Discovery of 3-Methyl-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (ABT-670), an Orally Bioavailable Dopamine D_4 Agonist for the Treatment of Erectile Dysfunction

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The goal of this study was to identify a structurally distinct D_4-selective agonist with superior oral bioavailability to our first-generation clinical candidate **1a** (ABT-724) for the potential treatment of erectile dysfunction. Arylpiperazines such as (heteroarylmethyl)piperazine **1a,** benzamide **2**, and acetamides such as **3a,b** exhibit poor oral bioavailability. Structure−activity relationship (SAR) studies with the arylpiperidine template provided potent partial agonists such as **4d** and **5k** that demonstrated no improvement in oral bioavailability. Further optimization with the (*N*-oxy-2-pyridinyl)piperidine template led to the discovery of compound **6b** (ABT-670), which exhibited excellent oral bioavailability in rat, dog, and monkey (68%, 85%, and 91%, respectively) with comparable efficacy, safety, and tolerability to **1a**. The *N*-oxy-2-pyridinyl moiety not only provided the structural motif required for agonist function but also reduced metabolism rates. The SAR study leading to the discovery of **6b** is described herein.

Introduction

Dopamine receptors belong to the superfamily of G-protein coupled receptors (GPCR) and have been classified as D_1-like and D_2-like on the basis of their binding properties and their ability to activate or to inhibit forskolin-induced adenylate cyclase activity.[1] The D_1-like receptors include D_1 and D_5 receptors, and the D_2-like receptors include D_2, D_3, and D_4 receptors.[2] The dopamine D_4 receptor is expressed predominantly within the central nervous system (CNS), and despite low abundance relative to the D_2 receptor, localization in the cortex suggests an important functional role. The role of D_4 receptor antagonists in CNS disorders such as schizophrenia has been extensively investigated and it has also been shown that the D_4 receptor could be associated with ADHD, depression, substance abuse, and cognitive disorders.[3,4] Apomorphine, a nonselective dopamine receptor agonist clinically effective in the treatment of patients with erectile dysfunction (ED), acts via a central dopaminergic mechanism.[5] We have proposed that the dopamine D_4 receptor subtype is primarily responsible for the erectogenic efficacy of apomorphine, while the dose-limiting side effects of nausea and emesis are mediated via the dopamine D_2 subtype.[6a,b,d] This breakthrough provided the impetus for the discovery of **1a** (ABT-724), a highly selective D_4 agonist for the potential treatment of ED.[6c] Since the discovery of **1a**, our goal was to identify a structurally distinct, selective D_4 agonist with improved in vitro efficacy and comparable in vivo efficacy and tolerability in animals but with substantially improved oral bioavailability.

SAR studies leading to **1a** indicated that the D_4 agonist function was incompatible with substitution other than hydrogen in the meta or para position of the terminal aryl ring.[6c] This SAR for agonist function appears to be a general trend and is exhibited by closely related D_4 ligands from the arylpiperazines reported in the literature[7b,c] where the agonists described are substituted in the 2-position (ortho) including **2** (PD168077) (Figure 1). We have reported that acetamide analogues[7d] such as **3a**,**b**, related to **2**, containing an *o*-cyanophenyl or 2-pyridinyl group, also exhibited this substituent effect on the terminal aryl ring, where even a small substituent such as fluorine or a lone pair of electrons on the pyridine nitrogen in the meta or para position showed complete loss of agonist activity. This remarkable SAR precluded a standard strategy of reducing the metabolism of the region B aryl ring by introduction of a halogen or other substituent at the site of metabolism in order to improve the oral bioavailability. The medicinal chemistry challenge in this or closely related series was finding substitution patterns on the region B aryl ring that would maintain agonist function and suppress the metabolism, thereby providing increased oral bioavailability.

To attenuate the metabolism of the region B aryl ring (Figure 2), we sought to decrease the electron density and make it less susceptible to putative oxidation. Our strategy was (1) to replace the 4-position piperazine nitrogen, which has an electron-donating resonance effect, with a carbon atom while keeping the basic nitrogen at the 1-position, which is required for activity.[6c] and (2) to deactivate the region B aryl ring (Ar_2) through substituent effects. The arylpiperidine templates generated by employing these strategies were utilized to conduct region A SAR studies with methylene, amide, and retroamide linkers (Figure 2).

According to our strategy, we initially synthesized benzimidazolylmethyl compound **1c,** a direct analogue of **1a** with the piperidine core (Figure 2). Region A analogues containing an amide linker (benzamides), such as compounds **4a**−**d**, and the retroamide linker analogues (acetamides), represented by **5a**−

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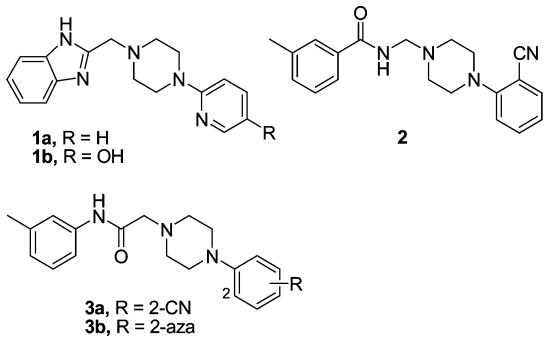


Figure 1. Dopamine D_4 agonists.

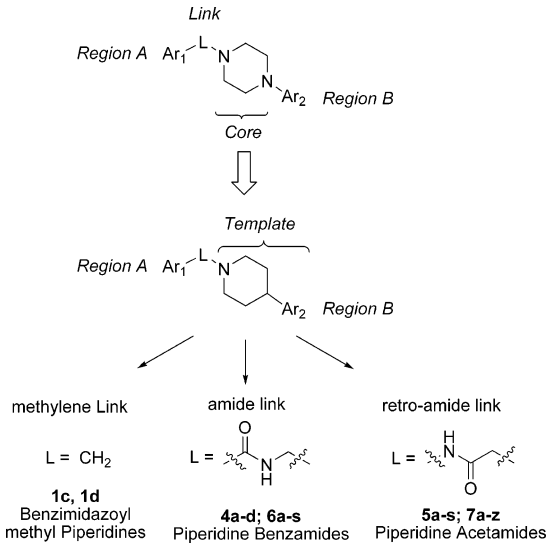


Figure 2. SAR strategy.

s, were also synthesized from the arylpiperidine templates. Pyridine N-oxidation of the (2-pyridinyl)piperidine template would potentially deactivate the pyridine ring toward putative oxidation and meet the structural requirements of having meta and para hydrogen substituents on the region B aromatic ring for agonist activity. The (*N*-oxy-2-pyridinyl)piperidine template was utilized to conduct a second SAR study of region A to obtain benzamides **6a**−**s** and acetamides **7a**−**z**. In this report we describe the discovery of **6b** (ABT-670) a novel, orally bioavailable, potent, and selective human dopamine D_4 receptor agonist.

Results and Discussion

Chemistry. General schemes 1−3 entail the synthesis of 4-heteroarylpiperidine templates, arylpiperidine benzamides, and arylpiperidine acetamides. 4-Substituted phenylpiperidines **12a**,**b**,**e**−**k** were obtained from commercial sources. The 4-heteroarylpiperidines **12c**,**d**,**l**,**m** were synthesized by the method depicted in Scheme 1. Commercially available 1-*t*-butoxycarbonyl-4-piperidinone **8** was converted to its *o*-triflyl enolate **9a** and then reacted with the appropriate intermediates under Pd-catalyzed Negishi cross-coupling[9a] conditions to provide 4-aryltetrahydropyridine intermediates **10c**,**d**,**m** that upon hydrogenation gave the corresponding arylpiperidines **11c**,**d.** The Boc group was removed by treatment with TFA to give **12c**,**d.** Compound **12l** was synthesized via Pd-mediated Suzuki cross-coupling[9b] of 2-chloro-3-cyanopyridine with vinyl boronates **9c**, followed by hydrogenation.

(*N*-Oxy-2-pyridinyl)piperidine[9c] **14** was obtained by *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of the 1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-carboxylic acid *t*-butyl ester **11d,** followed by Boc deprotection with HCl gas.

The benzimidazole analogues of **1a**, compounds **1c** and **1d**, were synthesized by the same method as compound **1a** reported earlier[6c] with heteroarylpiperidine cores **12d** and **14**. Some benzamide analogues (**4a**−**d**) were synthesized by the two-step methodology reported by Glase et al.[7b] (method A). We developed a new one-pot methodology (Scheme 2) avoiding $Pb(OAc)_4$ used in the synthesis reported by Glase et al.[7b] This new one-pot Mannich-type reaction (method B) enabled rapid access to a large number of region A analogues in good yields. In this methodology, (*N*-oxy-2-pyridinyl)piperidine **14** in toluene was treated with the appropriate benzamides and aqueous formaldehyde at 80 °C to give benzamides **6a**−**t** in good yield.

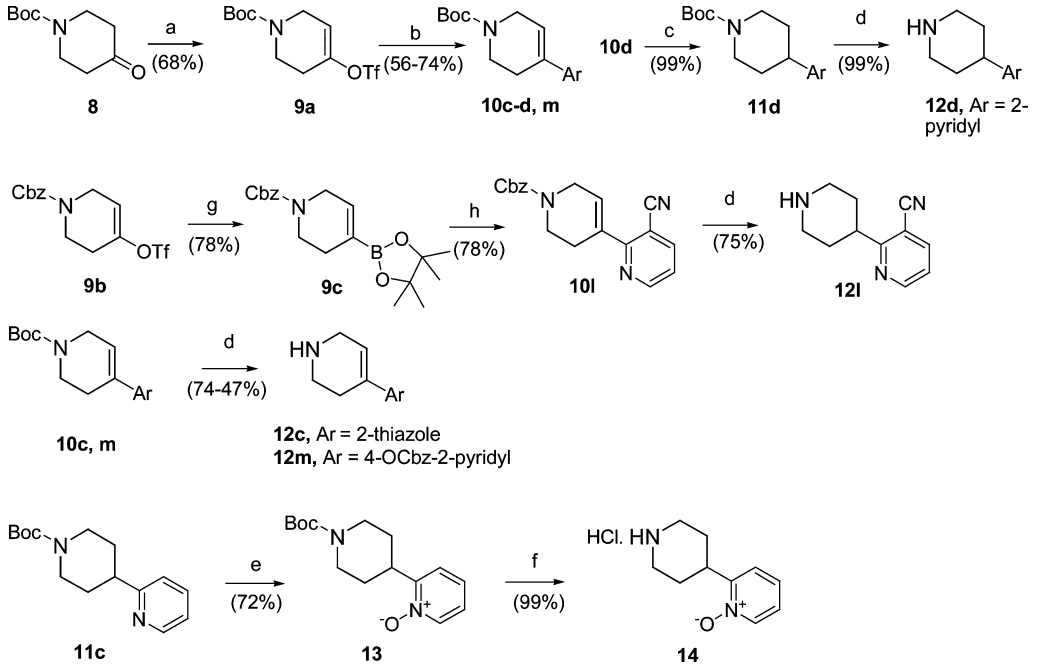
The bromo- and chloroacetamide precursors **17** were obtained through acylation of commercially available substituted anilines **15** with chloroacetyl bromide or chloride **16a** or **16b**, by methodologies[7d] described in the literature, in 50−70% yield. Coupling of *N*-arylchloroacetamides with piperidines was carried out in toluene at elevated temperatures in the presence of *N*,*N*-diisopropylethyl amine (method A) or by use of K_2CO_3 in *N*,*N*-dimethylformamide (DMF) at room temperature (method B) to obtain the acetamides **5a**−**s** and **7a**−**z** (Scheme 3).

In Vitro Activity of Compounds. D_4 agonist profile was measured by use of an in vitro Ca^{2+} flux assay through $G_{\alpha q0}$ coupling by FLIPR (fluorometric imaging plate reader) technology.[6c,8] This assay directly measures the activation of the receptor and provides both a measure of ligand potency and the agonist efficacy, also called intrinsic activity. One expression of the agonist potency is given by EC_{50}, the concentration of a compound giving half its maximal receptor activation. Agonist efficacy, %E, is the maximum calcium signal achieved by the compound, with efficacy normalized to the effect of 10 μM dopamine defined as full efficacy. The Ca^{2+} flux assay was used for SAR studies of D_4 agonists. In addition to the functional assay, binding affinities were used to confirm D_2/D_4 selectivity on selected compounds. Compounds that activated the D_4 receptor with efficacy ≥80% were defined as full agonists.

SAR of Agonist Potency and Efficacy. To determine the effect of replacing the piperazine core of **1a** with piperidine, **1c** (Figure 2) was synthesized. Compound **1c** retained the in vitro potency of **1a** but exhibited a 20% loss in agonist efficacy. A small set of benzamides, **4a**−**d** (Scheme 2, Table 1), was synthesized with the arylpiperidine templates. The unsubstituted phenyl analogue **4a** did not activate the D_4 receptor (%E = 17%). Ortho-substituted phenyl analogues such as the *o*-methoxy analogue **4b**, exhibited partial agonist activity (%E = 55%) for the D_4 receptor. Introduction of a heteroaryl group such as the 2-thiazolyl and 2-pyridinyl group provided compounds **4c** and **4d**. These analogues exhibited higher efficacies of 71% and 67%, respectively, at the D_4 receptor relative to the phenyl analogue **4b**.

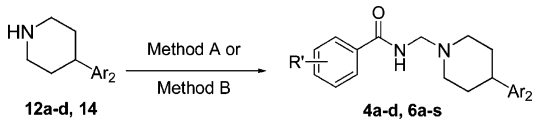
Data for the corresponding piperidine acetamide analogues, **5a**−**s**, are also shown in Table 1. Among the region B aryl analogues, the unsubstituted phenyl analogue **5a** also exhibited low efficacy (%E = 37%) as in the benzamide series. The *o*-cyano analogue **5b** was twice as effective (%*E* = 71%) as an agonist, and the *o*-fluoro analogue **5c** also had good potency and efficacy. Electron-donating groups such as methyl (**5d)** and methoxy (**5e)** in the ortho position showed lower potency and efficacy compared to **5b**. The *m*-fluoro analogue **5f** showed a significant drop in potency and efficacy compared to the *o*-fluoro analogue **5c**. A complete loss of agonist functional activity was observed in the para-substituted analogues such as **5h** (4-F) and

Scheme 1[a]



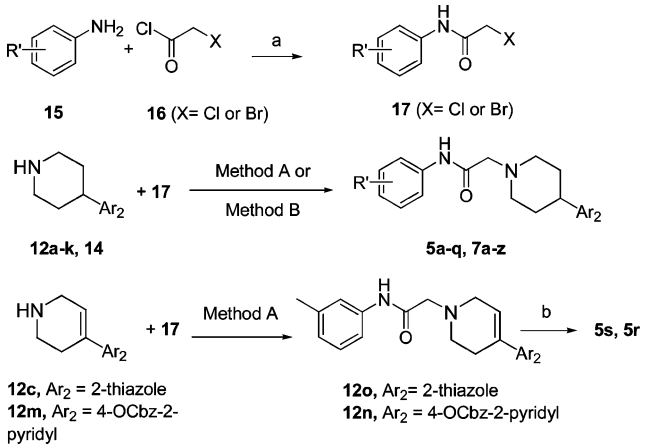
[a] Reagents and conditions: (a) LDA, −78 °C, $PhNTf_2$; (b) ArZnX, $Pd(PPh_3)_4$, Negishi cross-coupling conditions; (c) H_2/Pd; (d) CF_3COOH; (e) *m*-CPBA, CH_2Cl_2; (f) HCl gas, EtOAc; (g) $PdCl_2$dppf, dppf, dioxane, 80 °C; (h) $PdCl_2$dppf, K_2CO_3, 2-chloro-3-cyanopyridine, DMF, 80 °C.

Scheme 2[a]



[a] Reagents and conditions: method A, (a) $Pb(OAc)_4$, $Cu(OAc)_2$, C_6H_6, reflux, (b) arylpiperidine, Et_3N, CH_3CN, 25 °C; method B, benzamide, 37% aqueous CH_2O, K_2CO_3, toluene, 80 °C.

Scheme 3[a]

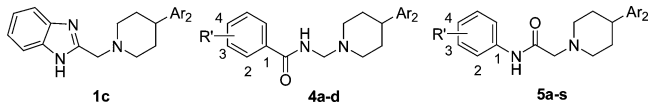


[a] Reagents and conditions: (a) 2 N NaOH, CH_2Cl_2, room temperature; method A, toluene, *N*,*N*-diisopropylethylamine, 80 °C or method B, K_2CO_3, DMF, 40 °C; (b) H_2/Pd.

