Synthesis, SAR, and Biological Evaluation of Oximino-Piperidino-Piperidine Amides. 1. Orally Bioavailable CCR5 Receptor Antagonists with Potent Anti-HIV Activity

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We previously reported the discovery of 4-[(*Z*)-(4-bromophenyl)(ethoxyimino)methyl]-1′-[(2,4-dimethyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-oxide **1** (SCH 351125) as an orally bioavailable human CCR5 antagonist for the treatment of HIV-1 infection. Herein, we describe in detail the discovery of **1** from our initial lead compound as well as the synthesis and SAR studies directed toward optimization of substitution at the phenyl, oxime, and right-hand side amide groups in the oximino-piperidino-piperidine series. Substitutions (4-Br, 4-CF_3, 4-OCF_3, 4-SO_2Me, and 4-Cl) at the phenyl group are well-tolerated, and small alkyl substitutions (Me, Et, ^{n}Pr, ^{i}Pr, and cyclopropyl methyl) at the oxime moiety are preferred for CCR5 antagonism. The 2,6-dimethylnicotinamide *N*-oxide moiety is the optimal choice for the right-hand side. Several compounds in this series, including compound **1**, exhibited excellent antiviral activity in vitro. Compound **1**, which has a favorable pharmacokinetic profile in rodents and primates, excellent oral bioavailability, and potent antiviral activity against a wide range of primary HIV-1 isolates, is a potentially promising new candidate for treatment of HIV-1 infection.

Introduction

The current therapies now approved for human immunodeficiency virus type I (HIV-1) include combinations of reverse transcriptase and protease inhibitors which are highly successful in reducing morbidity and mortality in HIV-1-infected individuals.[1] Although the use of combination therapy can be highly effective in suppressing viral replication, the emergence of drug resistant viruses and intolerance to available agents can lead to treatment failure. Hence, there remains a need for novel agents with better potency and less toxicity.

It has been established that HIV-1 enters macrophages and T-cells by attaching to the CD4 receptor and subsequent interactions with CCR5 chemokine receptors which serve as a viral coreceptor for the entry process.[2] The CCR5 receptor is a member of the G-protein-coupled receptor (GPCR) superfamily, for which small molecule inhibitors have been developed. The endogenous ligands which bind to the CCR5 receptor are the chemokines RANTES, MIP-1α, and MIP-1β which have been reported to inhibit HIV-1 infection.[3] The absence of CCR5 in humans who are homozygous for a defective CCR5-Δ32 allele has little impact on health, while being strongly protective against HIV-1 infection.[4] Furthermore, individuals who have reduced expression of CCR5 due to heterozygosity for the Δ32 allele advance more slowly to the disease than those with wild-type CCR5.[5] These observations provided compelling evidence that functional inhibition of the CCR5 receptor can be highly protective against HIV-1 infection. Therefore, it is hoped that the blockade of viral entry by a small molecule CCR5 receptor antagonist would represent a new class of anti-HIV therapeutics.

Various academic institutions[6a] and pharmaceutical companies, including ours, have reported structurally diverse small molecule CCR5 antagonists as shown in Figure 1.[6b] Researchers at Takeda Chemical Industries published their work on the discovery of the potent and selective small molecule CCR5 antagonist TAK-779.[7] In addition, the Takeda group disclosed patents claiming that derivatives of TAK-779 were potential orally bioavailable CCR5 antagonists.[8] Recently, research groups at Merck have published patents and papers highlighting the synthesis, SAR, and biological activity of structurally diverse antagonists.[9] Scientists at Glaxo Smithkline and Pfizer have also published patents covering potential CCR5 antagonists.[10] We have previously discussed our efforts in the optimization of our initial hits from our privileged piperazine- and piperidine-based structures. These efforts led to the discovery of the potent and orally bioavailable CCR5 antagonist SCH 350634, from the piperazino-piperidine series, and a clinical candidate SCH 351125 (**1**), from the piperidino-piperidine series.[11] In this paper, we describe in detail the identification of **1** as well as the design, synthesis, and biological activity of various analogues of **1**, with studies directed toward optimizing the left-hand side (LHS) phenyl, oxime, and right-hand side (RHS) amide regions of compound **1**, as shown in Figure 1.[12]

Chemistry

The general synthetic method for the preparation of aryl piperidino-piperidine amide analogues is shown in

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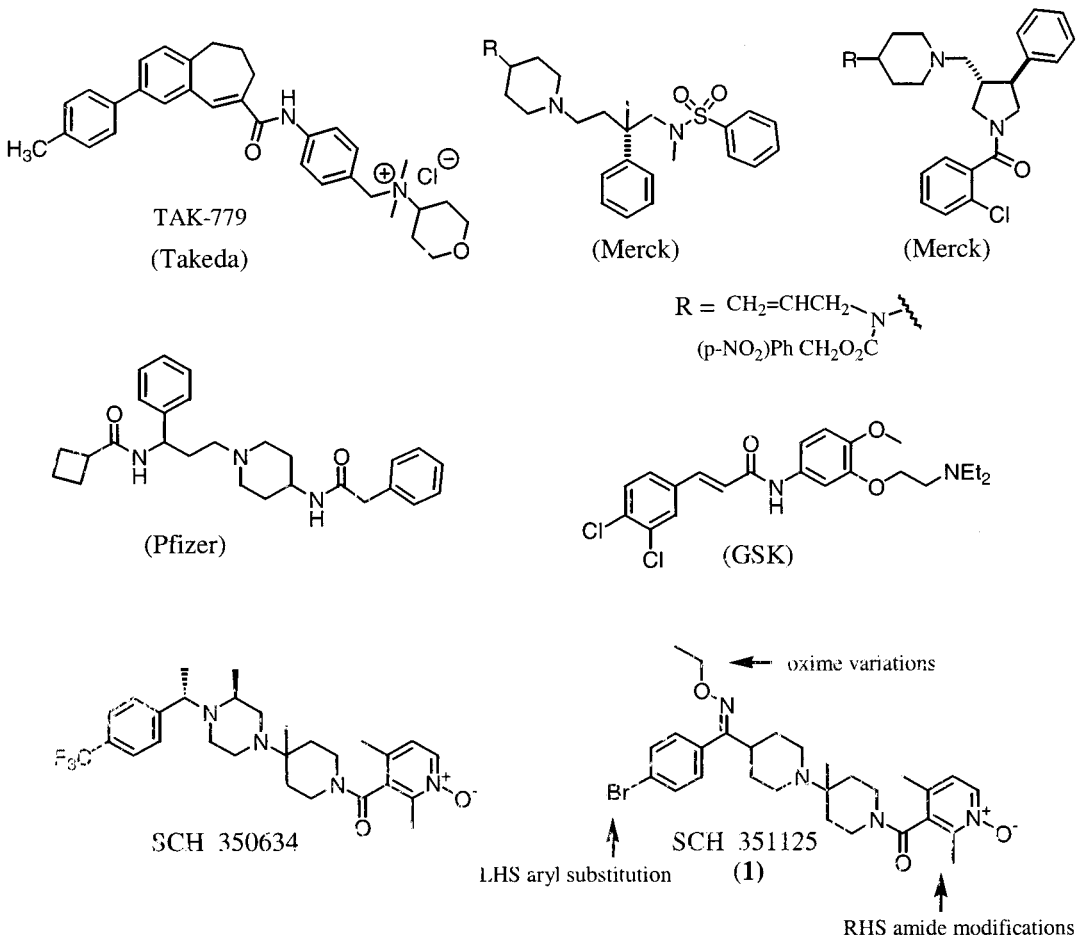
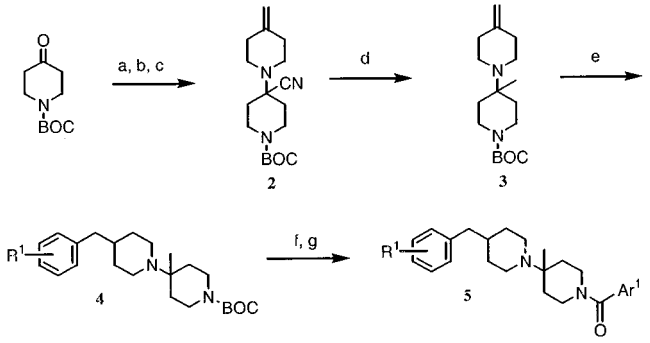


Figure 1. CCR5 antagonists.

Scheme 1. General Synthetic Scheme of Aryl Piperidino-Piperidine Amides[a]

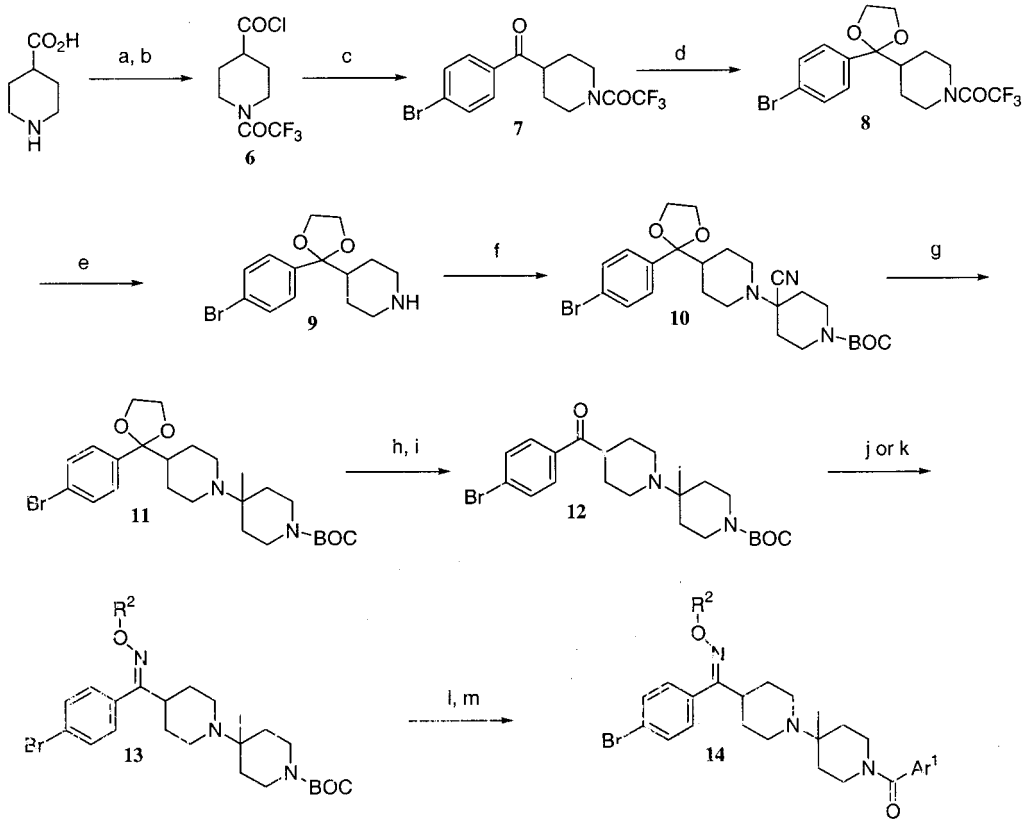


[a] Reagents and conditions: (a) $CH_3P^+Ph_3Br^-$, BuLi, −78 °C to rt, 24 h, 91%; (b) HCl, EtOAc, rt, 1.5 h; (c) *N*-Boc-piperidine-4-one, $Ti(O^iPr)_4$, 1,2-dichloroethane, rt, 12 h, and then Et_2AlCN, rt, 3 h, 96%; (d) MeMgBr, THF, rt, 2 h, 99%; (e) 9-BBN, THF, 70 °C, 3 h, cooled to rt, added aqueous K_3PO_4, R^1-substituted bromobenzene or iodobenzene, $PdCl_2(dppf)_2$, 70 °C, 24 h; (f) TFA, DCM, rt, 2 h; (g) Ar^1CO_2H, EDCI, DIPEA, HOBT, DCM, rt, 12 h.

Scheme 1. Wittig olefination of commercially available *N*-Boc-piperidine-4-one followed by Boc removal afforded the free amine. The amine was then treated with a second equivalent of *N*-Boc-piperidine-4-one under modified Strecker conditions to afford olefin **3** bearing a methyl group at the 4-position of the piperidine.[13] Hydroboration of the olefin with 9-BBN followed by palladium-catalyzed cross-coupling with a substituted bromobenzene gave the aryl-bipiperidine product **4**.[14] Boc removal with trifluoroacetic acid and coupling of the resulting free amine with the desired aromatic acids proceeded under standard conditions to afford the desired products **5**.

Oximino-piperidino-piperidine analogues containing a *p*-bromo aryl substituent were prepared according to Scheme 2. Protection of commercially available isonipecotic acid as the trifluoroacetamide followed by treatment with thionyl chloride afforded *N*-trifluoroacetylisonipecotyl chloride **6**. Friedel−Crafts condensation of acid chloride **6** and bromobenzene afforded ketone **7**, which was then converted to ketal **9**. Ketal **9** was allowed to react with *N*-Boc-piperidine-4-one in the presence of titanium isopropoxide. Subsequent treatment of the resulting intermediate with diethylaluminum cyanide gave aminonitrile **10**. This aminonitrile was treated with an excess of methylmagnesium bromide to afford the alkylated product **11**, which was then processed to ketone **12** in 2 steps. The ketone was then converted to the desired oximino-piperidino-piperidine analogue **13** by treatment with either alkyl or aryl hydroxylamine hydrochloride in the presence of sodium acetate. Boc removal and coupling of the resulting free amine with the desired aromatic acids proceeded under standard conditions. The oxime formation step afforded a mixture of *E* and *Z* oxime isomers in a ratio of 1.5:1 which was readily separated by silica gel chromatography. For subsequent large-scale preparation, the *E*/*Z* mixture was first equilibrated with 1 M hydrochloric acid in ether to provide a 1:2.5 mixture favoring the *Z*

Scheme 2. General Synthetic Scheme of 4-Bromophenyl Oximino-Piperidino-Piperidine Amides[a]



[a] Reagents and conditions: (a) TFAA (excess), reflux, 4 h; (b) $SOCl_2$ (excess), 12 h, 30% in two steps; (c) $AlCl_3$, bromobenzene (excess), reflux; (d) ethylene glycol, *p*-TSA, toluene, reflux (azeotropically remove water), 90% in two steps; (e) MeOH, H_2O, K_2CO_3, rt, 12 h, 99%; (f) *N*-Boc-piperidine-4-one, $Ti(O^iPr)_4$, 1,2-dichloroethane, rt, 12 h, and then Et_2AlCN, rt, 3 h, 63%; (g) MeMgBr, THF, rt, 2 h, 98%; (h) 6 N HCl, EtOAc, rt, 12 h; (i) Boc_2O, 10% NaOH, ether, rt, 12 h, 77%; (j) $NH_2OR^2 \cdot HCl$, NaOAc, MeOH, rt, 24 h, 94% when R^2 = Et, followed by 1 M HCl in ether (3 equiv), DCM, rt, 48 h, followed by chromatographic separation; (k) $NH_2OH \cdot HCl$, NaOAc, MeOH, rt, 24 h, followed by chromatographic separation, and then KHMDS, THF, 0 °C, 30 min, followed by R^2I or R^2Br, rt, 5 h, 35−80%; (l) TFA, DCM, rt, 2 h; (m) Ar_1CO_2H, EDCI, DIPEA, HOBT, DCM, rt, 12 h, 45% for compound **1**.

isomer, which was then separated as above following reprotection of the secondary amine with Boc anhydride.

Alternatively, the preparation of oximes wherein the alkyl hydroxylamine is not commercially available can be carried out via O-alkylation of the oxime. The ketone **12** was converted to the oxime **13**, where R^2 = H, by treatment with hydroxylamine hydrochloride in the presence of sodium acetate. Separation of *E* and *Z* oxime isomers could be readily carried out at this stage via silica gel chromatography. The *Z* isomer was then deprotonated with potassium bis(trimethylsilyl)amide followed by alkylation with alkyl halide to yield the desired oximino-piperidino-piperidine analogue **13** with retention of stereochemistry.

