3-thiazol-2-yl-piperidin-1-yl)-ethyl]-amine (16a). To a solution of the compound **15a** (70 mg, 0.33 mmol) in THF (5 mL) under N_2 were added 2-chlorobenzoxazole (26.5 μL, 0.23 mmol), $Pd_2(dba)_3$ (15.1 mg, 0.017 mmol), racemic BINAP (32 mg, 0.05 mmol), and sodium *tert*-butoxide (22 mg, 0.23 mmol). The reaction mixture was heated to 80 °C for 4 h. The reaction mixture was concentrated and purified by HPLC to give the desired product as TFA salt in 43% yield: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.49 (m, 1H), 7.34 (d, J = 6 Hz, 1H), 7.23 (m, 1H), 7.18 (m, 1H), 7.11 (m, 2H), 3.87 (m, 3H), 3.80 (m, 2H), 3.75 (m, 1H), 3.51 (m, 2H), 3.35 (m, 1H), 2.27 (m, 1H), 1.99 (m, 3H); MS (DCI/NH_3) *m/z* 329 $(M+H)^+$. Anal. Calcd for $C_{17}H_{20}N_4OS \cdot 2.0$ TFA: C, 45.33; H, 3.98; N, 10.07; Found: C, 45.47; H, 3.88; N, 9.99.

The following compounds were prepared in a manner similar to that of compound **16a**.

5.1.36. (1-Methyl-1*H*-benzoimidazol-2-yl)-[2-(3-thiazol-2-yl-piperidin-1-yl)-ethyl]-amine (16b). The compound was prepared and purified by flash chromatography (silica gel, 10:1 CH_2Cl_2/MeOH) in 45% yield as yellow oil: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.69 (d, J = 3.4 Hz, 1H), 7.44 (d, J = 3.4 Hz, 1H), 7.26 (m, 1H), 7.13 (m, 1H), 7.01 (m, 2H), 3.62 (t, J = 6.6 Hz, 2H), 3.52 (s, 3H), 3.23 (m, 1H), 2.95 (m, 1H), 2.75 (m, 2H), 2.41 (m, 1H), 2.29 (m, 1H), 2.12 (m, 1H), 1.75 (m, 4H); MS (DCI/NH_3) *m/z* 342 $(M+H)^+$. Anal. Calcd for $C_{18}H_{23}N_5S \cdot 0.7\ H_2O \cdot 0.2$ toluene: C, 62.33, H, 7.03; N, 18.80; Found: C, 62.49; H, 6.73; N, 18.44.

5.1.37. Benzooxazol-2-yl-[2-(3-phenyl-piperidin-1-yl)-ethyl]-amine (16c). The compound was prepared and purified as HCl salt as yellow oil in 30% yield: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.44 (m, 2H), 7.33 (m, 7H), 3.98 (t, J = 6 Hz, 2H), 3.75 (m, 2H), 3.54 (m, 2H), 3.19 (m, 3H), 2.09 (m, 3H), 1.85 (m, 1H); MS (DCI/NH_3) *m/z* 322 $(M+H)^+$. Anal. Calcd for $C_{20}H_{23}N_3O \cdot 2.1$ HCl·0.3 toluene: C, 62.36: H, 6.51; N, 9.87; Found: C, 62.00; H, 6.12; N, 9.56.

5.1.38. (1-Methyl-1*H*-benzoimidazol-2-yl)-[2-(3-phenyl-piperidin-1-yl)-ethyl]-amine (16d). The compound was prepared in 30% yield, purified by HPLC, and isolated as TFA salt as yellow oil: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.47 (m, 2H), 7.33 (m, 7H), 3.98 (t, J = 6 Hz, 2H), 3.73 (m, 2H), 3.69 (s, 3H), 3.55 (td, J = 6 Hz, 3 Hz, 2H), 3.16 (m, 3H), 2.06 (m, 3H), 1.85 (m, 1H); MS (DCI/NH_3) *m/z* 335 $(M+H)^+$; Anal. Calcd for $C_{21}H_{26}N_4 \cdot 2.2$ TFA: C, 52.12: H, 4.86; N, 9.57; Found: C, 52.04; H, 4.84; N, 9.50.