5i (4-OCH_3). This confirmed the SAR describing the substituent effect for agonist activity observed in previously reported arylpiperazine series[6c,7d]. However the *m*- and *p*-hydroxy analogues **5g** and **5j** exhibited low nanomolar partial agonist activity. Compound **5r,** the *p*-hydroxypyridine analogue of **5k**, maintained the low nanomolar potency of **5k** and exhibited full efficacy (%E = 83%). Additionally the *p*-hydroxy analogue of **1a,** compound **1b** (A-425444), which was found to be a major metabolite[10] of **1a**, also exhibited partial agonist activity (hD_4 EC_{50} = 2.4 nM, %E = 70%; rD_4 EC_{50} = 13.7 nM, %E = 66%). The hydroxy substituent is an exception to this SAR trend for functional activity. Among the region A analogues (**5k**−**p)** evaluated with the pyridinylpiperidine template, the 3-methylphenyl analogue **5k** exhibited low nanomolar potency and higher efficacy for the D_4 receptor. Other substituents such as chloro, ethyl, or methoxy (**5k**−**p**) reduced agonist efficacy. Several other region A analogues with various substituents on the phenyl ring were also synthesized by parallel synthesis with the (2-pyridinyl)piperidine template (data not shown in this paper). The in vitro potency and efficacy of these analogues was lower than that of **5k**. These data suggested that a small alkyl substituent on the region A phenyl ring with the pyridinylpiperidine template provided low nanomolar potency and good efficacy, exemplified by compound **5k**. Region B analogues with other heteroaryl groups such as thiazole (**5t**) displayed a loss in agonist efficacy compared to the pyridine analogue **5k**. Comparison of the results from the benzamide and acetamide analogues shown in Table 1 with the corresponding piperazine analogues[6c,7d] demonstrates that piperidine is bioisosteric with piperazine for this class of D_4 ligands.

Our second strategy to modulate the electron density of the aromatic ring, and subsequently attenuate its metabolism, was via oxidation of the pyridine nitrogen of the (2-pyridinyl)-piperidine template. Pyridine N-oxidation would inductively reduce the oxidation potential of the pyridine ring while maintaining the requirement of a mono-ortho-substituted aryl ring in region B for functional activity. To test this hypothesis, we synthesized the (*N*-oxy-2-pyridinyl)piperidine template **14** and synthesized direct analogues of **1c**, **4d**, and **5k**. The direct analogue of **1c**, 1′-(1*H*-benzimidazol-2-ylmethyl)-1′,2′,3′,4′,5′,6′-hexahydro-[2,4′-bipyridine] 1-oxide (**1d**), was found to be a potent partial agonist (hD_4 EC_{50} = 54 nM; %E = 54%). The benzamide analogue **6b** and its acetamide congener **7a** exhibited nearly full agonist efficacy while maintaining low nanomolar potency (hD_4 EC_{50} = 89 nM, %E = 77% for **6b**; hD_4 EC_{50} = 32 nM, %E = 79% for **7a**). The in vitro activity of compounds **6b** and **7a** met our potency and efficacy criteria and therefore an expanded SAR study of region A was conducted with the

Table 1. In Vitro Activity of Benzamides and Acetamides in FLIPR Assay[a]



compd	R	Ar_2	human D_4 FLIPR EC_{50},[b] nM (SEM)	% efficacy[c]
1a			12.4 ± 1.0	61
2			8.3 ± 1.1	62
1c		2-pyridinyl	12 ± 1	51
4a	3-methyl	phenyl	na[d]	
4b	3-methyl	2-methoxyphenyl	206 ± 16	55
4c	3-methyl	2-thiazole	9.8 ± 3.5	71
4d	3-methyl	2-pyridinyl	9 ± 2	67
5a	3-methyl	phenyl	170 ± 40	37
5b	3-methyl	2-cyanophenyl	8 ± 2	71
5c	3-methyl	2-fluorophenyl	1.0 ± 0.4	57
5d	3-methyl	2-methylphenyl	340 ± 20	43
5e	3-methyl	2-methoxyphenyl	420 ± 10	43
5f	3-methyl	3-fluorophenyl	512 ± 52	40
5g	3-methyl	3-hydroxyphenyl	8 ± 1	66
5h	3-methyl	4-fluorophenyl	na	
5i	3-methyl	4-methoxyphenyl	na	
5j	3-methyl	4-hydroxy-phenyl	70 ± 10	60
5k	3-methyl	2-pyridinyl	14 ± 2	75
5l	4-chloro-2,6-dimethyl	2-pyridinyl	240 ± 60	50
5m	2,4,6-trichloro	2-pyridinyl	145 ± 25	45
5n	2-ethyl-6-methyl	2-pyridinyl	111 ± 41	70
5o	2-chloro-6-methyl	2-pyridinyl	60 ± 10	70
5p	2-methyl-6-methoxy	2-pyridinyl	40 ± 4	69
5q	3-methyl	6-cyano-2-pyridinyl	36 ± 6	42
5r	3-methyl	2-(5-hydroxy-pyridinyl)	3.8 ± 0.8	83
5s	3-methyl	2-thiazolyl	1.0 (0.1	62

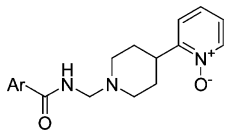
[a] In vitro activity was measured in FLIPR assays, using HEK-293 cells cotransfected with human $D_{4.4}$ receptor and G-protein $G\alpha_{qo5}$. [b] EC_{50} for agonists (SEM, $n \geq 3$). [c] Efficacy relative to 10 μM dopamine (100%), SEM ± 1−5%. [d] na = no agonist activity up to 10 μM.

(*N*-oxy-2-pyridinyl)piperidine template utilizing the amide and retroamide linkers (Tables 2 and 3).

Table 2 shows results of region A SAR studies of the benzamide series incorporating the (*N*-oxy-2-pyridinyl)piperidine template. The unsubstituted phenyl analogue **6a** showed partial agonist activity (%E = 66%). Adding an electron-donating substituent (methyl group) at the 3-position (**6b**) improved the potency by 9-fold and the efficacy by 10%, while electron-withdrawing groups in the 3-position, such as CN analogue **6e** and $CH{=}CH_2$ analogue **6c**, displayed slightly reduced agonist efficacy. Disubstituted analogue **6f**, bearing 3-methyl and 4-chloro groups, displayed a significant drop in potency and efficacy. The potency and efficacy was regained when a fluoro group was placed at the 4-position (**6g**) in region A. The di- and trisubstituted analogues such as **6h**−**p** did not show improvement in potency and efficacy compared to the monosubstituted analogue **6b**. The heteroaryl (pyridinyl) analogues such as **6q** and **6r** showed a significant drop in both potency and efficacy. The 2-thienyl analogue **6s** was found to be a nonagonist (%E < 10%). This region A SAR study confirmed that a small alkyl substituent in the 3-position, exemplified by compound **6b,** provided optimal potency and efficacy.

Several (*N*-oxy-2-pyridinyl)piperidine acetamide analogues were also examined (Table 3). Compound **7a**, a direct analogue of **5k** having a 3-methyl-substituted phenyl group in region A, also maintained the low nanomolar potency of **5k** and exhibited nearly full agonist activity (%E = 79%). Substituted phenyl analogues exhibited nanomolar potency as the substituent was moved from ortho to meta to para position (**7b**−**k**) but they exhibited lower efficacy compared to **7a** (%E ranging from 46% to 76%). Among the disubstituted analogues, compounds **7r** and **7s**, with a combination of a CH_3 group and a fluoro or NO_2 substituent, maintained agonist activity of the 3-methyl analogue

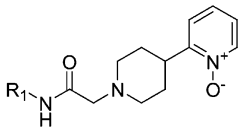
Table 2. In Vitro Activity of the (*N*-oxy-2-pyridinyl)piperidine Benzamides in the FLIPR Assay+*a*



compd	aromatic group	human D_4 FLIPR EC_{50},[b] nM (SEM)	% efficacy[c]
6a	Ph	532 ± 72	63
6b	Ph (3-CH_3)	89 ± 1	77[d]
6c	Ph(3-$CH{=}CH_2$)	68 ± 8	63
6d	Ph(3-OCH_2CH_3)	324 ± 20	54
6e	Ph(3-CN)	840 ± 100	69
6f	Ph(3-CH_3, 4-Cl)	2460 ± 500	62
6g	Ph(3-CH_3, 4-F)	50 ± 10	67
6h	Ph(3-Cl, 4-OCF_3)	170 ± 10	33
6i	Ph(3,5-di-Cl)	45 ± 10	64
6j	Ph(3-CF_3, 4-CH_3)	85 ± 20	59
6k	Ph(3,4-di-CH_3)	38 ± 4	65
6l	Ph(3-Cl, 4-F)	63 ± 10	67
6m	Ph(3,5-di-CH_3)	90 ± 4	56
6n	Ph(2-CH_3, 3-OCH_3)	685 ± 100	51
6o	Ph(3-OCH_3, 4-Cl)	159 ± 39	54
6p	2-napthyl	115 ± 20	67
6q	4-chloro-3-pyridinyl	1290 ± 40	44
6r	2-pyridinyl	3150 ± 7800	40
6s	2- thienyl		na[e]

[a] In vitro activity was measured in FLIPR assays, using HEK-293 cells cotransfected with human $D_{4.4}$ receptor and G-protein $G\alpha_{qo5}$. [b] EC_{50} for agonists (SEM, $n \geq 3$). [c] Efficacy relative to 10 μM dopamine (100%), SEM ± 1−5%. [d] SEM ± 0.6%, $n = 24$. [e] na = no agonist activity up to 10 μM.

Table 3. In Vitro Activity of the (*N*-Oxy-2-pyridinyl)piperidine Acetamides in the FLIPR Assay[a]



Region A

compd	R_1	human D_4 FLIPR EC_{50},[b] nM (SEM)	% efficacy[c]
7a	Ph (3-CH_3)	32 ± 2	79
7b	Ph (3-CF_3)	76 ± 10	75
7c	Ph (3-F)	160 ± 25	70
7d	Ph (4-F)	85 ± 10	71
7e	Ph (2-F)	270 ± 20	63
7f	Ph (3-Cl)	62 ± 10	76
7g	Ph (3-*i*PrO)	555 ± 100	48
7h	Ph (3-OCF_3)	135 ± 15	51
7i	Ph (3-SCH_3)	100 ± 15	56
7j	Ph (3-CH_2CH_3)	95 ± 30	62
7k	Ph (3-Ph)	360- ± 30	75
7l	Ph (3,5-di-Cl)	160 ± 50	68
7m	Ph (2,3-di-Cl)	180 ± 20	66
7n	Ph (2-OCH_3, 6-CH_3)	340 ± 75	56
7o	Ph (3,5-di-CH_3)	52 ± 2	76
7p	Ph (2-CH_3, 4-Br)	66 ± 16	61
7q	Ph (3-CH_3, 4-F)	18 ± 2	75
7r	Ph (2-CH_3, 4-F)	60 ± 5	84
7s	Ph (2-CH_3, 5-NO_2)	134 ± 34	76
7t	Ph (2,6-di-CH_3)	346 ± 33	68
7u	Ph (3-CH_3, 2,6-di-Cl)	346 ± 53	62
7v	Ph (2-CH_3, 5-Cl)	126 ± 22	58
7w	Ph (2,4-di-F)	103 ± 13	74
7x	Ph (2-CF_3, 4-F)	473 ± 93	65
7y	cyclohexyl	294 ± 52	58
7z	2-pyridinyl		na[d]

[a] In vitro activity was measured in FLIPR assays, using HEK-293 cells cotransfected with human $D_{4.4}$ receptor and G-protein $G\alpha_{qo5}$. [b] EC_{50} for agonists (SEM, $n \geq 3$). [c] Efficacy relative to 10 μM dopamine (100%), SEM ± 1−5%. [d] na = no agonist activity up to 10 μM.

7a. Compound **7y** containing a lipophilic cyclohexyl group showed only partial agonist activity, and compound **7z** bearing a polar pyridinyl group in region A was not an agonist as observed in the benzamide case. In summary, the 3-methyl analogue **7a** and the disubstituted analogues compounds **7r** and **7s** exhibited high potency and efficacy.

Selectivity. With the discovery of **1a** (ABT-724), it was demonstrated that the D_4 receptor subtype is responsible for the in vivo erectogenic activity, while the dose-limiting side effects of nausea and emesis seen in the nonselective dopamine agonist apomorphine are mediated via the dopamine D_2 subtype.[6d,h] Our goal was to maintain the selectivity of **1a** in order to avoid off-target side effects. The dopamine receptor subtype activation, as measured by a calcium flux assay of the lead compounds, is shown in Table 4. N-Oxy-2-pyridinyl analogues **6b**, **7a**, and **7r** and benzimidazolylmethyl arylpiperazine analogue **1b** were selective and potent D_4 agonists at human, ferret, and rat cell lines. These compounds were inactive as agonists at D_2 across the three species and were also inactive in the human D_3 cell line. Although **6b**, **7a**, and **7r** were clearly selective D_4 agonists, they could still have high affinity and potential antagonist activity at D_2 receptor.

Binding studies were conducted to determine selectivity based on binding affinities at D_2 and D_4 receptors for select compounds. To determine binding affinities at dopamine receptors, the functional profile of both competing ligand and radioligand must be considered.[7a] In general, agonists may show weak affinities against an antagonist radioligand, whereas antagonists usually show similar binding competition against both agonist and antagonist radioligand. The D_4 binding affinity of these compounds were assessed by use of the D_4 partial agonist radioligand [^{3}H]-A-369508[8] and a D_2-like receptor antagonist [^{3}H]spiperone (Table 5). The D_2 binding affinities were determined by use of radiolabeled D_2 agonist 7-OH-PIPAT.

The region B unsubstituted phenyl analogue **4a** had moderate binding affinity for the human D_{2L} receptor. The *o*-methoxy analogue **4b** also had binding affinity for the D_2 receptor; however, it did not activate the D_2 receptor (EC_{50} > 10 000). Region B pyridinyl analogue **4d** exhibited high affinity for the D_4 receptor in the binding assay versus spiperone with a K_i value of 32 nM and only low affinity for human D_2 receptor with a K_i value of 3.5 μM. Compound **5k** also exhibited high selectivity for the D_4 receptor. This data suggested that introduction of a heteroaryl group in region B provided high D_4/D_2 selectivity.

Compounds **6b**, **7a**, **7r**, and **1b** showed no binding for the human D_{2s} and D_{2L} receptor isoforms (K_i >10 μM) and they did not induce nausea or emesis in the ferret model of emesis.[6e] The *N*-oxy-2-pyridinyl analogues **6b**, **7a**, and **7r** exhibit modest D_4 binding affinity with the radioligand used. These binding affinities are considerably weaker than the EC_{50} values from the Ca^{2+} flux assay ($EC_{50} \ll K_i$), which may indicate a high agonist efficiency for the D_4 receptor.[6f] This may also reflect a considerable affinity of the partial agonist radioligand [^{3}H]-A-369508 for the antagonist conformation. In wider selectivity studies, both **6b** and **7a** at 10 μM did not show any activity against more than 70 different receptors, ion channels, and neuronal receptors (CEREP[11a]) including phosphodiesterases PDE1−6.

