Discovery of Bioavailable 4,4-Disubstituted Piperidines as Potent Ligands of the Chemokine Receptor 5 and Inhibitors of the Human Immunodeficiency Virus-1

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We describe robust chemical approaches toward putative CCR5 scaffolds designed in our laboratories. Evaluation of analogues in the ^{125}I-[MIP-1β] binding and Ba-L-HOS antiviral assays resulted in the discovery of **64** and **68** in the 4,4-disubstitited piperidine class **H**, both potent CCR5 ligands ($pIC_{50} = 8.30$ and 9.00, respectively) and HIV-1 inhibitors ($pIC_{50} = 7.80$ and 7.84, respectively, in Ba-L-HOS assay). In addition, **64** and **68** were bioavailable in rodents, establishing them as lead molecules for further optimization toward CCR5 clinical candidates.

Introduction

The AIDS epidemic continues to be a significant global threat with 33 million individuals infected with HIV, about 4 million new infections each year, and about 2.9 million AIDS-related deaths every year. Highly active antiretroviral therapy (HAART[a]) has been one of the key factors in a dramatic reduction of AIDS-related mortality rates, but there is still a continuing need for new medicines that address treatment complexity, high cost, unwanted side effects, drug−drug interactions, and viral resistance. In particular, anti-HIV drugs that exploit new mechanisms, such as inhibition of CCR5, are under intense development. Recent medicinal chemistry efforts have resulted in the discovery of several CCR5 antagonists currently in the clinic[1,2] and one FDA-approved drug for the treatment of ART-experienced patients.[3] Small molecule CCR5 inhibitors are allosteric ligands that, unlike the endogeneous CCR5 ligands, bind in a hydrophobic pocket inside CCR5, as demonstrated by single site mutagenesis studies with various small-molecule ligands. Progress in the discovery and development of CCR5 inhibitors has been summarized in recent reviews.[4−12]

In this report, we describe novel, small molecule CCR5 antagonists across eight chemical scaffolds. We pursued a modular, high-throughput chemistry approach by designing scaffolds with an amine and an aldehyde as points of diversity. Scaffolds were derivatized as amides/sulfonamides by reacting them with acyl chloride/sulfonyl chloride monomers, and as tertiary amines, by reductive alkylation with amine monomers, yielding putative CCR5 ligands (Figure 1a). To aid monomer selection, a six-feature, pharmacophore model for CCR5 inhibition (Figure 1b) was constructed via Catalyst[13] from structure−activity data culled from both an in-house CCR5 binding HTS assay[14] as well as from external sources. A multidimensional BCUT chemistry space was also constructed from the same available data.[15] Both computer-assisted drug design (CADD) methods were then used to select reagents from our amine and acyl monomer sets. Monomers were selected on the basis of the pharmacophore model such that the Catalyst-derived scores were maximized for the resultant products. Monomers were also selected from the BCUT chemistry space such that the distances between the resultant products and known CCR5 antagonists were minimized.

The scaffolds examined via the above computational approaches included **A**−**H**, Figure 2.[7−9,16−22]

The synthesis of azetidine **A**[16,18] was accomplished by sequentially alkylating 3,4-dichlorophenyl-acetonitrile with diethyl carbonate and then with 2-(2-bromoethyl)-1,3-dioxolane, resulting in **2** in 49% yield, Figure 3. Catalytic hydrogenation of **2** and cyclization to **3** proceeded in a cumulative 59% yield. Finally, LAH-mediated reduction of **3** afforded the azetidine-based two-point diversity scaffold, which was subsequently derivatized to **4** and analogues (not shown), as described above.

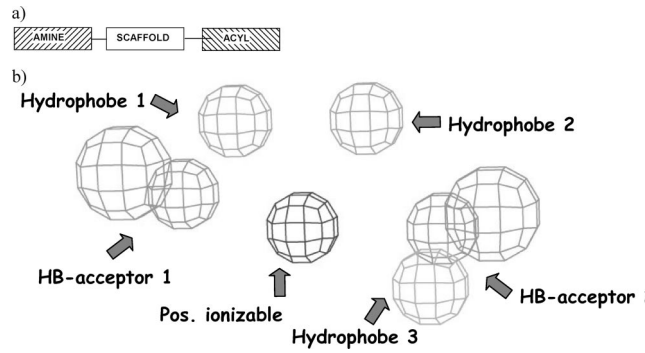

Figure 1. (a) Generalized modular structure of compounds described in this work. (b) Six-feature pharmacophore model for CCR5 antagonism constructed via Catalyst. Software version Catalyst v4.5, 2000, Accelrys, Inc., San Diego, CA.

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[a] Abbreviations: MIP-1β, macrophage inflammatory protein 1-β; CCR5, chemokine receptor 5; HOS, human osterosarcoma; HIV-1, human immunodeficiency virus-1; HAART, highly active antiretroviral therapy.

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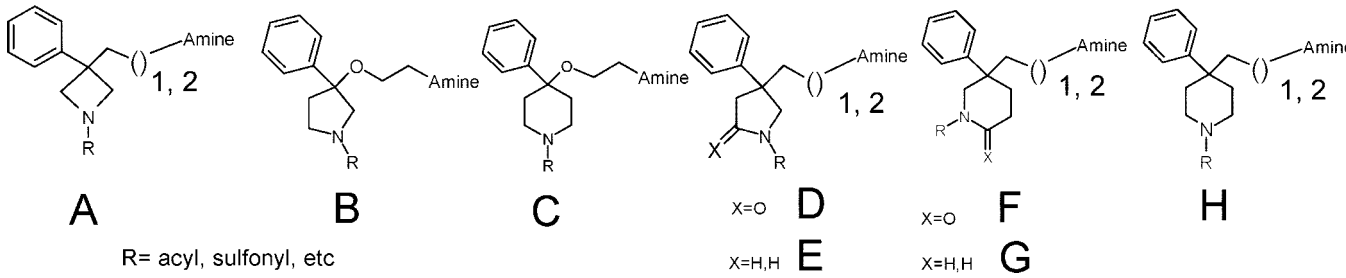


Figure 2. Scaffolds **A**−**H** described in this work.

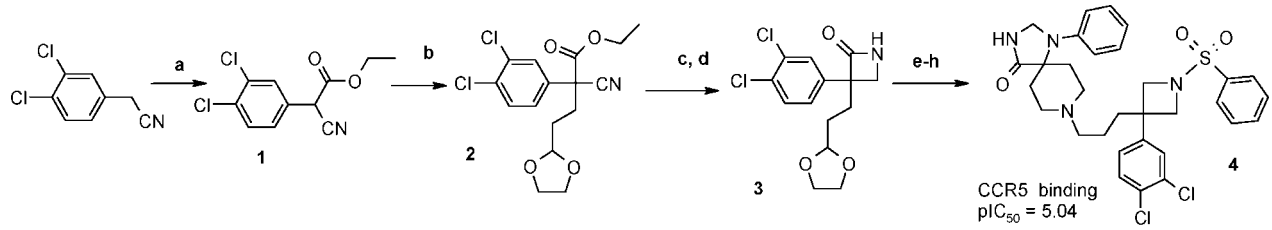


Figure 3. (a)Toluene, diethyl carbonate, NaH, reflux; (b) DMF, *t*-BuOK, 2-(2-bromoethyl)-1,3-dioxolane, −78 °C → rt, o/n; (c) MeOH/NH_4OH, Ra−Ni, 60 psi H_2, 50 °C; (d) THF/ethyl ether, CH_3MgI, rt; (e) THF/ethyl ether, LAH, reflux; (f) THF, benzenesulfonyl chloride, DIEA; (g) 10% HCl in THF; (h) dichloroethane, 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, $NaBH(OAc)_3$.

