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ARTICLE

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# Novel 4,4-Disubstituted Piperidine-Based C−C Chemokine Receptor-5 Inhibitors with High Potency against Human Immunodeficiency Virus-1 and an Improved human Ether-a-go-go Related Gene (hERG) Profile

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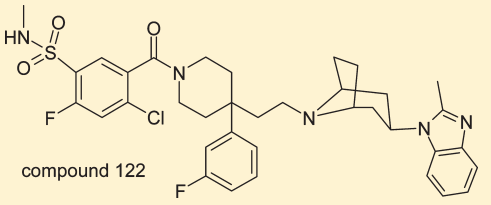
Supporting Information

**ABSTRACT:** We recently described (J. Med. Chem. 2008, 51, 6538−6546) a novel class of CCR5 antagonists with strong anti-HIV potency. Herein, we detail SAR converting leads **1** and **2** to druglike molecules. The pivotal structural motif enabling this transition was the secondary sulfonamide substituent. Further fine-tuning of the substituent pattern in the sulfonamide paved the way to enhancing potency and bioavailability and minimizing hERG inhibition, resulting in discovery of clinical compound **122** (GSK163929).



compound 122

## INTRODUCTION

The AIDS epidemic affects millions of individuals worldwide. Although highly active antiretroviral therapy (HAART) has resulted in a marked decline of AIDS-related deaths in the developed world, there is a continued need for new medicines that support simpler dosing, lower treatment cost, and fewer side effects. Recent efforts in the area of CCR5 antagonist discovery resulted in several advanced clinical compounds, such as vicriviroc,[1] (*S*,*E*)-8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-*N*-(4-(((1-propyl-1*H*-imidazol-5-yl)methyl)sulfinyl)phenyl)-1,2,3,4-tetrahydrobenzo[*b*]azocine-5-carboxamide (TAK-652),[2] and one FDA-approved drug (maraviroc).[3] Recent progress has been reviewed.[4−12]

In our previous communication we described the discovery of potent and bioavailable *endo* C2-4,4-disubstituted piperidine scaffold-based CCR5 antagonists **1** and **2**.[7−9,13−19,23]

Our subsequent investigations revealed that **1** and **2** (Table 1) also turned out to moderately inhibit hERG ion channels. In addition, both compounds were active (defined as QTc > 5% at 10 mg/kg dose)[20] in the in vivo guinea pig QTc prolongation assay, used successfully in predicting the risk of human QT prolongation.[20] The latter is a marker for ventricular arrhythmias, such as torsade de pointes (TdP), which has caused market withdrawal of several drugs, such as cisapride, grepafloxicin, and terfenadine. The incidence of TdP with noncardiac drugs is 0.01−0.001%, but it is significantly elevated (to 1−8% incidence) with cardiac proarrhythmic drugs. Consequently, we launched an effort designed to tune out hERG interaction and utilized hERG and QTc screens to make critical compound progression decisions.

A known approach to decreasing hERG inhibition is to increase the polarity, although this often results in lower membrane permeability and bioavailability and is illustrative of the challenges of multidimensional optimization.[21,22]

## RESULTS AND DISCUSSION

Herein, we describe SAR toward the discovery of clinical compound **122** (GSK163929). We believe that the SAR developed could also be applicable to other compound series.

**Linker Modifications.** Our previous work demonstrated preference for a two- over three-carbon linker in this series.[13,23] Analogues **3** and **4** (exo, data not shown), which feature a formal migration of nitrogen from tropane bridgehead to the linker, were less potent than **1** (Table 2, Figure 1). Low potency of amide **5** can be rationalized by the now well-established structural requirement for the basic amine moiety in CCR5 ligands. Similarly, poor potency of **6** can be attributed to low p$K_a$ of the bridgehead nitrogen (p$K_a$ = 6.37 for **6** vs 10.73 for **2**, calculated with ACD, version 11, software) due to the electron withdrawing effect of neighboring ketone (Table 2).

Analogues **3** and **4** were synthesized from dioxolane **7**, Figure 1. Both isomers, *endo* **8** and *exo* **9** were separated, and chemistry was carried out on individual isomers. Amine **10**, obtained from 4-phenyl-4-piperidinecarbonitrile **11**, was reductively alkylated with both **8** and **9**, yielding ligands **3** and **4**.