5.1.39. Quinoxalin-2-yl-[2-(3-thiazol-2-yl-piperidin-1-yl)-ethyl]-amine (16e). The title compound was prepared using a procedure similar to that outlined for compound **16c** substituting 2-chloroquinoxazoline for 2-chlorobenzoxazole and purified by HPLC as the TFA salt as yellow oil: ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.35 (s, 1H), 7.91 (m, 2H), 7.81 (m, 1H), 7.71 (m, 1H), 7.56 (t, J = 4.1 Hz, 2H), 7.38 (m, 1H), 4.00 (m, 1H), 3.83 (q, J = 5.9 Hz, 2H), 3.69 (m, 2H), 3.40 (m, 1H), 3.16 (m, 2H), 2.16 (m, 1H), 1.85 (m, 4H); MS (DCI/NH_3) *m/z* 340 $(M+H)^+$. Anal. Calcd for $C_{18}H_{21}N_5S \cdot 2.5$ TFA·0.3 ethanol: C, 44.41; H, 3.99; N, 10.97; Found: C, 44.80; H, 3.64; N, 10.68.

5.1.40. 2-(3-Thiazol-2-yl-piperidin-1-yl)-ethanol (17). A mixture of compound **9a** (1.80 g, 10.7 mmol), 2-bromoethanol (1.34 g, 10.7 mmol), K_2CO_3 (4.43 g, 32.1 mmol), NaI (790 mg, 5.3 mmol) in 1,2-dimethoxyethane (50 mL) was heated at 80 °C for 3 h before H_2O was added in. The water layer was extracted with EtOAc (3×30 mL). The organic layers were combined, dried

with Na_2SO_4, concentrated, and purified by flash chromatography (silica gel, 20:1:0.1 CH_2Cl_2/MeOH/NH_4OH) to give the desired product as yellow oil (1.80 g, 79%): ^1H NMR (300 MHz, MeOD-d_4) δ 7.69 (d, J = 3.4 Hz, 1H), 7.47 (d, J = 3.4 Hz, 1H), 3.70 (t, J = 6 Hz, 2H), 3.34 (m, 1H), 3.21 (m, 1H), 2.94 (m, 1H), 2.59 (t, J = 6.2 Hz, 2H), 2.33 (d, J = 9 Hz, 1H), 2.16 (m, 2H), 1.79 (m, 2H), 1.63 (m, 1H); MS (DCI/NH_3) m/z 213 $(M+H)^+$.

5.1.41. 2-[2-(3-Thiazol-2-yl-piperidin-1-yl)-ethoxy]-benzoxazole (18a). The title compound was prepared using a procedure similar to that outlined for compound **16c** substituting compound **17** for **15a** and purified by flash chromatography (silica gel, 20:1:0.1 CH_2Cl_2/MeOH/NH_4OH) in 42% yield: light tan solid; mp 112–114 °C. ^1H NMR (300 MHz, chloroform-d) δ 7.69 (d, J = 3.4 Hz, 1H), 7.48 (m, 1H), 7.35 (m, 1H), 7.35 (m, 1H), 7.20 (m, 3H), 4.69 (t, J = 5.6 Hz, 2H), 3.30 (m, 2H), 2.93 (m, 3H), 2.47 (m, 1H), 2.32 (m, 1H), 2.11 (m, 1H), 1.72 (m, 3H); MS (DCI/NH_3) m/z 330 $(M+H)^+$. Anal. Calcd for $C_{17}H_{19}N_3O_2S$: C, 61.98; H, 5.81; N, 12.76; Found: C, 61.85; H, 5.63; N, 12.46.

The following compounds were prepared in a manner similar to that of compound **18a**.