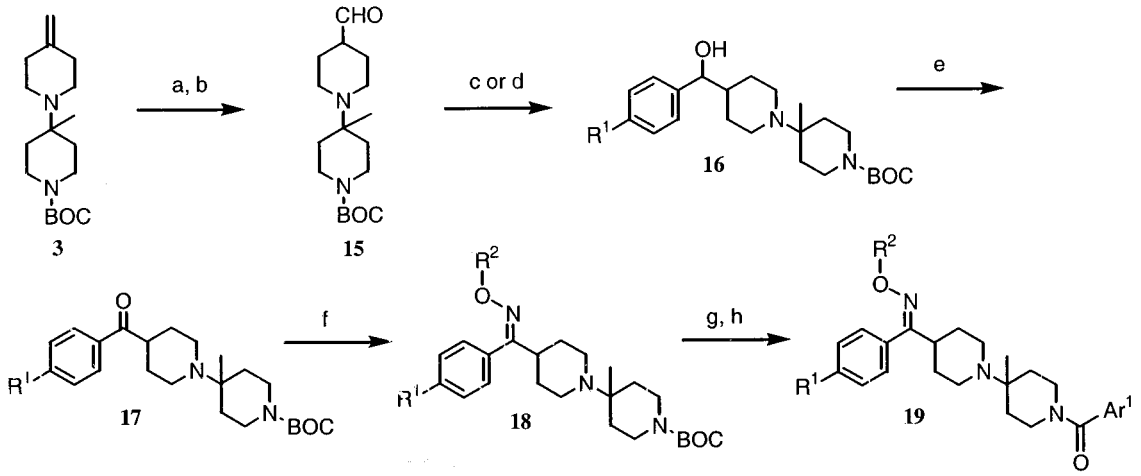
To investigate structure−activity relationships of the 4-aryl substituent in the oxime series, we developed a synthetic route, shown in Scheme 3, in which the desired left-hand aryl group was introduced via nucleophilic addition of 4-substituted aryllithium or arylmagnesium reagents to piperidino-piperidine carboxaldehyde. Hydroboration of olefin **3** followed by tetrapropylammonium perruthenate (TPAP) oxidation provided aldehyde **15**. It is important to note that in the hydroboration reaction, the oxidative workup in the presence of a pH = 7 buffer is necessary to prevent N-oxidation of piperidine. Addition of the arylmagnesium bromide or aryllithium reagent to the aldehyde gave alcohol **16** which was oxidized to the ketone **17** using TPAP, 4-methylmorpholine *N*-oxide (NMO), and molecular sieves. The ketone was then converted to the desired oximino-piperidino-piperidine analogue **19** by treatment with either methyl or ethyl hydroxylamine hydrochloride in the presence of sodium acetate. Boc removal and coupling of the resulting free amine with the desired aromatic acids proceeded under standard conditions.

In Vitro and in Vivo Studies. The in vitro activity of these CCR5 receptor antagonists was determined using a membrane binding assay, and the antiviral activity was evaluated using viral entry and replication assays.[15] Rat plasma levels after oral administration were evaluated using a rapid rat pharmacokinetic screen.[16] All the preliminary in vitro and in vivo studies on compounds were conducted using the amorphous tartrate or hydrochloride salts.

Results and Discussions

Screening of in-house compound collections using a high-throughput ^{125}I-labeled RANTES binding assay led to the identification of several structurally diverse compounds, including compound **20** with CCR5 receptor affinity (K_i = 1 μM). In addition to its CCR5 receptor activity, compound **20** was a potent antagonist of the muscarinic M2 receptor (M2, K_i = 1.3 nM); therefore, our goals at the beginning of the program were to improve the CCR5 binding affinity and increase selectivity versus the M2 receptor. In efforts parallel to those

Scheme 3. General Synthetic Scheme of 4-Phenyl Oximino-Piperidino-Piperidine Amides[a]



[a] Reagents and conditions: (a) BH_3·THF complex, THF, 0 °C to rt, 24 h, followed by workup with H_2O_2, pH = 7 buffer, THF, EtOH, 41%; (b) TPAP, NMO, molecular sieves, 0 °C to rt, 1 h, 64%; (c) R^1-substituted 4-bromobenzene, BuLi, −78 °C to rt, 2 h, 41%, $R^1 = CF_3$ or OCF_3; (d) 4-chlorophenylmagnesium bromide, THF, 0 °C to rt, 5 h, 47%; (e) TPAP, NMO, molecular sieves, 0 °C to rt, 1 h, 63%; (f) NH_2OR^2·HCl, NaOAc, MeOH, rt, 24 h, 94% when R^2 = Et; (g) TFA, DCM, rt, 2 h; (h) Ar^1CO_2H, EDCI, DIPEA, HOBT, DCM, rt, 12 h.

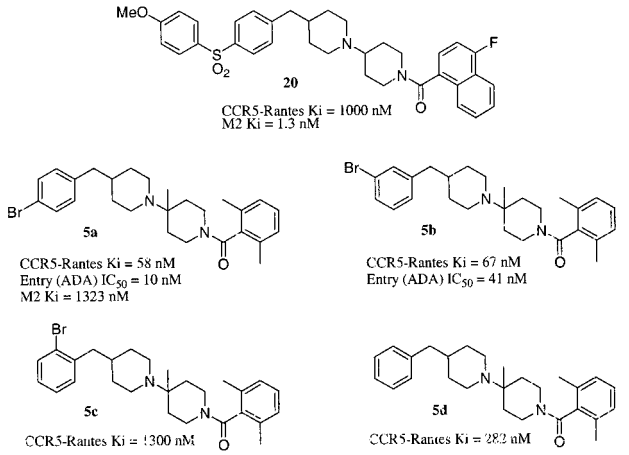


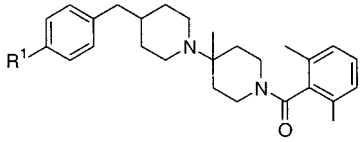
Figure 2. Piperidino-piperidine analogues.

carried out in a related piperazino-piperidine series, we studied structure−activity relationships at both ends of molecule **20**.[11c,17] Left-hand side truncation, along with replacement of 4-fluoronaphthamide with 2,6-dimethylbenzamide and the introduction of a methyl group at the 4-position of the piperidine, resulted in the identification of piperidino-piperidine compound **5a** which showed improvement in CCR5 activity and selectivity versus the M2 muscarinic receptor (CCR5, K_i = 58 nM; M2, K_i = 1323 nM). Antagonist **5a** provided an excellent starting point for further optimization. As described in Figure 2, the des-halo compound **5d** and the ortho-substituted derivative **5c** were significantly less active than **5a**. The meta-substituted derivative **5b** was slightly less active than **5a**, suggesting the requirement of a para substituent.

Optimization of the 4-phenyl substituent led to the discovery that other halogens and small polar groups are tolerated at this position, as shown in Table 1. The *p*-chloro and *p*-iodo substituents, as in **5e** and **5f**, as well as the medium-size halogenated and nonhalogenated groups, as in **5g**, **5h**, and **5l**, gave binding potency similar to that of antagonist **5a**.

Although the CCR5 antagonist potency of these compounds was promising, oral bioavailability was poor,

Table 1. 4-Aryl Substitution

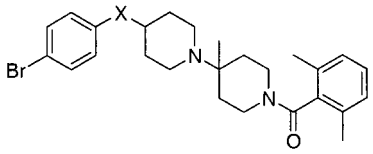


compound	R^1	K_i (nM)[a,b]	IC_{50} (nM)[c]
5a	Br	58	10
5e	Cl	68	23
5f	I	33	9
5g	CF_3	25	1
5h	OCF_3	55	5
5i	CH_3	113	38
5j	OCH_3	155	26
5k	SCH_3	86	
5l	SO_2CH_3	33	7
5m	$COCH_3$	596	
5n	Ph	363	

[a] The standard error was 10%, and variability was 2- to 3-fold from assay to assay. [b] Data for inhibition of RANTES binding. [c] Concentration required to inhibit the entry of HIV-1 reporter virus (ADA) into U-87 cells by 50%. For IC_{50} values, the 95% confidence limit was within 1 log and intra-assay variation was less than 0.5 log.

possibly due to metabolism at the benzylic site. Thus, subsequent SAR efforts were first focused at the benzylic site by introducing substituents that would either block or reduce metabolism (Table 2). Branching of the sp^3 benzylic carbon, as in **23**, had no effect on binding potency. However, rigidifying it in the form of an sp^2 center, as in **24**, provided an 8-fold improvement in binding at CCR5. Replacement with other linkers such as oxygen, alcohol, or carbonyl as in compound **25**, **22**, or **21**, respectively, offered no advantage in terms of CCR5 potency. The introduction of the oxime linker in **14a** not only improved the CCR5 binding affinity 6-fold but also substantially improved plasma levels in the rat after oral administration. Separation of the oxime geometric isomers led to the discovery that the *Z* isomer **14c** was 10-fold more potent than the *E* isomer **14b**. To determine the stability of compound **14c**, the compound was treated with 0.1 N HCl (pH = 1) at 37 °C for 12 h. No evidence of hydrolysis or oxime equilibration was observed.

Table 2. Linker Modifications



compound	X	K_i (nM)[a,b]	IC_{50} (nM)[c]	rat PK (10 mg/kg·po)[d] $AUC_{0-6\,h}$ (h·μg/mL)
5a	CH_2	66	10	0.04
21	C=O	54	12	
22	CH−OH	190	76	
23	$CH-CH_3$	62		
24	$C=CH_2$	8	1.0	0.59
25	O	29		
14a	C=NOMe (mix)	11	1.4	2.1
14b	C=NOMe (*E*)	25	2.8	1.2
14c	C=NOMe (*Z*)	2	1.2	1.4

[a] The standard error was 10%, and variability was 2- to 3-fold from assay to assay. [b] Data for inhibition of RANTES binding. [c] Concentration required to inhibit the entry of HIV-1 reporter virus (ADA) into U-87 cells by 50%. For IC_{50} values, the 95% confidence limit was within 1 log and intra-assay variation was less than 0.5 log. [d] See ref 16 for procedure.

With *Z* methoxime **14c** in hand (K_i = 2 nM), the next step was to study the significance of the oxime substitution and other substituted oximes. Table 3 displays the results for the inhibition of RANTES binding and viral entry for antagonists with the modifications of oxime. The oxime **14f** exhibited considerable loss in potency, indicating that alkyl substitution is required. Introduction of aromatic and other bulkier groups (**14k, 14l, 14m**, and **14n**) resulted in a loss of potency. It is clear from this study that the small alkyl-substituted oximes (**14c**, **14e**, **14g**, and **14h**) are the most potent. The ethoxime and methoxime are optimal for CCR5 activity. The introduction of a more polar substituent, such as **14i** and **14j**, onto the oxime alkyl side chain resulted in a moderate loss of activity.

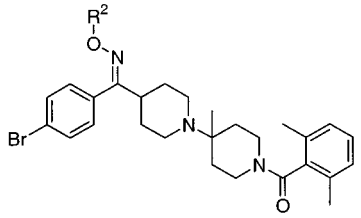
Having optimized the oxime geometry and alkyl substitution, we turned our attention to address the key metabolic issues associated with compounds **14c** and **14e**. We observed extensive oxidative metabolism (monohydroxylation) of the 2,6-dimethylbenzamide moiety in the rat, along with minor amounts of dihydroxylation and a carboxylic acid metabolite resulting from oxidation of one of the methyl groups. Therefore, our subsequent medicinal chemistry efforts were focused on replacements for the metabolically labile 2,6-dimethylbenzamide moiety (Table 4). Because 2,6-disubstitution is necessary for high binding potency, our initial approach was to replace the methyl groups with heteroatoms. This resulted in compounds **26**−**29**, which all showed a slight decrease in CCR5 binding potency or oral drug exposure in the rat. However, changing the benzamide to a nicotinamide while leaving the 2-methyl groups intact provided potent CCR5 antagonists with significantly improved rat plasma levels after oral administration (**30a** and **30b**). Compounds containing various nicotinamides (**31**−**35**) emphasized the fact that, like the benzamides, the 2,6-disubstitution is necessary for high binding potency. Substitution at the 4-position, as in **33** and **34**, provided no advantage in CCR5 binding or oral drug exposure in rats. Metabolite identification studies of these nicotinamides indicated less metabolism at the methyl and aryl groups but indicated the formation of a new major (M + 16) metabolite. We suspected that this was due to oxidation of the pyridine nitrogen, so the corresponding nicotinamide *N*-oxide **1** was prepared. Again, the necessity for 2,6-disubstitution was determined by compounds **36**−**38**, all of which resulted in a decrease in CCR5 binding potency.

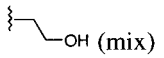
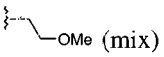
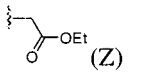
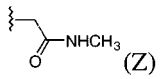
At this point, it was clear that the presence of either the methyl or ethyl oxime moiety in addition to the 2,6-dimethylnicotinamide *N*-oxide moiety was optimal for binding affinity and oral absorption. Analogues of **1** were prepared by varying the left-hand side aryl substituent as shown in Table 5. In general, the ethyl oxime derivatives (**1**, **39f**, **39g**, and **39i**) exhibited greater CCR5 binding affinity (K_i) and antiviral potency (IC_{50}) than the equivalent methyl derivatives (**39a, 39b, 39c**, and **39e**). The 4-fluoro derivative **39j** and methylsulfone derivatives **39h** and **39d** were significantly less active. Although the *p*-trifluoromethyl- and trifluoromethoxy-containing compounds (**39f** and **39g**) as well as the chloro compound (**39i**) compared well with compound **1** in terms of both inhibition of RANTES binding and inhibition of viral entry, these modifications resulted in lower oral blood levels of compound **1** in rats.

Compound **1** exhibited 2- to 3-fold higher oral plasma levels in the rat pharmacokinetic screen, in addition to satisfying our preliminary criteria of antiviral potency. Therefore, we selected compound **1** for detailed pharmacokinetic investigations in rats and monkeys (Table 6). Compound **1** was absorbed well in both species, providing oral bioavailability of 63% in rats and 52% in monkeys. More importantly, the plasma levels exceeding the mean in vitro IC_{90} inhibitory concentrations (IC_{90} values range from 3 to 78 nM) can be obtained and sustained at least 12−24 h after oral administration. The plasma concentrations of compound **1** at 12 and 24 h after the oral administrations were 330 and 16 nM in the rat and 300 and 40 nM in the monkey, respectively. In addition, compound **1** exhibited minimal or modest protein binding in human (16% free) and rat (11% free) plasma.

For the more potent compounds incorporating phenyl or oxime variations, CCR5 binding affinity correlated well with the inhibition of viral entry. It is important to note that IC_{50} values obtained from the viral entry assay were generally lower than the K_i values determined from the RANTES binding assay. This is probably due to differences in both the ligand (RANTES vs HIV) and the target (whole cells vs membrane) used in these assays. In addition, compounds with good activity against the ADA strain (**1**, **5a**, **5f**−**h**, **5l**, **14a**−**h**, **14l**, **24**, **26**−**31**, **33**, **34**, **38**, **39a**−**c**, **39f**, **39g**, and **39i**) inhibited the entry of other HIV-1 isolates as well as YU-2 or JRFL in U-87 cells with IC_{50} values less than 10 nM. Several compounds in this series, including **1**, were shown to be functional antagonists of the CCR5 receptor by their ability to block the effects of RANTES-induced calcium flux in cells.[11a,b] Also, antagonist **1** showed no appreciable affinity (less than 15% inhibition at concentrations of 2−20 μM) for muscarinic receptors or the closely related chemokine receptors, including CCR1, CCR2, CCR3, and CCR7.[11a,b] The cytotoxicity

Table 3. Oxime Substitutions



Compound	R^2	Ki (nM)[a,b]	IC_{50} (nM)[c]	Rat PK (10 mg/kg po)[d] $AUC_{0\text{-}6h}$ (hr μg/ml)
14a	Me (mix)	11	1.4	2.1
14b	Me (E)	25	2.8	1.2
14c	Me (Z)	2	1.2	1.4
14d	Et (E)	48	9.2	
14e	Et (Z)	2	1.1	1.0
14f	H (Z)	78	10	
14g	^{t}Bu (Z)	9	5.7	
14h	^{i}Pr (Z)	4	1.7	1.7
14i		62		
14j		12		
14k		33		
14l		33	4.4	
14m	Ph (Z)	>30		
14n	Bn (mix)	>500		

(CC_{50}) of antagonist **1** is 92 μM in PBMC cultures using the MTS cell titer 96 protocol which is well above its therapeutic concentration.

Compound **1** has been advanced to clinical studies due to its superior antiviral potency, receptor specificity, and pharmacokinetic profile. Compound **1** inhibits the replication of a wide range of genetically diverse HIV-1 isolates with geometric mean IC_{50} values ranging from 0.40 to 8.9 nM and IC_{90} values from 3 to 78 nM.[11a,b] More importantly, compound **1**, when dosed orally (30 mg/kg/day) for 28 days after inoculation with HIV-1, showed a 3.6 log reduction in viral RNA levels compared to those of the untreated mice in the SCID-hu Thy/Liv mouse infection model.[11b]

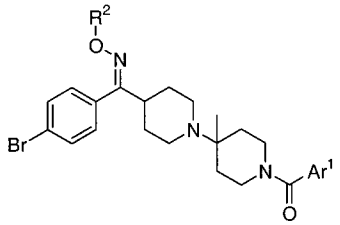
Conclusion

In summary, the identification of compound **1** as well as complete SAR investigations of the phenyl, oxime, and right-hand side amide groups of oximino-piperidino-piperidine series were described. The substituents Br, Cl, CF_3, OCF_3, and $MeSO_2$ at the 4-phenyl group; small alkyl groups Me, Et, ^{n}Pr, and ^{i}Pr; and 2,6-dimethylnicotinamide are optimal for antiviral activity. On the basis of extensive structure−activity studies, we have chosen compound **1** for human clinical trials for the treatment of HIV-1 infection because of its potent antiviral activity and favorable in vivo pharmacokinetic profile. Compound **1** exists as a mixture of 4 rotational isomers due to hindered bond rotation caused by the steric and unsymmetrical nature of the tertiary amide. Our ongoing studies on rotational isomers of **1** and subsequent amide SAR investigations on this promising oximino-piperidino-piperidine series will be reported in due course.