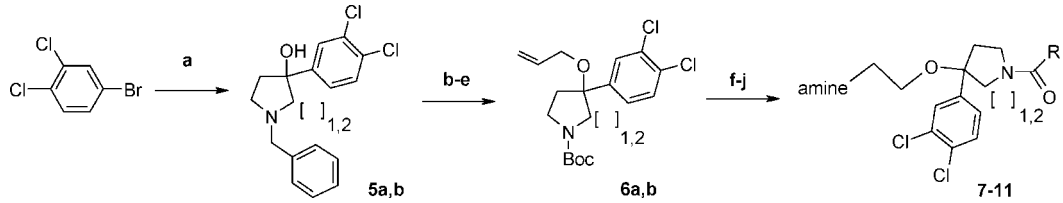


Figure 4. (a)THF, *t*-BuLi, −78 °C, 1-(benzyl)-3-pyrroldinone or 1-(benzyl)-4-piperidinone; (b) DMF, NaH, allyl bromide; (c) toluene, 1-chloroethyl chloroformate; (d) MeOH, K_2CO_3; (e) THF, $(Boc)_2O$, TEA; (f) THF, OsO_4, NMO; (g) THF/H_2O, $NaIO_4$; (h) DCE, amine, $NaBH(OAc)_3$; (i) TFA/DCM (1/4); (j) DCM, acid chloride, polystyrene-DIEA.

Table 1. Inhibitory Potency pIC_{50} of 4-(Alkyloxy)-4-phenylpyrrolidine (**B**) and 4-(Alkyloxy)-4-phenylpiperidine (**C**) Analogues **7**−**11** in the ^{125}I-[MIP-1β] Binding Assay

	C	pIC_{50} CCR5 binding		B	pIC_{50} CCR5 binding
7		5.46	9		5.40
			10		5.32
8		5.62	11		4.69

These azetidine-based analogues were found to exhibit low affinity to CCR5, with $pIC_{50} < 5.50$ in the ^{125}I-[MIP-1β] binding assay.[14,18]

We next synthesized 3-(alkyloxy)-3-phenyl-pyrrolidine **B** and 4-(alkyloxy)-4-phenyl-piperidine **C** scaffolds[16,17] by alkylating 1-(benzyl)-3-pyrroldinone and 1-(benzyl)-4-piperidinone with 4-bromo-1,2-dichlorobenzene, yielding **5a**,**b**. Oxidation of ethers **6a**,**b** afforded aldehyde scaffolds, which were subsequently derivatized to inhibitors **7**−**11**, Figure 4, Table 1.

Compounds in both **B** and **C** classes also turned out to exhibit low affinity to CCR5. There was no scaffold ring-size effect when 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one amine-was employed in **7** and **9**. Similarly, the use of unsaturated acyl moiety in **10**, vs an aromatic one in **9**, did not affect binding. On the other hand, the SAR diverged between **B** and **C** when a sulfonamide moiety was employed, with potency of piperidine-based **8** being approximately 10-fold higher than that of pyrrolidine-based **11**.[16,17]

We next synthesized analogues in the pyrrolidinone **D** and pyrrolidine **E** scaffold series.[16,18] Alkylation of 3,4-dichlorophenyl-acetonitrile with methyl bromoacetate yielded chromatographically separable bis-alkylated **12** (yield 35%) and monoalkylated **13** (yield 51%) applicable toward C2-**E** and C3-**E**, respectively, Figure 5. Reduction and an in situ cyclization of **12** to pyrrolidinone **14** enabled synthesis of analogues **15**−**18** in the **D** and **E** series. Alkylation of **13** with 2-(3-bromopropoxy)-tetrahydro-2*H*-pyran afforded **20**, which after cyclization to **21** enabled C3-**E** analogues **22**−**26**, Figure 5, Table 2.

Data in Table 2 suggests that the C3-linker in the pyrrolidinone series **D** supports approximately 10-fold stronger binding than the C2-linker (**15** vs **16**, respectively). Similar trends can be observed in the pyrrolidine **E** series (**22** vs **17**). The 3,4-dichloro motif substantially increased potency compared to the unsubstituted phenyl ring, in both C2-**E** (**17** and **18**) and C3-**E** series (data not shown). Formal removal of the carbonyl moiety in **23** resulted in an approximately 40-fold potency decrease vs **22**, suggesting possible involvement of the carbonyl moiety in hydrogen bonding. Modifications in the 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one moiety were deleterious to potency in cyclohexyl **24**, hydantoine **25**, and *N*-Me **26** analogues, Table 2. Finally, the conformationally restricted *endo* tropane[23] moiety did not significantly influence the potency of **19** in the C2-**E** series, in contrast to a very significant effect of this moiety observed later in another scaffold (vide infra).

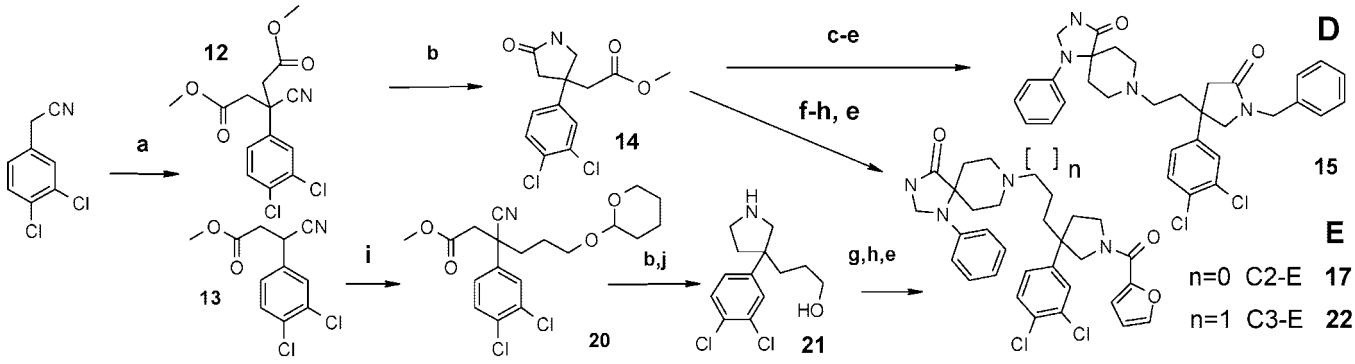


Figure 5. (a) THF, LHMDS, methyl bromoacetate, −78 °C, chromatographic separation; (b) MeOH, NH_4OH, H_2, 40 psi, Ra−Ni; rt; (c) THF, NaH, BnBr; (d) toluene, DIBAL; (e) DCE, amine, $NaBH(OAc)_3$; (f) THF, LAH; (g) DMF, HATU, DIEA, acid; (h) DCM, Dess−Martin periodane; (i) THF, LHMDS, 2-(3-bromopropoxy)tetrahydro-2*H*-pyran; (j) 10% HCl in dioxane.

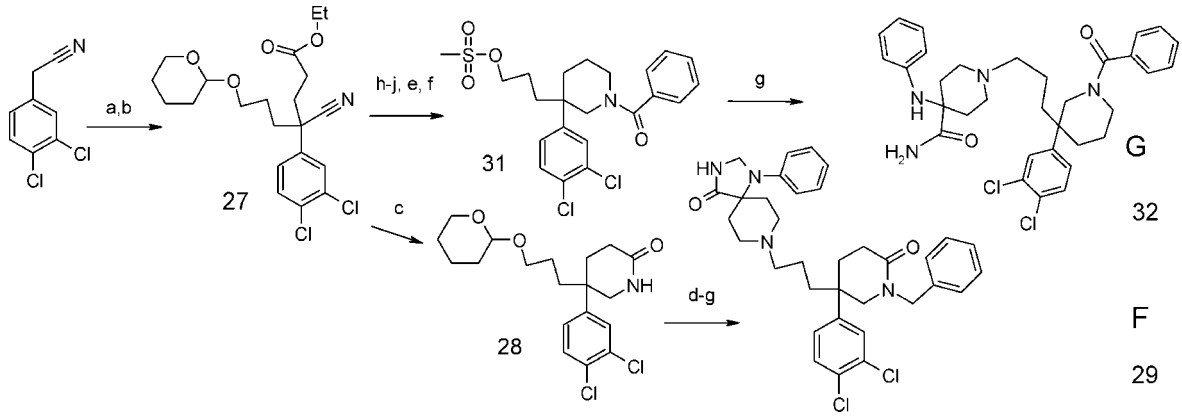


Figure 6. (a) THF, NaH, Br-$(CH_2)_3$-O-THP; (b) dioxane, Triton B, ethyl acrylate; (c) MeOH, NH_4OH, H_2, 40 psi, Ra−Ni; rt; (d) THF, NaH, $C_6H_5CH_2Cl$; (e) 10% HCl in THF; (f) DCM, MsCl, TEA; (g) DMSO, amines, 100 °C; (h) THF, LAH; (i) DCM, triphenyl phosphine, DEAD; (j) DCM, DIEA, C_6H_5COCl.