5.1.42. 1-Methyl-2-[2-(3-thiazol-2-yl-piperidin-1-yl)-ethoxy]-1H-benzoimidazole (18b). The compound was prepared in 76% yield as yellow oil: ^1H NMR (300 MHz, chloroform-d) δ 7.69 (d, J = 3.4 Hz, 1H), 7.54 (m, 1H), 7.19 (d, J = 3.4 Hz, 1H), 7.15 (m, 3H), 4.70 (m, 2H), 3.55 (s, 3H), 3.31 (m, 2H), 2.93 (m, 3H), 2.50 (m, 1H), 2.34 (m, 1H), 2.13 (m, 1H), 1.79 (m, 1H), 1.65 (m, 2H); MS (DCI/NH_3) m/z 343 $(M+H)^+$. Anal. Calcd for $C_{18}H_{22}N_4OS$: C, 63.12; H, 6.48; N, 16.36; Found: C, 62.61; H, 6.45; N, 16.01.

5.1.43. 2-[2-(3-Thiazol-2-yl-piperidin-1-yl)-ethoxy]-benzothiazole (18c). The compound was prepared in 42% yield: ^1H NMR (300 MHz, MeOD-d_4) δ 7.72 (dd, J = 7.5 Hz, 0.8 Hz, 1H), 7.69 (d, J = 3.4 Hz, 1H), 7.62 (dd, J = 7.5 Hz, 0.8 Hz, 1H), 7.42 (d, J = 3.4 Hz, 1H), 7.37 (td, J = 7.5 Hz, 0.8 Hz, 1H), 7.24 (td, J = 7.5 Hz, 0.8 Hz, 1H), 4.72 (t, J = 5.6 Hz, 2H), 3.35 (m, 1H), 3.23 (m, 1H), 2.93 (m, 3H), 2.46 (m, 1H), 2.35 (m, 1H), 2.11 (m, 1H), 1.80 (m, 1H), 1.65 (m, 2H); MS (DCI/NH_3) m/z 346 $(M+H)^+$. Anal. Calcd for $C_{17}H_{19}N_3OS_2$: C, 59.10; H, 5.54; N, 12.16; Found: C, 59.17; H, 5.37; N, 11.91.

5.1.44. 2-[2-(3-Thiazol-2-yl-piperidin-1-yl)-ethoxy]-quinoxaline (18d). The compound was prepared in 40% yield, purified by reverse HPLC, and isolated as TFA salt as amorphous solid: ^1H NMR (300 MHz, MeOD-d_4) δ 8.59 (b, 1H), 8.03 (dd, J = 8.7 Hz, 1.5 Hz, 1H), 7.86 (m, 1H), 7.76 (m, 1H), 7.66 (m, 1H), 7.56 (m, 1H), 7.52 (m, 1H), 4.97 (m, 2H), 4.16 (m, 1H), 3.87 (m, 1H), 3.75 (m, 2H), 3.61 (m, 1H), 3.32 (m, 1H), 3.21 (m, 1H), 2.35 (m, 1H), 2.17 (m, 1H), 1.97 (m, 2H); MS (DCI/NH_3) m/z 341 $(M+H)^+$. Anal. Calcd for $C_{18}H_{20}N_4OS \cdot 1.6$ TFA: C, 48.70; H, 4.16; N, 10.71; Found: C, 48.80; H, 4.22; N, 10.84.

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.[25] 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. Radioligand binding assay

Binding assays were initiated by addition of 250 μL of membrane to 200 μL of 2-[4-(4-[^{3}H]-2-cyanophenyl)-piperazinyl]-*N*-(2,4,6-[^{3}H]$_3$-3-methylphenyl)acetamide, 88.1 Ci/mmol)[26] and were incubated at room temperature for 1 h. Nonspecific binding was determined in the presence of 10 μM PD 168077 (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 2-[4-(4-[^{3}*H*]-2-cyanophenyl)piperazinyl]-*N*-(2,4,6-[^{3}H]$_3$-3-methylphenyl)acetamide was 2.0 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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