Experimental Section

Elemental analyses were performed by the Physical-Analytical Chemistry Department, Schering-Plough Research Institute, either on a Leeman CE 440 or on a FISONS EA 1108 elemental analyzer. Mass spectra were recorded using an

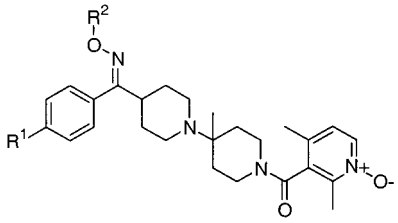
Table 4. Right-Hand Side Amide Substitution



Compound	Ar^1	R^2	Ki (nM)[a,b]	IC_{50} (nM)[c]	Rat PK (10 mg/kg po)[d] $AUC_{0\text{-}6h}$ (hr·μg/ml)
14c		Me	2.0	1.2	1.4
26		Me	3.4	0.6	0.62
27		Me	18	4.0	3.0
28		Me	4.5	0.5	1.3
29		Et	3.0	2.1	2.7
30a		Me	1.1	0.5	1.9
30b		Et	1.1	0.2	2.1
31		Et	26	1.4	
32		Et	>30		
33		Et	7	0.9	0.21
34		Et	43	6.4	
35		Et	>30		
1		Et	2.1	0.6	6.5
36		Et	>30		
37		Et	>30		
38		Et	16	1.7	3.2

[a] The standard error was 10%, and variability was 2- to 3-fold from assay to assay. [b] Data for inhibition of RANTES binding. [c] Concentration required to inhibit the entry of HIV-1 reporter virus (ADA) into U-87 cells by 50%. For IC_{50} values, 95% confidence limit was within 1 log and intra-assay variation was less than 0.5 log. [d] See ref 16 for procedure.

Table 5. 4-Aryl Modifications of Compound **1**



compound	R^1	R^2	K_i (nM)[a,b]	IC_{50} (nM)[c]	rat PK (10 mg/kg·po)[d] $AUC_{0-6\ h}$ (h·μg/mL)
39a	Br	Me	19	5.6	2.4
39b	CF_3	Me	5.3	1.1	0.35
39c	OCF_3	Me	7.6	5.1	3.3
39d	$MeSO_2$	Me	30		
39e	Cl	Me	24		
1	Br	Et	2.1	0.6	6.5
39f	CF_3	Et	3.8	1.3	2.2
39g	OCF_3	Et	4.4	1.8	3.0
39h	$MeSO_2$	Et	20		0
39i	Cl	Et	5.6	1.4	1.7
39j	F	Et	30		

[a] The standard error was 10%, and variability was 2- to 3-fold from assay to assay. [b] Data for inhibition of RANTES binding. [c] Concentration required to inhibit the entry of HIV-1 reporter virus (ADA) into U-87 cells by 50%. For IC_{50} values, the 95% confidence limit was within 1 log and intra-assay variation was less than 0.5 log. [d] See ref 16 for procedure.

EXTREL 401 (CI), JEOL or MAT-90 (FAB), VG ZAB-SE (SIMS), or Finnigan MAT-CH-5 (EI) spectrometer. In general, NMR structure determinations of the compounds were made using chemical shifts, coupling constants, coupling information from COSY spectra, and 1D NOE experiments. The ^1H and ^{13}C NMR spectra were obtained on a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz, ^1H; 75.5 MHz, ^{13}C), or XL-400 (400 MHz, ^1H; 100 MHz, ^{13}C) spectrometer and are reported as parts per million downfield from Me_4Si with the number of protons, multiplicities, and coupling constants in hertz (Hz) indicated parenthetically. For ^{13}C NMR, a Nalorac Quad nuclei probe was used. Compound purity was checked by TLC and LC/MS analysis using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column (Altech platinum C18, 3 μm, 33 × 7 mm i.d.). A gradient flow was used as follows: 0 min, 10% CH_3CN; 5 min, 95% CH_3CN; 7 min, 95% CH_3CN; 7.5 min, 10% CH_3CN; 9 min, stop; retention times are reported (t_R) for the final targets.

In vitro and in vivo data given throughout the text for compounds **1**, **14a**−**n**, and **26**−**39j** were collected for the amorphous tartrate salts. The tartrate salts were prepared by mixing the final compound with 1 equiv of a 1.0 M tartaric acid solution in methylene chloride followed by evaporation of the solvent. In vitro and in vivo data given throughout the text for final compounds **5a**−**n** and **21**−**25** were collected for the amorphous hydrochloride salts. The hydrochloride salts were prepared by mixing the final compound with an excess of a 3.0 M hydrogen chloride solution in diethyl ether followed by evaporation of the solvent.

Preparation of 4-Methylene-1′-(*tert*-butoxycarbonyl)-4′-cyano-1,4′-bipiperidine (2). To a solution of methyl triphenylphosphonium bromide (60.8 g, 168.8 mmol) in THF (400 mL) was slowly added 2.5 M *n*-butyllithium in THF (65.2 mL, 163.2 mmol) at −78 °C, and the mixture was stirred for 1 h. 4-Boc-piperidinone (22.4 g, 112.8 mmol) in THF (80 mL) was added dropwise to the mixture, and then the reaction mixture was warmed to ambient temperature and stirred overnight. The reaction was then quenched with water, and the mixture was extracted with hexanes (3 times). The combined extracts were concentrated and filtered through silica gel to give 20.2 g (91%) of the crude olefin. To a stirred solution of this crude olefin (20.0 g, 101.5 mmol) in ethyl acetate (100 mL) were added water (100 mL) and concentrated hydrochloric acid (30 mL), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture layers were separated, and the aqueous layer was concentrated to afford 12.8 g (95%) of crude amine. To a stirred solution of this amine (12.8 g, 97.0 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (14.6 mL, 97.0 mmol), and 4-Boc-piperidinone (27.8 g, 145.4 mmol) in 1,2-dichloroethane (200 mL) was added titanium isopropoxide (30.4 mL, 145.4 mmol), and the mixture was stirred for 18 h at room temperature. The mixture was concentrated, and a 1.0 M solution of diethylaluminum cyanide (145.4 mL, 145.4 mmol) was added at room temperature. The mixture was stirred for 3 h, and then diluted with EtOAc. The reaction was quenched with water (20 mL), and the mixture was stirred a further 2 h. The mixture was then filtered through Celite, and the resulting filtrate was concentrated and chromatographed to afford 20.0 g (67%) of cyano compound: ^1H NMR $CDCl_3$ δ 4.74 (s, 2 H), 4.00 (m, 2 H), 3.20 (m, 2 H), 2.69 (m, 4 H), 2.32 (m, 4 H), 2.17 (m, 2 H), 1.76 (m, 2 H), 1.51 (s, 9 H).

Preparation of 4-Methylene-1′-(*tert*-butoxycarbonyl)-4′-methyl-1,4′-bipiperidine (3). To a stirred solution of cyanide **2** (20.0 g, 71.4 mmol) in THF (200 mL) was added a 3.0 M solution of MeMgBr in ether (71.4 mL, 214.3 mmol), and the mixture was stirred for 2 h at room temperature. The reaction was then quenched with saturated aqueous ammonium chloride, and the mixture was extracted twice with methylene chloride. The extracts were concentrated to afford 20.0 g (90%) of the desired methylated compound **3**: R_f 0.68 (20% EtOAc/hexanes); ^1H NMR $CDCl_3$ δ 4.58 (s, 2 H), 3.34 (m, 2 H), 3.33 (m, 2 H), 2.47 (m, 4 H), 2.17 (m, 4 H), 1.78 (m, 2 H), 1.42 (s, 9 H), 1.32 (m, 2 H), 0.85 (s, 3 H).

General Procedure for Preparation of Substituted Benzyl Bipiperidines 5a−j, 5m, and 5n. (1) To a stirred solution of the olefin **3** (1.56 g, 5.33 mmol) in THF (5 mL) was added a 0.5 M 9-BBN solution in THF (10.66 mL, 5.33 mmol), and the mixture was heated to 70 °C for 3 h. The reaction mixture was cooled to room temperature, and a 3.0 M aqueous K_3PO_4 (3 mL) solution was added followed by the substituted bromo- or iodobenzene (4.44 mmol) in DMF and $PdCl_2(dppf)_2$ (0.18 g, 0.22 mmol). The solution was reheated to 70 °C for 18 h. The mixture was cooled to room temperature. The reaction was quenched with water, and the mixture was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried, concentrated, and chromatographed to yield 1.4 g of (60% for R^1 = 4-CF_3) compound **4**. For R^1 = 4-CF_3 compound: R_f 0.38 (20% EtOAc/hexanes); ^1H NMR $CDCl_3$ δ 7.50 (d, 2 H), 7.21 (d, J = 7.8 Hz, 2 H), 3.39−3.43 (m, 4 H), 2.85 (m, 2 H), 2.54 (m, 2 H), 1.99 (m, 2 H), 1.75 (m, 2 H), 1.60 (m, 2 H), 1.43 (s, 9 H), 1.13−1.39 (m, 5 H), 0.87 (s, 3 H).

(2) To a stirred solution of **4** (R^1 = 4-CF_3, 1.4 g, 3.16 mmol) in methylene chloride (20 mL) was added trifluoroacetic acid (TFA) (2.5 mL), and the mixture was stirred at room temperature for 2 h. The mixture was concentrated, poured into 10% NaOH, and extracted twice with methylene chloride. The combined extracts were dried and concentrated to afford 1.05 g (97%) of crude amine. To a stirred solution of this crude amine (0.10 g, 0.29 mmol) in methylene chloride (1 mL) were added 2,6-dimethylbenzoic acid (0.066 g, 0.44 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.084 g, 0.44 mmol), diisopropylethylamine (DIPEA) (0.5 mL), and 1-hydroxybenzotriazole hydrate (HOBT) (0.060 g, 0.44 mmol), and the mixture was stirred for 18 h at room temperature. The reaction was quenched with 10% NaOH, and the mixture was extracted twice with methylene chloride. The combined extracts were dried, concentrated, and chromatographed to give amide (67% for 4-CF_3 compound) **5**. Purity was checked by LC/MS analysis.

4-[(4-Bromophenyl)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (5a). The compound was prepared from 1-bromo-4-iodobenzene by following the general procedure described above to afford **4** where R^1 = 4-Br, which was then converted to compound **5a** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.60 (96:4:1 ratio of CH_2Cl_2:MeOH:NH_4OH); HPLC t_R = 4.50 min; ^1H NMR $CDCl_3$ δ 7.35 (d, J = 7.6 Hz, 2 H), 7.09 (m, 1 H), 6.98 (m, 4 H), 4.09 (m,

Table 6. Pharmacokinetic Parameters of Compound **1**

			iv administration		oral administration			
	dose (iv/po) (mg/kg)	*A* (%)[a]	CL (mL/min/kg)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (μM)	$AUC_{(0-24\ h)}$ (μM·h)	BA (%)
rat	10/10	57	12.8	5.4	0.5	2.5	15	63
monkey	2/2	80	4.28	6.0	2.0	0.76	6.9	52

[a] A = absorption.

1 H), 3.48 (m, 1 H), 3.26 (m, 1 H), 2.97 (m, 1 H), 2.87 (m, 1 H), 2.72 (m, 1 H), 2.44 (d, J = 3.3 Hz, 2 H), 2.23 (s, 3 H), 2.21 (s, 3 H), 1.86−2.06 (m, 3 H), 1.34−1.76 (m, 4 H), 1.05−1.28 (m, 4 H), 0.87 (s, 3 H); mass spectrum FAB+ observed = 483.2006, estimated = 483.2011.

4-[(3-Bromophenyl)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (5b). The compound was prepared from 1-bromo-3-iodobenzene by following the general procedure described above to afford **4**, where R^1 = 3-Br, which was then converted to compound **5b** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.60 (96:4:1 ratio of CH_2Cl_2:MeOH:NH_4OH); HPLC t_R = 5.21 min; ^{1}H NMR $CDCl_3$ δ 7.25−7.31 (m, 2 H), 6.96−7.14 (m, 5 H), 4.09 (m, 1 H), 3.49 (m, 1 H), 3.26 (m, 1 H), 2.97 (m, 1 H), 2.88 (m, 1 H), 2.73 (m, 1 H), 2.47 (d, 2 H), 2.24 (s, 3 H), 2.22 (s, 3 H), 1.87−2.08 (m, 3 H), 1.10−1.76 (m, 8 H), 0.87 (s, 3 H); mass spectrum FAB+ observed = 483.2014, estimated = 483.2011.

4-[(2-Bromophenyl)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (5c). The compound was prepared from 1-bromo-2-iodobenzene by following the general procedure described above to afford **4** where R^1 = 2-Br, which was then converted to compound **5c** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.60 (96:4:1 ratio of CH_2Cl_2:MeOH:NH_4OH); HPLC t_R = 5.06 min; ^{1}H NMR $CDCl_3$ δ 7.53 (d, J = 7.8 Hz, 2 H), 6.98−7.24 (m, 5 H), 4.13 (m, 1 H), 3.54 (m, 1 H), 3.31 (m, 1 H), 2.37−3.06 (m, 7 H), 2.29 (s, 3 H), 2.27 (s, 3 H), 1.90−2.22 (m, 5 H), 1.20−1.66 (m, 4 H), 0.90 (s, 3 H); mass spectrum FAB+ observed = 483.2002, estimated = 483.2011.

1′-(2,6-Dimethylbenzoyl)-4-(phenylmethyl)-4′-methyl-1,4′-bipiperidine (5d). The compound was prepared from bromobenzene by following the general procedure described above to afford **4** where R^1 = H, which was then converted to compound **5d** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: HPLC t_R = 4.86 min; ^{1}H NMR $CDCl_3$ δ 7.07−7.28 (m, 6 H), 6.97 (m, 2 H), 4.10 (m, 1 H), 3.49 (m, 1 H), 3.27 (m, 1 H), 2.97 (m, 1 H), 2.87 (m, 1 H), 2.72 (m, 1 H), 2.50 (d, J = 3.9 Hz, 2 H), 2.23 (s, 3 H), 2.21 (s, 3 H), 1.87−2.07 (m, 3 H), 1.08−1.79 (m, 8 H), 0.89 (s, 3 H); mass spectrum FAB+ observed = 405.2918, estimated = 405.2906.

4-[(4-Chlorophenyl)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (5e). The compound was prepared from 1-chloro-4-iodobenzene by following the general procedure described above to afford **4** where R^1 = 4-Cl, which was then converted to compound **5e** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: HPLC t_R = 5.06 min; ^{1}H NMR $CDCl_3$ δ 7.18−7.25 (m, 3 H), 6.95−7.12 (m, 4 H), 4.08 (m, 1 H), 3.49 (m, 1 H), 3.27 (m, 1 H), 2.67−3.03 (m, 3 H), 2.46 (d, J = 3.9 Hz, 2 H), 2.23 (s, 3 H), 2.21 (s, 3 H), 1.85−2.05 (m, 3 H), 1.33−1.75 (m, 4 H), 1.08−1.28 (m, 4 H), 0.87 (s, 3 H); mass spectrum FAB+ observed = 439.2511, estimated = 439.2516.

4-[(4-Iodophenyl)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (5f). The compound was prepared from 1-bromo-4-iodobenzene by following the general procedure described above to afford **4** where R^1 = 4-Br. To this compound in THF at −78 °C was added *n*BuLi (1.1 equiv), and the mixture was stirred for 10 min followed by the dropwise addition of a solution of I_2 (1.2 equiv) in THF. The mixture was stirred for 1 h to afford **4** where R^1 = 4-I, which was then converted to compound **5f** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: HPLC t_R = 5.31 min; ^{1}H NMR $CDCl_3$ δ 7.57 (d, J = 7.7 Hz, 2 H), 7.14 (m, 1 H), 7.01 (d, J = 7.8 Hz, 2 H), 6.88 (d, J = 7.8 Hz, 2 H), 4.12 (m, 1 H), 3.52 (m, 1 H), 3.29 (m, 1 H), 3.01 (m, 1 H), 2.90 (m, 1 H), 2.75 (m, 1 H), 2.47 (d, J = 3.9 Hz, 2 H), 2.28 (s, 3 H), 2.24 (s, 3 H), 1.90−2.08 (m, 3 H), 1.36−1.79 (m, 4 H), 1.08−1.30 (m, 4 H), 0.90 (s, 3 H); mass spectrum FAB+ observed = 531.1878, estimated = 531.1872.