Table 2. Inhibitory Potency pIC_{50} of Pyrrolidinone **D** (**15**, **16**), Pyrrolidine C2-**E** (**17**−**19**) and Pyrrolidine C3-**E** (**22**−**26**) Analogues in the ^{125}I-[MIP-1β] Binding Assay

D		pIC_{50} CCR5 binding	C2-E		pIC_{50} CCR5 binding
15	i=1	5.03	**17**	X, X= Cl, Cl	5.83
16	i=2	5.99	**18**	X, X= H, H	5.03
C3-E			**19**		6.11
24		<4.50	C3-E		
25		<4.50	**22**		6.85
26		5.15	**23**		5.28

Table 3. Inhibitory Potency pIC_{50} of Piperidones **F** and Piperidines **G** in the ^{125}I-[MIP-1β] Binding Assay

G		pIC_{50} CCR5 binding	F		pIC_{50} CCR5 binding
32		<4.50	**29**		6.00
33		5.80	**30**		4.70
34		6.35			

We then examined the SAR and the potential to achieve strong binding to CCR5 in the piperidinone **F** and piperidine **G** scaffold families by synthesizing **29**,**30** and **32**−**34**.[16,24−26] Key intermediate **27**, obtained via a two-step alkylation of 3,4-dichlorophenyl-acetonitrile with 2-[(2-bromoethyl)oxy]tetrahydro-2*H*-pyran and ethyl acrylate,[24] could then be either reduced to the piperidinone **28** or converted to the piperidine **31** by reduction and Mitsunobu cyclization, Figure 6.

Piperidine **G**-based inhibitors turned out to be more potent than piperidinone **F** analogues (**34** vs **29** and **33** vs **30**). As in other scaffold series examined, the 1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one moiety in **34** and **29** resulted in superior binding (e.g., vs **33** and **30**), while the use of 4-(phenylamino)-4-piperidinecarboxamide in **32**, a formal ring-open homologue of **30**, resulted in a greater than 80-fold loss in potency, Table 3.

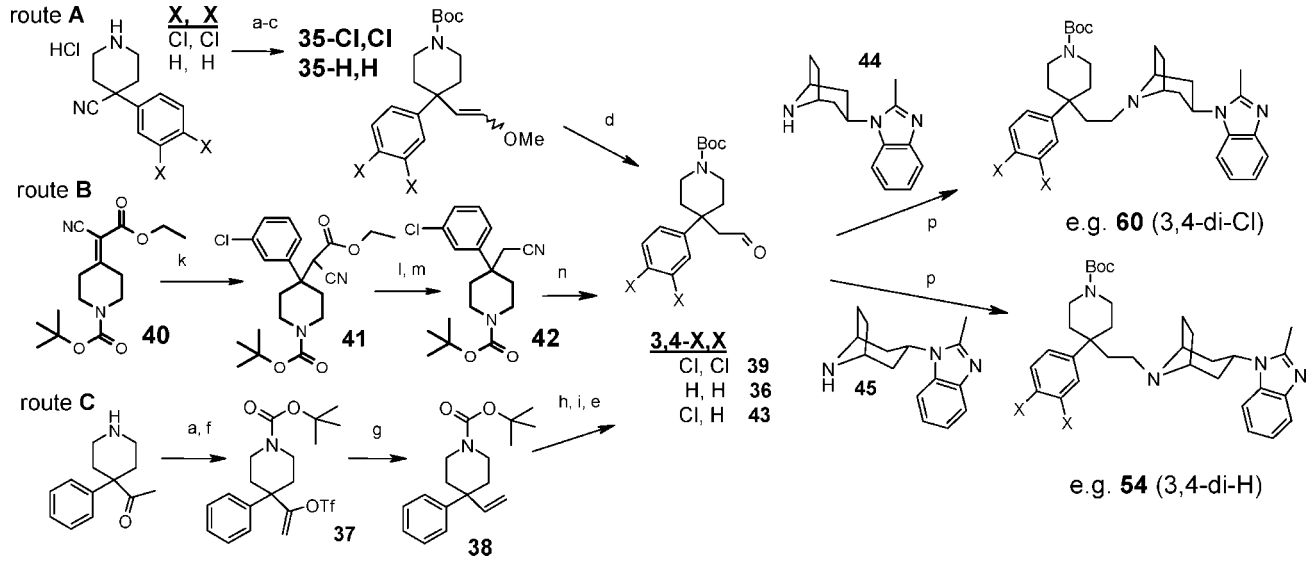


Figure 7. (a) THF, $(Boc)_2O$, TEA; (b) toluene, DIBAL in toluene, −78 °C to −35 °C, 2.5 h; (c) THF, *t*-BuOK, methyloxymethyl triphenylphosphonium chloride, 0 to 60 °C over 2 h; (d) water/acetone, *p*-TsOH, rt; (e) DCM, Dess−Martin periodinane, *t*-BuOH, rt; (f) toluene, KHMDS, $(CF_3SO_2)_2NPh$; (g) CH_3CN, K_2CO_3, $Pd(PPh_3)_4$, $(CH_3)_2NH\cdot BH_3$, 65 °C, sealed tube, overnight; (h) THF, 9-BBN, reflux, o/n; (i) NaOH aq, H_2O_2; (k) 1-chloro-3-iodobenzene, ethyl ether, magnesium turnings, rt, add to cyano(1-Boc-4-piperidinylidene)acetate in THF, CuI; (l) ethanol, sodium hydroxide, rt, 1 M HCl workup; (m) acetonitrile, Cu_2O, reflux, 30 min; (n) DCM, −30 °C, DIBAL in DCM; (p) dichloroethane, sodium triacetoxyborohydride.

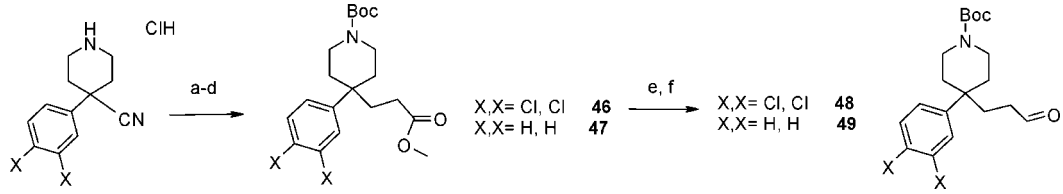


Figure 8. (a) dichloromethane, $(Boc)_2O$, TEA; (b) toluene, DIBAL in toluene, −78 °C to −35 °C, 2.5 h; (c) DMF, NaH, trimethylphosphonoacetate; (d) MeOH, H_2, Pd−C, overnight; (e) toluene, DIBAL in toluene, −78 °C, 20 min; (f) DCM, Dess−Martin periodinane.