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Table 1

| Analogue | | $pIC_{50}$ CCR5 binding [MIP-1β] | Ba-L-HOS $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | QTc (%) | RAT PO DNAUC [ng.hr/mL] |
|---|---|---|---|---|---|---|
| 1 |  | 7.8 | 7.80 | 5.7 | 9.4 | 16 |
| 2 |  | 9.45 | 8.01 | 6.0 | 6.5 | 144 |

Table 2

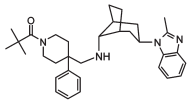
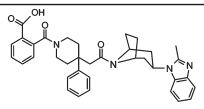
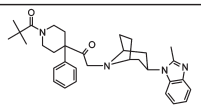
| Analogue | | $pIC_{50}$ CCR5 binding [MIP-1β] | Ba-L-HOS $pIC_{50}$ |
|---|---|---|---|
| 3 |  | 5.65 | n.t. |
| 5 |  | <5.50 | <4.70 |
| 6 |  | 5.75 | <5.00 |

Table 3

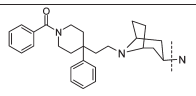
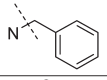
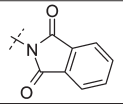
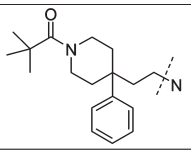
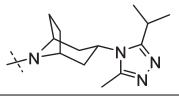
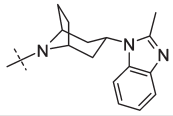
| Analogue | | $pIC_{50}$ CCR5 binding [MIP-1β] | Ba-L-HOS $pIC_{50}$ |
|---|---|---|---|
| |  | | |
| 17 |  | <5.50 | 5.20 |
| 18 |  | <5.50 | 5.53 |
| 19 |  | 5.60 | <6.00 |

Table 4

| Analogue | | $pIC_{50}$ CCR5 binding assay [$^{125}$I-[MIP-1β] | Ba-L-HOS $pIC_{50}$ |
|---|---|---|---|
| |  | | |
| 24 |  | n.t. | 5.55 |
| 25 |  | n.t. | 7.72 |

Analogue **5** was synthesized from acid **13**, which was derived from **11** and amine **14**.[13,23] Ligand **6** was obtained by acylation of ketone **15**, followed by its bromination to **16** and final alkylation with amine **14**.

**Benzimidazole Modifications.** We probed the consequences of replacing benzimidazole moiety in **1** with other aromatic moieties, using ligands **17**−**19**.

Compounds **17** and **18** were synthesized using known chemistry,[13,23] while **19** was obtained by converting tropinone to *endo* amine **20**, subsequent derivatization to phthaloates **21** and **22**, and reductive alkylation with aldehyde **23** (X, Y, Z, W = H) (Figure 2).

Analogues **17**−**19** were found to be virtually inactive in both CCR5 binding and the antiviral assay (Table 3).

Inhibitor **24** incorporates the (3-*exo*)-3-[3-methyl-5-(1-methylethyl)-4*H*-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]octane moiety also found in maraviroc, and we were surprised to find **24** to be essentially inactive (Table 4). A comparison with much more potent *exo*-benzimidazole **25** may suggest that compounds in our series may interact with CCR5 in a different binding mode than maraviroc.

Both **24** and **25** were synthesized from aldehyde 23(X, Y, Z, W = H) using chemistry described elsewhere.[3,23−25]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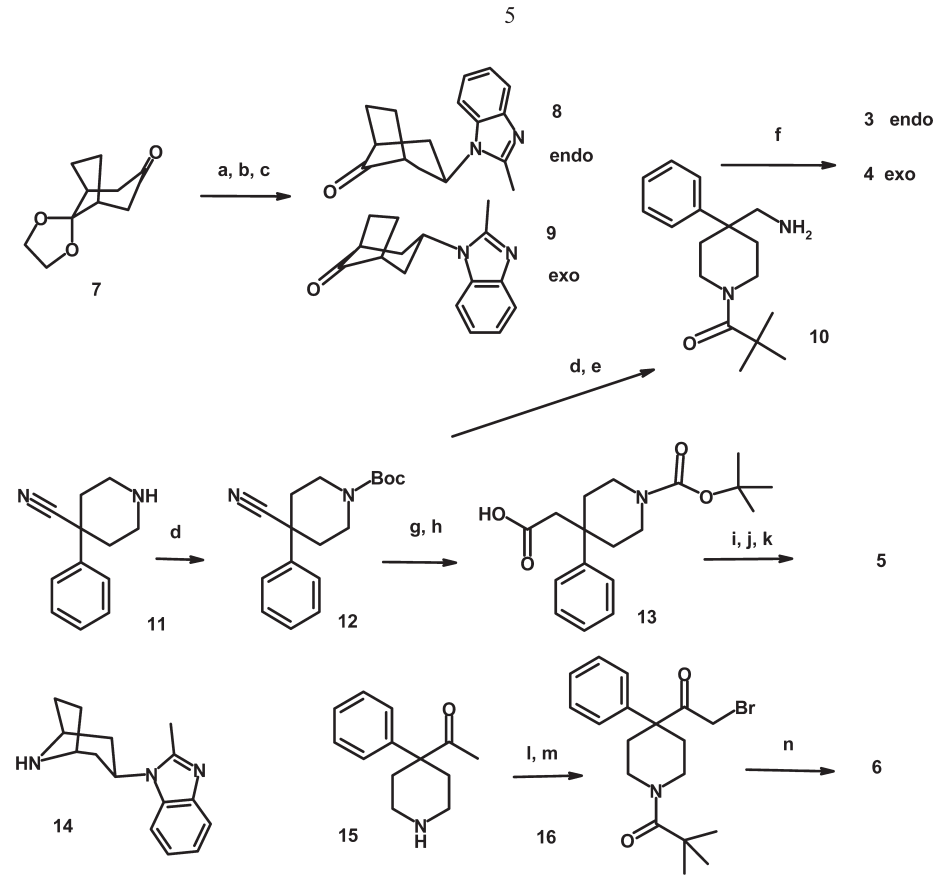