1′-(2,6-Dimethylbenzoyl)-4′-methyl-4-[[4-(trifluoromethyl)phenyl]methyl]-1,4′-bipiperidine (5g). The compound was prepared from 4-bromobenzotrifluoride by following the general procedure described above to afford **4** where R^1 = 4-CF_3, which was then converted to compound **5g** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.58 (50% EtOAc/hexanes); HPLC t_R = 5.16 min; ^{1}H NMR $CDCl_3$ δ 7.52 (d, J = 7.8 Hz, 2 H), 7.24 (d, J = 7.7 Hz, 2 H), 7.12 (m, 1 H), 7.00 (d, J = 7.8 Hz, 2 H), 4.11 (m, 1 H), 3.51 (m, 1 H), 3.29 (m, 1 H), 3.00 (m, 1 H), 2.91 (m, 1 H), 2.75 (m, 1 H), 2.58 (d, J = 3.9 Hz, 2 H), 2.26 (s, 3 H), 2.24 (s, 3 H), 1.99−2.09 (m, 3 H), 1.38−1.78 (m, 4 H), 1.16−1.32 (m, 4 H), 0.90 (s, 3 H); mass spectrum FAB+ observed = 473.2788, estimated = 473.2780.

1′-(2,6-Dimethylbenzoyl)-4′-methyl-4-[[4-(trifluoromethoxy)phenyl]methyl]-1,4′-bipiperidine (5h). The compound was prepared from 1-bromo-4-(trifluoromethoxy)benzene by following the general procedure described above to afford **4** where R^1 = 4-OCF_3, which was then converted to compound **5h** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: HPLC t_R = 5.00 min; ^{1}H NMR $CDCl_3$ δ 7.05−7.15 (m, 5 H), 6.98 (d, J = 7.7 Hz, 2 H), 4.09 (m, 1 H), 3.49 (m, 1 H), 3.27 (m, 1 H), 2.83−3.03 (m, 2 H), 2.73 (m, 1 H), 2.49 (d, 2 H), 2.23 (s, 3 H), 2.21 (s, 3 H), 1.85−2.07 (m, 3 H), 1.34−1.75 (m, 4 H), 1.07−1.30 (m, 4 H), 0.86 (s, 3 H); mass spectrum FAB+ observed = 489.2741, estimated = 489.2729.

1′-(2,6-Dimethylbenzoyl)-4′-methyl-4-[(4-methylphenyl)methyl]-1,4′-bipiperidine (5i). The compound was prepared from 4-iodotoluene by following the general procedure described above to afford **4** where R^1 = 4-CH_3, which was then converted to compound **5i** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: HPLC t_R = 4.96 min; ^{1}H NMR $CDCl_3$ δ 6.98−7.14 (m, 7 H), 4.12 (m, 1 H), 3.53 (m, 1 H), 3.30 (m, 1 H), 2.99 (m, 1 H), 2.89 (m, 1 H), 2.75 (m, 1 H), 2.48 (d, J = 3.9 Hz, 2 H), 2.31 (s, 3 H), 2.23 (s, 3 H), 1.87−2.08 (m, 3 H), 1.73 (m, 2 H), 1.61 (s, 3 H), 1.37−1.51 (m, 2 H), 1.08−1.31 (m, 4 H), 0.89 (s, 3 H); mass spectrum FAB+ observed = 419.3064, estimated = 419.3062.

1′-(2,6-Dimethylbenzoyl)-4′-methyl-4-[(4-methoxyphenyl)methyl]-1,4′-bipiperidine (5j). The compound was prepared from 4-iodoanisole by following the general procedure described above to afford **4** where R^1 = 4-OCH_3, which was then converted to compound **5j** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.49 (97:3:1 ratio of CH_2Cl_2:MeOH:NH_4OH); HPLC t_R = 4.66 min; ^{1}H NMR $CDCl_3$ δ 6.96−7.13 (m, 5 H), 6.79 (d, J = 7.7 Hz, 2 H), 4.09 (m, 1 H), 3.76 (s, 3 H), 3.49 (m, 1 H), 3.28 (m, 1 H), 2.97 (m, 1 H), 2.87 (m, 1 H), 2.71 (m, 1 H), 2.44 (d, 2 H), 2.23 (s, 3 H), 2.21 (s, 3 H), 1.86−2.07 (m, 3 H), 1.33−1.76 (m, 4 H), 1.05−1.29 (m, 4 H), 0.86 (s, 3 H); mass spectrum FAB+ observed = 435.3004, estimated = 435.3012.

4-[(4-Acetylphenyl)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (5m). The compound was prepared from 4-iodoacetophenone by following the general procedure

described above to afford **4** where R^1 = 4-$COCH_3$, which was then converted to compound **5m** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: ^{1}H NMR $CDCl_3$ δ 7.83 (d, J = 7.8 Hz, 2 H), 7.19 (m, 2 H), 7.09 (m, 1 H), 6.97 (d, J = 7.7 Hz, 2 H), 4.08 (m, 1 H), 3.50 (m, 1 H), 3.27 (m, 1 H), 2.97 (m, 1 H), 2.89 (m, 1 H), 2.74 (m, 1 H), 2.55 (d, 2 H), 2.54 (s, 3 H), 2.24 (s, 3 H), 2.23 (s, 3 H), 1.87−2.08 (m, 3 H), 1.33−1.78 (m, 4 H), 1.08−1.31 (m, 4 H), 0.87 (s, 3 H); mass spectrum FAB+ observed = 447.3016, estimated = 447.3012.

4-[[(1,1′-Biphenyl)-4-yl]methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (5n). The compound was prepared from 4-bromobiphenyl by following the general procedure described above to afford **4** where R^1 = 4-Ph, which was then converted to compound **5n** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.45 (96:4:1 ratio of CH_2Cl_2:MeOH:NH_4OH); HPLC t_R = 5.33 min; ^{1}H NMR $CDCl_3$ δ 7.29−7.57 (m, 7 H), 7.17 (d, J = 7.8 Hz, 2 H), 7.09 (m, 1 H), 6.99 (m, 2 H), 4.09 (m, 1 H), 3.22−3.71 (m, 2 H), 2.63−3.05 (m, 3 H), 2.54 (d, J = 3.9 Hz, 2 H), 2.36 (m, 1 H), 2.23 (s, 6 H), 1.86−2.06 (m, 3 H), 1.10−1.77 (m, 7 H), 0.87 (s, 3 H); mass spectrum FAB+ observed = 481.3221, estimated = 481.3219.

Preparation of *N*-Trifluoroacetylisonipecotyl Chloride (6). Trifluoroacetic anhydride (TFAA) (300 mL, 210 mmol) was added to isonipecotic acid (96 g, 740 mmol) at 0 °C. Afterward, the mixture was heated at reflux for 4 h. Excess TFAA was removed, and the reaction mixture was taken up in EtOAc, washed with water, and concentrated to give 160 g of the amide. The crude amide (50 g) was treated with 300 mL of thionyl chloride, and the mixture was heated at reflux overnight. Excess thionyl chloride was then removed in vacuo to give 54 g (32%) of the acid chloride **6** which was used in the next step without further purification.

Preparation of 4-(4-Bromobenzoyl)trifluoroacetylpiperidine (7). Aluminum chloride (11.0 g, 82.5 mmol) was added slowly to a solution of acid chloride **6** (10.0 g, 41.0 mmol) in bromobenzene (40 mL, 380 mmol) at ambient temperature, after which the reaction mixture was heated at reflux for 4 h. It was then cooled and poured into a mixture of concentrated HCl and ice, and the product was extracted with EtOAc. The organic layer was separated, washed with water and half-saturated sodium bicarbonate solution, and concentrated to give 16.2 g of the crude ketone **7**: ^{1}H NMR $CDCl_3$ δ 7.75 (d, J = 7.8 Hz, 2 H), 7.60 (d, J = 7.7 Hz, 2 H), 4.41(m, 1 H), 4.00 (m, 1 H), 3.50 (m, 1 H), 3.30 (m, 1 H), 3.07 (m, 1 H), 1.70−2.05 (m, 4 H).

Preparation of 4-[2-(4-Bromophenyl)-1,3-dioxolan-2-yl]-1-triflouroacetylpiperidine (8). The crude ketone **7** (16.2 g, 44.5 mmol) was dissolved in toluene (200 mL) containing ethylene glycol (25 mL) and *p*-toluenesulfonic acid (0.5 g). The mixture was heated at reflux with azeotropic removal of water until no further water was collected. The mixture was concentrated to give 17.4 g of the crude ketal **8**: ^{1}H NMR $CDCl_3$ δ 7.75 (d, J = 7.8 Hz, 2 H), 7.60 (d, J = 7.7 Hz, 2 H), 4.51 (m, 1 H), 3.90−4.00 (m, 3 H), 3.70 (m, 2 H), 2.90 (m, 1 H), 2.55 (m, 1 H), 2.01 (m, 1 H), 1.30−1.80 (m, 4 H).

Preparation of 4-[2-(4-Bromophenyl)-1,3-dioxolan-2-yl]-piperidine (9). The crude ketal **8** (17.4 g, 42 mmol) was dissolved in methanol (100 mL), and to this were added 25 mL of water and 12 g of potassium carbonate. Themixture was stirred at ambient temperature overnight. The mixture was diluted with water and extracted with EtOAc. The organic layer was separated, washed with water and brine, and concentrated to give 12.55 g (95%) of amine **9**: ^{1}H NMR $CDCl_3$ δ 7.45 (d, J = 7.8 Hz, 2 H), 7.25 (d, J = 7.7 Hz, 2 H), 3.98 (m, 2 H), 3.70 (m, 2 H), 3.09 (m, 2 H), 2.40−2.55 (m, 3 H), 1.85 (m, 1 H), 1.70 (m, 1 H), 1.20−1.35 (m, 2 H).

Preparation of 4-[2-(4-Bromophenyl)-1,3-dioxolan-2-yl]-1′-(*tert*-butoxycarbonyl)-4′-cyano-1,4′-bipiperidine (10). To a stirred solution of amine **9** (7.2 g, 23 mmol) and *N*-*tert*-butoxycarbonyl-4-piperidinone (4.8 g, 24 mmol) in 1,2-dichloroethane (20 mL) was added titanium isopropoxide (6.7 mL, 32.3 mmol), and the mixture was stirred for 12 h at room temperature. The mixture was concentrated, and a 1.0 M solution of diethylaluminum cyanide (35 mL) was added at room temperature. The mixture was stirred for 3 h and then diluted with EtOAc. The reaction was quenched with water (5 mL), and the mixture was stirred a further 2 h. The mixture was then filtered through Celite, and the resulting filtrate was concentrated and chromatographed to afford 7.3 g (63%) of compound **10**: R_f 0.25 (20% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.45 (d, J = 7.8 Hz, 2 H), 7.25 (d, J = 7.7 Hz, 2 H), 3.90−4.00 (m, 4 H), 3.70 (m, 2 H), 3.00−3.25 (m, 4 H), 2.00−2.15 (m, 3 H), 1.60−1.85 (m, 4 H), 1.45 (s, 9 H), 1.30−1.45 (m, 4 H).

Preparation of 4-[2-(4-Bromophenyl)-1,3-dioxolan-2-yl]-1′-(*tert*-butoxycarbonyl)-4′-methyl-1,4′-bipiperidine (11). To a stirred solution of cyanide **10** (7.3 g, 14.03 mmol) in THF (100 mL) was added a 3.0 M solution of MeMgBr in ether (14.0 mL, 42 mmol) at room temperature, and the mixture was stirred for 2 h. The reaction was then quenched with saturated aqueous ammonium chloride, and the mixture was extracted twice with methylene chloride. The extracts were concentrated to afford 7.0 g (98%) of the desired methylated compound **11**: R_f 0.36 (35% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.45 (d, J = 7.8 Hz, 2 H), 7.25 (d, J = 7.7 Hz, 2 H), 3.95 (m, 2 H), 3.73 (m, 2 H), 3.25 (m, 2 H), 2.85 (m, 2 H), 1.75−2.00 (m, 3 H), 1.45 (s, 9 H), 1.20−1.75 (m, 10 H), 0.95 (s, 3 H).

Preparation of 4-(4-Bromobenzoyl)-1′-(*tert*-butoxycarbonyl)-4′-methyl-1,4′-bipiperidine (12). The crude ketal **11** was dissolved in EtOAc (100 mL) and 6 N HCl (40 mL), and the mixture was stirred at room temperature for 24 h. The mixture was then neutralized with 20% NaOH and extracted with EtOAc. The organic layer was dried and concentrated to yield 5.0 g (98%) of crude amine. To a stirred solution of this crude amine (5.0 g, 13.6 mmol) in ether (200 mL) were added 10% NaOH (50 mL) and di-*tert*-butylcarbonate (BOC_2O) (2.97 g, 13.6 mmol), and the mixture was stirred at room temperature overnight. The layers were separated, and the organic layer was washed with brine, dried, concentrated, and chromatographed to yield 5.1 g (79%) of Boc-protected amine **12**: R_f 0.50 (35% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.80 (d, J = 7.8 Hz, 2 H), 7.60 (d, J = 7.7 Hz, 2 H), 3.50 (m, 2 H), 3.10−3.25 (m, 3 H), 2.95 (m, 2 H), 2.20 (m, 2 H), 1.75−1.90 (m, 6 H), 1.45 (s, 9 H), 1.20−1.40 (m, 2 H), 0.90 (m, 3 H).

General Procedure for Preparation of Oximes 1, 14a−g, 14l−n, 26−42, 43a, 43d, and 43h. (1) To a stirred solution of ketone **12** (1.5 g, 3.22 mmol) in MeOH (50 mL) were added sodium acetate (5.0 g, 47 mmol) and *O*-alkyl or *O*-aryl hydroxylamine hydrochloride, and the mixture was stirred at room temperature for 24 h. The resulting mixture was then poured into aqueous NaOH (10%) and extracted twice with methylene chloride. The combined extracts were then dried and chromatographed to yield 1.5 g of oxime **13** (94% for ethyl oxime) as a mixture of *E* and *Z* isomers. The isomers could be separated at this point by chromatography. For the ethyl compound: *E* isomer, R_f 0.70 (35% EtOAc/hexanes); *Z* isomer, R_f 0.61 (35% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.50 (d, J = 7.7 Hz, 2 H), 7.09 (d, J = 7.8 Hz, 2 H), 4.05 (q, 2 H), 3.24−3.49 (m, 4 H), 2.94 (m, 2 H), 2.40 (m, 1 H), 2.10 (m, 2 H), 1.76 (m, 4 H), 1.54 (m, 2 H), 1.44 (s, 9 H), 1.33 (m, 2 H), 1.18 (t, 3 H), 0.89 (s, 3 H).

(2) To a stirred solution of **13** (1.5 g, 3.0 mmol) in methylene chloride (10 mL) was added trifluoroacetic acid (3 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated, poured into 10% NaOH, and extracted twice with methylene chloride. The combined extracts were dried and concentrated to afford 1.2 g (100%) of amine. To a stirred solution of this crude amine (1.3 g, 3.2 mmol) in methylene chloride (50 mL) were added substituted benzoic, nicotinic, or nicotinic *N*-oxide acid (4.94 mmol), EDCI (0.94 g, 4.94 mmol), DIPEA (0.84 g, 6.58 mmol), and HOBT (0.66 g, 4.94 mmol), and the mixture was stirred for 12 h at room temperature. The reaction was quenched with saturated $NaHCO_3$, and the mixture was extracted twice with methylene chloride. The combined extracts were dried and concentrated to yield 1.6 g of oxime **14**. The isomers can also be separated

at this point by chromatography. Purity was checked by LC/MS analysis.

General Procedure for Preparation of Oximes 14h−k. (1) To a stirred solution of ketone **12** (2.0 g, 4.30 mmol) in MeOH (50 mL) and THF (50 mL) were added sodium acetate (7.1 g, 86 mmol) and hydroxylamine hydrochloride (5.98 g, 86 mmol), and the mixture was stirred at room temperature for 24 h. The resulting mixture was then poured into aqueous NaOH (10%) and extracted twice with methylene chloride. The combined extracts were then dried and concentrated to give 2.27 g of oxime **13**, where R = H, as a mixture of *E* and *Z* isomers. Oxime isomers could be separated at this point by chromatography: *Z* isomer, R_f 0.25 (35% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.55 (d, J = 7.8 Hz, 2 H), 7.14 (d, J = 7.7 Hz, 2 H), 3.22−3.50 (m, 4 H), 2.94 (m, 2 H), 2.41 (m, 1 H), 2.10 (m, 2 H), 1.78 (m, 4 H), 1.45 (s, 9 H), 1.24−1.60 (m, 4 H), 0.90 (s, 3 H).