In Vivo Studies. Potent agonists **4d**, **5k**, **6b**, **7a**, **7s**, and **7r** demonstrated similar in vivo efficacy to **1a** in the rat penile erection assay[6d] when administered subcutaneously (Table 6). The in vivo potencies ranged from 0.003 to 1 μmol/kg with maximal erectile incidence to at least 70−85%. The maximally efficacious dose of compound **1b** was 0.1 μmol/kg. Agonist **6b** robustly induced a high (75%) incidence of erections in male rats, at a maximally efficacious dose of 0.1 μmol/kg. In this model, apomorphine also efficiently induced erections in rat at a high incidence rate (91%).[6]

Table 4. In Vitro Agonist Activity in Cellular FLIPR Assays[a]

compd	EC_{50} ± SEM, nM (%E)[b] human D_4	ferret D_4	rat D_4	human D_2	ferret D_2	rat D_2	human D_3
dopamine	2.2 ± 0.2 (100%)	2.7 ± 0.3 (100%)	2.4 ± 0.2 (100%)	18 ± 2 (100%)	8 ± 0.4 (100%)	1.1 ± 0.1 (100%)	
apomorphine	4.3 ± 0.2 (84%)	1.5 ± 0.1 (84%)	5.5 ± 0.3 (87%)	5.8 ± 0.3 (86%)	1.8 ± 0.2 (91%)	0.4 ± 0.1 (103%)	
6b	89 ± 1 (77%)[c]	160 ± 8 (76%)	93 ± 3 (78%)	na[d]	na	na	na
7a	32 ± 2 (79%)		57 ± 3 (80%)	na	na	na	na
7r	60 ± 5 (84%)		100 ± 5 (76%)	na	na	na	na
1b	2.4 ± 0.1 (70%)	5 ± 0.1 (48%)	13.7 ± 0.5 (66%)	na	na	na	na

[a] In vitro activity was measured in FLIPR assays, using HEK cells cotransfected with the target receptor and G protein $G\alpha_{qo5}$. [b] EC_{50} for agonists (SEM, $n \geq 3$). Efficacy relative to 10 μM dopamine (100%), SEM ± 1−5%. [c] SEM ± 0.6%, $n = 24$. [d] na = no agonist (<10%) activity up to 10 μM.

Table 5. Radioligand Binding Affinity for Select Agonists

compd	human D_{2L} binding K_i,[a] nM	human D_4 binding K_i,[b] nM
apomorphine	3.6	8.9
4a	235	
4b	27	1.3
4d	3500	32[c]
5k	2900	8
7a	>10 000	294
6b	>10 000	1445
7r	>10 000	405
1b	>10 000	17

[a] Radioligand binding affinity for the dopamine agonists was measured using membrane expressing the human D_{2L} receptor and functional efficacy in HEK-293 cells expressing the cloned human D_{2L} receptor and the chimeric G-protein G_{q05}. In the D_{2L} binding studies, data represent the mean K_i calculated from at least four determinations ±15% standard error of the mean (SEM) with [^{125}I]-7-OH-PIPAT as ligand. [b] Radioligand binding affinity (K_i, nanomolar) for the DA agonists was measured by use ofthe D_4 agonist [^{3}H]-A-369508. Data represent the mean K_i calculated from at least four determinations ± 15% mean SEM. [c] Binding assay using a D_2-like receptor antagonist [^{3}H]spiperone, K_i calculated from at least four determinations ± 15% mean SEM.

Table 6. In Vivo Proerectile Activity of Compounds in Rats during 60 Min Following Subcutaneous Injection

compd	max. effective dose, μmol/kg, sc	max. incidence of penile erections, [a] % ± SEM
6b	0.1	75 ± 9** (n = 24)
apomorphine	0.1	91 ± 1*** (n = 32)
5k	0.1	75 ± 10*** (n = 24)
4d	0.03	83 ± 10** (n =12)
7a	0.3	75 ± 10*** (n = 12)
7s	0.01	83 ± 10** (n = 12)
7r	0.03	67 ± 15** (n = 12)
1b	0.1	60 ± 15* (n = 12)

[a] Level of statistical significance relative to control: *p < 0.1; **p < 0.05; ***p < 0.001; n = number of animals tested.

Table 7. Pharmacokinetic Properties of Lead Compounds in Rat

compd	dose[a]	$T_{1/2}$ (h)	F%[b] (SEM)
4d	sc	0.6	76 (5)
4d	po	UC[c]	2 (1)
5k	sc	0.7	57 (11)
5k	po	UC	0
5r	po	UC	0
7a	sc[d]	0.5	61 (4)
7a	po[d]	0.3	11 (1)
7r	po[d]	UC	7 (1)

[a] Pharmacokinetic properties were evaluated in Sprague-Dawley rats, after administration of 1 mg/kg drug; sc, subcutaneous; po, per os (oral). n = 3 except as marked. [b] F = oral bioavailability, %; data are provided as mean (SEM). [c] UC, unable to calculate. [d] n = 6.

Clozapine (3 μmol/kg, ip) and haloperidol (1 μmol/kg, ip) blocked the erectogenic effect of **6b**, but domperidone (10 μmol/kg, ip) did not. These data indicate that the effect is mediated via central dopaminergic mechanisms, as the peripheral dopamine antagonist domperidone did not block the proerectile effect of **6b**.

Preclinical Pharmacokinetics. Potent partial agonists such as **4d**, **5k**, and **5s** were selected for pharmacokinetic (PK) studies. An initial PK study with benzamide **4d** and acetamide **5k** showed moderate bioavailabilty upon subcutaneous dosing in rat (Table 7); however, like **1a**, the oral bioavailability was still extremely low. This data suggested that the primary oxidative metabolism route had not been altered by replacing the piperazine core with piperidine. An in vitro metabolism study of **5k** showed hydroxylation of the pyridine ring to produce the major metabolite. The para-hydroxylated analogue of **5k**, compound **5r**, also exhibited low oral bioavailability in rat.

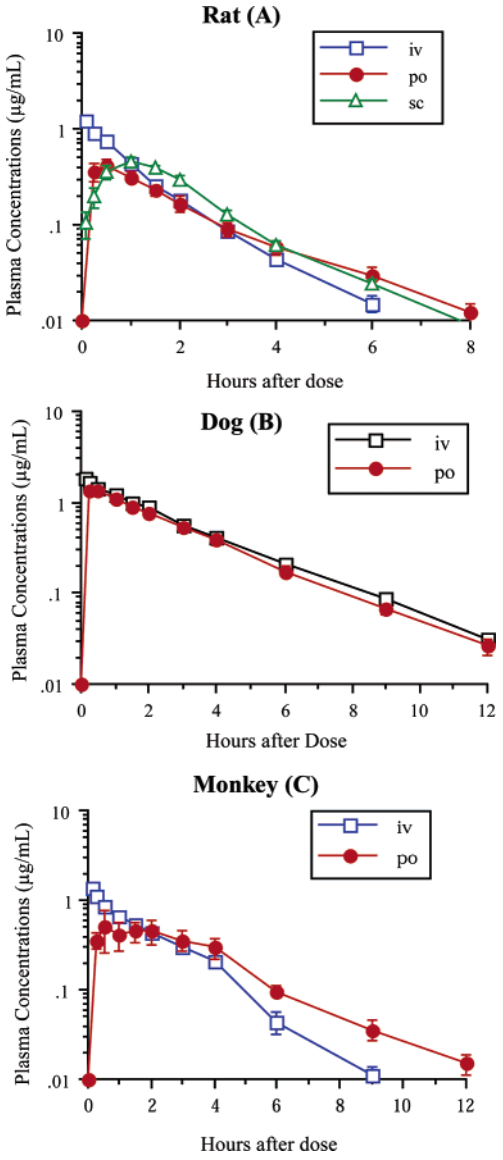


Figure 3. Mean (±SEM, n = 3) plasma concentrations of **6b**, ABT-670, after a 1 mg/kg intravenous, subcutaneous, or oral dose in (A) rat, (B) dog, and (C) monkey.

The (*N*-oxy-2-pyridinyl)piperidine analogues such as **6b**, **7a**, and **7r** from our second strategy were selected for PK evaluation. Compound **7a** exhibited a remarkable improvement in PK profile compared to **5k** with oral bioavailability in rat, dog, and monkey of 11%, 70%, and 28%, respectively. PK profile of the benzamide analogue **6b** was superior to that of **7a**, exhibiting high oral bioavailability in all three species. Plasma concentration curves for **6b** after intravenous (iv), oral (po), and subcutaneous (sc) dosing are shown in Figure 3. The calculated PK parameters across three species are shown in Table 8. Compound **6b** was slowly cleared after iv dosing in rat, dog, and monkey, with values ranging from 0.74 L/(h·kg) in rat to 0.2 L/(h·kg) in dog. SC bioavailability was high in the rat, with peak concentration of 465 ng/mL and bioavailability of 84% following a 1 mg/kg dose. Compound **6b** reached similar C_{max} and AUC when dosed both po and sc. Dosing po in monkey and dog at 1 mg/kg dose produced a higher C_{max} and AUC with a calculated oral bioavailability of 91% (Figure 3, Table 8). This remarkable oral bioavailability of **6b** indicated that the oxidation of the pyridine nitrogen not only had attenuated the first-pass metabolism of the pyridine ring but also may have provided improved solubility and absorption.[11b]

Table 8. Pharmacokinetics of **6b** (ABT-670) after a Single Dose in Rat, Monkey, or Dog[a]

species	dose[b]	$T_{1/2}$, h	*F*% (SEM)	C_{max}, ng/mL (SEM)	AUC, ng·h/mL (SEM)
rat	sc	1.2	84 (6)	465 (50)	1138 (81)
rat	po	1.8	68 (9)	417 (70)	922 (121)
monkey	po	2.0	91 (18)	660 (201)	2280 (449)
dog	po	2.1	85 (7)	1418 (66)	4275 (356)

[a] Pharmacokinetic data are provided as mean (SEM). [b] 1.0 mg/kg dose; sc, subcutaneous; po, per os (oral).

Table 9. In Vitro Effects on hERG Current and Cardiac Purkinje Fiber Repolarization[a]

compd	dose, ng/mL	hERG blockade, %	dose, ng/mL	Purkinje RP, %
6b	3000	14.5 ± 3.5	3000	4.3 ± 1.0
7a	3000	44.8 ± 4.6	1600	12.0 ± 2.0

[a] DMSO, 11.0% ± 4.0% block; $n = 4-6$ per group.

In Vitro Effects on HERG Current and Cardiac Purkinje Fiber Repolarization. Since different classes of dopaminergic agents can induce both central and peripheral side effects such as pressor effects on the cardiovascular system, compounds **6b** and **7a** were profiled in cardiovascular safety studies. Compounds **6b** and **7a** were tested by in vitro assays to measure their effects on hERG tail currents[12a] as a primary screen (Table 9). Compound **7a** exhibited a 45% reduction in hERG current at 3 μg/mL concentrations indicating that it could have some cardiovascular liability. In contrast, compound **6b** did not reduce hERG current at the 1 and 3 μg/mL concentrations tested (14.4% and 14.5% block, respectively) compared to vehicle [dimethyl sulfoxide (DMSO), 11% block; $n = 4-6$ per group].

To evaluate the possible effects of **6b** and **7a** on ventricular repolarization, changes in action potential duration (APD) of canine cardiac Purkinje fibers were assessed in vitro (Table 9). For compound **6b**, no significant prolongation (0.6%) of the action potential duration was elicited at 1 μg/mL. A higher concentration of **6b** (3 μg/mL) elicited minimal (4.3%) prolongation of the action potential duration that attained statistical significance. However, the higher concentration of **7a** elicited 12% prolongation of the action potential duration.

As shown in Table 9, compound **6b** did not elicit meaningful prolongation of canine Purkinje fiber repolarization and it did not block hERG current at concentrations 200-fold greater than efficacious plasma concentrations (15 ng/mL at 0.1 μmol/kg dose). Compound **6b** appears to have a large preclinical cardiovascular safety index. The hERG and Purkinje fiber repolarization data on **7b** indicated low cardiovascular liability.

Conclusion

Arylpiperidine acetamides and benzamides have been discovered as a new class of selective D_4 agonists. Arylpiperidine analogues demonstrated the same remarkable SAR trend observed in the arylpiperazine series reported earlier, wherein substitution at the meta or para position of the terminal aryl ring was found to be detrimental to the D_4 functional activity, precluding blockage of the site of metabolism with a substituent. The N-oxidation of the pyridine ring of (2-pyridinyl)piperidine provided an alternative pharmacophore that retained structural requirements for receptor activation. Optimization of region A provided compound **6b** (ABT-670), which exhibited nearly full agonist activity and demonstrated excellent oral bioavailability in rat, dog, and monkey (68%, 85%, and 91%, respectively). In addition to attenuated first-pass metabolism, the remarkable oral bioavailability may also be a result of better physicochemical properties of the pyridine *N*-oxide analogue compared to the pyridine analogue. Compound **6b** exhibited erectogenic activity in rats with no overt side effects such as emesis, nausea, or cardiovascular liability. Since compound **6b** (ABT-670) exhibited superior PK as well as cardiovascular safety profile, it was selected for advanced toxicological and safety evaluation and subsequently selected as a development candidate for erectile dysfunction.

Experimental Section

Chemistry Methods. All solvents were of anhydrous reagent grade from commercial sources. Unless otherwise noted, all chemicals and reagents were obtained commercially and used without purification. The ^{1}H NMR spectra were obtained at 300 MHz on a Nicolet/GE QE300 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) or (trimethylsilyl)propionate-d_4 (TSP) as in internal standard. Mass spectra were obtained on a Kratos MS-50 instrument, in desorption chemical ionization (DCI)/NH_3 mode. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Flash chromatography was carried out on silica gel 60 (E. Merck, 230−400 mesh), or prepacked 40 mm silica gel columns from Biotage. Thin-layer chromatography was performed on 250 μM silica-coated glass plates from EM Science. Samples were analyzed by high-performance liquid chromatography (HPLC)−mass spectrometry (MS)−evaporative light scattering detection (ELSD) on an Open Access Finnigan Navigator/Agilent 1100/Sedere Sedex 75 system using a Phenomenex Luna C_8 column (5 μm, 2.1 × 50 mm). The elution system used was a gradient of 10−100% over 4.5 min at 1.5 mL/min, and the solvent was either acetonitrile/0.1% aqueous trifluoroacetic acid (TFA), or acetonitrile/10 mM ammonium acetate. The MS was operated in the atmospheric pressure chemical ionization (+APCI) mode. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected.

General Procedure for Compounds 4a−c (Method A): 2-Methoxy-*N*-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)-benzamide (4b). Step 1. *N*-(3-Methylbenzoyl)glycine (10 g, 51.7 mmol), lead tetraacetate (25.25 g, 56.94 mmol), and copper(II) acetate monohydrate (0.94 g, 5.17 mmol) were combined in toluene and heated at reflux overnight. The reaction mixture was cooled to room temperature (rt) and filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (elution with 25% EtOAc/hexanes) to provide [(3-methylbenzoyl)amino]methyl acetate (7.95 g, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.40 (s, 3H), 5.45 (d, $J = 9$ Hz, 2H), 7.35 (m, 2H), 7.55 (m, 1H), 7.62 (s, 1H); MS (DCI/NH_3) *m*/*e* 208 $(M + H)^+$

Step 2. 4-(2-Methoxyphenyl)piperidine **12b** (286 mg, 1.5 mmol), [(3-methylbenzoyl)amino]methyl acetate (310 mg, 1 mmol), and triethylamine (0.42 mL, 3 mmol) were combined in acetonitrile (8 mL) and stirred at rt for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (elution with CH_2Cl_2/CH_3OH 9.5:0.5) to provide **4b**(285 mg, 56.2% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65 (m, 4H), 2.31 (m, 2H), 2.37 (s, 3H), 2.79 (m, 1H), 2.93 (m, 2H), 3.75 (s, 3H), 4.15 (d, $J = 6$ Hz, 2H), 6.90 (m, 2H), 7.15 (m, 2H), 7.36 (m, 2H), 7.68 (m, 2H), 8.69 (t, $J = 6$ Hz, 1H); MS (DCI/NH_3) *m*/*e* 339 $(M + H)^+$; Anal. ($C_{21}H_{26}N_2O_2 \cdot 0.15H_2O$) C, H, N.

***N*-(3′,4′,5′,6′-Tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)-benzamide (4a)** was prepared in the same manner as compound **4b** but with substitution of 4-phenylpiperidine in place of 4-(2-methoxyphenyl)piperidine (90 mg, 62% yield). ^{1}H NMR (300 MHz,

DMSO-d_6) δ 1.70 (m, 4H), 2.31 (m, 2H), 2.36 (s, 3H), 2.45 (m, 1H), 2.95 (m, 2H), 4.17 (d, J = 6 Hz, 2H), 7.23 (m, 5H), 7.35 (d, J = 6 Hz, 2H), 7.69 (m, 2H), 8.71 (m, 1H); MS (DCI-NH_3) *m*/*e* 309 $(M + H)^+$. Anal. ($C_{20}H_{24}N_2O$) C, H, N.