Table 4. Inhibitory Potency pIC_{50} of C3-4,4-Disubstituted Piperidines **50**−**56** in the CCR5 ^{125}I-[MIP-1β] Binding Assay

	H	X, X	pIC_{50} CCR5 binding		H	X, X	pIC_{50} CCR5 binding
50		H, H	<4.50	**54**		Cl, Cl	5.10
51		Cl, Cl	4.70	**55**		H, H	5.40
52		H, H	5.30				
53		H, H	5.90	**56**			5.07

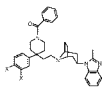
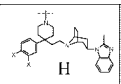
Table 5. Inhibitory Potency pIC_{50} of Selected C2-4,4-Disubstituted Piperidines **57**−**62** in the CCR5 ^{125}I-[MIP-1β] Binding and Ba-L-HOS Antiviral Assay[a]

		pIC_{50} CCR5 binding		H	pIC_{50} CCR5 binding	Bal-HOS pIC_{50}
57		<5.50	**59**		7.20	5.90
			60		7.45	6.64
			61		7.20	n.t.
58		5.34	**62**		7.70	n.t.

[a] n.t.: not tested.

The most potent ligand identified thus far, **22**, turned out to be a weak HIV inhibitor (binding $pIC_{50} = 6.85$, antiviral $pIC_{50} = 5.2$ in the Ba-L-HOS assay). While the cause of this discrepancy is under investigation, it is potentially caused by allosterism of **22**. Similar findings were reported for another class of CCR5 ligands,[27] strongly suggesting that this effect is scaffold-related. We thus hypothesized that such discrepancy could be addressed with another scaffold and next explored the 4,4-disubstituted piperidines **H** series, Figure 2. Because the SAR of the scaffolds examined thus far indicated significant phenyl ring substitution effects, we therefore developed several

Table 6. Inhibitory Potencies pIC_{50} of *endo* C2-4,4-Disubstituted Piperidines **63**−**69** in the CCR5 ^{125}I-[MIP] Binding and Cellular Antiviral Assays[a]

H  3,4-X, X		pIC_{50} CCR5 binding	pIC_{50} HOS-Ba-L	pIC_{50} PBL-Ba-L		 H 3,4-X, X		pIC_{50} CCR5 binding	pIC_{50} HOS-Ba-L	pIC_{50} PBL-Ba-L
63	Cl, Cl	7.80	n.t	n.t.	**66**		Cl, Cl	8.14	7.47	n.t.
64	H, H	8.30	7.80	7.12	**67**		Cl, Cl	7.53	n.t	n.t.
65	Cl, H	8.28	6.96	n.t	**68**		Cl, H	9.00	7.84	8.72
					69		Cl, II	8.30	n.t	n.t.

[a] n.t.: not tested.

synthetic strategies (routes **A**−**C**), applicable to range of substituted phenyl and heteroaromatic rings, toward diverse aldehydes, exemplified here by **36**, **39**, and **43**, Figure 7.

Aldehyde **39** was obtained by nitrile to aldehyde reduction in *N*-Boc-protected 4-(3,4-dichlorophenyl)-4-piperidinecarbonitrile (route **A**), followed by conversion to enolate **35-Cl**,**Cl**, Figure 7. Chemoselective deprotection of the latter proved nontrivial, but after considerable exploration, *p*-toluenesulfonic acid was successfully employed, yielding **39**. The synthesis of **36** (route **C**) was accomplished in a cumulative 45% yield by reduction of triflate **37** to olefin **38**, followed by BBN-mediated hydroboration-hydroxylation and Dess−Martin oxidation. Aldehyde **36** was also independently obtained via route **A** from **35-H**,**H**. Finally, route **B**, applicable for large-scale synthesis of a range of aldehydes, employed conjugative addition of X-Ar-MgBr to cyano(1-Boc-4-piperidinylidene)acetate **40**, followed by hydrolysis and decarboxylation of cyanoester **41** (X = m-F). Resulting nitrile **42** was further reduced with DIBAL to **43**, Figure 7.[28,29]

The C3 linker-containing scaffolds were accessed by nitrile reduction in N-Boc-protected 4-(3,4-X,X-phenyl)-4-piperidinecarbonitrile as in route **A**, followed by Horner−Emmons−Wadsworth olefination of thus resulting aldehydes and double bond reduction to yield esters **46** and **47**. DIBAL-mediated reduction and Dess−Martin oxidation was then used to secure **48** and **49**, Figure 8.

Analogues **50**−**69** (Tables 4, 5) were synthesized from aldehydes **36**, **39**, **44**, **48**, and **49** and were then evaluated in the CCR5 ^{125}I-[MIP-1β] binding as well as HOS and PBL cell-based antiviral assays.[14,30,31]

Significant differences emerged between the SAR in series **H** and previously discussed series. While pyrrolidine **E** and pyrrolidinone **D** series exhibited preference for the C3 linker, compounds in the C3-linker **H** class were found to exhibit low affinity to CCR5, Table 4. Furthermore, the use of the previously found preferred 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one moiety did not significantly improve the binding of **56** (e.g., vs **55**). Incorporation of the conformationally restricted 1-[(3-*exo*)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole moiety in **50** yielded an inactive analogue, although replacement of the carbamate with amide moieties in **52** and **53** resulted in some potency increase. Finally, in contrast to findings in scaffold **E**, there was no significant advantage of the 3,4-dichloro moiety on binding in series **H** (**55** vs **54** and **50** vs **51**), Table 4.

Among the C2 linker-containing analogues **57**−**62**, many tropane-containing compounds, exemplified here by **57**, were found to be inactive. In addition, **58** was practically equipotent to its C3-analogue **56** and thus did not initially indicate any linker effect. However, unlike **50** ($pIC_{50} < 4.50$) in the C3-series, the 1-[(3-*exo*)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole moiety in **59** in the C2-series resulted in moderate binding to CCR5 ($pIC_{50} = 7.2$), corresponding to unexpectedly large (and reversed) linker effect (ΔpIC_{50} (**59**−**50**)$_{binding} > 2.6$). Similar trends were observed for amides **60** and **53** (ΔpIC_{50} (**60**−**53**)$_{binding} = 1.55$), which confirmed this surprising reversal of linker effect in scaffold **H** series (Table 4, Table 5) versus previous scaffolds.

Encouraged by the potent binding of the *exo*-tropane **60**, we synthesized *endo*-tropanes **63**−**69**, Table 6. In particular, **64** was found to be a potent ligand ($pIC_{50} = 8.3$) and antiviral ($pIC_{50} = 7.8$ in the Ba-L-HOS assay), Table 6. This compound was inactive against HIV-1 pseudotyped with the G envelope glycoprotein of vesicular stomatitis virus (VSVg HIV), resulting in a VSVg/Ba-L selectivity ≥790, consistent with HIV inhibition through CCR5 (data not shown). As was found in the C3-**H** class, replacement of the carbamate moiety in **67** with amides in **66** and **63** improved binding and/or antiviral potency. To probe the influence of ring substitution on potency, we also synthesized and evaluated 3-Cl substituted analogues **65**, **68**, and **69**. Comparison of **69** to **67** and **68** to **66** suggested that 3-Cl substitution resulted in more potent analogues than the 3,4-di-Cl moiety, Table 6.

We further characterized **64** and **68** in rodent PK models. Inhibitor **64** had a moderate clearance in rats (22 mL/kg·min, 40% liver blood flow) and a dose-dependent bioavailability ($F = 5\%$, 12.5%, and 19% at 1, 5, and 10 mg/kg oral doses, respectively). Inhibitor **64** also had a moderate clearance in mice (38 mL/kg·min, 42% liver blood flow) and dose-independent bioavailability $F = 22\%$, 30%, and 20% at 1, 5, and 10 mg/kg oral dose, respectively. Similarly, rat clearance (21 mL/kg·min, 38% liver blood flow) and bioavailability of inhibitor **68** at 1 mg/kg oral dose ($F = 26\%$) were quite encouraging.