(2) To a stirred solution of **13** (0.25 g, 0.52 mmol), where R = H, in THF (3 mL) was added a 0.5 M solution KHMDS (3 equiv) in toluene at 0 °C, and the mixture was stirred at 0 °C for 1 h. Then the alkyl halide (3 equiv) was added, and the mixture was stirred at room temperature for 6 h. The reaction was quenched with water. The resulting mixture was then poured into aqueous NaOH (10%) and extracted twice with methylene chloride. The combined extracts were then dried, concentrated, and chromatographed to yield 0.24 g of oxime **13** (84% for methoxy ethyl). Oxime isomers could be separated at this point by chromatography if not done previously. For the methoxy ethyl compound: R_f 0.47 (35% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.48 (d, J = 7.8 Hz, 2 H), 7.11 (d, J = 7.9 Hz, 2 H), 4.11 (m, 2 H), 3.57 (m, 2 H), 3.25−3.50 (m, 4 H), 3.31 (s, 3 H), 2.91 (m, 2 H), 2.40 (m, 1 H), 2.08 (m, 2 H), 1.75 (m, 4 H), 1.53 (m, 2 H), 1.45 (s, 9 H), 1.31 (m, 2 H), 0.87 (s, 3 H).

(3) Compound **13** was then converted to compound **14** via the procedure described above in the general procedure for oxime **1**. Purity was checked by LC/MS analysis.

4-[(*E*)-(4-Bromophenyl)(methoxyimino)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14b). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **14b** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: HPLC t_R = 4.71 min; ^{1}H NMR $CDCl_3$ δ 7.50 (d, J = 7.7 Hz, 2 H), 7.23 (m, 2 H), 7.10 (m, 1 H), 6.90 (d, J = 7.7 Hz, 2 H), 4.03 (m, 1 H), 3.90 (s, 3 H), 3.55 (m, 1 H), 3.20 (m, 3 H), 3.00 (m, 3 H), 2.82 (m, 1 H), 2.24 (s, 3 H), 2.23 (s, 3 H), 2.15 (m, 3 H), 1.80−1.20 (m, 5 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 526.2070, estimated = 526.2069.

4-[(*Z*)-(4-Bromophenyl)(methoxyimino)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14c). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **14c** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: HPLC t_R = 4.51 min; ^{1}H NMR $CDCl_3$ δ 7.50 (d, J = 7.7 Hz, 2 H), 7.15−6.95 (m, 5 H), 4.15 (m, 1 H), 3.80 (s, 3 H), 3.45 (m, 1 H), 3.25 (m, 1 H), 3.00 (m, 3 H), 2.83 (m, 2 H), 2.24 (s, 3 H), 2.25 (s, 3 H), 2.10 (m, 2 H), 1.80−1.50 (m, 7 H), 0.92 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.3, 159.9, 136.7, 133.7, 133.5, 132.9, 131.4, 129.2, 128.0, 127.4, 122.5, 61.7, 53.9, 44.8, 42.6, 41.7, 36.5, 36.4, 35.6, 32.5, 30.6, 30.5, 19.1, 17.8; mass spectrum FAB+ observed = 526.2072, estimated = 526.2069. Anal. Calcd for $C_{28}H_{36}BrN_3O_2$: C, 63.87; H, 6.89; N, 7.98. Found: C, 63.62; H, 6.91; N, 8.03.

4-[(*E*)-(4-Bromophenyl)(ethoxyimino)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14d). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **14d** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.43 (50% EtOAc/hexanes); HPLC t_R = 5.08 min; ^{1}H NMR $CDCl_3$ δ 7.49 (d, J = 7.8 Hz, 2 H), 7.25 (m, 2 H), 7.21 (m, 1 H), 7.00 (d, J = 7.7 Hz, 2 H), 4.17 (q, 2 H), 4.08 (m, 1 H), 3.54 (m, 1 H), 3.20−3.33 (m, 3 H), 2.98 (m, 2 H), 2.81 (m, 2 H), 2.26 (s, 3 H), 2.23 (s, 3 H), 2.16 (m, 2 H), 1.93 (m, 1 H), 1.56−1.80 (m, 4 H), 1.44 (m, 1 H), 1.29 (t, 3 H), 0.93 (s, 3 H); mass spectrum FAB+ observed = 540.2222, estimated = 540.2226.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14e). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **14e** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.36 (50% EtOAc/hexanes); HPLC t_R = 4.91 min; ^{1}H NMR $CDCl_3$ δ 7.50 (d, J = 7.7 Hz, 2 H), 7.15−6.95 (m, 5 H), 4.15 (m, 1 H), 4.05 (q, J = 7.1 Hz, 2 H), 3.20−3.55 (m, 2 H), 2.90−3.05 (m, 2 H), 2.80 (m, 1 H), 2.35 (m, 1 H), 2.24 (m, 3 H), 2.25 (s, 3 H), 2.10 (m, 2 H), 1.40−2.00 (m, 7 H), 1.25 (m, 1 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 540.5210, estimated = 540.5269.

4-[(*Z*)-(4-Bromophenyl)(hydroxyimino)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14f). The compound was prepared from hydroxylamine hydrochloride by following the general procedure described above to afford the hydroxyoxime, which was then converted to compound **14f** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.20 (75% EtOAc/hexanes); HPLC t_R = 4.66 min; ^{1}H NMR $CDCl_3$ δ 7.49 (d, J = 7.8 Hz, 2 H), 7.24 (m, 2 H), 7.08−7.17 (m, 1 H), 6.99 (d, J = 7.8 Hz, 2 H), 3.98 (m, 1 H), 3.65 (m, 1 H), 3.25 (m, 2 H), 3.02 (m, 2 H), 2.86 (m, 1 H), 2.26 (s, 3 H), 2.24 (s, 3 H), 2.15 (m, 2 H), 1.93 (m, 1 H), 1.60−1.84 (m, 4 H), 1.49 (m, 1 H), 1.22−1.38 (m, 2 H), 0.96 (s, 3 H); mass spectrum FAB+ observed = 514.1896, estimated = 514.1892.

4-[(*Z*)-(4-Bromophenyl)[(1,1-dimethylethoxy)imino]-methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14g). The compound was prepared from *O*-(*tert*-butyl)hydroxylamine hydrochloride by following the general procedure described above to afford the *tert*-butyloxime, which was then converted to compound **14g** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.40 (35% EtOAc/hexanes); HPLC t_R = 5.26 min; ^{1}H NMR $CDCl_3$ δ 7.48 (d, J = 7.8 Hz, 2 H), 7.08−7.18 (m, 3 H), 7.00 (d, J = 7.7 Hz, 2 H), 4.10 (m, 1 H), 3.54 (m, 1 H), 3.29 (m, 1 H), 2.98 (m, 2 H), 2.82 (m, 1 H), 2.43 (m, 1 H), 2.29 (s, 3 H), 2.25 (s, 3 H), 1.65−2.20 (m, 8 H), 1.31−1.58 (m, 2 H), 1.26 (s, 9 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 568.2554, estimated = 568.2539.

4-[(4-Bromophenyl)[(*Z*)-(1-methylethyl)imino]methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14h). The compound was prepared from 2-iodopropane by following the general procedure described above to afford the isopropyloxime, which was then converted to compound **14h** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.51 (35% EtOAc/hexanes); HPLC t_R = 5.56 min; ^{1}H NMR $CDCl_3$ δ 7.50 (d, J = 7.7 Hz, 2 H), 7.09−7.16 (m, 3 H), 7.00 (d, J = 7.8 Hz, 2 H), 4.28 (m, 1 H), 4.12 (m, 1 H), 3.47 (m, 1 H), 3.28 (m, 1 H), 2.97 (m, 2 H), 2.82 (m, 1 H), 2.40 (m, 1 H), 2.27 (s, 3 H), 2.24 (s, 3 H), 2.10 (m, 2 H), 1.96 (m, 1 H), 1.22−1.82 (m, 7 H), 1.17 (s, 3 H), 1.15 (s, 3 H), 0.91 (s, 3 H); mass spectrum FAB+ observed = 554.2387, estimated = 554.2382.

4-[(*Z*)-(4-Bromophenyl)[(2-hydroxyethoxy)imino]-methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14i). The compound was prepared from (2-bromoethoxy)-*tert*-butyldimethylsilane by following the general procedure described above to afford the TBS-protected ethoxyoxime. The protected alcohol was then treated with tetrabutylammonium fluoride (3 equiv) in THF for 1.5 h to afford the hydroxyethoxyoxime, which was then converted to compound **14i** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.51 (100% EtOAc); HPLC t_R = 4.40 min; ^{1}H NMR $CDCl_3$ δ 7.54 (d, 2 H),

7.10−7.16 (m, 3 H), 7.00 (d, 2 H), 4.13 (br t, 2 H), 3.85 (br t, 2 H), 3.45 (m, 1 H), 3.27 (m, 1 H), 2.99 (m, 2 H), 2.85 (m, 1 H), 2.65 (m, 1 H), 2.40 (m, 1 H), 2.26 (s, 3 H), 2.23 (s, 3 H), 2.20 (m, 2 H), 1.95 (m, 1 H), 1.18−1.83 (m, 7 H), 0.91 (s, 3 H); mass spectrum FAB+ observed = 558.2166, estimated = 558.2154.

4-[(4-Bromophenyl)[(2-methoxyethoxy)imino]methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14j). The compound was prepared from 2-bromoethyl methyl ether by following the general procedure described above to afford the methoxyethoxyoxime, which was then converted to compound **14j** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.43 (50% EtOAc/hexanes); HPLC t_R = 4.91 min; ^{1}H NMR $CDCl_3$ δ (mix of isomers) 7.50 (m, 2 H), 7.25 (m, 2 H), 7.12 (m, 1 H), 7.01 (d, J = 7.8 Hz, 2 H), 4.15 and 4.27 (m, 2 H), 3.58 and 3.68 (m, 2 H), 3.35 and 3.42 (s, 3 H), 3.25 (m, 1 H), 2.77−3.06 (m, 3 H), 2.40 (m, 1 H), 2.28 (s, 3 H), 2.24 (s, 3 H), 1.14−2.19 (m, 12 H), 0.93 and 0.91 (s, 3 H); mass spectrum FAB+ observed = 570.2325, estimated = 570.2331.

Ethyl[(4-bromophenyl)[1′-(2,6-dimethylbenzoyl)-4′-methyl-[1,4′-bipiperidin]-4-yl]methylene]aminooxyacetate (14k). The compound was prepared from ethyl bromoacetate by following the general procedure described above to afford the ethylacetateoxime, which was then converted to compound **14k** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.49 (50% EtOAc/hexanes); HPLC t_R = 5.01 min; ^{1}H NMR $CDCl_3$ δ (mix of isomers) 7.51 (m, 2 H), 7.24 (m, 2 H), 7.20 (m, 1 H), 7.00 (d, J = 7.7 Hz, 2 H), 4.54 and 4.69 (s, 2 H), 4.10−4.25 (q, 2 H), 4.04 (m, 1 H), 3.55 (m, 1 H), 3.26 (m, 2 H), 2.99 (m, 2 H), 2.82 (m, 1 H), 2.41 (m, 1 H), 2.24 (s, 3 H), 2.22 (s, 3 H), 2.15−2.21 (m, 2 H), 1.36−1.99 (m, 7 H), 1.25−1.31 (t, 3 H), 0.93 and 0.91 (s, 3 H); mass spectrum FAB+ observed = 598.2272, estimated = 598.2280.

(*Z*)-2-[(4-Bromophenyl)[1′-(2,6-dimethylbenzoyl)-4′-methyl-[1,4′-bipiperidin]-4-yl]methylene]aminooxy-*N*-methylacetamide (14l). The compound was prepared from carboxymethoxylamine hemihydrochloride by following the general procedure described above to afford the carboxymethoxime, which was then converted to the amide in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid. The carboxymethoxime was then converted to compound **14l** by treatment with methylamine (1 equiv), EDCI (1 equiv), and HOBT (1 equiv) in methylene chloride for 10 h followed by purification via chromatography: R_f 0.55 (20% EtOH/EtOAc); ^{1}H NMR $CDCl_3$ δ 7.47 (d, J = 7.7 Hz, 2 H), 7.25 (m, 2 H), 7.12 (m, 1 H), 6.99 (d, J = 7.8 Hz, 2 H), 4.81 (s, 2 H), 4.04 (m, 1 H), 3.55 (m, 1 H), 3.28 (m, 2 H), 2.80−3.02 (m, 3 H), 2.98 (s, 3 H), 2.27 (s, 3 H), 2.24 (s, 3 H), 2.18 (m, 2 H), 1.55−1.97 (m, 5 H), 1.20−1.52 (m, 3 H), 0.91 (s, 3 H); mass spectrum FAB+ observed = 583.2295, estimated = 583.2284.

4-[(*Z*)-(4-Bromophenyl)(phenoxyimino)methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14m). The compound was prepared from *O*-phenylhydroxylamine hydrochloride by following the general procedure described above to afford the phenyloxime, which was then converted to compound **14m** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.55 (50% EtOAc/hexanes); HPLC t_R = 5.76 min; ^{1}H NMR $CDCl_3$ δ 7.55 (d, J = 7.8 Hz, 2 H), 6.95−7.30 (m, 10 H), 4.18 (m, 1 H), 3.49 (m, 2 H), 3.30 (m, 1 H), 3.01 (m, 2 H), 2.89 (m, 1 H), 2.54 (m, 1 H), 2.27 (s, 3 H), 2.24 (s, 3 H), 2.15 (m, 1 H), 1.82−2.04 (m, 3 H), 1.58−1.81 (m, 3 H), 1.20−1.50 (m, 2 H), 0.93 (s, 3 H); mass spectrum FAB+ observed = 588.2222, estimated = 588.2228.

4-[(*E*/*Z*)-(4-Bromophenyl)[(phenylmethoxy)imino]methyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (14n). The compound was prepared from *O*-benzylhydroxylamine hydrochloride by following the general procedure described above to afford the benzyloxime, which was then converted to compound **14n** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: R_f 0.57 (50% EtOAc/hexanes); HPLC t_R = 5.43 min; ^{1}H NMR $CDCl_3$ δ 7.50 (d, J = 7.7 Hz, 2 H), 7.24−7.39 (m, 5 H), 7.00−7.17 (m, 5 H), 5.05 (s, 2 H), 4.13 (m, 1 H), 3.47 (m, 1 H), 3.28 (m, 1 H), 2.97 (m, 2 H), 2.80 (m, 1 H), 2.40 (m, 1 H), 2.27 (s, 3 H), 2.23 (s, 3 H), 1.89−2.17 (m, 3 H), 1.69−1.82 (m, 3 H), 1.19−1.65 (m, 4 H), 0.91 (s, 3 H); mass spectrum FAB+ observed = 602.2388, estimated = 602.2382.

1′-(2-Amino-6-chlorobenzoyl)-4-[(*Z*)-(4-bromophenyl)(methoxyimino)methyl]-4′-methyl-1,4′-bipiperidine (26). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **26** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2-amino-6-chlorobenzoic acid. Compound **26** exists as a mixture of nonseparable rotational isomers: HPLC t_R = 4.56 min; ^{1}H NMR $CDCl_3$ δ 7.55 (m, 2 H), 7.30 (m, 2 H), 7.15 (t, J = 7.7 Hz, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.60 (d, J = 7.8 Hz, 1 H), 4.25 (m, 2 H), 3.80 (s, 2 H), 3.40 (m, 2 H), 2.80−3.20 (m, 4 H), 2.40 (m, 2 H), 1.40−2.20 (m, 8 H), 0.90 (s, 3 H); mass spectrum FAB+ observed = 549.2133, estimated = 526.2130.

1′-(2-Hydroxy-6-methylbenzoyl)-4-[(*Z*)-(4-bromophenyl)(methoxyimino)methyl]-4′-methyl-1,4′-bipiperidine (27). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **27** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2-hydroxy-6-methyl benzoic acid. Compound **27** exists as a mixture of nonseparable rotational isomers: HPLC t_R = 4.41 min; ^{1}H NMR $CDCl_3$ δ 7.55 (m, 2 H), 7.15 (m, 1 H), 6.90 (m, 2 H), 6.35 (m, 1 H), 6.20 (m, 1 H), 4.40 (m, 2 H), 4.00−4.20 (m, 1 H), 3.80 and 3.75 (s, 3 H), 3.20−3.56 (m, 3 H), 2.80−3.20 (m, 4 H), 2.40 (m, 2 H), 2.10 (s, 3 H), 1.20−1.90 (m, 6 H), 0.90 (s, 3 H); Anal. Calcd for $C_{27}H_{35}BrClN_3O_3 \cdot H_2O$ (hydrochloride salt): C, 55.72; H, 6.01; N, 7.22. Found: C, 55.91; H, 6.36; N, 6.86.