Preparation of 3-Methyl-*N*-(4-thiazol-2-ylpiperidin-1-ylmethyl)-benzamide (4c): Step 1. The procedure described below for **10d** was followed, with substitution of 2-thiazolylzinc bromide in place of 3-methyl-2-pyridylzinc bromide, to provide 3-methyl-*N*-(4′-thiazol-2-yl-2′,3′,4′,5′-tetrahydropyridin-1′-ylmethyl)benzamide **10c** (56% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5 (s, 9H), 2.7 (m, 2H), 3.33 (t, J = 6 Hz, 2H), 4.10 (q, J = 3 Hz, 2H), 6.60 (m, 1H), 7.21 (d, J = 3 Hz, 1H), 7.78 (d, J = 3 Hz, 1H); MS (DCI/NH_3) *m*/*e* 267 $(M + H)^+$.

Step 2. A solution of **10c** (3.62 g, 13.6 mmol) in 25% trifluoroacetic acid in CH_2Cl_2 (30 mL) was stirred at rt for 2 h. The reaction was concentrated under reduced pressure to afford 4-thiazol-2-yl-1,2,3,6-tetrahydropyridine as a brown oil (1.69 g, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (m, 2H), 3.12 (t, J = 6 Hz, 2H), 3.59 (m, 2H), 6.63 (m, 1H), 7.20 (d, J = 3 Hz, 1H), 7.75 (d, J = 3 Hz, 1H); MS (DCI/NH_3) *m*/*e* 167 $(M + H)^+$.

Step 3. The procedure described for **4b** was followed, with substitution of 4-thiazol-2-yl-1,2,3,6-tetrahydropyridine in place of 4-(2-methoxyphenyl)piperidine, to provide 3-methyl-*N*-{[4-(1,3-thiazol-2-yl)-3,6-dihydro-1(2*H*)-pyridinyl]methyl}benzamide as a yellow sticky residue (680 mg, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H), 2.8 (m, 2H), 2.95 (t, 2H, 4.5 Hz), 3.42 (m, 2H), 4.5 (d, J = 6 Hz, 2H), 6.6 (m, 1H), 7.2 (d, J = 3 Hz, 1H), 7.35 (dd, J = 4.5 and 1.5 Hz, 2H), 7.49 (m, 1H), 7.52 (s, 1H), 7.78 (d, J = 3 Hz, 1H); MS (DCI/NH_3) *m*/*e* 314 $(M + H)^+$.

Step 4. 3-Methyl-*N*-{[4-(1,3-thiazol-2-yl)-3,6-dihydro-1(2*H*)-pyridinyl]methyl}benzamide (490 mg, 1.5 mmol) was hydrogenated with 10% Pd/C catalyst under hydrogen gas pressure (60 psi) for 42 h in methanol. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% ethanol/EtOAc) to provide the title compound **4c** (100 mg, 22% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (dq, J = 12 and 6 Hz, 2H), 2.20 (m, 2H), 2.40 (s, 3H), 2.48 (m, 2H), 3.10 (m, 3H), 4.35 (d, J = 6 Hz, 2H), 6.50 (m, 1H), 7.20 (d, J = 3.3 Hz, 1H), 7.35 (m, 2H), 7.60 (m, 2H), 7.70 (d, J = 3.3 Hz, 1H); MS (DCI/NH_3) *m*/*e* 316 $(M + H)^+$. Maleate salt: Anal. ($C_{17}H_{21}N_3OS \cdot 1.2C_4H_4O_4$) C, H, N.

3-Methyl-*N*-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (4d): (A) 4-Trifluoromethanesulfonyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *t*-Butyl Ester (9a). To a solution of diisopropylamine (13.4 mL, 96 mmol) in tetrahydrofuran (THF) (350 mL) at −78 °C was added 1.6 M *n*-BuLi in hexanes (60 mL, 96 mmol). The reaction mixture was stirred for 5 min at −78 °C. A solution of *t*-butoxycarbonyl-4-piperidone (16 g, 80 mmol) in THF (100 mL) was added, and the reaction mixture was stirred for 10 min. Then a solution of *N*-phenyltrifluoromethanesulfonimide (31.4 g, 88 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min and the cooling bath was removed to warm it up to rt for 1.5 h until all piperidone was utilized (determined by thin-layer chromatography, TLC). The reaction was quenched by saturated $NaHCO_3$, followed by extraction with ethyl ether and 5% citric acid. The organic layer was then washed with 1 N NaOH (4 × 200 mL), water (2 × 200 mL), and brine (1 × 200 mL), dried over $MgSO_4$, and evaporated on a rotary evaporator to give a yellowish oil. Purification by flash chromatography with hexanes/EtOAc 8:2 as eluent gave 18 g (68% yield) of pure colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41 (s, 9H), 2.41 (m, 2H), 3.54 (t, 2H), 3.98 (m, 2H), 6.02 (m, 1H).

(B) 3′,6′-Dihydro-2′*H*-[2,4′-bipyridine]-1′-carboxylic Acid *t*-Butyl Ester (10d). Pure 4-trifluoromethanesulfonyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *t*-butyl ester (18 g, 54 mmol) in THF (~200 mL) was treated with 2-pyridylzinc bromide (0.5 M solution in THF; Aldrich, brown color, 124 mL, 62.5 mmol, 1.15 equiv) followed by $Pd(PPh_3)_4$ (from Strem Chemicals) (625 mg). The reaction mixture was heated at 60 °C for 90 min. All of the triflate was utilized (checked by TLC). The THF was removed by rotary evaporation. EtOAc (300 mL) and 1 N NaOH (200 mL) were added to the residue. Zinc salts were filtered and the organic layer was separated, washed with brine (300 mL), dried ($MgSO_4$), and concentrated on the rotary evaporator to give a brown oil. Purification by flash chromatography with hexanes/EtOAc 6:4 as eluent gave 9.0 g (64% yield) of the desired product as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43 (s, 9H), 2.56 (m, 2H), 3.54 (t, 2H), 4.04 (m, 2H), 6.08 (m, 1H), 7.25 (dd, 1H), 7.56 (d, J = 9 Hz, 1H), 7.77 (m, 1H), 8.54 (m, 1H); MS (DCI-NH_3) *m*/*e* 259 $(M + H)^+$, 277 $(M + H + 18)^+$

(C) 3′,4′,5′,6′-Tetrahydro-2′*H*-[2,4′-bipyridine]-1′-carboxylic Acid *t*-Butyl Ester (11d). 3′,6′-Dihydro-2′*H*-[2,4′-bipyridine]-1′-carboxylic acid *t*-butyl ester (9.0 g) was hydrogenated by use of 10%Pd/C (dry, 900 mg) at 60 psi at room temperature for 1.5 h to give 8.9 g (99%) of the desired product as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41 (s, 9H), 1.58 (m, 2H), 1.81 (m, 2H), 2.85 (m, 3H), 4.06 (m, 2H), 7.20 (dd, 1H), 7.28 (d, J = 9 Hz, 1H), 7.70 (m, 1H), 8.48 (m, 1H).

(D) 1′,2′,3′,4′,5′,6′-Hexahydro-2′*H*-[2,4′-bipyridine] (12d). Compound **11d** (6.57 g) was dissolved in EtOAc (50 mL) and cooled to −78 °C. HCl gas was bubbled through the reaction mixture for 15 min. The reaction mixture was allowed to warm up to room temperature, upon which an off-white precipitate was formed. This precipitate was filtered, washed with EtOAc, and dried under high vacuum to give the dihydrochloride salt (5.03 g, 99%) of the desired product (**12d**).

(E) The procedure described for **4b** was followed, with substitution of compound **12d** in place of **12b**, to provide the title compound **4d** (480 mg, 64% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75 (m, 4H), 2.31 (m, 2H), 2.36 (s, 3H), 2.59 (m, 1H), 2.95 (m, 2H), 4.17 (d, J = 6 Hz, 2H), 7.18 (m, 1H), 7.25 (d, J = 6 Hz, 1H), 7.35 (m, 2H), 7.69 (m, 3H), 8.48 (m, 1H), 8.71 (m, 1H); MS (DCI/NH_3) *m*/*e* 310 (M + H)+. Anal. ($C_{19}H_{23}N_3O \cdot 0.25\ H_2O$): C, H, N.

General Procedure for Compounds 5a−s (Method B): 2-(3′,4′,5′,6′-Tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)-*N*-(*m*-tolyl)acetamide (5k). A mixture of 4-(2-pyridinyl)piperidine 12d (900 mg, 3.86 mmol), 2-bromo-*N*-(*m*-tolyl)acetamide (880 mg, 3.86 mmol) and K_2CO_3 (1.6 g, 11.58 mmol) in DMF (20 mL) was stirred at rt for 18 h. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo, and purified by flash chromatography with EtOAc/EtOH, 9.2:0.8, to give the desired product (850 mg, yield 71%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (m, 4H), 2.24 (m, 5H), 2.64 (m, 1H), 2.98 (m, 2H), 3.12 (s, 2H), 3.78 (s, 3H), 6.88 (d, J = 6 Hz, 1H), 7.20 (m, 2H), 7.30 (d, J = 6 Hz, 1H), 7.45 (d, J = 6 Hz, 2H), 7.71 (m, 1H), 8.51 (m, 1H), 9.59 (br s, 1H); MS (DCI-NH_3) *m*/*e* 310 $(M + H)^+$. Anal. ($0.15H_2O \cdot C_{19}H_{23}N_3O$) C, H, N.

2-(4-Phenylpiperidin-1-yl)-*N*-(*m*-tolyl)acetamide (5a) was prepared in the same manner as **5k** but with substitution of 4-phenylpiperidine in place of 4-(2-pyridinyl)piperidine (150 mg, 99% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.76 (m, 4H), 2.28 (m, 5H), 2.51 (m, 1H), 2.98 (m, 2H), 3.12 (s, 2H), 6.88 (d, J = 6 Hz, 1H), 7.19 (m, 2H), 7.29 (m, 4H), 7.46 (d, 2H), 9.61 (br s, 1H); MS (DCI-NH_3) *m*/*e* 39 $(M + H)^+$. Anal. ($C_{20}H_{24}N_2O \cdot 0.2H_2O$) C, H, N.

2-[1-[2-(*m*-Tolylamino)allyl]piperidin-4-yl]benzonitrile (5b) was prepared in the same manner as **5k** but with substitution of 2-piperidin-4-ylbenzonitrile in place of 4-(2-pyridinyl)piperidine (133 mg, 70% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (s, 1H), 7.79 (dd, J = 7.8 and 1.0 Hz, 1H), 7.70 (ddd, J = 7.8, 7.8, and 1.4 Hz, 1H), 7.60 (br d, J = 7.1 Hz, 1H), 7.44 (m, 3H), 7.19 (dd, J = 7.8 and 7.8 Hz, 1H), 6.88 (br d, J = 7.5 Hz, 1H), 3.17 (s, 2H), 3.02 (br d, J = 11.5 Hz, 2H), 2.86 (m, 1H), 2.34 (m, 2H), 2.29 (s, 3H), 1.96−1.75 (m, 4H). MS (DCI/NH_3) *m*/*e* 334 $(M + H)^+$. This material was converted to the maleate salt. Anal. ($C_{21}H_{23}N_3O \cdot 1.2C_4H_4O_4 \cdot 0.2H_2O$) C, H, N.

2-[4-(2-Fluorophenyl)piperidin-1-yl]-*N*-(*m*-tolyl)acetamide (5c) was prepared in the same manner as **5k** but with substitution of 4-(2-fluorophenyl)piperidine in place of 4-(2-pyridinyl)piperidine (89 mg, 80.9% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.72 (m, 2H), 1.85 (m, 2H), 2.29 (m, 5H), 2.51 (m, 1H), 2.80 (m, 1H), 2.97

(m, 2H), 3.12 (s, 2H), 6.88 (d, $J = 6$ Hz, 1H), 7.19 (m, 4H), 7.42 (m, 3H), 9.61 (br s, 1H); MS (DCI/NH_3) *m/e* 327 $(M + H)^+$. Anal. ($C_{20}H_{23}FN_2O$) C, H, N.

***N*-(*m*-Tolyl)-2-[4-(*o*-tolyl)piperidin-1-yl]acetamide (5d)** was prepared in the same manner as **5k** but with substitution of 4-(2-methylphenyl)piperidine in place of 4-(2-pyridinyl)piperidine (65 mg, 87.8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.72 (m, 2H), 1.79 (m, 2H), 2.29 (m, 8H), 2.69 (m, 1H), 2.97 (m, 2H), 3.12 (s, 2H), 6.88 (d, $J = 6$ Hz, 1H), 7.13 (m, 4H), 7.28 (d, $J = 6$ Hz, 1H), 7.47 (m, 2H), 9.61 (br s, 1H); MS (DCI/NH_3) *m/e* 323 $(M + H)^+$. Anal. ($C_{21}H_{26}N_2O$) C, H, N.

2-[4-(2-Methoxyphenyl)piperidin-1-yl]-*N*-(*m*-tolyl)acetamide (5e) (Method A). 4-(2-Methoxyphenyl)piperidine (200 mg, 1 mmol), 2-bromo-*N*-(3-methylphenyl)acetamide (228 mg, 1 mmol), and *N*,*N*-diisopropylethylamine (0.185 mL, 1.1 mmol) in toluene (8 mL) were stirred at 60 °C for 18 h. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (2 × 30 mL), dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (elution with CH_2Cl_2/methanol, 9.5:0.5) to provide the title compound (177 mg, 52.3% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71 (m, 4H), 2.28 (m, 5H), 2.89 (m, 1H), 2.96 (m, 2H), 3.13 (s, 2H), 3.78 (s, 3H), 6.91 (m, 3H), 7.20 (m, 3H), 7.45 (m, 2H), 8.69 (s, 1H); MS (DCI/NH_3) *m/e* 339 $(M + H)^+$. Anal. ($C_{21}H_{26}N_2O_2$) C, H, N.

2-[4-(3-Fluorophenyl)piperidin-1-yl]-*N*-(*m*-tolyl)acetamide (5f) was prepared in the same manner as **5k** but with substitution of 4-(3-fluorophenyl)piperidine in place of 4-(2-pyridinyl)piperidine (68 mg, 61.8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75 (m, 4H), 2.29 (m, 5H), 2.55 (m, 1H), 2.96 (m, 2H), 3.12 (s, 2H), 6.88 (d, $J = 6$ Hz, 1H), 7.01 (m, 1H), 7.14 (m, 3H), 7.35 (m, 1H), 7.45 (m, 2H), 9.61 (br s, 1H); MS (DCI/NH_3) *m/e* 327 $(M + H)^+$. Anal. ($C_{20}H_{23}FN_2O$) C, H, N.

2-[4-(3-Hydroxyphenyl)piperidin-1-yl]-*N*-(*m*-tolyl)acetamide (5g) was prepared in the same manner as **5k** but with substitution of 4-(3-hydroxyphenyl)piperidine in place of 4-(2-pyridinyl)piperidine (190 mg, 60% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.61−1.87 (m, 4H), 2.16−2.34 (m, 5H), 2.33−2.46 (m, 1H), 2.88−3.01 (m, 2H), 3.25−3.41 (m, 2H), 6.54−6.61 (m, 1H), 6.62−6.73 (m, 2H), 7.08 (t, 1H), 7.14−7.24 (m, 1H), 7.20 (t, 1H), 7.40−7.51 (m, 2H), 9.19−9.30 (m, 1H), 9.56−9.66 (m, 1H); MS (DCI/NH_3) *m/e* 325 $(M + H)^+$. Anal. ($C_{20}H_{24}N_2O_2 \cdot 0.2H_2O$) C, H, N.

2-[4-(4-Fluorophenyl)piperidin-1-yl]-*N*-(*m*-tolyl)acetamide (5h) was prepared in the same manner as **5k** but with substitution of 4-(4-fluorophenyl)piperidine in place of 4-(2-pyridinyl)piperidine (125 mg, 83.8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75 (m, 4H), 2.29 (m, 5H), 2.55 (m, 1H), 2.96 (m, 2H), 3.12 (s, 2H), 6.88 (d, $J = 7.5$ Hz, 1H), 7.13 (m, 3H), 7.31 (m, 2H), 7.45 (m, 2H), 9.61 (br s, 1H); MS (DCI-NH_3) *m/e* 327 $(M + H)^+$. Anal. ($C_{20}H_{23}FN_2O$) C, H, N.