In summary, our investigation of the SAR of scaffolds **A**−**G** revealed a preference for the C3 linker and the 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one moiety (Figure 1a). There was no significant effect on potency when 1-[(3-*endo*)-8-azabicyclo[3.2.1]-oct-3-yl]-2-methyl-1*H*-benzimidazole was incorporated in **19** in class **E**. The 3,4-dichloro phenyl moiety also provided a significant potency advantage versus unsubstituted phenyl in both C2-**E** and C3-**E**. These findings contrasted with SAR in scaffold **H**. There, key structural contributors to binding, exemplified by potent inhibitors **60**, **64**, and **68**, were both the C2 linker and 1-[(3-*endo* or *exo*)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole moiety. In addition, there was no substantial influence of the 3,4-dichloro phenyl moiety on binding, Table 6. This work utilized high-throughput modular chemistry approach, with monomers optimized for best fit to accelerate discovery of potent ligands. We were able to rapidly evaluate and evolve scaffolds toward ones supporting increased potency, culminating in discovery of novel and potent HIV-1 CCR5 inhibitors **64** and **68**. In addition, **64** and **68** demonstrated

promising PK in rodents, supporting further lead optimization of scaffold **H** toward clinically viable candidate molecules.

Experimental Section

Unless stated otherwise, the reagents were obtained from commercial sources and were used directly. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. The reactions were carried out at ambient temperature unless otherwise indicated. Silica gel (EM Science, 230−400 mesh) was used for chromatographic purification unless otherwise indicated. Anhydrous solvents were obtained from Aldrich (Sure Seal). ^{1}H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometers; the chemical shifts are reported in parts per million (ppm) relative to TMS. The following abbreviations are used to describe peak patterns when appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. ^{1}H NMR analyses were carried out in deuterated chloroform unless otherwise indicated. Mass spectra (ms) were obtained using electrospray (positive or negative ion).

Synthesis of Inhibitors 53, 55, 60, 62, 63, 66, 64, 68, and 69 and of Key Intermediates. (a) Compound **40**. A mixture of *tert*-butyl 4-oxo-1-piperidinecarboxylate (25.25 g, 127 mmol), ethyl cyanoacetate (13.8 mL, 130 mmol), ammonium acetate (2.73 g, 35.4 mmol), glacial acetic acid (6.3 mL), and benzene (250 mL) was heated for 4 h at reflux under Dean−Stark conditions. The reaction mixture was cooled to room temperature and washed successively with water, sodium bicarbonate solution, and brine. Drying, filtration, and evaporation of the organic phase provided *tert*-butyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate as an oil that crystallized on standing (37 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28 (q, 2H, J = 7 Hz), 3.60 (br t, 2H, J = 6 Hz), 3.54 (br t, 2H, J = 6 Hz), 3.12 (t, 2H, J = 6 Hz), 2.76 (t, 2H, J = 6 Hz), 1.47 (s, 9H), and 1.35 (t, 3H, J = 7 Hz). ES-LCMS m/z 293 (M − 1).

(b) Compound **41**. A solution of 1-chloro-3-iodobenzene (14.1 g, 59.28 mmol) in diethyl ether (12 mL) was added dropwise to a mixture of magnesium turnings (1.59 g, 65.4 mmol) in diethyl ether (50 mL) at room temperature. When the Grignard reaction was complete, the resulting organomagnesium reagent was added dropwise to a stirred mixture of **40** (5.0 g, 17 mmol) and cuprous iodide (800 mg, 4.2 mmol) in tetrahydrofuran (30 mL) cooled to 0 °C. The reaction mixture was stirred 1 h at 0 °C and then quenched with saturated ammonium chloride solution. Ethyl acetate (500 mL) was added, and the mixture was washed successively with saturated ammonium chloride, water, and brine. The organic layer was dried and concentrated, and the resulting crude material was purified by column chromatography on silica gel eluting with 4:1 hexane:ethyl acetate. This afforded *tert*-butyl 4-(3-chlorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate **41** as an oil (5.2 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.26 (m, 4H), 3.99 (br q, 2H, J = 6 Hz), 3.91 (br m, 2H), 3.58 (s, 1H), 2.88 (br m, 2H), 2.52 (ddd, 2H, J = 6, 4, 3 Hz), 2.04 (m, 2H), 1.43 (s, 9H), and 1.06 (t, 3H, J = 6 Hz). ES-LCMS m/z 429 (M + Na^+).

(c) Compound **42**. Four M aqueous sodium hydroxide (30 mL, 120 mmol) was added to solution of **41** (5.2 g, 12.8 mmol) in ethanol (30 mL). After stirring at room temperature for 6.5 h, concentrated HCl was added dropwise at 0 °C to reach pH ∼ 4. The mixture was then subjected to ethyl acetate/water extraction, organic phases collected, and concentrated to afford [1-(*tert*-butoxycarbonyl)-4-(3-chlorophenyl) piperidin-4-yl](cyano)acetic acid as a foam (3.75 g, 77%). This material (used without further purification) was dissolved in acetonitrile (30 mL), and cupric oxide (355 mg, 0.025 mmol) was added. The mixture was heated at reflux with stirring for 30 min and then cooled to room temperature, filtered through celite, and evaporated to give *tert*-butyl 4-(3-chlorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate **42** (3.0 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.27 (m, 4H), 3.74 (br m, 2H), 3.08 (br t, 2H, J = 11 Hz), 2.55 (s, 2H), 2.27 (br dd, 2H, J = 11, 3 Hz), 1.86 (ddd, 2H, J = 14, 11, 4 Hz), and 1.44 (s, 9H).

(d) Compound **43**. A solution of **42** (1.96 g, 5.85 mmol) in dichloromethane (25 mL) was cooled to −30 °C, and a 1 M solution of diisobutyl aluminum hydride in dichloromethane (15.5 mL, 17.5 mmol) was added dropwise at-35 °C. The reaction mixture was stirred 30 min and then quenched at −35 °C with methanol (0.7 mL) followed by saturated citric acid solution (50 mL), allowed to warm to room temperature, and extracted with dichloromethane. Combined dichloromethane layers were dried, filtered, and evaporated to provide *tert*-butyl 4-(3-chlorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate **43** as an oil (1.3 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (t, 1H, J = 3 Hz), 7.34−7.22 (m, 4H), 3.61 (m, 2H), 3.26 (ddd, 2H, J = 13, 9, 3 Hz), 2.66 (d, 2H, J = 3 Hz), 2.19 (m, 2H), 1.86 (ddd, 2H, J = 13, 9, 3 Hz), and 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4 (CH), 154.97 (C), 145.8 (C), 135.2 (C), 130.4 (CH), 127.3 (CH), 127.0 (CH), 124.9 (CH), 79.9 (C), 54.6 ($2CH_2$), 53.3 (C), 39.2 (CH_2), 35.5 ($2CH_2$), and 28.6 ($3CH_3$).

Synthesis of Aldehyde 36: Vinyl Enolate Route A. (a) Triethylamine (95 mL) was added to a suspension of 4-cyano-4-phenylpiperidine hydrochloride (50.4 g, 0.266 mol) in tetrahydrofuran (440 mL), followed by di-*tert*-butyl dicarbonate (47.95 g, 0.22 mol) in tetrahydrofuran (150 mL). After stirring at room temperature for 2 h, 200 mL of ethyl acetate was added and washed with 200 mL of 1N citric acid, 200 mL of brine, dried over sodium sulfate, and concentrated to yield 1-Boc-4-phenyl-4-piperidinecarbonitrile (64.40 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.34 (m, 5H), 4.33−4.18 (m, 2H), 3.27−3.19 (m, 2H), 2.14−1.92 (m, 4H), and 1.51 (s, 9H). ES-LCMS m/z 308 (M + H).