**Figure 1.** Reagents and conditions: (a) DCM, 1,2-diaminobenzene, $NaBH(OAc)_3$, molecular sieves, silica chromatography separation of *exo* and *endo* isomers; (b) $MeC(OEt)_3$, 100 °C, quant; (c) 1 N HCl, acetone; (d) THF, $(Boc)_2O$, TEA; (e) $LiAlH_4$, $Et_2O$; (f) DCM, molecular sieves, $NaBH(OAc)_3$; (g) toluene, DIBAL in toluene, −78 to −35 °C, 2.5 h; (h) $NaClO_2$, $NaH_2PO_4$, *t*-BuOH, water; (i) **14**, HATU, $Et_3N$, $CH_3CN$; (j) 4N HCl dioxane; (k) benzoic acid derivative, HATU, $Et_3N$, $CH_3CN$; (l) dichloromethane, pivaloyl chloride, triethylamine; (m) methanol, 0 °C, $Br_2$; (n) ethyl ether, TEA, **14**, benzene, 90 °C, 12 h.

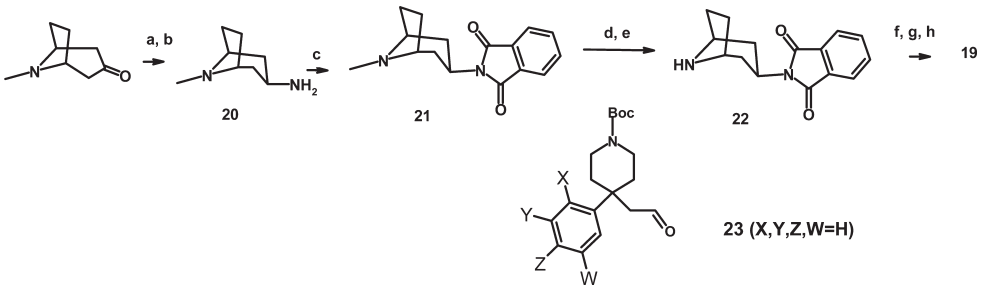


**Figure 2.** Reagents and conditions: (a) benzylamine, DCE, $NaBH(OAc)_3$; (b) methanol, 10% Pd/C, $H_2$, 45 psi; (c) $THF/Et_3N$, *N*-carbethoxyphthalimide, reflux; (d) $ClCO_2CH(Cl)CH_3$, 1.2 equiv, DCE, reflux; (e) MeOH, $K_2CO_3$, reflux; (f) dichloroethane, sodium triacetoxyborohydride, **23** (X, Y, Z, W = H); (g) 4 N HCl in dioxane; (h) DMF, HATU, DIEA, benzoic acid.

On the basis of these data, a conclusion was made that the benzimidazole moiety was preferred in our series.

**Substitutions on Benzimidazole Moiety.** We examined the influence of benzimidazole substitutions in analogues **24**−**34**. Tropanes **35**−**45** were synthesized from pivotal intermediates **46** and **47** (Figure 3) and further elaborated into inhibitors **24**−**34** using reductive alkylation chemistry, analogous to one described in Figure 2.