2-[4-(4-Methoxyphenyl)piperidin-1-yl]-*N*-(*m*-tolyl)acetamide (5i) wasprepared in the same manner as **5k** but with substitution of 4-(4-methoxyphenyl)piperidine in place of 4-(2-pyridinyl)piperidine (120 mg, 83.8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.73 (m, 4H), 2.14−2.35 (m, 5H), 2.38−2.61 (m, 1H), 2.81−2.99 (m, 2H), 3.04−3.18 (m, 2H), 3.61−3.87 (m, 3H), 6.71−7.00 (m, 3H), 7.10−7.29 (m, 3H), 7.36−7.62 (m, 2H), 9.47−9.71 (m, 1 H); MS (DCI-NH_3) *m/e* 339 $(M + H)^+$. HRMS Calcd for $C_{21}H_{26}N_2O_2$: 339.1994 $(M + H)^+$. Found: 339.2067.

2-[4-(4-Hydroxyphenyl)piperidin-1-yl]-*N*-(*m*-tolyl)acetamide (5j) was prepared in the same manner as **5k** but with substitution of 4-(4-hydroxyphenyl)piperidine in place of 4-(2-pyridinyl)piperidine and $NaHCO_3$ as a base (120 mg, 83.8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54−1.89 (m, 4H), 2.14−2.36 (m, 4H), 2.27 (m, 3H), 2.33−2.46 (m, 1H), 2.84−3.02 (m, 2H), 3.04−3.21 (m, 2H), 6.56−6.78 (m, 2H), 6.81−6.94 (m, 1H), 6.97−7.15 (m, 2H), 7.14−7.26 (m, 1H), 7.36−7.57 (m, 2H), 9.02−9.23 (m, 1H), 9.48−9.76 (m, 1H); MS (DCI-NH_3) *m/e* 325 $(M + H)^+$. Anal. ($C_{20}H_{24}N_2O_2 \cdot 0.2H_2O$) C, H, N.

***N*-(4-Chloro-2,6-dimethylphenyl)-2-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (5l)** was prepared in the same manner as **5k** but with substitution of 2-bromo-*N*-(4-chloro-2,6-dimethylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (22.9 mg, 25% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (m, 4H), 2.05 (s, 3H), 2.14 (s, 6H), 2.30 (m, 2H), 2.67 (m, 1H), 3.04 (m, 2H), 3.16 (s, 2H), 4.67 (br s, 1H), 6.83 (s, 2H), 7.16 (s, 2H), 7.20 (m, 1H), 7.29 (br d, $J = 7.5$ Hz, 1H), 7.72 (ddd, $J = 2.1$, 7.5, 7.5 Hz, 1H), 8.48 (m, 1H), 9.27 (br s, 1H); MS (ESI) *m/e* 358 $(M + H)^+$; Anal. ($C_{20}H_{24}ClN_3O \cdot 0.35C_2H_4O_2 \cdot 0.15H_2O$) C, H, N.

2-(3′,4′,5′,6′-Tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)-*N*-(2,4,6-trichlorophenyl)acetamide (5m) was prepared in the same manner as **5k** but with substitution of 2-bromo-*N*-(2,4,6-trichlorophenyl)-acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (21.2 mg, 21% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84 (m, 4H), 2.48 (m, 2H), 2.67 (m, 1H), 3.10 (br d, $J = 10.5$ Hz, 2H), 3.17 (s, 2H), 7.21 (m, 1H), 7.30 (d, $J = 7.8$ Hz, 1H), 7.72 (ddd, $J = 2.1$, 7.5, and 7.5 Hz, 1H), 7.77 (s, 2H), 8.48 (m, 1H); MS (ESI) *m/e* 400 $(M + H)^+$; Anal. ($C_{18}H_{18}Cl_3N_3O \cdot 0.1C_4H_4O_4 \cdot 0.55H_2O$) C, H, N.

***N*-(2-Ethyl-6-methylphenyl)-2-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (5n)** was prepared in the same manner as **5k** but with substitution of 2-bromo-*N*-(2-ethyl-6-methylphenyl)-acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (48.5 mg, 28% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, $J = 7.5$ Hz, 3H), 1.90 (m, 4H), 2.14 (s, 3H), 2.32 (m, 2H), 2.50 (q, $J = 7.5$ Hz, 2H), 2.68 (m, 1H), 3.04 (br d, $J = 11.4$ Hz, 2H), 3.15 (s, 2H), 7.10 (m, 3H), 7.21 (ddd, $J = 1.5$, 4.5, and 7.5 Hz, 1H), 7.30 (d, $J = 8.4$ Hz, 1H), 7.72 (ddd, $J = 2.1$, 7.5, and 7.5 Hz, 1H), 8.28 (m, 1H), 9.22 (br s, 1H); MS (ESI) *m/e* 338 $(M + H)^+$; Anal. ($C_{21}H_{27}N_3O \cdot 0.3H_2O$) C, H, N.

***N*-(2-Chloro-6-methylphenyl)-2-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (5o)** was prepared in the same manner as **5k** but with substitution of 2-bromo-*N*-(2-chloro-6-methylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (62.8 mg, 36% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88 (m, 4H), 2.20 (s, 3H), 2.30 (m, 2H), 2.68 (m, 1H), 3.12 (m, 2H), 3.17 (s, 2H), 7.21 (m, 2H), 7.29 (d, $J = 8.4$ Hz, 1H), 7.36 (m, 1H), 7.73 (ddd, $J = 2.1$, 7.5, and 7.5 Hz, 1H), 8.48 (m, 1H), 9.43 (br s, 1H); MS (ESI) *m/e* 344 $(M + H)^+$; Anal. ($C_{19}H_{22}ClN_3O \cdot 0.1CH_2Cl_2$) C, H, N.

***N*-(2-Methoxy-6-methylphenyl)-2-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (5p)** was prepared in the same manner as **5k** but with substitution of 2-bromo-*N*-(2-methoxy-6-methylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (38 mg, 22% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.87 (m, 4H), 2.14 (s, 3H), 2.29 (m, 2H), 2.69 (m, 1H), 3.08 (m, 4H), 3.72 (s, 3H), 6.84 (m, 2H), 7.13 (dd, $J = 8.4$ and 8.4 Hz, 1H), 7.20 (ddd, $J = 1.5$, 4.5, and 7.5 Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.72 (ddd, $J = 2.1$, 7.5, and 7.5 Hz, 1H), 8.48 (m, 1H), 8.94 (br s, 1H); MS (ESI) *m/e* 340 $(M + H)^+$; Anal. ($C_{20}H_{25}N_3O \cdot 0.4H_2O$) C, H, N.

2-(3-Cyano-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)-*N*-(*m*-tolyl)acetamide (5q): (A) 4-Trifluoromethanesulfonyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (9b). Benzyl 4-oxo-1-piperidinecarboxylate (0.5 g, 2.1 mmol) and *N*-phenyltrifluoromethanesulfonimide (1.15 g, 3.2 mmol) in tetrahydrofuran (10 mL) at −78 °C was treated with lithium hexamethyldisilazide (2.14 mL, 2.1 mmol). After 4 h at −78 °C, the mixture was quenched with water and extracted with a large excess of diethyl ether (3×). The ethereal layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on flash silica gel (20% EtOAc/hexanes) to provide the title compound (0.471 g, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (m, 2H), 3.72 (m, 2H), 4.13 (m, 2H), 5.16 (s, 2H), 5.78 (br m, 1H), 7.36 (m, 5H); MS (ESI) *m/e* 366 $(M + H)^+$.

(B) 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (9c). Bis-(pinacolato)diborane (338 mg, 1.33 mmol), potassium acetate (356 mg, 3.63 mmol), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) ($PdCl_2$dppf; 30 mg, 0.04 mmol), and 1,1′-

bis(diphenylphosphino)ferrocene (20 mg, 0.04 mmol) were combined and treated with compound **9b** (440 mg, 1.21 mmol) in degassed 1,4-dioxane (7 mL). The reaction mixture was heated at 80 °C for 16 h, allowed to cool to 23 °C, diluted with water, and extracted with CH_2Cl_2 (3×). The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on flash silica gel (20% EtOAc/hexanes) to provide the title compound (323 mg, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 12H), 2.24 (m, 2H), 3.52 (dd, J = 5.7 and 5.7 Hz, 2H), 4.03 (dd, J = 3 and 6 Hz, 2H), 5.14 (s, 2H), 6.46 (br m, 1H), 7.32 (m, 5H); MS (ESI) m/e 344 $(M + H)^+$.

(C) Benzyl 3-Cyano-3′,6′-dihydro-2′*H*-[2,4′-bipyridine]-1′-carboxylate 4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-ol Complex (10l). Compound **9c** (200 mg, 0.58 mmol), potassium carbonate (241 mg, 1.75 mmol), $PdCl_2$dppf (29 mg, 0.035 mmol), and 2-chloro-3-cyanopyridine (85 mg, 0.61 mmol) were combined in degassed DMF (4 mL). The reaction mixture was heated at 80 °C for 16 h, allowed to cool to 23 °C, and diluted with water and CH_2Cl_2, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×). All the CH_2Cl_2 phases were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on flash silica gel (50% EtOAc/hexanes) to provide the title compound sufficiently pure to carry on in further reactions (323 mg, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 12H), 2.74 (br s, 2H), 3.75 (dd, 2H, J = 6 Hz), 4.26 (m, 2H), 5.19 (s, 2H), 6.57 (br m, 1H), 7.32 (m, 6H), 7.98 (dd, J = 1.8 and 7.8 Hz, 1H), 8.76 (dd, J = 1.8 and 4.5 Hz, 1H); MS (ESI) m/e 320 $(M + H)^+$.

(D) 2-(4-Piperidinyl)nicotinonitrile (12l). A steady stream of H_2 was bubbled through a stirred solution of **10l** (70 mg, 0.15 mmol), Pd/C (5 mg), and ethanol (2 mL) at 23 °C for 24 h. The H_2 bubbling was stopped and N_2 was bubbled through for a few minutes. The reaction mixture was passed through Celite and the filtrate was concentrated under reduced pressure to provide the title compound sufficiently pure to carry into further reactions (30 mg). MS (ESI) m/e 188 $(M + H)^+$.

(E) 2-(3-Cyano-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)-*N*-(*m*-tolyl)acetamide (5q). 2-(4-Piperidinyl)nicotinonitrile **12l** (30 mg, 0.15 mmol), 2-bromo-*N*-(3-methylphenyl)acetamide (37 mg, 0.16 mmol), and DMF (31 mg, 0.24 mmol) in toluene (3 mL) were combined and heated at 60 °C. After 16 h, the mixture was allowed to cool to 23 °C and concentrated under reduced pressure. The residue was purified by thin-layer chromatography (7% EtOAc/hexanes) to provide the title compound (9 mg, 17% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79 (br d, J = 12 Hz, 2H), 2.02 (m, 2H), 2.27 (s, 3H), 2.32 (m, 2H), 3.04 (m, 3H), 3.16 (s, 2H), 6.88 (br d, J = 8 Hz, 1H), 7.18 (dd, J = 7.2 and 7.2 Hz, 1H), 7.45 (m, 3H), 8.26 (dd, J = 1 and 2 Hz, 1H), 8.82 (dd, J = 1 and 4.4 Hz, 1H), 9.58 (s, 1H); MS (APCI/ESI) m/e 335 $(M + H)^+$.

2-(5-Hydroxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)-*N*-(*m*-tolyl)acetamide (5r): (A) 5-Benzyloxy-2-bromopyridine. 6-Chloropyridin-3-ol (6 g, 46 mmol) in DMF (50 mL) was treated with benzyl bromide (5.5 mL, 46 mmol) and potassium carbonate (12.8 mmol), and the reaction mixture was heated to 40 °C for 18 h. The reaction was cooled to rt, poured into brine (200 mL), and extracted with EtOAc (200 mL). The organic layer was washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 5-benzyloxy-2-chloropyridine. This crude product was dissolved in propionitrile (50 mL) and treated with trimethylsilyl bromide (12.36 mL, 92 mmol), and the reaction mixture was heated at 100 °C for 113 h. The reaction mixture was cooled to rt and poured into 2.0 M sodium hydroxide solution to which 50 g of ice had been added. The aqueous phase was extracted with diethyl ether (3 × 75 mL). The organic layers were combined and washed with water (2 × 100 mL) and brine (75 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue (light brown oil) was purified by flash column chromatography on silica gel with 8% EtOAc/hexanes as eluent to give 4.72 g of the 5-benzyloxy-2-bromopyridine as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.19 (s, 2H), 7.42 (m, 6H), 7.57 (d, J = 6 Hz, 1H), 8.19 (d, J = 3 Hz, 1H), MS (DCI/NH_3) m/e 365 $(M + H)^+$.

(B) *t*-Butyl 5-Benzyloxy-3′,6′-dihydro-2′*H*-[2,4′-bipyridine]-1′-carboxylate (12m). The 5-benzyloxy-2-bromopyridine (0.33 g, 17.7 mmol) in diethyl ether (10 mL) was added rapidly to a solution of 2.5 M *n*-butyllithium (0.98 mL, 1.56 mmol) in diethyl ether (8 mL) at −78 °C. The resulting brown solution was stirred at −78 °C for 10 min. To this was added 0.5 M zinc chloride solution (2.75 mL, 1.37 mmol), and the reaction mixture was warmed to 0 °C and stirred at 0 °C for 15 min. To this reaction mixture was added 4-trifluoromethanesulfonyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *t*-butyl ester (0.5 g, 1.5 mmol) and tetrakis-(triphenylphosphine)palladium(0) (175 mg, 0.15 mmol). The reaction was heated to 60 °C for 4 h. The mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and 1 N sodium hydroxide (50 mL). The inorganic salts were filtered, and the filtrate was washed with brine (50 mL), dried ($MgSO_4$), and concentrated on the rotary evaporator to give a brown oil. The crude compound was purified by flash column chromatography on silica gel with 80% hexanes/EtOAc as eluent to give 0.209 g (47% yield) of the desired product **12m** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (s, 9H), 2.52 (m, 2H), 3.51 (t, J = 6 Hz, 2H), 4.01 (m, 2H), 5.19 (s, 2H), 6.52 (m, 1H), 7.41 (m, 7H), 8.31 (d, J = 1.5 Hz, 1H), MS (DCI/NH_3) m/e 367 $(M + H)^+$.

(C) 2-[5-Benzyloxy-3′,6′-dihydro-2′*H*-[2,4′-bipyridine]-1′-yl]-*N*-(3-methylphenyl)acetamide (12n). A mixture of 5-benzyloxy-3′,6′-dihydro-2,4′-bipyridine (175 mg, 0.46 mmol), the product from example 1A (125 mg, 0.54 mmol), and potassium carbonate (164 mg, 1.1 mmol) in DMF (8 mL) was stirred at rt for 18 h. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash column chromatography with 70% hexanes/EtOAc to give the desired product (105 mg, 55% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.60 (m, 2H), 2.76 (t, J = 4.5 Hz, 2H), 3.27 (m, 2H), 3.97 (d, J = 6 Hz, 2H), 5.19 (s, 2H), 6.54 (m, 1H), 6.87 (m, 2H), 7.18 (t, J = 6 Hz, 2H), 7.42 (m, 7H), 8.31 (d, J = 3 Hz, 1H), 9.52 (s, 0.5H), 9.64 (s, 0.5H); MS (DCI/NH_3) m/e 414 $(M + H)^+$.

(D) 2-[4-(5-Hydroxypyridin-2-yl)piperidin-1-yl]-*N*-(3-methylphenyl)acetamide (5r). Compound **12n** (105 mg, 0.2 mmol) in methanol (50 mL) was treated with 10% Pd/C (58 mg) at 60 psi for 16 h. The catalyst was filtered and the filtrate was concentrated under reduced pressure to give a pale yellow foamy solid. This crude product was purified by flash column chromatography on silica gel with 4% ethanol/EtOAc to give the title compound (50 mg, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (m, 4H), 2.31 (s, 3H), 2.41 (m, 2H), 2.71 (m, 1H), 3.04 (m, 2H), 3.16 (s, 2H), 6.92 (d, J = 7.5 Hz, 1H), 7.20 (m, 4H), 7.40 (d, J = 9 Hz, 2H), 8.26 (m, 1H), 9.24 (br s, 1H); MS (DCI/NH_3) m/e 326 $(M + H)^+$; Anal. ($C_{19}H_{23}N_3O_2$) C, H, N.