1′-(2-Amino-6-methylbenzoyl)-4-[(*Z*)-(4-bromophenyl)(methoxyimino)methyl]-4′-methyl-1,4′-bipiperidine (28). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **28** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2-amino-6-methylbenzoic acid. Compound **28** exists as a mixture of nonseparable rotational isomers: HPLC t_R = 4.36 min; ^{1}H NMR $CDCl_3$ δ 7.55 (d, J = 7.8 Hz, 2 H), 7.25 (m, 2 H), 7.15 (m, 1 H), 6.50−6.60 (m, 2 H), 4.25 (m, 1 H), 4.05 (m, 1 H), 3.80 (s, 3 H), 3.50 (m, 1 H), 3.40 (m, 2 H), 3.17 (m, 1 H), 2.95 (m, 1 H), 2.83 (m, 1 H), 2.40 (m, 1 H), 2.02 and 1.98 (s, 3 H), 2.20 (m, 2 H), 1.95 (m, 1 H), 1.78 (m, 1 H), 1.22−1.65 (m, 4 H), 0.90 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.6, 168.4, 159.8, 143.0, 142.7, 134.7, 134.6, 132.9, 132.8, 131.3, 129.1, 129.0, 123.1, 122.9, 122.4, 120.0, 113.4, 113.4, 61.7, 53.9, 44.7, 42.6, 42.1, 42.0, 36.9, 36.8, 35.7, 36.5, 35.7, 35.6, 30.5, 35.7, 35.6, 30.6, 30.5, 19.2, 19.1, 17.9, 16.6; mass spectrum FAB+ observed = 529.1017, estimated = 529.1015.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-1′-[2-fluoro-6-(trifluoromethyl)benzoyl]-4′-methyl-1,4′-bipiperidine (29). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **29** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2-fluoro-6-(trifluoromethyl)benzoic acid. Compound **29** exists as a mixture of nonseparable rotational isomers: R_f 0.65 (35% EtOAc/hexanes); HPLC t_R = 5.36 min; ^{1}H NMR $CDCl_3$ δ 7.48−7.54 (m, 4 H), 7.30 (m, 1 H), 7.12 (d, J = 7.7 Hz, 2 H), 4.19 (m, 1 H), 4.07 (q, J = 8.0 Hz, 2 H), 3.39 (m, 2 H), 2.76−3.05 (m, 3 H), 2.40 (m, 1 H), 1.90−2.17 (m, 3 H), 1.78 (m, 3 H), 1.25−1.62 (m, 4 H), 1.20 (t, J = 8.0 Hz, 3 H), 0.91 (s, 3 H); mass spectrum FAB+ observed = 600.1688, estimated = 600.1672.

4-[(*Z*)-(4-Bromophenyl)(methoxyimino)methyl]-1′-[(2,6-dimethyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipiperidine (30a). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure de-

scribed above to afford the methoxime, which was then converted to compound **30a** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid: R_f 0.72 (20% EtOH/EtOAc); HPLC t_R = 3.66 min; ^{1}H NMR $CDCl_3$ δ 8.33 (d, J = 7.8 Hz, 1 H), 7.51 (d, J = 7.7 Hz, 2 H), 7.09 (d, J = 7.8 Hz, 2 H), 6.98 (d, J = 7.8 Hz, 1 H), 4.26 (m, 1 H), 3.80 (s, 3 H), 3.31 (m, 1 H), 2.91−3.04 (m, 4 H), 2.85 (m, 1 H), 2.48 and 2.45 (s, 3 H), 2.25 and 2.23 (s, 3 H), 1.71−2.19 (m, 7 H), 1.20−1.63 (m, 3 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 527.2021, estimated = 527.2022.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-1′-[(2,6-dimethyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipiperidine (30b). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **30b** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid: R_f 0.75 (20% EtOH/EtOAc); HPLC t_R = 3.98 min; ^{1}H NMR $CDCl_3$ δ 8.35 (d, J = 7.8 Hz, 1 H), 7.51 (d, J = 7.7 Hz, 2 H), 7.11 (d, J = 7.6 Hz, 2 H), 6.97 (d, J = 7.8 Hz, 1 H), 4.19 (m, 1 H), 4.06 (q, J = 7.1 Hz, 2 H), 3.24−3.50 (m, 2 H), 2.97 (m, 2 H), 2.81 (m, 1 H), 2.47 and 2.49 (s, 3 H), 2.40 (m, 1 H), 2.26 and 2.28 (s, 3 H), 1.92−2.18 (m, 3 H), 1.35−1.85 (m, 7 H), 1.19 (t, J = 7.1 Hz, 3 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 541.2188, estimated = 541.2178.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-4′-methyl-1′-[(2-methyl-3-pyridinyl)carbonyl]-1,4′-bipiperidine (31). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **31** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2-methylnicotinic acid: HPLC t_R = 3.90 min; ^{1}H NMR $CDCl_3$ δ 8.53 (d, J = 7.8 Hz, 1 H), 7.45−7.55 (m, 3 H), 7.09−7.55 (m, 3 H), 4.13 (m, 1 H), 4.01 (m, 2 H), 3.72 (m, 1 H), 3.39 (m, 2 H), 3.00 (m, 2 H), 2.83 (m, 1 H), 2.54 (s, 3 H), 2.41 (m, 1 H), 2.11 (m, 2 H), 1.98 (m, 1 H), 1.67−1.86 (m, 3 H), 1.35−1.67 (m, 3 H), 1.18−1.24 (m, 3 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 527.2025, estimated = 527.2022.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-4′-methyl-1′-(3-pyridinylcarbonyl)-1,4′-bipiperidine (32). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **32** in the subsequent steps by removal of the Boc and treatment of the resulting amine with nicotinic acid: HPLC t_R = 4.15 min; ^{1}H NMR $CDCl_3$ δ 8.66 (br s, 2 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.56 (d, J = 7.7 Hz, 2 H), 7.34 (m, 1 H), 7.11 (d, J = 7.8 Hz, 2 H), 4.03−4.10 (m, 2 H), 3.49 (m, 2 H), 3.30 (m, 1 H), 2.78−3.02 (m, 2 H), 2.43 (m, 1 H), 2.12 (m, 2 H), 1.97 (m, 1 H), 1.79 (m, 3 H), 1.24−1.65 (m, 5 H), 1.18−1.22 (m, 3 H), 0.93 (s, 3 H); mass spectrum FAB+ observed = 513.1863, estimated = 513.1865.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-1′-[(6-hydroxy-2,4-dimethyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipiperidine (33). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **33** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 6-hydroxy-2,4-dimethylnicotinic acid: R_f 0.60 (20% EtOH/EtOAc); HPLC t_R = 4.17 min; ^{1}H NMR $CDCl_3$ δ 7.53 (d, J = 7.8 Hz, 2 H), 7.12 (d, J = 7.8 Hz, 2 H), 6.28 (s, 1 H), 4.15 (m, 1 H), 4.07 (q, J = 7.7 Hz, 2 H), 3.38 (m, 2 H), 3.17 (m, 1 H), 2.71−3.01 (m, 2 H), 2.02 (m, 1 H), 2.28 and 2.31 (s, 3 H), 2.13 and 2.15 (s, 3 H), 1.72−2.09 (m, 5 H), 1.24−1.65 (m, 5 H), 1.20 (t, J = 7.7 Hz, 3 H), 0.93 (s, 3 H); mass spectrum FAB+ observed = 557.2124, estimated = 557.2127.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-1′-[(2-hydroxy-4,6-dimethyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipiperidine (34). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **34** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2-hydroxy-4,6-dimethylnicotinic acid: ^{1}H NMR $CDCl_3$ δ 7.50 (d, J = 7.8 Hz, 2 H), 7.11 (d, J = 7.7 Hz, 2 H), 5.89 (s, 1 H), 4.11 (m, 1 H), 4.01−4.08 (q, 2 H), 3.10−3.53 (m, 3 H), 2.80−2.99 (m, 2 H), 2.39 (m, 1 H), 2.23 (s, 3 H), 2.15 and 2.12 (s, 3 H), 1.67−2.01 (m, 5 H), 1.24−1.63 (m, 5 H), 1.18 (t, 3 H), 0.90 and 0.89 (s, 3 H).

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-1′-[(4-hydroxy-2-methyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipiperidine (35). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **35** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2-hydroxy-4-methylnicotinic acid: HPLC t_R = 4.21 min; ^{1}H NMR $CDCl_3$ δ 7.51 (d, J = 7.3 Hz, 2 H), 7.30 (d, J = 10.3 Hz, 1 H), 7.10 (d, J = 7.3 Hz, 2 H), 6.42 (d, J = 10.3 Hz, 1 H), 4.10 (m, 1 H), 4.04 (q, J = 7.7 Hz, 2 H), 3.41 (m, 2 H), 3.22 (m, 2 H), 2.90 (m, 2 H), 2.37 (s, 3 H), 2.12 (m, 2 H), 1.73−1.96 (m, 4 H), 1.35−1.60 (m, 4 H), 1.21 (t, J = 7.7 Hz, 3 H), 0.91 (s, 3 H); mass spectrum FAB+ observed = 543.1974, estimated = 543.1971.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-1′-[(2,6-dimethyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (1). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **1** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: R_f 0.29 (20% EtOH/EtOAc); HPLC t_R = 4.43 min; ^{1}H NMR $CDCl_3$ δ 8.15 (d, J = 7.8 Hz, 1 H), 7.25 (AB system, 4 H), 7.00 (d, J = 7.8 Hz, 1 H), 4.20 (m, 1 H), 4.02 (q, J = 7.1 Hz, 2 H), 3.25−3.45 (m, 2 H), 2.80−3.00 (m, 3 H), 2.47 and 2.44 (s, 3 H), 2.24 and 2.27 (s, 3 H), 2.10 (m, 3 H), 1.20−1.85 (m, 8 H), 1.20 (t, J = 7.1 Hz, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.1, 164.7, 159.1, 145.0, 138.3, 133.0, 131.3, 129.3, 124.8, 122.3, 69.4, 53.8, 44.8, 44.7, 42.4, 42.0, 37.0, 36.9, 36.4, 36.3, 35.5, 32.5, 30.6, 18.4, 18.0, 17.8, 15.2, 15.2, 14.6; mass spectrum FAB+ observed = 557.2130, estimated = 557.2127. Anal. Calcd for $C_{32}H_{43}BrN_4O_9$ (tartarate salt): C, 54.32; H, 6.13; N, 7.92. Found: C, 54.37; H, 6.43; N, 7.58.

Preparation of 2,6-Dimethylnicotinic Acid *N*-Oxide. To a stirred solution of 2,6-dimethylnicotinic acid (2.0 g, 13.2 mmol) in DMF-MeOH (100−40 mL) was added a 48% solution of THF (1.0 mL, 23.8 mmol) followed by 3-chloroperoxybenzoic acid (6.1 g, 26.5 mmol). The reaction mixture was stirred at room temperature for 24 h before being poured into cold water (300 mL) with stirring. The reaction mixture was then filtered, and the filtrate was concentrated in vacuo. The resulting precipitate was then washed with chloroform and dried to afford 1.36 g (61%) of the *N*-oxide as a white solid: ^{1}H NMR DMSO-d_6 δ 8.2 (d, J = 6.9 Hz, 1 H), 7.15 (d, J = 6.9 Hz, 1 H), 2.30 (s, 3 H), 2.00 (s, 3 H).

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-4′-methyl-1′-(3-pyridinylcarbonyl)-1,4′-bipiperidine *N*-Oxide (36). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **36** in the subsequent steps by removal of the Boc and treatment of the resulting amine with nicotinic acid *N*-oxide: HPLC t_R = 4.12 min; ^{1}H NMR $CDCl_3$ δ 8.22 (br s, 2 H), 7.54 (d, J = 7.8 Hz, 2 H), 7.24−7.35 (m, 2 H), 7.10 (d, J = 7.7 Hz, 2 H), 4.10 (m, 1 H), 4.03−4.08 (q, 2 H), 3.20−3.55 (m, 3 H), 2.78−3.00 (m, 2 H), 2.44 (m, 1 H), 2.14 (m, 2 H), 1.98 (m, 1 H), 1.67−1.89 (m, 3 H), 1.25−1.61 (m, 4 H), 1.18−1.22 (t, 3 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 529.1803, estimated = 529.1814.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-4′-methyl-1′-[(2-methyl-3-pyridinyl)carbonyl]-1,4′-bipiperidine *N*-Oxide (37). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then

converted to compound **37** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2-methylnicotinic acid *N*-oxide: R_f 0.43 (20% EtOH/EtOAc); HPLC t_R = 4.36 min; ^{1}H NMR $CDCl_3$ δ 8.25 (d, 1 H), 7.51 (d, J = 7.6 Hz, 2 H), 7.09−7.20 (m, 4 H), 4.14 (m, 1 H), 4.04 (q, J = 8.0 Hz, 2 H), 3.38 (m, 2 H), 2.76−3.05 (m, 3 H), 2.49 and 2.46 (s, 3 H), 2.40 (m, 1 H), 2.10 (m, 2 H), 1.97 (m, 1 H), 1.78 (m, 3 H), 1.32−1.65 (m, 4 H), 1.20 (t, J = 8.0 Hz, 3 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 543.1969, estimated = 543.1971.

4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)methyl]-4′-methyl-1′-[(3-methyl-2-pyridinyl)carbonyl]-1,4′-bipiperidine *N*-Oxide (38). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **38** in the subsequent steps by removal of the Boc and treatment of the resulting amine with 2-methylpicolinic acid *N*-oxide: ^{1}H NMR $CDCl_3$ δ 8.03 (m, 2 H), 7.51 (d, J = 7.8 Hz, 2 H), 7.12 (m, 3 H), 4.17 (m, 1 H), 3.99−4.08 (q, 2 H), 3.24−3.75 (m, 5 H), 2.39 (m, 1 H), 2.31 and 2.27 (s, 3 H), 1.83−2.18 (m, 5 H), 1.45−1.82 (m, 5 H), 1.15−1.22 (t, 3 H), 0.89 (s, 3 H).

4-[(*Z*)-(4-Bromophenyl)(methoxyimino)methyl]-1′-[(2,6-dimethyl-3-pyridinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (39a). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **39a** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: R_f 0.55 (20% EtOH/EtOAc); HPLC t_R = 4.16 min; ^{1}H NMR $CDCl_3$ δ 8.15 (d, J = 7.8 Hz, 1 H), 7.53 (d, J = 7.7 HZ, 2 H), 7.09 (d, J = 7.6 Hz, 2 H), 6.99 (d, J = 7.8 Hz, 1 H), 4.19 (m, 1 H), 3.81 (s, 3 H), 3.33 (m, 2 H), 2.97 (m, 2 H), 2.82 (m, 1 H), 2.44 (s, 3 H), 2.25 (s, 3 H), 1.96−2.20 (m, 2 H), 1.70−1.90 (m, 5 H), 1.16−1.65 (m, 4 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 545.1949, estimated = 545.1920.

1′-[(2,4-Dimethyl-3-pyridinyl)carbonyl]-4′-methyl-4-[(*Z*)-[4-(methylsulfonyl)phenyl](methoxyimino)methyl]-1,4′-bipiperidine *N*-Oxide (39d). The bromide **12** was treated with sodium thiomethoxide (2.5 equiv) in DMF at 70 °C for 24 h to afford the methylsulfide compound. The sulfide was then oxidized with Oxone (3 equiv) in methanol at 0 °C for 4 h, concentrated, and chromatographed to afford the methylsulfone (82%). The compound was then prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **39d** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: R_f 0.51 (20% EtOH/EtOAc); HPLC t_R = 3.16 min; ^{1}H NMR $CDCl_3$ δ 8.14 (d, J = 7.8 Hz, 1 H), 7.95 (d, J = 7.3 Hz, 2 H), 7.39 (d, J = 7.0 Hz, 2 H), 6.99 (d, J = 7.8 Hz, 1 H), 4.16 (m, 1 H), 3.79 (s, 3 H), 3.24−3.40 (m, 2 H), 3.07 (s, 3 H), 2.97 (m, 2 H), 2.82 (m, 1 H), 2.43 and 2.42 (s, 3 H), 2.24 (br s, 3 H), 1.95−2.18 (m, 3 H), 1.70−1.88 (m, 3 H), 1.16−1.66 (m, 5 H), 0.92 (br s, 3 H); mass spectrum FAB+ observed = 543.2654, estimated = 543.2641.

1′-[(2,4-Dimethyl-3-pyridinyl)carbonyl]-4′-methyl-4-[(*Z*)-[4-(methylsulfonyl)phenyl](ethoxyimino)methyl]-1,4′-bipiperidine *N*-Oxide (39h). The bromide **12** was treated with sodium thiomethoxide (2.5 equiv) in DMF at 70 °C for 24 h to afford the methylsulfide compound. The sulfide was then oxidized with Oxone (3 equiv) in methanol at 0 °C for 4 h, concentrated, and chromatographed to afford the methylsulfone (82%). The compound was then prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **39h** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: R_f 0.49 (20% EtOH/EtOAc); HPLC t_R = 3.43 min; ^{1}H NMR $CDCl_3$ δ 8.13 (d, J = 7.8 Hz, 1 H), 7.95 (d, J = 7.7 Hz, 2 H), 7.40 (d, J = 7.7 Hz, 2 H), 6.99 (d, J = 7.6 Hz, 1 H), 4.20 (m, 1 H), 4.01−4.10 (q, 2 H), 3.24−3.38 (m, 2 H), 3.18 (s, 3 H), 2.97 (m, 2 H), 2.82 (m, 1 H), 2.43 and 2.41 (s, 3 H), 2.23 (br s, 3 H), 1.92−2.19 (m, 3 H), 1.70−1.87 (m, 3 H), 1.23−1.63 (m, 5 H), 1.15−1.19 (t, 3 H), 0.92 (br s, 3 H); mass spectrum FAB+ observed = 557.2800, estimated = 557.2798.