(b) A 1 M solution of diisobutylaluminum hydride in toluene (248 mL) was added over 3 h to a solution of 33.32 g (0.116 mol) of 1-Boc-4-phenyl-4-piperidinecarbonitrile (procedure a) in toluene (600 mL) at −78 °C. The reaction mixture was allowed to warm up to −35 °C over 2 h and stirred at −35 °C for 1 h. After quenching with methanol, aqueous workup yielded 29.71 g (88%) of the 1-Boc-4-phenyl-4-piperidinecarbaldehyde. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.43 (s, 1H), 7.55−7.18 (m, 5H), 3.92−3.82 (m, 2H), 3.31−3.18 (m, 2H), 2.40−1.92 (m, 4H), and 1.38 (s, 9H). ES-LCMS m/z 290 (M + H).

(c) A 1 M solution of potassium *tert*-butoxide in tetrahydrofuran (22 mL) was added dropwise to a slurry of (methoxymethyl)triphenyl-phosphonium chloride (7.39 g, 21.56 mmol) in tetrahydrofuran (90 mL) and the reaction mixture was stirred at room temperature for 30 min, followed by addition of the solution of 6.24 g, (21.56 mmol) 1-Boc-4-phenyl-4-piperidinecarbaldehyde (step b) in tetrahydrofuran (18 mL). The mixture was stirred at room temperature for 16 h, heated to reflux for 2 h. Aqueous workup and silica gel chromatography afforded 4.64 g, (68%) of **35**-**H**,**H** as a 1:1 mixture of *E*/*Z* isomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.19 (m, 5H), 6.07 and 4.84 (d, J = 13.0 Hz, 1H), 5.95 and 4.23 (d, J = 7.1 Hz, 1H), 3.95−3.78 (m, 2H), 3.54 and 3.51 (s, 3H), 3.30−3.06 (m, 2H), 2.20−2.09 (m, 2H), 1.98−1.76 (m, 2H), and 1.52 and 1.49 (s, 9H). ES-LCMS m/z 318 (M + H).

(d) Compound **36**. Solution of *p*-toluenesulfonic acid monohydrate (1.95 g, 10.28 mmol) in water (24 mL) was added to solution of **35**−**H**,**H** (4.64 g, 14.61 mmol) in acetone (48 mL) and reaction stirred at room temperature for 48 h. After acetone was removed, solid sodium bicarbonate was added until pH 9, and the aqueous layer extracted with several volumes of DCM and organic fractions were combined and then dried over sodium sulfate. After silica gel purification, 2.23 g of **36** (50%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.39 (s, 1H), 7.43−7.25 (m, 5H), 3.69−3.61 (m, 2H), 3.31−3.22 (m, 2H), 2.65 (s, 2H), 2.28−2.23 (m, 2H), 1.92−1.83 (m, 2H), and 1.46 (s, 9H). ES-LCMS m/z 304 (M + H).

Synthesis of 44, *endo*-1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole. (a) *endo*-1,1-Dimethylethyl 3-[(phenylmethyl)-amino]-8-azabicyclo[3.2.1]octane-8-carboxylate. Sodium triacetoxyborohydride (125 g, 0.59 mol) was added portionwise during 45 min to a mechanically stirred mixture of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (88.3 g, 0.39 mol), pulverized 4A molecular sieves (88 g), and benzylamine (44.1 g, 0.41 mol) in

dichloromethane (1 L) at rt under N_2. The mixture was stirred at rt for 2 days. Saturated sodium carbonate solution (1 L) was added, the mixture stirred for 1 h at room temperature, filtered, and the aqueous layer was further extracted with dichloromethane, and combined organic layers were dried and concentrated to a white solid endo 1,1-dimethylethyl 3-[(phenylmethyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (123 g, 99%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.24−7.33 (m, 5H), 4.19 (m, 1H), 4.10 (m, 1H), 3.76 (s, 2H), 3.00 (t, 1H), 2.15 (m, 3H), 1.91 (m, 2H), 1.60 (m, 1H), 1.57 (m, 1H), 1.49 (m, 1H), 1.48 (m, 1H), 1.45 (s, 9H). AP-LCMS *m*/*z* 317 (M + 1).

(b) *endo*-1,1-Dimethylethyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate. A stirred mixture of 123 g (0.39 mol) of endo 1,1-dimethylethyl 3-[(phenylmethyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (section a), ammonium formate (175 g, 2.78 mol), and 20% palladium hydroxide on carbon (12.3 g) in absolute ethanol (1.5 L) was heated to 50 °C under nitrogen for 7 h. The mixture was filtered and the filtrate was concentrated, dissolved in ethyl acetate, and was washed with water, dried, and concentrated to give the desired *endo*-1,1-dimethylethyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate product (65.4 g, 74%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.19 (m, 1H), 4.10 (m, 1H), 3.30 (t, 1H), 3.03−2.19 (m, 4H), 1.94 (m, 2H), 1.58 (m, 2H), 1.44 (s, 9H). AP-LCMS *m*/*z* 127 (M-99).

(c) *endo-t*-Butyl3-[(2-Nitrophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate). A mixture of 65.4 g (0.29 mol) of *tert*-butyl-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (section b), *N,N*-diisopropylethylamine (56 mL, 0.32 mol) and 1-fluoro-2-nitrobenzene (40.9 g, 0.29 mol) in 1-methyl-2-pyrrolidinone (200 mL) was heated at 70 °C under nitrogen for 16 h. The reaction mixture was diluted with water (500 mL) and extracted with ethyl acetate (3 × 300 mL), and combined organic layers dried and purified on silica gel to give the desired endo-*tert*-butyl 3-[(2-nitrophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate derivative (98.2 g, 98%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.74 (m, 1H), 8.18 (m, 1H), 7.43 (m, 1H), 6.61−6.73 (m, 2H), 4.26 (m, 2H), 3.90 (t, 1H), 2.26−2.32 (m, 2H), 2.03 (m, 4H), 1.83 (m, 2H), 1.44 (s, 9H).

(d) *endo-t*-Butyl3-[(2-Aminophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate. A mixture of 98.2 g (0.28 mol) of *tert*-butyl-3-[(2-nitrophenyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (procedure c), 10% Pd/C (10 g) in ethanol:ethyl acetate 1:1 (1 L) was hydrogenated for 24 h at atmospheric pressure (uptake 17.4 L). The mixture was filtered through celite and concentrated to give the title product (76.2 g, 86%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.67−6.83 (m, 3H), 6.57 (m, 1H), 4.25 (m, 1H), 4.17 (m, 1H), 3.70 (m, 2H), 3.32 (br s, 2H), 2.28 (m, 2H), 1.98−2.07 (m, 4H), 1.76 (m, 2H), 1.47 (s, 9H). AP-LCMS *m*/*z* 318 (M + 1).

(e) *endo*-1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole hydrochloride **44**. A solution of 76.2 g (0.24 mol) of *tert*-butyl 3-[(2-aminophenyl) amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (obtained in procedure d) in triethylorthoacetate (250 mL) was refluxed under nitrogen for 2.5 h. The mixture was concentrated, redissolved in ethyl acetate (500 mL), washed with water (2 × 200 mL), washed with brine, dried, and concentrated. The residue was dissolved in ethanol (250 mL), 6N hydrochloric acid (200 mL) was added and the mixture was refluxed for 2 h. The reaction mixture was concentrated to the desired title product (61.5 g, 92%). ^{1}H NMR (400 MHz; DMSO-d_6) δ 10.16 (d, J = 10 Hz, 1H), 9.47 (d, J = 10 Hz, 1H), 7.95 (d of d, J = 3.6 Hz, 1H), 7.79 (d of d, J = 4.8 Hz, 1H), 7.54 (m, 2H), 5.63 (m, 1H), 4.13 (d, J = 9 Hz, 2H), 2.88 (s, 3H), 2.71 (m, 2H), 2.17 (m, 6H). ES-LCMS *m*/*z* 242 (M + 1).