2-(4-Thiazol-2-ylpiperidin-1-yl)-*N*-(*m*-tolyl)acetamide (5s): 2-(4-Thiazol-2-yl-3,6-dihydro-2*H*-pyridin-1-yl)-*N*-(*m*-tolyl)acetamide (12o) was prepared in the same manner as **5k** but with substitution of 4-(1,3-thiazol-2-yl)-3,6-dihydropyridine in place of 1′,2′,3′,4′,5′,6′-hexahydro-2′*H*-[2,4′-bipyridine] (**12d**) to provide the title compound as a yellow sticky residue (450 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.3 (s, 3H), 3.8 (m, 2H), 2.9 (m, 2H), 3.31 (s, 2H), 3.4 (m, 2H), 6.6 (m, 1H), 6.9 (m, 1H), 7.2 (m, 1H), 7.25 (d, J = 3 Hz, 1H), 7.4 (m, 2H), 7.8 (d, J = 3 Hz, 1H), 9.15 (br s, 1H); MS (DCI/NH_3) m/e 314 $(M + H)^+$. This product was hydrogenated under the same conditions as compound **4c** to provide the desired product 5s. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.8−1.95 (m, 2H), 2.0−2.15 (m, 2H), 2.22 (s, 3H), 2.25−2.35 (m, 2H), 2.85−2.98 (m, 2H), 3.0 (m, 1H), 3.15 (s, 2H), 6.82 (d, J = 9 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.45 (m, 2H), 7.6 (d, J = 3 Hz, 1H), 7.7 (d, J = 3 Hz, 1H), 9.6 (br s, 1H); MS (DCI/NH_3) m/e 316 $(M + H)^+$.

General Procedure for Compounds 6a−s (Method B).3-Methyl-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-

ylmethyl)benzamide (6b): (A) 1-Oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-carboxylic Acid *t*-Butyl Ester (13). 3′,4′,5′,6′-Tetrahydro-2′*H*-[2,4′-bipyridine]-1′-carboxylic acid *t*-butyl ester (8.9 g, 33.9 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C and treated with 77% *m*-chloroperbenzoic acid (10.5 g, 61.06 mmol, 1.8 equiv). The reaction mixture was stirred at 0 °C for 30 min and then at rt for 2 h; CH_2Cl_2 (50 mL) was added to the reaction mixture, which was washed with saturated $NaHCO_3$ and then with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was triturated with 5% CH_2Cl_2 in hexanes to give a white solid (6.57 g, 72%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41 (s, 9H), 1.42 (m, 2H), 1.90 (m, 2H), 2.83 (m, 2H), 3.45 (m, 1H), 4.09 (m, 2H), 7.30 (m, 2H), 7.40 (m, 1H), 8.26 (m, 1H).

(B) 1′,2′,3′,4′,5′,6′-Hexahydro-[2,4′-bipyridine] *N*-Oxide (14). Compound **13** (6.57 g) was dissolved in EtOAc (150 mL) and cooled to −78 °C. HCl gas was bubbled through the reaction mixture for 15 min. The reaction mixture was allowed to warm up to rt, upon which an off-white precipitate was formed. This precipitate was filtered, washed with EtOAc, and dried under high vaccum to give the hydrochloride salt of the desired product 1′,2′,3′,4′,5′,6′-hexahydro-[2,4′-bipyridine] *N*-oxide (5.04 g, 99% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.82 (m, 2H), 2.10 (m, 2H), 3.06 (m, 2H), 3.36 (m, 2H), 3.58 (m, 1H), 7.45 (m, 3H), 8.39 (d, J = 9 Hz, 1H), 9.04 (br s, 1H); MS (DCI-NH_3) *m*/*e* 179 (M + H) $^+$, 163 (M + H − 16)$^+$

(C) 3-Methyl-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6b). 2-Piperidin-4-ylpyridinium *N*-oxide hydrochloride (4.16 g, 16.4 mmol) in toluene/dioxane (60 mL/6 mL) was treated with powdered potassium carbonate (2.69 g, 19.37 mmol) at rt and stirred for 30 min. To this mixture were added 3-methylbenzamide (7.89 g, 58.4 mmol) and 37% aqueous formaldehyde (4.7 mL, 58 mmol). The reaction mixture was heated at 80 °C for 3 h, cooled to rt, and treated with additional portions of 3-methylbenzamide (2.63 g, 19.5 mmol) and 37% formaldehyde (1.57 mL, 19.5 mmol). The reaction mixture was stirred at 80 °C for 1 h, cooled, and concentrated under reduced pressure. Toluene was used to remove the water (2 × 75 mL). To the residue was added 3% methanol/CH_2Cl_2, and the inorganic salts were filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with 10% methanol/CH_2Cl_2 followed by 15% methanol/CH_2Cl_2 to provide the title compound as a solid (4.53 g, 85% yield). mp 177−180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 2H), 1.89 (m, 2H), 2.33 (m, 2H), 2.38 (s, 3H), 2.96 (m, 2H), 3.19 (m, 1H), 4.17 (d, J = 6 Hz, 2H), 7.31 (m, 5H), 7.69 (m, 2H), 8.23 (m, 1H), 8.71 (m, 1H); MS (DCI/NH_3) *m*/*e* 310 (M + H − 16)$^+$; Anal. ($C_{19}H_{23}N_3O_2$) C, H, N.

***N*-(1-Oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6a)** waspPrepared in the same manner as compound **6b** but with substitution of benzamide in place of 3-methylbenzamide (27 mg, 30% yield). ^{1}H NMR (300 MHz, CD_3-OD) δ 1.71 (dd, J = 12.4 and 3.6 Hz, 2H), 2.04 (m, 2H), 2.54 (m, 2H), 3.12 (m, 3H), 3.37 (s, 2H), 7.46 (m, 5H), 7.87 (m, 3H), 8.33 (d, J = 6.4 Hz, 1H); MS (ESI) *m*/*e* 312 (M + H)$^+$; Anal. ($C_{18}H_{21}N_3O_2$.2.0 H_2O) C, H, N.

***N*-(1-Oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)-3-vinylbenzamide (6c)** was prepared in the same manner as compound **6b** but with substitution of 3-vinylbenzamide in place of 3-methylbenzamide (84 mg, 67% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 1.75 (dd, J = 12.6 and 3.7 Hz, 2H), 2.10 (d, J = 12.6 Hz, 2H), 2.63 (m, 2H), 3.21 (m, 2H), 3.46 (m, 1H), 4.38 (s, 2H), 5.34 (d, J = 11.2 Hz, 1H), 5.90 (d, J = 17.3 Hz, 1H), 6.81 (dd, J = 17.6 and 10.9 Hz, 1H), 7.50 (m, 5H), 7.76 (d, J = 7.5 Hz, 1H), 7.95 (s, 1H), 8.33 (d, J = 6.4 Hz, 1H), MS (ESI) *m*/*e* 338 (M + H)$^+$. HRMS Calcd for $C_{20}H_{23}N_3O_2Na$: 360.4503. Found: 360.1682.

3-Ethoxy-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6d) was prepared in the same manner as compound **6b** but with substitution of 3-ethoxybenzamide in place of 3-methylbenzamide (65 mg, 47% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (t, J = 7.5 Hz, 3H), 1.52 (m, 2H), 1.89 (d, J = 12 Hz, 2H), 2.36 (t, J = 12 Hz, 2H), 2.95 (d, J = 12 Hz, 2H), 3.20 (m, 1H), 4.08 (q, J = 6 Hz, 2H), 4.18 (d, J = 6 Hz, 2H), 7.08 (m, 1H), 7.27 (m, 2H), 7.39 (m, 4H), 8.23 (dd, J = 6 and 1.5 Hz, 1H), 8.72 (t, J = 6 Hz, 1H); MS (DCI/NH_3) *m*/*e* 340 (M + H − 16)$^+$; 356 (M + H)$^+$; Anal. ($C_{20}H_{25}N_3O_3$·0.75H_2O) C, H, N.

3-Cyano-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6e) was prepared in the same manner as compound **6b** but with substitution of 3-cyanobenzamide in place of 3-methylbenzamide (55 mg, 55% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 1.73 (dd, J = 12.5 and 3.6 Hz, 2H), 2.11 (m, 2H), 2.69 (d, J = 2.0 Hz, 2H), 3.27 (m, 2H), 3.46 (m, 1H), 4.43 (s, 2H), 7.41 (d, J = 2.4 Hz, 1H), 7.56 (m, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.24 (s, 1H), 8.34 (d, J = 6.4 Hz, 1H), MS (ESI) *m*/*e* 337 (M + H)$^+$. HRMS Calcd for $C_{19}H_{20}N_4O_2Na$: 359.14843. Found: 359.1478.

3-Chloro-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6f) was prepared in the same manner as compound **6b** but with substitution of 4-chloro-3-methylbenzamide in place of 3-methylbenzamide (60 mg, 56% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (m, 6H), 2.51 (m, 2H), 2.73 (m, 1H), 2.88 (s, 3H), 4.80 (s, 2H), 7.34 (m, 1H), 7.52 (m, 2H), 7.71 (m, 2H), 7.90 (m, 2H), 9.21 (br s, 1H); MS (ESI) *m*/*e* 360 (M + H)$^+$; Anal. ($C_{19}H_{22}ClN_3O_2$·1.0$C_2HF_3O_2$) C, H, N.

3-Fluoro-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6g) was prepared in the same manner as compound **6b** but with substitution of 4-fluoro-3-methylbenzamide for 3-methylbenzamide (82 mg, 82.8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 2H), 1.89 (d, J = 12 Hz, 2H), 2.29 (s, 3H), 2.36 (t, J = 12 Hz, 2H), 2.95 (d, J = 12 Hz, 2H), 3.19 (m, 1H), 4.17 (d, J = 6 Hz, 2H), 7.27 (m, 3H), 7.39 (dd, J = 7.5 and 1.5 Hz, 1H), 7.75 (m, 1H), 7.85 (dd, 7.5 and 1.5 Hz, 1H), 8.23 (dd, J = 6 and 1.5 Hz, 1H), 8.72 (t, J = 6 Hz, 1H); MS (DCI/NH_3) *m*/*e* 328 (M + H − 16)$^+$; 344 (M + H)$^+$; Anal. ($C_{19}H_{22}N_3FO_2$) C, H, N.

3-Chloro-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)-4-trifluoromethylbenzamide (6h) was prepared in the same manner as compound **6b** but with substitution of 3-chloro-4-trifluoromethoxybenzamide in place of 3-methylbenzamide (98 mg, 62% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 2H), 1.89 (d, J = 12 Hz, 2H), 2.36 (t, J = 12 Hz, 2H), 2.95 (d, J = 12 Hz, 2H), 3.20 (m, 1H), 4.18 (d, J = 6 Hz, 2H), 7.27 (m, 3H), 7.39 (dd, J = 7.5 and 1.5 Hz, 1H), 7.75 (m, 1H), 7.85 (dd, 7.5 and 1.5 Hz, 1H), 8.23 (dd, J = 6 and 1.5 Hz, 1H), 8.72 (t, J = 6 Hz, 1H); MS (DCI/NH_3) *m*/ *e* 414 (M + H − 16)$^+$; 430 (M + H)$^+$; Anal. ($C_{19}H_{19}ClF_3O_3$) C, H, N.

3,5-Dichloro-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6i) was prepared in the same manner as compound **6b** but with substitution of 3,5-dichlorobenzamide in place of 3-methylbenzamide (46 mg, 33.3% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ1.52 (m, 2H), 1.89 (d, J = 12 Hz, 2H), 2.36 (t, J = 12 Hz, 2H), 2.95 (d, J = 12 Hz, 2H), 3.20 (m, 1H), 4.18 (d, J = 6 Hz, 2H), 7.29 (m, 2H), 7.39 (m, 1H), 7.83 (t, J = 1.5 Hz, 1H), 7.92 (d, J = 1.5 Hz, 2H), 8.23 (dd, J = 6 and 1.5 Hz, 1H), 8.98 (t, J = 6 Hz, 1H); MS (DCI/NH_3) *m*/*e* 365 (M + H − 16)$^+$; 381 (M + H)$^+$; Anal. ($C_{18}H_{19}Cl_2N_3O_2$) C, H, N.

4-Methyl-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)-3-trifluoromethylbenzamide (6j) was prepared in the same manner as compound **6b** but with substitution of 3-trifluoromethyl-4-methylbenzamide in place of 3-methylbenzamide (75 mg, 66.3% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 2H), 1.89 (d, J = 12 Hz, 2H), 2.36 (t, J = 12 Hz, 2H), 2.95 (d, J = 12 Hz, 2H), 3.20 (m, 1H), 3.25 (s, 3H), 4.18 (d, J = 6 Hz, 2H), 7.29 (m, 2H), 7.39 (m, 1H), 7.58 (d, J = 9 Hz, 1H), 8.08 (d, J = 9 Hz, 1H), 8.19 (s, 1H), 8.23 (dd, J = 6 and 1.5 Hz, 1H), 8.98 (t, J = 6 Hz, 1H); MS (DCI/NH_3) *m*/*e* 378 (M + H − 16)$^+$; 394 (M + H)$^+$; Anal. ($C_{20}H_{22}F_3N_3O_2$·0.3H_2O) C, H, N.

3,4-Dimethyl-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6k) was prepared in the same manner as compound **6b** but with substitution of 3,4-dimethylbenzamide in place of 3-methylbenzamide (85 mg, 89% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ1.52 (m, 2H), 1.89 (d, J = 12 Hz, 2H), 2.28 (s, 6H), 2.36 (m, 2H), 2.95 (d, J = 12 Hz, 2H), 3.20 (m,

1H), 4.18 (d, $J = 6$ Hz, 2H), 7.21 (d, $J = 9$ Hz, 1H), 7.29 (m, 2H), 7.39 (m, 1H), 7.62 (d, $J = 9$ Hz, 1H), 7.68 (s, 1H), 8.23 (dd, $J =$ 6 and 1.5 Hz, 1H), 8.64 (t, $J = 6$ Hz, 1H); MS (DCI/NH_3) *m/e* 324 $(M + H - 16)^+$; 340 $(M + H)^+$; Anal. ($C_{20}H_{25}N_3O_2 \cdot 0.3H_2O$) C, H, N.

3-Chloro-4-fluoro-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6l) was prepared in the same manner as compound **6b** but with substitution of 3-chloro-4-fluorobenzamide in place of 3-methylbenzamide (85 mg, 89% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 2H), 1.89 (d, J = 12 Hz, 2H), 2.36 (m, 2H), 2.95 (d, $J = 12$ Hz, 2H), 3.20 (m, 1H), 4.18 (d, $J = 6$ Hz, 2H), 7.24 (m, 2H), 7.39 (dd, $J = 6$ and 1.5 Hz, 1H), 7.53 (t, $J = 9$ Hz, 1H), 7.93 (m, 1H), 8.13 (dd, $J = 6$ and 1.5 Hz, 1H), 8.23 (dd, $J = 6$ and 1.5 Hz, 1H), 8.90 (t, $J = 6$ Hz, 1H); MS (DCI/ NH_3) *m/e* 348 $(M + H - 16)^+$; 364 $(M + H)^+$; Anal. ($C_{18}H_{19}N_3O_2ClF \cdot 0.8H_2O$) C, H, N.

3,5-Dimethyl-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6m) was prepared in the same manner as compound **6b** but with substitution of 3,5-dimethylbenzamide in place of 3-methylbenzamide (140 mg, 60% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 1.76 (dd, $J = 12.4$ and 3.6 Hz, 2H), 2.11 (d, $J = 12.6$ Hz, 2H), 2.36 (s, 6H), 2.66 (m, 2H), 3.23 (d, J = 12.2 Hz, 2H), 3.47 (m, 1H), 4.38 (s, 2H), 7.22 (s, 1H), 7.41 (m, 1H), 7.52 (m, 2H), 7.56 (m, 2H), 8.34 (d, $J = 6.4$ Hz, 1H); MS (ESI) *m/e* 340 $(M + H)^+$. HRMS Calcd for $C_{20}H_{25}N_3O_2Na$: 362.1844. Found: 362.1839

3-Methoxy-2-methyl-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6n): 3-Methoxy-2-methylbenzamide. A reaction mixture containing 3-methoxy-2-methylbenzoic acid (2 g, 12.04 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.76 g, 14.4 mmol), and 1-hydroxybenzotriazole hydrate (1.95 g, 14.4 mmol) in chloroform was stirred at rt for 1 h. The reaction was quenched with 30% ammonium hydroxide solution (35 mL), and stirring was continued for another 1.5 h. The layers were separated, and the organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to afford a white powder (1.2 g, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.3 (s, 3H), 3.82 (s, 3H), 6.9 (d, J = 9 Hz, 1H), 7.02 (d, $J = 9$ Hz, 1H), 7.18 (t, $J = 9$ Hz, 1H); MS (DCI/NH_3) *m/e* 166 $(M + H)^+$.