Preparation of 1′-(2,6-Dimethylbenzoyl)-4′-methyl-4-[[4-(methylthio)phenyl]methyl]-1,4′-bipiperidine (5k). Compound **12** was converted to the amide in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid. The aryl bromide was then treated with sodium thiomethoxide (2.5 equiv) in DMF at 70 °C for 24 h to afford the methylsulfide compound. Next, the ketone was reduced with $NaBH_4$ (2.5 equiv) in methanol for 1 h followed by treatment with excess triethylsilane (50 equiv) and excess TFA (100 equiv) at 50 °C for 1 h. The mixture was concentrated and chromatographed to afford compound **5k**: R_f 0.29 (75% EtOAc/hexanes); HPLC t_R = 4.85 min; ^{1}H NMR $CDCl_3$ δ 7.18 (d, J = 7.8 Hz, 2 H), 6.98−7.15 (m, 5 H), 4.10 (m, 1 H), 3.52 (m, 1 H), 3.30 (m, 1 H), 3.00 (m, 1 H), 2.90 (m, 1 H), 2.74 (m, 1 H), 2.48 (m, 2 H), 2.45 (s, 3 H), 2.25 (s, 3 H), 2.22 (s, 3 H), 1.87−2.08 (m, 3 H), 1.64 (m, 2 H), 1.44 (m, 2 H), 1.10−1.33 (m, 4 H), 0.90 (s, 3 H); mass spectrum FAB+ observed = 451.2776, estimated = 451.2783.

Preparation of 1′-(2,6-Dimethylbenzoyl)-4′-methyl-4-[[4-(methylsulfonyl)phenyl]methyl]-1,4′-bipiperidine (5l). Compound **5k** was treated with sodium perborate (2.1 equiv) in acetic acid for 24 h, concentrated, and chromatographed to afford compound **5l**: HPLC t_R = 4.11 min; ^{1}H NMR $CDCl_3$ δ 7.85 (d, J = 7.8 Hz, 2 H), 7.32 (d, J = 7.7 Hz, 2 H), 7.12 (m, 1 H), 7.00 (d, J = 7.8 Hz, 2 H), 4.11 (m, 1 H), 3.52 (m, 1 H), 3.29 (m, 1 H), 3.04 (s, 3 H), 3.00 (m, 1 H), 2.92 (m, 1 H), 2.78 (m, 1 H), 2.62 (m, 2 H), 2.27 (s, 3 H), 2.25 (s, 3 H), 1.89−2.09 (m, 3 H), 1.37−1.80 (m, 4 H), 1.16−1.33 (m, 4 H), 0.90 (s, 3 H); mass spectrum FAB+ observed = 483.2690, estimated = 483.2681.

Preparation of 4-(4-Bromobenzoyl)-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (21). Compound **12** was converted to the amide in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid to afford compound **21**: HPLC t_R = 4.86 min; ^{1}H NMR $CDCl_3$ δ 7.80 (d, J = 9.7 Hz, 2 H), 7.60 (d, J = 9.7 Hz, 2 H), 7.00 (m, 3 H), 4.07 (m, 1 H), 2.86−3.51 (m, 6 H), 2.32 (s, 6 H), 2.24 (m, 2 H), 1.68−2.02 (m, 6 H), 1.49 (m, 1 H), 1.31 (m, 1 H), 0.96 (s, 3 H); mass spectrum FAB+ observed = 497.1801, estimated = 497.1804.

Preparation of 4-[(4-Bromophenyl)hydroxymethyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (22). Compound **12** was converted to the amide in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid. The ketone was then reduced by treatment with $NaBH_4$ (25 equiv) in methanol for 1 h. The mixture was concentrated and chromatographed to afford the alcohol **22**: HPLC t_R = 4.61 min; ^{1}H NMR $CDCl_3$ δ 7.47 (d, J = 7.8 Hz, 2 H), 7.09−7.20 (m, 3 H), 6.99 (d, J = 7.7 Hz, 2 H), 4.37 (m, 1 H), 4.10 (m, 1 H), 2.67−3.58 (m, 6 H), 2.25 (s, 6 H), 1.15−2.14 (m, 11 H), 0.89 (s, 3 H); mass spectrum FAB+ observed = 501.1944, estimated = 501.1944.

Preparation of 4-[1-(4-Bromophenyl)ethyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (23). Compound **12** was converted to the amide in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid. The ketone was then treated with a 3.0 M MeMgBr solution (3 equiv) in THF for 1 h to afford the tertiary alcohol, which was then reduced by treatment with excess triethylsilane (50 equiv) and excess TFA (100 equiv) at 50 °C for 24 h. The mixture was concentrated and chromatographed to afford compound **23**: ^{1}H NMR $CDCl_3$ δ 7.40 (d, J = 7.7 Hz, 2 H), 7.13 (m, 1 H), 7.02 (m, 4 H), 4.98 (m, 1 H), 4.07 (m, 1 H), 3.19−3.75 (m, 5 H), 2.30−3.04 (m, 5 H), 2.25 (s, 3 H), 2.23 (s, 3 H), 1.35−2.19 (m, 6 H), 1.21 (br d, 3 H), 0.89 (s, 3 H); mass spectrum FAB+ observed = 499.2142, estimated = 499.2147.

Preparation of 4-[1-(4-Bromophenyl)ethenyl]-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (24). Methyl triphenylphosphonium bromide (1.6 equiv) was dissolved in THF, and BuLi (1.6 equiv) was added dropwise at −78 °C. The

mixture was stirred at −40 °C for 30 min. The mixture was recooled to −78 °C, and **12** (1 equiv) in THF was added dropwise. The mixture was stirred for 20 h, gradually warming to room temperature. The crude material was then converted to **24** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylbenzoic acid: ^{1}H NMR $CDCl_3$ δ 7.41 (d, J = 7.6 Hz, 2 H), 7.15 (d, J = 7.7 Hz, 2 H), 7.09 (m, 1 H), 6.98 (d, J = 7.6 Hz, 2 H), 5.14 (s, 1 H), 5.01 (s, 1 H), 4.13 (m, 1 H), 3.46 (m, 1 H), 3.27 (m, 1 H), 2.99 (m, 2 H), 2.81 (m, 1 H), 2.25 (s, 3 H), 2.22 (s, 3 H), 1.90−2.19 (m, 3 H), 1.61−1.84 (m, 4 H), 1.18−1.50 (m, 4 H), 0.91 (s, 3 H); mass spectrum FAB+ observed = 495.2002, estimated = 495.2011.

Preparation of 4-(4-Bromophenoxy)-1′-(2,6-dimethylbenzoyl)-4′-methyl-1,4′-bipiperidine (25). (1) To a stirred solution of 1,4-dioxa-8-azaspiro[4.5]decane (32 mL, 249.6 mmol) and *N*-*tert*-butoxycarbonyl piperidinone (52.2 g, 262.1 mmol) in 1,2-dichloroethane (200 mL) was added titanium isopropoxide (104 mL, 349.5 mmol), and the mixture was stirred for 19 h at room temperature. The reaction mixture was concentrated, and a 1.0 M solution of diethylaluminum cyanide (27.2 mL) was added at room temperature. The mixture was stirred for 4 h at room temperature; it was then cooled to 0 °C, diluted with EtOH (500 mL) and water (50 mL), and stirred a further 1 h. The mixture was then filtered through Celite, and the resulting filtrate was then concentrated to afford 48.9 g (61%) of cyano compound: R_f 0.73 (50% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 3.91−4.07 (m, 6 H), 3.15 (m, 2 H), 2.75 (m, 4 H), 2.12 (m, 2 H), 1.61−1.81 (m, 6 H), 1.46 (s, 9 H).

(2) To a stirred solution of the above cyanide (48.9 g, 153.45 mmol) in THF (300 mL) was added a 3.0 M solution of MeMgBr in ether (153.4 mL, 460.2 mmol) at room temperature, and the mixture was stirred for 4.5 h. The reaction was quenched with saturated aqueous ammonium chloride, and the mixture was extracted twice with methylene chloride. The extracts were concentrated to afford 46.41 g (89%) of methylated compound: R_f 0.61 (50% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 3.90 (m, 4 H), 3.41 (m, 2 H), 3.30 (m, 2 H), 2.52 (m, 4 H), 1.59−1.81 (m, 6 H), 1.42 (s, 9 H), 1.31 (m, 2 H), 0.89 (s, 3 H).

(3) To a stirred solution of the above ketal (46.41 g, 136.5 mmol) in EtOAc (350 mL) were added 6 N HCl (200 mL) and concentrated HCl (75 mL), and the mixture was stirred at room temperature for 4 h. Concentration gave 30.0 g (100%) of crude ketone. To a stirred solution of this crude ketone (136.5 mmol) were added diethyl ether (500 mL) and 20% aqueous NaOH (500 mL), and the solution was stirred for 30 min. BOC_2O (35.7 g, 163.8 mmol) was added incrementally, and the mixture was stirred for 48 h. The layers were separated, and the organic layer was washed with brine, dried, concentrated, and chromatographed to afford 17.1 g (42%) of Boc-protected amine: R_f 0.68 (50% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 3.55 (m, 2 H), 3.36 (m, 2 H), 2.80 (m, 4 H), 2.40 (m, 4 H), 1.85 (m, 2 H), 1.48 (s, 9 H), 1.38−1.48 (m, 2 H), 0.95 (s, 3 H).

(4) To a stirred solution of the above ketone (1.7 g, 5.74 mmol) in methanol (7 mL) was added $NaBH_4$ (0.33 g, 8.61 mmol) at 0 °C. The mixture was stirred for 1.5 h, gradually warming to room temperature. The mixture was concentrated, diluted with EtOAc, washed with water and brine, dried, concentrated, and chromatographed to afford 0.82 g (50%) of alcohol: R_f 0.23 (75% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 3.66 (m, 1 H), 3.27−3.55 (m, 4 H), 2.79 (m, 2 H), 2.21 (m, 2 H), 1.71−1.96 (m, 4 H), 1.44 (s, 9 H), 1.29−1.57 (m, 4 H), 0.90 (s, 3 H).

(5) To a stirred solution of the above alcohol (0.25 g, 0.84 mmol) in THF (6 mL) were added 4-bromophenol (0.146 g, 0.84 mmol), triphenylphosphine (0.26 g, 1.10 mmol), and diethyl azodicarboxylate (0.16 mL, 1.01 mmol). The mixture was stirred for 18 h at room temperature. The reaction was quenched with saturated aqueous bicarbonate, and the mixture was extracted twice with diethyl ether. The extracts were washed with water and brine, dried, concentrated, and chromatographed to afford 0.08 g (22%) of Mitsunobu product: R_f 0.61 (50% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.33 (d, J = 7.6 Hz, 2 H), 6.77 (d, J = 7.8 Hz, 2 H), 4.23 (m, 1 H), 3.47 (m, 2 H), 3.34 (m, 2 H), 2.79 (m, 2 H), 2.35 (m, 2 H), 1.97 (m, 2 H), 1.12−1.87 (m, 4 H), 1.46 (s, 9 H), 1.37 (m, 2 H), 0.93 (s, 3 H).

(6) To a stirred solution of the above Boc compound (0.08 g, 0.18 mmol) in methylene chloride (5 mL) was added TFA (0.5 mL), and the mixture was stirred at room temperature for 2 h. The mixture was concentrated, poured into 10% NaOH, and extracted twice with methylene chloride. The combined extracts were dried and concentrated to afford 0.065 g (100%) of amine. To a stirred solution of this crude amine (0.05 g, 0.14 mmol) in methylene chloride (3 mL) were added 2,6-dimethylbenzoic acid (0.03 g, 0.21 mmol), EDCI (0.04 g, 0.21 mmol), DIPEA (0.3 mL), and HOBT (0.03 g, 0.21 mmol), and the mixture was stirred for 18 h at room temperature. The reaction was quenched with 10% NaOH, and the mixture was extracted twice with methylene chloride. The combined extracts were dried, concentrated, and chromatographed to afford 0.034 g (50%) of amide **25**: R_f 0.40 (50% EtOAc/hexanes); HPLC t_R = 4.61 min; ^{1}H NMR $CDCl_3$ δ 7.35 (d, J = 7.7 Hz, 2 H), 7.11 (m, 1 H), 7.00 (d, J = 7.6 Hz, 2 H), 6.76 (d, J = 7.7 Hz, 2 H), 4.22 (m, 2 H), 3.48 (m, 1 H), 3.30 (m, 1 H), 3.03 (m, 1 H), 2.77 (m, 2 H), 2.34 (m, 1 H), 2.25 (s, 6 H), 1.96 (m, 3 H), 1.74 (m, 3 H), 1.20−1.53 (m, 3 H), 0.95 (s, 3 H); mass spectrum FAB+ observed = 485.1790, estimated = 485.1763.

Preparation of 4-Formyl-1′-(*tert*-butoxycarbonyl)-4′-methyl-1,4′-bipiperidine (15). (1) To a stirred solution of the olefin **3** (15.6 g, 66.4 mmol) in THF (100 mL) was added a 1.0 M solution of borane in THF (79.7 mL, 79.7 mmol) at 0 °C dropwise. The mixture was stirred for 18 h, gradually warming to room temperature. The mixture was recooled to 0 °C, and a THF/EtOH (1:1, 50 mL) solution was added followed by a pH = 7 buffer (50 mL) and a 30% aqueous H_2O_2 solution (50 mL). The mixture was stirred at room temperature for 24 h. The mixture was basified with 10% NaOH and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried, concentrated, and chromatographed to yield 7.0 g (41%) of alcohol: R_f 0.45 (20% EtOH/EtOAc); ^{1}H NMR $CDCl_3$ δ 3.43 (d, 2 H), 3.35 (m, 4 H), 2.89 (m, 2 H), 2.05 (m, 2 H), 1.73 (m, 4 H), 1.41 (s, 9 H), 1.07−1.40 (m, 5 H), 0.88 (s, 3 H).

(2) To a stirred solution of the above alcohol (2.33 g, 9.21 mmol) in methylene chloride (100 mL) at 0 °C were added 4-methylmorpholine *N*-oxide (NMO) (1.62 g, 13.81 mmol) and tetrapropylammonium perruthenate (TPAP) (0.323 g, 0.92 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with Et_2O and passed through a pad of silica gel and Celite eluting with EtOAc. The filtrate was concentrated to afford 1.47 g (64%) of crude aldehyde **15**: R_f 0.67 (20% EtOH/EtOAc); ^{1}H NMR $CDCl_3$ δ 9.63 (s, 1 H), 3.46 (m, 2 H), 3.30 (m, 2 H), 2.84 (m, 2 H), 2.20 (m, 2 H), 1.48−2.00 (m, 6 H), 1.44 (s, 9 H), 1.34 (m, 3 H), 0.89 (s, 3 H).

General Procedure for Preparation of Oximes 39b, 39c, 39f, and 39g. (1) To a stirred solution of 1-bromo-4-(trifluoromethoxy)benzene (1.4 equiv) or 4-bromobenzotrifluoride (1.4 equiv) in THF was added *n*BuLi (1.3 equiv) at −78 °C, and the mixture was stirred at −78 °C for 20 min. Aldehyde **15** (1 equiv) was added as a THF solution at −78 °C, and the mixture was stirred at −78 °C for 1 h, warmed to room temperature, and stirred for 1 h. The reaction was quenched with water, and the mixture was extracted with methylene chloride (3 times). The combined extracts were washed with brine, dried, concentrated, and chromatographed to afford **16** (62% for CF_3, 78% for OCF_3). For the CF_3 compound: R_f 0.40 (100% EtOAc); ^{1}H NMR $CDCl_3$ δ 7.61 (d, J = 8.7 Hz, 2 H), 7.43 (d, J = 8.7 Hz, 2 H), 4.49 (m, 1 H), 3.27−3.52 (m, 4 H), 2.96 (m, 1 H), 2.87 (m, 1 H), 1.87−2.11 (m, 4 H), 1.75 (m, 2 H), 1.59 (m, 2 H), 1.46 (s, 9 H), 1.22−1.42 (m, 4 H), 0.88 (s, 3 H).

(2) To a stirred solution of the above alcohol **16** (1 equiv) in methylene chloride at 0 °C were added NMO (1.5 equiv) and TPAP (0.1 equiv), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with Et_2O and passed through a pad of silica gel and Celite eluting with EtOAc. The filtrate was concentrated to afford crude ketone **17** (63% for CF_3, 65% for OCF_3). To a stirred solution of this

crude ketone **17** (1 equiv) in MeOH were added sodium acetate (20 equiv) and *O*-methyl or *O*-ethyl hydroxylamine hydrochloride (20 equiv), and the mixture was stirred at room temperature for 24 h. The resulting mixture was then poured into aqueous NaOH (10%) and extracted twice with methylene chloride. The combined extracts were then dried, concentrated, and chromatographed to yield oxime **18** as a mixture of *E* and *Z* isomers. The isomers were separated by chromatography. For the CF_3 (*Z*)-ethyl oxime compound: R_f 0.35 (20% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.45 (d, J = 8.7 Hz, 2 H), 7.15 (d, J = 8.7 Hz, 2 H), 3.89 (q, J = 8.0 Hz, 2 H), 3.07−3.31 (m, 4 H), 2.75 (m, 2 H), 2.28 (m, 1 H), 1.93 (m, 2 H), 1.60 (m, 4 H), 1.39 (m, 2 H), 1.28 (s, 9 H), 1.19 (m, 2 H), 1.02 (t, J = 8.0 Hz, 3 H), 0.73 (s, 3 H).