Compound 45: *exo*-1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole. (a) 8-Benzyl-8-azabicyclo[3.2.1]octan-3-one. First, 60 g (454 mmol) of 2,5-dimethoxytetrahydrofuran was added to 192 mL of 0.025 M HCl at 0 °C and the mixture was stirred at 0 °C for 17 h. Then 78 g (543.6 mmol) of benzyl amine, 66 g (452.0 mmol) of 3-oxopentanedioic acid, and 20.4 g (248.4 mmol) of sodium acetate in 360 mL of water were sequentially added at 0 °C. The reaction was allowed to proceed at room temperature for 1 h, then heated to 50 °C for 2 h, cooled to ambient temperature, pH adjusted to 12, product extracted with ethyl acetate (×3), dried, and solvents removed. Distillation at ~120 °C yielded 25 g of the title crude product.

(b) 8-Benzyl-8-azabicyclo[3.2.1]octan-3-one oxime. To 4.85 g (22.56 mmol) of 8-benzyl-8-azabicyclo[3.2.1]octan-3-one (from step a) was dissolved in 60 mL of ethanol, and 3.13 g (45 mmol) hydroxylamine hydrochloride was added, followed by the addition of 1.8 g (45 mmol) of NaOH in 15 mL water. The mixture was refluxed for 20 h and solvents removed in vacuo to give 4.28 g of the product.

(c) *exo*-8-Benzyl-8-azabicyclo[3.2.1]octan-3-amine. First 3.5 g of sodium in 200 mL of pentanol was added portionwide over 1 h to 3.9 g (16.9 mmol) of 8-benzyl-8-azabicyclo[3.2.1]octan-3-one oxime (step b). The mixture was then refluxed for 3 h, cooled to ambient temperature, quenched with water, and extracted with 6N HCl. The aqueous layer was basified using NaOH pellets and the compound extracted with EtOAc, the organic layer dried, and solvents removed to afford 2.9 g (80%) of crude title product.

(d) *exo*-8-Benzyl-*N*-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine. First 4.32 g (30.60 mmol) 1-fluoro-2-nitrobenzene was added to 5.62 g (27.82 mmol) of exo-8-benzyl-8-azabicyclo[3.2.1]octan-3-amine (from step c) and 9.7 mL (55.46 mmol) of Hunig base dissolved in 200 mL of NMP. Then the mixture was stirred at RT for 3 h, diluted with EtOAc, washed with water, the organic layer dried, and solvents removed, affording 8.62 g of the title product.

(e) *exo*-*N*-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)benzene-1,2-diamine. To 2.92 g (9.04 mmol) of *exo*-8-benzyl-*N*-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine (procedure d) dissolved in 150 mL of EtOAc and 25 mL of methanol, 1 g Pd/C was added and the mixture stirred at 1 atm H_2 for 3.5 h, filtered through celite, and solvents removed to afford 2.2 g of the desired solid.

(f) *exo*-1-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole. First 7.7 g (25.08 mmol) of *exo*-*N*-(8-benzyl-8-azabicyclo [3.2.1]oct-3-yl)benzene-1,2-diamine (procedure e) was refluxed in 200 mL of 1,1,1-triethoxyethane for 18 h. The mixture was cooled, solvents removed, and the residue redissolved in toluene, 1.8 g (9.47 mmol) of *p*-toluenesulfonic acid was added, and the reaction mixture was heated to reflux for 18 h. Purification resulted in 2.2 g of the desired product.

(g) *exo*-1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole **45**. First 2.2 g (6.65 mmol) of *exo*-1-(8-benzyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (procedure f) was dissolved in 150 mL of ethanol, followed by addition of 2.09 g (33.23 mmol) of ammonium formate and 0.4 g palladium hydroxide (20% on carbon), and the mixture was refluxed for 2.5 h and filtered through celite to yield after solvent removal 1.06 g of the desired product **45**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (m, 1H), 7.55 (m, 1H), 7.20 (m, 2H), 4.52 (m, 1H), 3.72 (m, 2H), 2.65 (s, 3H), 2.50 (m, 2H), 1.96 (m, 2H); 1.80 (m, 4H).

Compound 69. (a) *tert*-Butyl *endo*-4-(3-chlorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate. Sodium triacetoxyborohydride (286 mg, 1.35 mmol) was added in one portion to a stirred mixture of the dihydrochloride salt of **44** (250 mg, 0.90 mmol), **43** (304 mg, 0.90 mmol), triethylamine (0.25 mL, 1.79 mmol), and powdered sieves (250 mg) in dichloromethane (3 mL). After stirring for 1 h at room temperature, the reaction was quenched with saturated sodium bicarbonate solution and the dichloromethane layer was removed. The aqueous layer was extracted with dichloromethane and after workup afforded *tert*-butyl *endo*-4-(3-chlorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate **69** (500 mg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47 (dd, 1H, J = 7.2 Hz), 7.40 (br s, 1H), 7.39−7.35 (m, 3H), 7.27 (d, 1H, J = 7 Hz), 7.11 (dd, 1H, J = 7.6 Hz), 7.08 (dd, 1H, J = 7.6 Hz), 4.50 (m, 1H, J = 8 Hz), 3.48 (m, 2H), 3.24 (m, 2H), 3.11 (m, 2H), 2.48 (s, 3H), 2.35 (br dd, 2H, J = 15.9 Hz), 1.98 (m, 2H), 1.90−1.70 (m, 10H), 1.59 (d, 2H, J = 8 Hz), and 1.36 (s, 9H). ES-LCMS *m*/*z* 585 (M + Na^+).

Compound 68, *endo*-1-(8-{2-[4-(3-Chlorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole.

Deprotection

First, 4 M HCl in dioxane (7 mL, 28 mmol) was added to a stirred solution of **69** (500 mg, 0.888 mmol) in dichloromethane (6 mL). After 15 min, solvents were removed, affording *endo*-1-(8-{2-[4-(3-chlorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (548 mg, 100%). This material was used without further purification. ES-LCMS *m*/*z* 463 (M + H).

Amide Formation

Pivaloyl chloride (0.040 mL, 0.325 mmol) was added to the solution of *endo*-1-(8-{2-[4-(3-chlorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (165 mg, 0.308 mmol) and triethylamine (0.086 mL, 0.616 mmol) in dichloromethane (3 mL). After stirring 1 h at room temperature, the reaction mixture was quenched with saturated sodium bicarbonate solution and after aqueous workup and purification on silica gel gave *endo*-1-(8-{2-[4-(3-chlorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole **68** (100 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, 1H, J = 7 Hz), 7.42 (s, 1H), 7.41−7.34 (m, 3H), 7.28 (d, 1H, J = 7 Hz), 7.11 (br t, 1H, J = 7 Hz), 7.08 (br t, 1H, J = 7), 4.50 (m, 1H, J = 8 Hz), 3.73 (m, 2H), 3.29 (s, 3H), 3.25 (m, 4H), 2.35 (br dd, 2H, $J \sim$ 22.9 Hz), 2.02 (m 2H), 1.84−1.73 (m, 10H), 1.59 (d, 2H, J = 8 Hz), and 1.16 (s, 9H). ES-LCMS *m*/*z* 547 (M + H). HRMS $C_{33}H_{43}ClN_4O$ *m*/*z* 547.3186 $(M + H)_{calcd}$ 547.3204 $(M + H)_{obs}$.