Compound **6n** was prepared in the same manner as compound **6b** but with substitution of 3-methoxy-2-methylbenzamide in place of 3-methylbenzamide (45 mg, 16% yield; white solid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45−1.55 (m, 2H), 2.05−2.15 (m, 2H), 2.25 (s, 3H), 2.55−2.65 (m, 2H), 3.05−3.10 (m, 2H), 3.40−3.50 (m, 1H), 3.81 (s, 3H), 4.40 (d, $J = 6$ Hz, 2H), 6.4 (br s, 1H), 6.85 (d, $J = 9$ Hz, 1H), 7.0 (d, $J = 9$ Hz, 1H), 7.10−7.20 (m, 2H), 7.25−7.32 (m, 2H), 8.20 (d, $J = 6$ Hz, 1H); MS (DCI/NH_3) *m/e* 356 $(M + H)^+$; Anal. ($C_{20}H_{25}N_3O_3$) C, H, N.

3-Methoxy-4-chloro-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide (6o) was prepared in the same manner as compound **6b** but with substitution of 4-chloro-3-methoxybenzamide in place of 3-methylbenzamide (75 mg, 17% yield; yellow solid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6−1.68 (m, 2H), 2.05−2.20 (m, 2H), 2.50−2.65 (m, 2H), 3.05−3.20 (m, 2H), 3.42−3.55 (m, 1H), 3.98 (s, 3H), 4.40 (d, $J = 6$ Hz, 2H), 6.65 (br s, 1H), 7.15 (m, 1H), 7.2−7.35 (m, 3H), 7.40 (d, $J = 9$ Hz, 1H), 7.45 (d, $J = 3$ Hz, 1H), 8.22 (d, $J = 6$ Hz, 1H); MS (DCI/NH_3) *m/e* 376 $(M + H)^+$; Anal. ($C_{19}H_{22}ClN_3O_3$) C, H, N.

Naphthalene-2-carboxylic Acid (1-Oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)amide (6p) was prepared in the same manner as compound **6b** but with substitution of 2-naphthoylamide in place of 3-methylbenzamide (75 mg, 56% yield; white solid). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (q, $J = 12.2$ Hz, 1H), 1.57 (q, $J = 11.9$ Hz, 1H), 1.92 (d, $J = 11.2$ Hz, 2H), 2.41 (t, $J = 11.2$ Hz, 2H), 3.02 (d, $J = 11.5$ Hz, 2H), 3.25 (m, J = 12.9 Hz, 1H), 4.24 (d, $J = 5.8$ Hz, 2H), 7.30 (m, 2H), 7.40 (dd, $J = 7.5$ and 2.4 Hz, 1H), 7.62 (m, 2H), 8.01 (m, 4H), 8.24 (d, $J =$ 5.8 Hz, 1H), 8.51 (s, 1H), 8.97 (s, 1H); MS (DCI/ NH_3) *m/e* 362 $(M + H)^+$; Anal. ($C_{22}H_{23}N_3O_2 \cdot 0.2CH_2Cl_2 \cdot 1.2H_2O$) C, H, N.

6-Chloro-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)nicotinamide (6q) was prepared in the same manner as compound **6b** but with substitution of 6-chloronicotinamide in place of 3-methylbenzamide (20 mg, 25% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 2H), 1.89 (d, $J = 12$ Hz, 2H), 2.36 (m, 2H), 2.98 (d, $J = 12$ Hz, 2H), 3.22 (m, 1H), 4.19 (d, $J = 6$ Hz, 2H), 7.29 (m, 2H), 7.30 (dd, $J = 6$ and 1.5 Hz, 1H), 7.65 (d, $J =$ 9 Hz, 1H), 8.26 (m, 2H), 8.88 (d, $J = 3$ Hz, 1H), 9.02 (t, $J = 6$ Hz, 1H); MS (DCI/NH_3) *m/e* 331 $(M + H - 16)^+$; Anal. ($C_{17}H_{19}N_4O_2Cl \cdot 0.4H_2O$) C, H, N.

Pyridine-2-carboxylic Acid (1-Oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)amide (6r) was prepared in the same manner as compound **6b** but with substitution of pyridine-2-carboxylic acid amide in place of 3-methylbenzamide (51 mg, 57% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 2H), 1.89 (d, J = 12 Hz, 2H), 2.36 (m, 2H), 2.98 (d, $J = 12$ Hz, 2H), 3.18 (m, 1H), 4.22 (d, $J = 6$ Hz, 2H), 7.27 (m, 2H), 7.28 (dd, $J = 6$ and 1.5 Hz, 1H), 7.63 (m, 1H), 8.03 (m, 1H), 8.22 (dd, $J = 6$ and 1.5 Hz, 1H), 8.23 (dd, $J = 6$ and 1.5 Hz, 1H), 8.68 (dd, $J = 6$ and 1.5 Hz, 1H), 9.02 (t, $J = 6$ Hz, 1H); MS (DCI/NH_3) *m/e* 297 $(M + H - 16)^+$; 313 $(M + H)^+$; Anal. ($C_{17}H_{20}N_4O_2 \cdot 0.3H_2O$) C, H, N.

Thiazole-2-carboxylic Acid (1-Oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)amide (6s) was prepared in the same manner as compound **6b** but with substitution of thiophene-2-carboxylic acid amide in place of 3-methylbenzamide (100 mg, 56.6% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 2H), 1.89 (d, $J = 12$ Hz, 2H), 2.36 (m, 2H), 2.98 (d, $J = 12$ Hz, 2H), 3.18 (m, 1H), 4.12 (d, $J = 6$ Hz, 2H), 7.18 (dd, $J = 4.5$ and 3.0, 1H), 7.28 (m, 2H), 7.39 (dd, $J = 9.0$ and 3 Hz, 1H), 7.78 (dd, $J = 4.5$ and 1.5 Hz, 1H), 7.85 (dd, $J = 4.5$ and 1.5 Hz, 1H), 8.22 (dd, $J =$ 6 and 1.5 Hz, 1H), 8.79 (t, $J = 6$ Hz, 1H); MS (DCI/NH_3) *m/e* 297 $(M + H - 16)^+$; 313 $(M + H)^+$. HRMS Calcd for $C_{16}H_{19}N_3O_2SNa$: 340.1096 $(M + H)^+$. Found: 340.1090

General Procedure for Compounds 7a−z: 2-(1-Oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)-*N*-(*m*-tolyl)acetamide (7a). A mixture of 2-bromo-*N*-(*m*-tolyl)acetamide (8.903 g, 39.03 mmol), and 1′,2′,3′,4′,5′,6′-hexahydro-[2,4′-bipyridine] *N*-oxide (8.38 g, 39.03 mmol) and K_2CO_3 (10.78 g, 78.06 mmol) in DMF (100 mL) was stirred at rt for 20 h. The reaction mixture was checked by TLC. Both starting materials were present along with the product; therefore, the reaction mixture was heated at 40 °C for 4 h. TLC still showed starting materials 1 and 2, but to avoid any side reactions due to prolonged heating, the reaction mixture was worked up. DMF was removed on the rotary evaporator. The residue was extracted between brine and EtOAc. The aqueous layer was extracted with EtOAc (3 × 200 mL). Combined organics were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography with 4% MeOH in CH_2Cl_2 to give the desired product as an off-white solid (8.065 g, 63.5%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.80 (m, 2H), 1.91 (m, 2H), 2.30 (m, 5H), 2.99 (m, 2H), 3.14 (s, 2H), 3.25 (m, 1H), 6.88 (d, $J = 7.5$ Hz, 1H), 7.19 (t, $J = 7.5$ Hz, 1H), 7.31 (m, 2H), 7.45 (m, 2H), 8.24 (m, 1H), 9.6 (br s, 1H); MS (DCI-NH_3) *m/e* 310 $(M + H - 16)^+$; 326 $(M + H)^+$. Anal. ($C_{19}H_{23}N_3O_2$) C, H, N.

2-(1-Oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)-*N*-(3-trifluoromethylphenyl)acetamide (7b) was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3-trifluoromethylphenyl)acetamide in place of 2-bromo-*N*-(3-tolyl)acetamide (191 mg, 17% yield). This material was converted to the maleate salt: ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (br d, J = 6.5 Hz, 1H), 8.08 (br s, 1H), 7.77 (br d, $J = 8.1$ Hz, 1H), 7.65−7.44 (m, 5H), 6.26 (s, 2H), 4.12 (s, 2H), 3.77 (br d, $J = 11.9$ Hz, 2H), 3.69 (ddd, $J = 12.2$, 3.4, and 3.4 Hz, 1H), 3.30 (m, 2H), 2.35 (br d, $J = 13.9$ Hz, 2H), 2.10 (m, 2H); MS (ESI) *m/e* 380 $(M + H)^+$; Anal. ($C_{19}H_{20}F_3N_3O_2 \cdot 1.2C_4H_4O_4 \cdot 0.1H_2O$) C, H, N.

***N*-(3-Fluorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7c)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3-fluorophenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (157 mg, 68% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68 (m, 2H), 1.92 (d, $J = 5.8$ Hz, 2H), 2.30 (m, 2H), 3.01 (m, 2H), 3.19 (s, 2H), 3.25

(m, 1H), 6.89 (m, 1H), 7.35 (m, 3H), 7.42 (m, 2H), 7.68 (m, 1H), 8.26 (d, $J = 4.5$ Hz, 1H), 9.91 (s, 1H); MS (DCI/NH_3) *m/e* 330 (M + H)$^+$. Maleate salt (190 mg): Anal. ($C_{18}H_{20}N_3O_2F \cdot 1.0C_4H_4O_4 \cdot 0.2H_2O$) C, H, N.

***N*-(4-Fluorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7d)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(4-fluorophenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (245 mg, 45% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68 (m, 2H), 1.92 (d, $J = 5.8$ Hz, 2H), 2.30 (m, 2H), 3.01 (m, 2H), 3.19 (s, 2H), 3.25 (m, 1H), 6.89 (m, 1H), 7.35 (m, 3H), 7.42 (m, 2H), 7.68 (m, 1H), 8.26 (d, $J = 4.5$ Hz, 1H), 9.91 (s, 1H); MS (DCI/NH_3) *m/e* 314 (M + H − 16)$^+$; 330 (M + H)$^+$. Maleate salt (190 mg): Anal. ($C_{18}H_{20}N_3O_2F \cdot 1.0C_4H_4O_4 \cdot 1.1H_2O$) C, H, N.

***N*-(2-Fluorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7e)** was pPrepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(2-fluorophenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (126 mg, 54% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68 (m, 2H), 1.92 (d, $J = 6$ Hz, 2H), 2.30 (m, 2H), 3.01 (m, 2H), 3.19 (s, 2H), 3.25 (m, 1H), 7.15 (m, 1H), 7.30 (m, 3H), 7.42 (m, 2H), 7.68 (m, 1H), 8.26 (d, $J = 4.5$ Hz, 1H), 9.81 (s, 1H); MS (DCI/NH_3) *m/e* 314 (M + H − 16)$^+$; 330 (M + H)$^+$. Maleate salt (190 mg): Anal. ($C_{18}H_{20}N_3O_2F \cdot 1.0C_4H_4O_4 \cdot 0.2H_2O$) C, H, N.

***N*-(3-Chlorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7f)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3-chlorophenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (226 mg, 66% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68 (m, 2H), 1.92 (d, $J = 5.7$ Hz, 2H), 2.30 (m, 2H), 3.01 (m, 2H), 3.19 (s, 2H), 3.25 (m, 1H), 6.89 (m, 1H), 7.35 (m, 3H), 7.42 (m, 2H), 7.68 (m, 1H), 8.26 (d, $J = 4.5$ Hz, 1H), 9.91 (s, 1H); MS (DCI/NH_3), *m/e* 330 (M + H − 16)$^+$, 346 (M + H)$^+$. Maleate salt (294 mg): Anal. ($C_{18}H_{20}N_3O_2Cl \cdot 1.0C_4H_4O_4 \cdot 0.2H_2O$) C, H, N.

***N*-(3-Isopropoxyphenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7g)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3-isopropoxyphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)-acetamide (74 mg, 52.8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (d, $J = 6$ Hz, 6H), 1.70 (m, 2H), 1.91 (m, 2H), 2.30 (m, 2H), 3.01 (m, 2H), 3.15 (m, 1H), 3.31 (m, 1H), 4.55 (m, 1H), 6.62 (m, 1H), 7.16 (m, 2H), 7.30 (m, 3H), 7.45 (m, 1H), 8.15 (dd, $J =$ 6 and 1.5 Hz, 1H), 9.65 (s, 1H); MS (DCI/NH_3) *m/e* 354 (M + H − 16)$^+$; 370 (M + H)$^+$; Anal. ($C_{21}H_{27}N_3O_3 \cdot 0.4H_2O$) C, H, N.

***N*-(3-Trifluoromethoxyphenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7h)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3-trifluoromethoxyphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (176 mg, 77% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68 (q, $J = 11.9$ Hz, 1H), 1.69 (q, $J =$ 12.4 Hz, 1H), 1.91 (d, $J = 11.9$ Hz, 2H), 2.31 (t, $J = 11.5$ Hz, 2H), 3.00 (d, $J = 11.5$ Hz, 2H), 3.19 (s, 2H), 3.28 (m, 1H), 7.05 (m, $J = 8.3$, 2.4, 1.0, and 0.9 Hz, 1H), 7.31 (m, 2H), 7.44 (m, 2H), 7.62 (ddd, $J = 8.2$, 2.0, and 1.0 Hz, 1H), 7.85 (s, 1H), 8.26 (d, J = 5.8 Hz, 1H), 10.01 (s, 1H); MS (DCI/NH_3) *m/e* 396 (M + H)$^+$; Anal. ($C_{19}H_{20}F_3N_3O_3 \cdot 0.4H_2O$) C, H, N.

***N*-(3-Methylsulfanylphenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7i)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3-thiomethylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)-acetamide (17 mg, 21% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.60−1.78 (m, 2H), 1.63−1.95 (m, 2H), 2.12−2.18 (m, 2H), 2.70 (s, 3H), 2.9−3.12 (m, 2H), 3.22−3.30 (m, 3H), 6.9−7.0 (m, 1H), 7.2−7.3 (m, 2H), 7.3−7.35 (m, 2H), 7.62 (t, $J = 3$ Hz, 1H), 7.8 (s, 1H), 8.23−8.27 (m, 1H), 9.75 (s, 1H); MS (DCI/NH_3) *m/e* 358 (M + H)$^+$.

***N*-(3-Ethylphenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7j)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3-ethylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (38 mg, 26% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, $J = 7.6$ Hz, 3H), 1.70 (m, 8H), 2.64 (m, 3H), 4.26 (s, 2H), 6.91 (s, 1H), 7.25 (m, 3H), 7.42 (m, 2H), 7.60 (m, 1H), 8.28 (d, $J = 6.1$ Hz, 1H); MS (ESI) *m/e* 340 (M + H)$^+$. HRMS Calcd for $C_{20}H_{25}N_3O_2$: 340.4314 (M + H)$^+$. Found: 340.2020.

***N*-(Biphenyl-3-yl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7k)** was prepared in the same manner as compound **7a** but with substitution of *N*-(biphenyl-3-yl)-2-bromoacetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (38.5 mg, 26% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (m, 2H), 2.09 (m, 2H), 2.55 (m, 2H), 3.08 (m, 2H), 3.22 (s, 2H), 3.48 (m, 1H), 7.19 (m, 4H), 7.39 (m, 3H), 7.61 (m, 5H), 8.28 (d, $J = 6.10$ Hz, 1H) 9.21 (s, 1H); MS (ESI) *m/e* 390 (M + H)$^+$; Anal. ($C_{24}H_{25}N_3O_2$) C, H, N.