(3) To a stirred solution of **18** (1 equiv) in methylene chloride was added trifluoroacetic acid (20 equiv), and the mixture was stirred at room temperature for 2 h. The mixture was concentrated, poured into 10% NaOH, and extracted twice with methylene chloride. The combined extracts were dried and concentrated to afford an amine. To a stirred solution of this crude amine (1 equiv) in methylene chloride were added 2,6-dimethylnicotinic acid *N*-oxide (1.5 equiv), EDCI (1.5 equiv), DIPEA (2 equiv), and HOBT (1.5 equiv), and the mixture was stirred for 12 h at room temperature. The reaction was quenched with saturated $NaHCO_3$, and the mixture was extracted twice with methylene chloride. The combined extracts were dried and concentrated to yield oxime **19**. Purity was checked by LC/MS analysis.

General Procedure for Preparation of Oximes 39e and 39i. To a stirred solution of aldehyde **15** (0.67 g, 2.07 mmol) in THF (15 mL) at 0 °C was added a 1.0 M solution of 4-chlorophenylmagnesium bromide (4.14 mL) in THF. The mixture was stirred for 5 h, gradually warming to room temperature. The reaction was quenched with saturated NH_4-Cl, and the mixture was extracted with methylene chloride (3 times). The combined extracts were washed with brine, dried, concentrated, and chromatographed to afford **16** (47%): ^{1}H NMR $CDCl_3$ δ 7.16−7.27 (m, 4 H), 4.27 (d, 1 H), 3.31 (m, 4 H), 2.90 (m, 1 H), 2.79 (m, 1 H), 1.85−2.05 (m, 4 H), 1.56−1.80 (m, 4 H), 1.40 (s, 9 H), 1.10−1.32 (m, 4 H), 0.83 (s, 3 H).

Alcohol **16** was converted to oxime **19** by following the general procedure described above for compounds **39b**, **39c**, **39f**, and **39g**.

4-[(*Z*)-(Methoxyimino)[4-(trifluoromethyl)phenyl]methyl]-1′-[(2,4-dimethyl-3-piperidinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (39b). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **39b** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: HPLC t_R = 3.86 min; ^{1}H NMR $CDCl_3$ δ 8.14 (d, J = 7.3 Hz, 1 H), 7.64 (d, J = 7.3 Hz, 2 H), 7.31 (d, J = 7.0 Hz, 2 H), 6.98 (d, J = 7.6 Hz, 1 H), 4.20 (m, 1 H), 3.80 (s, 3 H), 3.32−3.40 (m, 2 H), 2.95 (m, 2 H), 2.71 (m, 1 H), 2.40 and 2.44 (s, 3 H), 2.21 and 2.25 (s, 3 H), 1.98−2.19 (m, 2 H), 1.81 (m, 5 H), 1.43−1.55 (m, 4 H), 0.92 (br s, 3 H); mass spectrum FAB+ observed = 533.2758, estimated = 533.2740.

4-[(*Z*)-(Methoxyimino)[4-(trifluoromethoxy)phenyl]methyl]-1′-[(2,4-dimethyl-3-piperidinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (39c). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **39c** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: R_f 0.27 (96:4:1 ratio of CH_2Cl_2:MeOH:NH_4OH); ^{1}H NMR $CDCl_3$ δ 8.12 (d, J = 7.8 Hz, 1 H), 7.12−7.25 (m, 4 H), 6.95 (d, J = 7.8 Hz, 1 H), 4.25 (m, 1 H), 3.75 (s, 3 H), 3.20−3.45 (m, 2 H), 2.90 (m, 2 H), 2.78 (m, 2 H), 2.38 and 2.42 (s, 3 H), 2.19 and 2.22 (s, 3 H), 1.85−2.15 (m, 2 H), 1.65−1.85 (m, 4 H), 1.10−1.84 (m, 4 H), 0.88 (br s, 3 H); mass spectrum FAB+ observed = 549.2686, estimated = 549.2689.

4-[(*Z*)-(4-Chlorophenyl)(methoxyimino)methyl]-1′-[(2,4-dimethyl-3-piperidinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (39e). The compound was prepared from methyl hydroxylamine hydrochloride by following the general procedure described above to afford the methoxime, which was then converted to compound **39e** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: HPLC t_R = 3.91 min; ^{1}H NMR $CDCl_3$ δ 8.12 (d, J = 7.8 Hz, 1 H), 7.33 (d, J = 7.7 Hz, 2 H), 7.12 (d, J = 7.6 Hz, 2 H), 6.98 (d, J = 7.7 Hz, 1 H), 4.20 (m, 1 H), 3.79 (s, 3 H), 3.22−3.48 (m, 2 H), 2.95 (m, 2 H), 2.80 (m, 1 H), 2.40 and 2.44 (s, 3 H), 2.21 and 2.24 (s, 3 H), 1.90−2.18 (m, 4 H), 1.70−1.88 (m, 3 H), 1.30−1.68 (m, 4 H), 0.92 (br s, 3 H); mass spectrum FAB+ observed = 499.2471, estimated = 499.2476.

4-[(*Z*)-(Ethoxyimino)[4-(trifluoromethyl)phenyl]methyl]-1′-[(2,4-dimethyl-3-piperidinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (39f). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **39f** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: HPLC t_R = 4.56 min; ^{1}H NMR $CDCl_3$ δ 8.18 (d, J = 7.8 Hz, 1 H), 7.65 (d, J = 7.8 Hz, 2 H), 7.33 (d, J = 7.6 Hz, 2 H), 6.97 (d, J = 7.6 Hz, 1 H), 4.15 (m, 1 H), 4.05−4.09 (q, 2 H), 3.25−3.55 (m, 2 H), 2.98 (m, 2 H), 2.82 (m, 1 H), 2.42 and 2.46 (s, 3 H), 2.23 and 2.26 (s, 3 H), 1.92−2.20 (m, 2 H), 1.72−1.90 (m, 4 H), 1.35−1.68 (m, 4 H), 1.20−1.29 (m, 1 H), 1.14−1.20 (t, 3 H), 0.92 (br s, 3 H); mass spectrum FAB+ observed = 547.2901, estimated = 547.2896.

4-[(*Z*)-(Ethoxyimino)[4-(trifluoromethoxy)phenyl]methyl]-1′-[(2,4-dimethyl-3-piperidinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (39g). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **39g** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: R_f 0.47 (1:1 ratio of CH_2Cl_2:acetone); HPLC t_R = 4.43 min; ^{1}H NMR $CDCl_3$ δ 8.12 (d, J = 7.8 Hz, 1 H), 7.15−7.30 (m, 4 H), 6.95 (d, J = 7.8 Hz, 1 H), 4.15 (m, 1 H), 3.95−4.15 (q, 2 H), 3.20−3.45 (m, 2 H), 2.93 (m, 2 H), 2.78 (m, 1 H), 2.40 and 2.44 (s, 3 H), 2.35−2.45 (m, 1 H), 2.19 and 2.23 (s, 3 H), 1.70−2.20 (m, 6 H), 1.20−1.65 (m, 4 H), 1.10−1.25 (t, 3 H), 0.89 (br s, 3 H); mass spectrum FAB+ observed = 563.2855, estimated = 563.2845.

4-[(*Z*)-(4-Chlorophenyl)(ethoxyimino)methyl]-1′-[(2,4-dimethyl-3-piperidinyl)carbonyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (39i). The compound was prepared from ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **39i** in subsequent steps by removal of the Boc and treatment of the resulting amine with 2,6-dimethylnicotinic acid *N*-oxide: R_f 0.49 (20% EtOH/EtOAc); HPLC t_R = 4.01 min; ^{1}H NMR $CDCl_3$ δ 8.15 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.6 Hz, 2 H), 7.18 (d, J = 7.7 Hz, 2 H), 6.98 (d, J = 7.7 Hz, 1 H), 4.04 (q, 2 H), 3.73−3.83 (m, 1 H), 3.25−3.53 (m, 2 H), 2.76−3.02 (m, 3 H), 2.46 and 2.42 (s, 3 H), 2.25 and 2.21 (s, 3 H), 1.95−2.19 (m, 1 H), 1.70−1.95 (m, 6 H), 1.35−1.66 (m, 4 H), 1.15−1.20 (t, 3 H), 0.92 (br s, 3 H); mass spectrum FAB+ observed = 513.2642, estimated = 513.2632.

1′-[(2,4-Dimethyl-3-pyridinyl)carbonyl]-4-[(*Z*)-(4-fluorophenyl)(ethoxyimino)methyl]-4′-methyl-1,4′-bipiperidine *N*-Oxide (39j). (1) To a stirred solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (4.9 g, 20 mmol) in ether (200 mL) were added 10% NaOH (100 mL) and BOC_2O (4.4 g, 20 mmol), and the mixture was stirred at room temperature overnight. The layers were separated, and the organic layer was washed with brine, dried, and concentrated to give a crude Boc-protected amino ketone. To a stirred solution of this crude ketone (5.0 g, 17.3 mmol) in MeOH were added sodium acetate (7.3 g, 86.8 mmol) and *O*-ethyl hydroxylamine hydrochloride (8.4 g, 86.8 mmol), and the mixture was stirred at room temperature for 24 h. The resulting mixture

was then poured into aqueous NaOH (10%) and extracted twice with methylene chloride. The combined extracts were then dried and concentrated to yield 5.36 g (94%) of crude oxime as a mixture of *E* and *Z* isomers: ^{1}H NMR $CDCl_3$ δ 7.20−7.37 (m, 2 H), 7.00−7.10 (m, 2 H), 4.18 and 4.05 (q, 2 H), 3.30 and 2.60 (m, 1 H), 2.75 (m, 2 H), 1.62−1.80 (m, 6 H), 1.44 (s, 9 H), 1.22 and 1.30 (t, 3 H).

(2) To a stirred solution of the above oxime (5.4 g, 16.2 mmol) in methylene chloride (50 mL) was added trifluoroacetic acid (25 mL, 324 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was concentrated, poured into 10% NaOH, and extracted twice with methylene chloride. The combined extracts were dried and concentrated to afford 2.25 g (61%) of crude amine. To a stirred solution of this crude amine (2.2 g, 9 mmol) and *N*-*tert*-butoxycarbonyl-4-piperidinone (1.9 g, 9.5 mmol) in 1,2-dichloroethane (20 mL) was added titanium isopropoxide (5.6 mL, 18.9 mmol), and the mixture was stirred for 12 h at room temperature. The mixture was concentrated, and a 1.0 M solution of diethylaluminum cyanide (18.9 mL) was added at room temperature. The mixture was stirred for 3 h, and then diluted with EtOAc. The reaction was quenched with water (5 mL), and the mixture was stirred a further 2 h. The mixture was then filtered through Celite, and the resulting filtrate was then concentrated to afford 4.61 g of crude cyano compound: *E* isomer, R_f 0.54 (20% EtOAc/hexanes); *Z* isomer, R_f 0.48 (20% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.22−7.37 (m, 2 H), 7.00−7.10 (m, 2 H), 4.18 and 4.04 (q, 2 H), 3.95 (m, 2 H), 3.10 (m, 4 H), 2.22 (m, 2 H), 2.10 (m, 2 H), 1.58−1.90 (m, 7 H), 1.44 (s, 9 H), 1.30 and 1.20 (t, 3 H).

(3) To a stirred solution of the above cyanide (4.5 g, 9.8 mmol) in THF (100 mL) was added a 1.4 M solution of MeMgBr in toluene/THF (35.0 mL, 49.1 mmol) at room temperature, and the mixture was stirred for 4 h. The reaction was then quenched with saturated aqueous ammonium chloride, and the mixture was extracted twice with methylene chloride. The extracts were washed with brine, dried, concentrated, and chromatographed to afford 0.93 g (22%) of the desired methylated *Z* isomer: R_f 0.26 (20% EtOAc/hexanes); ^{1}H NMR $CDCl_3$ δ 7.00 (m, 2 H), 6.85 (m, 2 H), 3.85 (q, 2 H), 3.23 (m, 2 H), 3.09 (m, 2 H), 2.70 (m, 2 H), 2.21 (m, 1 H), 1.89 (m, 2 H), 1.57 (m, 4 H), 1.36 (m, 2 H), 1.24 (s, 9 H), 1.10 (m, 2 H), 0.99 (t, 3 H), 0.68 (s, 3 H).

(4) To a stirred solution of the above *Z* oxime (0.93 g, 2.08 mmol) in methylene chloride (10 mL) was added trifluoroacetic acid (3.2 mL, 41.6 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was concentrated, poured into 10% NaOH, and extracted twice with methylene chloride. The combined extracts were dried and concentrated to afford 0.73 g (100%) of crude amine. To a stirred solution of this crude amine (0.05 g, 0.16 mmol) in methylene chloride (3 mL) were added 2,6-dimethylnicotinic acid *N*-oxide (0.05 g, 0.32 mmol), EDCI (0.06 g, 0.32 mmol), DIPEA (0.3 mL), and HOBT (0.04 g, 0.32 mmol), and the mixture was stirred for 12 h at room temperature. The reaction was quenched with saturated $NaHCO_3$, and the mixture was extracted twice with methylene chloride. The combined extracts were dried, concentrated, and chromatographed to yield 0.052 g (67%) of oxime **39j**: R_f 0.38 (20% EtOH/EtOAc); HPLC t_R = 3.88 min; ^{1}H NMR $CDCl_3$ δ 8.15 (d, J = 7.8 Hz, 1 H), 7.20 and 7.28 (d, J = 7.7 Hz, 2 H), 7.03 and 7.10 (d, J = 7.7 Hz, 2 H), 7.00 (d, J = 7.6 Hz, 1 H), 4.18 (m, 1 H), 4.01−4.10 (q, 2 H), 3.27−3.42 (m, 2 H), 2.97 (m, 2 H), 2.82 (m, 1 H), 2.46 and 2.44 (s, 3 H), 2.26 and 2.24 (s, 3 H), 1.93−2.20 (m, 3 H), 1.72−1.90 (m, 3 H), 1.23−1.68 (m, 5 H), 1.17−1.22 (t, 3 H), 0.93 (s, 3 H); mass spectrum FAB+ observed = 497.2927, estimated = 497.2928.

RANTES Binding Assay. Membranes from NIH 3T3 cells expressing CCR5 were incubated with ^{125}I-labeled RANTES in the presence or absence of compound for 1 h at room temperature. The reaction cocktails (buffer: 50 mM HEPES, pH = 7.4, 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.2% BSA) were harvested through glass fiber filters, washed with 10 mM HEPES (pH = 7.4, 150 mM NaCl) at 4 °C, and counted to determine the amount of bound RANTES. The binding affinity constant, K_i, was determined from the experimental IC_{50} values using GraphPad PRISM software analysis.

Viral Entry Assay. Replication-defective HIV-1 virus containing the reported gene for luciferase was used to infect U-87 cells expressing CD4 and CCR5. Infections were carried out in the presence or absence of compound, and luciferase activity was measured after 3 days. The data are reported as the concentration of compound required to reduce luciferase production by 50% compared with control cultures. Compounds were tested in triplicate at 8 concentrations ranging from 0.1 to 100 nM. The triplicates were averaged, and dose−response curves were generated using GraphPad PRISM software. Typically, the 95% confidence limit for experimental IC_{50} was within 1 log and the R^2 variance between 0.9 and 1.0. Intra-experimental IC_{50} values typically varied less than 0.5 log.

HIV-1 Replication Assay. Peripheral blood mononuclear cells (PBMCs) were pretreated with compound for 1 h at 37 °C and subsequently infected in triplicate with a panel of CCR5-tropic HIV-1 isolates for 3 h. Following infection, the cells were washed to remove residual viral inoculum and cultured in the presence of compound for 4−6 days. Culture supernatants were harvested, and viral replication was measured by determination of viral p24 antigen concentration by ELISA. Compounds were tested in triplicate at 11 concentrations ranging from 1000 to 0.001 nM. The triplicates were averaged, and dose−response curves were generated using GraphPad PRISM software. Typically, the 95% confidence limit for experimental IC_{50} was within 1 log or less and the R^2 variance between 0.85 and 1.0. Because primary PBMCs from different donors can vary widely in both CCR5 expression and viral infectivity, the IC_{50} values for a single viral isolate could vary as much as 1.5 log between experiments using different donor cells. Therefore, compounds were typically compared head to head in the same experiment using the same donor and viral inoculum.

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