Compound 64. (a) *endo*-2-Methyl-1-((1*R*,5*S*)-8-{2-[4-phenyl-1-(phenylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole Compound **64** was obtained from intermediates **36** and **44** using the procedure described for **68**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, m), 6.94 (7H, m), 6.82 (4H, m), 6.70 (2H, m), 4.15 (1H, m), 3.75 (1H, m), 3.11 (1H, m), 2.98 (4H, m), 2,93 (1H, m), 2.78 (3H, m), 2.05 (3H, s), 2.04 (2H, m), 1.88 (3H, m), 1.70 (1H, m), 1.59−1.24 (4H, m), 1.14 (2H, m). HRMS *m*/*z* $(M + H)^+_{calcd}$ 533.3280; $(M + H)^+_{obs}$ 533.3300.

Alternatively, **64** was synthesized by reductive alkylation of **44** with (1-benzoyl-4-phenylpiperidine-4-yl) acetaldehyde using the procedure described for **69**. To that end, the synthesis of (1-benzoyl-4-phenylpiperidine-4-yl) acetaldehyde was accomplished by stirring 4 M HCl in dioxane (9 mL) and **36** (8.75 g, 27.57 mmol) in THF (27 mL) for 1 h at rt. The solvents were evaporated and product redissolved in DCM (40 mL), cooled to 0 °C, and benzoyl chloride (4.65 g, 33.08 mmol) in DCM (5 mL) was added, followed by triethylamine 8.37 g, 82.71 mmol) in DCM (5 mL). After stirring for 1 h at rt, aqueous workup and silica gel chromatography afforded the desired (1-benzoyl-4-phenylpiperidine-4-yl) acetaldehyde (3.47 g, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.37 (s, 1H), 7.42−7.25 (m, 10H), 4.14−4.09 (m, 1H), 3.54−3.30 (m, 3H), 2.67 (s, 2H), 2.38−2.24 (m, 2H), and 1.97−1.85 (m, 2H). ES-LCMS *m*/*z* 308 (M + H).

Compound 60, *exo*-2-Methyl-1-(8-{2-[4-phenyl-1-(phenylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole. Obtained analogously to **68**. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.80 (m, 1H), 7.62−7.17 (m, 13H), 4.74 (m, 1H), 4.30−4.13 (m, 1H), 4.02 (m, 2H), 3.71−3.55 (m, 1H), 3.32 (s, 2H), 2.84−2.71 (m, 4H), 2.65 (s, 3H), 2.45 (m, 1H), 2.29−1.81 (m, 11H). HRMS (M + H) calcd, 533.3280; found, 533.3267.

Compound 62, *exo*-1-(8-{2-[1-(Cyclopentylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole. Obtained analogously to **60**. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.65 (m, 1H), 7.48−7.32 (m, 5H), 7.26−7.06 (m, 3H), 4.65 (m, 1H), 4.04−3.71 (m, 4H), 3.20 (m, 1H), 3.09−2.94 (m, 2H), 2.71−2.46 (m, 7H), 2.32−2.16 (m, 2H), 2.10−1.86 (m, 8H), 1.83−1.47 (m, 10H). HR MS (M + H) calcd, 525.3593; found, 525.3595.

Compound 63, *endo*-1-(8-{2-[4-(3,4-Dichlorophenyl)-1-(phenylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole. Compound **63** was prepared according to procedures applied toward **68**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H, J = 7.2 Hz), 7.44 (app t) overlapping 7.39 (br s, 7H total), 7.32−7.25 (m) overlapping 7.26 (s, $CHCl_3$, 2H total), 7.18−7.14 (m, 2H), 4.60 (app quint, 1H, J = 8.8 Hz), 4.13 (br s, 1H), 3.57, 3.40, 3.27 (three overlapping br s, 6H total), 2.55 (s, 3H), 2.44−2.34 (m, 2H), 2.21−1.66 (m, 13H). FAB HRMS (calcd for MH^+, $C_{35}H_{38}Cl_2N_4O$) 601.2501; found 601.2501.

Compound 66, *endo*-1-(8-{2-[4-(3,4-Dichlorophenyl)-1-(2,2-dimethylpropanoyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole. Prepared according to procedures used for **68**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H, J = 6.9 Hz), 7.45 (d, 1H, J = 8.3 Hz), 7.39 (br. s, 1H), 7.32−7.27 (m, 1H), 7.20−7.14 (br. m, 3H), 4.62 (app quint, 1H, J = 9.2 Hz), 3.97−3.87 (m, 2H), 3.41−3.25 (m, 4H), 2.58 (s, 3H), 2.44−2.34 (m, 2H), 2.16−2.10 (m, 2H), 1.97−1.65 (m, 12H), 1.27 (s, 9H). LRMS (ES, +ve ion) *m*/*z* 581.0 (M^+), 583.3 (M + 2,^{37Cl}).

The Synthesis of C3-linker Analogues 53 and 55. 1-Boc-4-formyl-4-phenyl-1-piperidine was obtained as described in steps a and b in procedure leading to **36**.

Intermediate **47** was synthesized by adding trimethyl phosphonoacetate (4.28 mL, 26.45 mmol) dropwise to a suspension of NaH (1.15 g, 60% in mineral oil, 28.86 mmol) in toluene (100 mL) at 0 °C, stirring at rt for 1 h, followed by addition of 6.95 g (24.05 mmol) off 1-Boc-4-formyl-4-phenyl-1-piperidine in 50 mL toluene and stirring the mixture stirred at rt overnight. Following aqueous workup, solvent were removed, and the desired product was obtained as a colorless oil (8.26 g). Residue was dissolved in MeOH (200 mL), Pd/C (1 g, 5%) was added and stirred under 1 atm H_2 for 2.5 h, filtered through celite, and purified, resulting in 6.5 g of **47** (78% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47−7.18 (5H, m), 3.70−3.64 (2H, m), 3.54 (3H, s), 3.12 (2H, m), 2.16−2.12 (2H, m), 1.98−1.87 (4H, m), 1.71−1.64 (2H, m), 1.43 (9H, s). LRMS: *m*/*z* calcd for $C_{20}H_{29}NO_4$, 347.2; found, 347.3 (M^+).

DIBAL (38 mL, 1 M in toluene, 38 mmol) was cooled to −78 °C and added into a solution of **47** (6.5 g, 18.73 mmol) in toluene (80 mL) cooled to −78 °C. The reaction was carried out at −78 °C for 2.5 h, quenched with cooled MeOH (−78 °C), and after standard workup gave 5.72 g of **49**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.53 (1H, s), 7.46−7.25 (5H, m), 3.73−3.67 (2H, m), 3.10−3.05 (2H, m), 2.17−2.09 (4H, m), 1.90−1.86 (2H, t, J = 8.0 Hz), 1.71−1.64 (2H, m), 1.43 (9H, s). LRMS: *m*/*z* calcd for $C_{19}H_{27}NO_3$, 317.2; found, 317.3 (M^+).

Compound 53, 2-Methyl-1-(8-{3-[4-phenyl-1-(phenylcarbonyl)-4-piperidinyl]propyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole. Obtained from **49** and **45** as described for **64**. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.80 (m, 1H), 7.62−7.17 (m, 13H), 4.74 (m, 1H), 4.30−4.13 (m, 1H), 4.02 (m, 2H), 3.71−3.55 (m, 1H), 3.32 (s, 2H), 2.84−2.71 (m, 4H), 2.65 (s, 3H), 2.45 (m, 1H), 2.29−1.81 (m, 11H). HRMS (M + H) calcd, 533.3280; found, 533.3267.

Compound 55, *tert*-Butyl-4-{3-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]propyl}-4-phenylpiperidine-1-carboxylate. Obtained from **49** and 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one as described for **69**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (m, 1H), 7.32−6.98 (m, 10H), 4.28 (m, 1H), 3.65 (m, 2H), 3.09 (m, 2H), 2.87−2.84 (m, 2H), 2.37 (m, 2H), 2.18 (m, 4H), 1.95 (m, 1H), 1.70 (m, 4H), 1.54 (m, 2H), 1.41 (s, 9H), 1.14−1.00 (m, 2H). MS (electrospray +) 519.27 (M + 1).

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