***N*-(3,5-Dichlorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7l)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3,5-dichlorophenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (36 mg, 34% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71 (m, 2H), 1.92 (m, 2H), 2.30 (m, 2H), 2.98 (m, 2H), 3.19 (s, 2H), 3.25 (m, 1H), 7.30 (m, 2H), 7.42 (m, 1H), 7.80 (d, $J = 3$ Hz, 2H), 8.26 (d, $J = 4.5$, 1H), 10.05 (s, 1H); MS (DCI/NH_3) *m/e* 365 (M + H − 16)$^+$; 381 (M + H)$^+$; Anal. calcd for acetate salt ($C_{18}H_{19}Cl_2N_3O_2 \cdot 1.0C_2H_4O_2$) C, H, N.

***N*-(2,3-Dichlorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7m)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(2,3-dichlorophenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (25 mg, 22% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71 (m, 2H), 1.99 (m, 2H), 2.43 (m, 2H), 3.03 (m, 2H), 3.25 (s, 2H), 3.35 (m, 1H), 7.38 (m, 5H), 8.26 (dd, $J = 4.5$ and 1.5 Hz, 2H), 10.15 (s, 1H). MS (DCI/NH_3) *m/e* 365 (M + H − 16)$^+$; 381 (M + H)$^+$. Anal. calcd for acetate salt ($C_{18}H_{19}Cl_2N_3O_2 \cdot 1.0C_2H_4O_2$) C, H, N.

***N*-(2-Methoxy-6-methylphenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7n)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(2-methoxy-6-methylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (45 mg, 44% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71 (m, 2H), 1.99 (m, 4H), 2.15 (m, 3H), 2.30 (m, 2H), 3.10 (m, 1H), 3.15 (s, 2H), 3.75 (s, 3H), 6.86 (dd, $J = 9$ and 1.5 Hz, 2H), 7.16 (t, $J = 9$ Hz, 1H), 7.30 (m, 2H), 7.45 (m, 1H), 8.26 (dd, $J = 4.5$ and 1.5 Hz, 1H), 8.95 (s, 1H); MS (DCI/NH_3) *m/e* 340 (M + H − 16)$^+$; 356 (M + H)$^+$. Acetate salt was obtained after purification. HRMS Calcd for $C_{20}H_{26}N_3O_3$: 356.4308 (M + H)$^+$. Found: 356.1969.

***N*-(3,5-Dimethylphenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7o)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(3,5-dimethylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (38 mg, 26% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (d, $J = 3.39$ Hz, 2H), 2.05 (d, $J = 12.55$ Hz, 2H), 2.28 (s, 6H), 2.43 (m, 2H), 3.11 (m, 3H), 3.21 (s, 2H), 6.78 (s, 1H), 7.21 (s, 2H), 7.41 (m, 2H), 7.60 (d, $J = 4.07$ Hz, 1H), 8.34 (d, $J = 6.44$ Hz, 1H); MS (ESI) *m/e* 340 (M + H)$^+$. HRMS Calcd for $C_{20}H_{25}N_3O_2$: 340.1947 (M + H)$^+$. Found: 340.2020.

***N*-(2-Methyl-4-bromophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7p)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(4-bromo-2-methylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (25 mg, 60% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.67 (ddd, $J = 24.6$, 12.2, and 3.6 Hz, 2H), 1.96 (d, $J = 12.5$ Hz, 2H), 2.25 (s, 3H), 2.37 (t, $J = 11.7$ Hz, 2H), 3.04 (d, $J = 11.5$ Hz, 2H), 3.18 (s, 2H), 3.26 (m, 1H), 7.37 (m, 5H), 7.76 (d, $J = 8.8$ Hz, 1H), 8.26 (m, 1H), 9.46 (s, 1H); MS (DCI/NH_3) *m/e* 404/406 (M + H)$^+$; Anal. ($C_{19}H_{22}BrN_3O_2 \cdot 0.1K_2CO_3$) C, H, N.

***N*-(3-Methyl-4-fluorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7q)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(4-bromo-2-methylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (139 mg, 57% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68 (m, 2H), 1.92 (d, $J = 5.8$ Hz, 2H), 2.22 (s, 3H), 2.46 (m, 2H), 3.04 (m, 2H), 3.25 (s, 3H), 7.03 (t, $J = 6$ Hz, 1H), 7.35

(m, 2H), 7.44 (dd, J = 4.5 and 1.5 Hz, 1H), 7.48 (m, 1H), 7.54 (dd, J = 4.5 and 1.5 Hz, 1H), 8.26 (d, J = 4.5 Hz, 1H), 9.79 (s, 1H); MS (DCI/NH_3) m/e 328 $(M + H - 16)^+$; 344 $(M + H)^+$. Maleate salt (171 mg): Anal. ($C_{19}H_{22}N_3O_2F \cdot 1.0C_4H_4O_4$) C, H, N.

***N*-(2-Methyl-4-fluorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7r)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(2-methyl-4-fluorophenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68 (m, 2H), 1.92 (d, J = 5.8 Hz, 2H), 2.24 (s, 3H), 2.36 (m, 2H), 3.04 (d, J = 11.5 Hz, 2H), 3.17 (s, 2H), 3.29 (m, 2H), 7.03 (m, 1H), 7.11 (dd, J = 9.7 and 2.9 Hz, 1H), 7.35 (m, 2H), 7.67 (dd, J = 8.8 and 5.8 Hz, 1H), 8.26 (m, 1H), 9.40 (s, 1H); MS (DCI/NH_3) m/e 328 $(M + H - 16)^+$; 344 $(M + H)^+$. Maleate salt (856 mg): Anal. ($C_{19}H_{22}N_3O_2F \cdot 1.0C_4H_4O_4 \cdot 0.75H_2O$) C, H, N.

***N*-(2-Methyl-5-nitrophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7s)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(2-nitro-5-methylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (75% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (q, J = 11.9 Hz, 1H), 1.71 (q, J = 12.4 Hz, 1H), 2.21 (d, J = 13.2 Hz, 2H), 2.40 (s, 3H), 2.62 (t, J = 11.9 Hz, 2H), 3.11 (d, J = 11.9 Hz, 2H), 3.28 (s, 2H), 3.55 (tt, J = 12.0 and 3.4 Hz, 1H), 7.19 (ddd, J = 12.9, 6.4, and 2.7 Hz, 1H), 7.31 (m, 2H), 7.91 (dd, J = 8.1 and 2.4 Hz, 1H), 8.28 (d, J = 6.4 Hz, 1H), 9.08 (d, J = 2.4 Hz, 1H), 9.55 (s, 1H); MS (DCI/NH_3) m/e 371 $(M + H)^+$; Anal. ($C_{19}H_{22}N_4O_4 \cdot 1.1H_2O$) C, H, N.

***N*-(2,6-Dimethylphenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7t)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(2,6-dimethylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (27 mg, 8% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 1.88 (dd, J = 12.4 and 3.6 Hz, 2H), 2.07 (m, 2H), 2.22 (s, 6H), 2.50 (m, 2H), 3.11 (m, 3H) 3.21 (s, 2H), 7.10 (m, 1H), 7.42 (m, 2H), 7.58 (m, 1H), 7.86 (m, 1H), 7.93 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 6.4 Hz, 1H); MS (ESI) m/e 354 $(M + H)^+$. Anal. ($C_{20}H_{25}N_3O_2$) C, H, N.

***N*-(3-Methyl-2,6-dichlorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7u)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(2,6-dichloro-3-methylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (86 mg, 64% yield; off-white solid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (q, J = 12.4 Hz, 1H), 1.73 (q, J = 12.3 Hz, 1H), 2.17 (d, J = 12.9 Hz, 2H), 2.39 (s, 3H), 2.56 (t, J = 11.9 Hz, 2H), 3.25 (d, J = 12.2 Hz, 2H), 3.27 (s, 2H), 3.58 (t, J = 12.2 and 3.3 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 7.17 (m, 4H), 8.27 (d, J = 6.4 Hz, 1H), 9.03 (s, 1H); MS (DCI/NH_3) m/e 394 $(M + H)^+$; Anal. ($C_{19}H_{21}Cl_2N_3O_2 \cdot 1.3H_2O$) C, H, N.

***N*-(2-Methyl-5-chlorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7v)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(5-chloro-2-methylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (15 mg, 13% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68−1.73 (m, 2H), 2.15−2.22 (m, 2H), 2.25 (s, 3H), 2.6 (t, J = 12 Hz, 2H), 3.05−3.18 (m, 2H), 3.22 (s, 2H), 3.50−3.60 (m, 1H), 7.05 (dd, J = 6 and 3 Hz, 1H), 7.10 (d, J = 9 Hz, 1H), 7.18−7.2 (m, 1H), 7.22−7.28 (m, 2H), 8.22 (d, J = 6 Hz, 2H), 9.38 (br s, 1H); MS (DCI/NH_3) m/e 360 $(M + H)^+$; Anal. ($C_{19}H_{22}ClN_3O_2 \cdot 0.5H_2O$) C, H, N.

***N*-(2,4-Difluorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7w)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(2,4-difluorophenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (1100 mg, 86% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50−1.80 (m, 2H), 1.84−2.02 (m, 2H), 2.20−2.45 (m, 2H), 2.92−3.10 (m, 2H), 3.23−3.39 (m, 3H), 6.94−7.17 (m, 1H), 7.23−7.53 (m, 4H), 7.78−8.01 (m, 1H), 8.16−8.44 (m, 1H), 9.52−9.69 (m, 1H). MS (DCI/NH_3) m/e 332 $(M + H - 16)^+$; 348 $(M + H)^+$; Anal. ($C_{18}H_{19}N_3O_2F_2$) C, H, N.

***N*-(2-trifluoromethyl-4-fluorophenyl)-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2, 4′-bipyridine]-1′-yl)acetamide (7x)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-(4-fluoro-2-trifluoromethylphenyl)acetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (120 mg, 14% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 1.80 (m, 2H), 2.10 (br d, 2H, 12.5), 2.53 (ddd, J = 12.2, 12.2, and 2.4 Hz, 2H), 3.12 (br d, J = 11.5 Hz, 2H), 3.26 (s, 2H), 3.50 (dddd, J = 12.6, 12.6, 4.1, and 4.1 Hz, 1H), 7.42 (m, 2H), 7.53 (ddd, J = 8.1, 8.1, and 2.4 Hz, 2H), 7.61 (ddd, J = 8.5, 8.5, and 1.4 Hz, 1H), 8.15 (dd, J = 8.8 and 4.7 Hz, 1H), 8.35 (dd, J = 6.1 and 1.0 Hz, 1H). MS (DCI/NH_3) m/e 398 $(M + H)^+$; Anal. ($C_{19}H_{19}F_4N_3O_2$) C, H, N.

***N*-Cyclohexyl-2-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-yl)acetamide (7y)** was prepared in the same manner as compound **7a** but with substitution of 2-bromo-*N*-cyclohexylacetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (153 mg, 21% yield). This material was converted to the maleate salt. ^{1}H NMR (300 MHz, CD_3OD) δ 1.47−1.18 (m, 6H), 1.64 (m, 1H), 1.78 (m, 2H), 1.90 (m, 2H), 2.05 (m, 2H), 2.33 (m, 2H), 3.24 (dd, J = 12.6 and 2.4 Hz, 1H,), 3.70 (m, 4H), 3.90 (s, 2H), 6.26 (s, 2H), 7.45 (m, 1H), 7.53 (dd, J = 8.1 and 2.0 Hz, 1H), 7.61 (ddd, J = 8.5, 8.5,and 1.4 Hz, 1H), 8.37 (dd, J = 6.4 and 1.0 Hz, 1H). MS (ESI) m/e 318 $(M + H)^+$. Anal. ($C_{18}H_{27}N_3O_2 \cdot 1.2C_4H_4O_4 \cdot 0.4H_2O \cdot 0.2CH_2Cl_2$) C, H, N.

2-(1-Oxy-3′,4′,5′,6′-tetrahydro-2′H-[2,4′-bipyridine]-1′-yl)-*N*-pyridin-2-ylacetamide (7z) was prepared in the same manner as compound **7a** but with substitution of 2-chloro-*N*-pyridin-3-ylacetamide in place of 2-bromo-*N*-(*m*-tolyl)acetamide (392 mg, 30% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 1.83 (dd, J = 12.2 and 3.4 Hz, 1H), 1.91 (dd, J = 12.2 and 3.4 Hz, 1H), 2.05 (br d, J = 11.9 Hz, 2H), 2.44 (ddd, J = 11.9, 11.9, and 2.4 Hz, 2H), 3.13 (m, 2H), 3.28 (s, 2H), 3.46 (m, 1H), 7.41 (m, 2H), 7.60 (m, 2H), 8.18 (ddd, J = 8.5, 2.7, and 1.7 Hz, 1H), 8.28 (dd, J = 5.1 and 1.4 Hz, 1H), 8.34 (br d, J = 6.4 Hz, 1H), 8.80 (br d, J = 2.4 Hz, 1H), MS (DCI/NH_3) m/e 313 $(M + H)^+$; Anal. ($C_{17}H_{20}N_4O_2 \cdot 0.3 H_2O$) C, H, N.

FLIPR Assay of Receptor Activation by Agonists. Test compounds were evaluated for their ability to activate the human $D_{4.4}$ receptors coexpressed with $G\alpha_{qo5}$ in HEK293 cells according to the method described by Moreland et al.[8]

Conscious Rat Penile Erection Model. Test compounds were evaluated for their ability to induce erections in rat according to the method described by Brioni et al.[6b]

hERG Ionic Current Studies. hERG channels were stably expressed in HEK 293 cells. Cells were maintained in minimal Eagle medium (MEM) supplemented with 10% fetal bovine serum. 1% penicillin−streptomycin, 2 mM L-glutamine, 0.1 mM nonessential amino acids, 1 mM sodium pyruvate, and 200 mg/mL G418. Medium was changed every 48 h and cells were passaged weekly.

Currents were recorded by use of an Axopatch 200 and pClamp data acquisition software. Patch pipettes were constructed with borosilicate glass capillary tubes (resistance 1.8−3.8 MΩ). The pipet solution contained 125 mM potassium aspartate, 20 mM KCl, 10 mM ethylene glycol bis(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA), 1 mM $MgCl_2$, 5 mM *N*-(2-hydroxyethyl)-piperazine-*N*′-2-ethanesulfonic acid (HEPES), and 5 mM MgATP; pH = 7.3. The bath solution contained 140 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 5 mM glucose, and 20 mM HEPES; pH = 7.4. Compounds were dissolved in DMSO and then diluted in the bath solution. Cells were exposed to a single concentration of drug. DMSO concentrations never exceeded 0.1% (by volume).

Effects of compounds on hERG current were assessed by a voltage clamp protocol that stepped to −25, 0, 25, and 50 mV for 3 s, followed by a step to −50 mV for 4 s from a holding potential of −80 mV once every 15 s. Current measurements were made at 36.5−37 °C. IC_{50} values were calculated from the effect of compounds on hERG tail current at −50 mV corrected for run down/DMSO vehicle effects.

Action Potential Duration Studies. Free-running canine cardiac Purkinje fibers were removed and placed in a warmed (37 °C) superfusion chamber (8−10 mL/min) and stimulated (2× threshold, biphasic waveform, typically 1−2 ms in duration) by use of platinum electrodes located in the chamber floor. Fibers were

impaled with 3 M KCl-filled microelectrodes (resistance 10−30 MΩ), and electrical activity was monitored with high-input impedance electrometers. Studies were initiated after a minimum of 30 min in vitro equilibration with stimulation. Fibers were considered suitable for study if the following criteria were satisfied: (a) the membrane potential just prior to the action potential (AP) upstroke was more negative than −80 mV, (b) the AP duration was between 300 and 500 ms, and (c) the normal automatic rate did not exceed the stimulation cycle length. The AP duration was defined as the interval between the maximum upstroke velocity and 90% of repolarization (APD_{90}). Fibers were exposed to two concentrations of compounds, with electrophysiological effects at each concentration evaluated at three different stimulation rates. Fibers were paced in control bath solution (131 mM NaCl, 18 mM $NaHCO_3$, 1.8 mM NaH_2PO_4, 0.5 mM $MgCl_2$, 5.5 mM dextrose, 4 mM KCl, and 2 mM $CaCl_2$) for a minimum of 20 min at a basic cycle length (BCL) of 2 s, then consecutively paced at 800 and 400 ms for at least 2 min at each rate to establish a baseline AP recording. Following return to the stimulation BCL of 2 s, superfusion with the lowest compound concentration was initiated. After a 25 min drug equilibration period, APs were again obtained at the three different stimulation rates. The protocol was then repeated with the higher compound concentration.

Supporting Information Available: Elemental analysis data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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