Modifications of 2- benzimidazole moiety by truncation (**25**), homologation (**34**), isosteric or heteroatom substitution (**24**, **26**, **28**), and aromatic ring substitutions (**29**−**31**) were found to be deleterious to anti-HIV potency (Table 5).

**Tropane Ring Modification.** We probed the apparent preference for tropane moiety in CCR5 analogues by synthesizing both the expanded ring size oxo analogue **48** and fused 5−3 ring analogue **49** (Figure 4).[23,26] Both compounds were found to be essentially inactive ($pIC_{50}$ CCR5 binding assay $^{125}I$-[MIP-1$\beta$] of <5.50 and 5.47; HOS $pIC_{50}$ of 5.05 and 6.00, respectively).


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Table 5

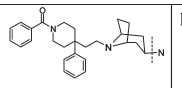
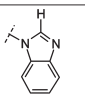
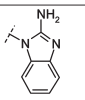
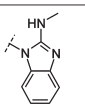
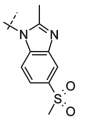
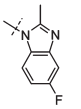
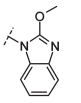
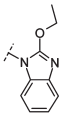
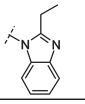
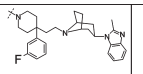
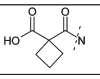
| Analogue | Amine Fragment |  | $pIC_{50}$ CCR5 binding [$^{125}$I-[MIP-1β] | Ba-L-HOS $pIC_{50}$ |
|---|---|---|---|---|
| 24 | 35 |  | <5.50 | 5.13 |
| 25 | 36 |  | 6.40 | 5.04 |
| 26 | 37 |  | 6.59 | 5.90 |
| 27 | 38 |  | 6.60 | 5.80 |
| 28 | 39 |  | 7.00 | 5.70 |
| 29 | 40 |  | 5.80 | 5.13 |
| 30 | 41 |  | 8.00 | 6.76 |
| 31 | 42 |  | 7.70 | 6.46 |
| 32 | 43 |  | 6.60 | 5.60 |
| 33 | 44 |  | 5.70 | 5.85 |
| 34 | 45 |  | 8.05 | 6.85 |

Table 6

| Analogue |  | Ba-L-HOS $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | RAT PO DNAUC [ng.h/mL] | RAT iv CL [mL/min/kg] | MDCK Papp [nm/sec] |
|---|---|---|---|---|---|---|
| 50 |  | 7.54 | 5.8 | 128 | 24 | 248 |
| 51 |  | 7.56 | 4.25 | n.t. | n.t. | 0.9 |
| 52 |  | 7.77 | 4.35 | 0 | 136 | 1.5 |


dx.doi.org/10.1021/jm200279v |*J. Med. Chem.* 2011, 54, 3756–3767

Table 7

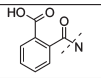
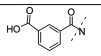
| Analogue | | Ba-L-HOS $pIC_{50}$ | hERG $pIC_{50}$ | QTc (%) | RAT PO DNAUC [ng.h/mL] | RAT iv CL [mL/min/kg] | MDCK Papp [nm/sec] |
|---|---|---|---|---|---|---|---|
| **53** |  | 7.51 | 3.9 | n.t. | 0 | 114 | 2.6 |
| **54** |  | 7.58 | 4.3 | -2% | 0 | 62 | 4.2 |

Table 8

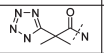
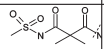
| Analogue | | Ba-L-HOS $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | QTc (%) | RAT PO DNAUC [ng.h/mL] | RAT iv CL [mL/min/kg] | MDCK Papp [nm/sec] |
|---|---|---|---|---|---|---|---|
| **55** |  | 7.34 | 4.74 | n.t. | 0 | 156 | 1.3 |
| **56** |  | 8.13 | 4.6 | n.t. | 0 | 53 | 1.5 |

Table 9

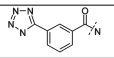
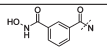
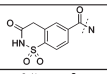
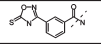
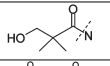
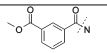
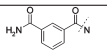
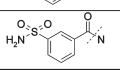
| Analogue | | Ba-L-HOS $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | QTc (%) | RAT PO DNAUC [ng.h/mL] | RAT iv CL [mL/min/kg] | MDCK Papp [nm/sec] |
|---|---|---|---|---|---|---|---|
| **60** |  | 8.11 | 4.5 | n.t. | n.t. | n.t. | n.t. |
| **61** |  | 7.60 | 4.1 | n.t. | 0 | n.t. | 1.7 |
| **62** |  | 7.33 | <4.5 | n.t. | 0 | 26 | 6.7 |
| **63** |  | 7.53 | <4.5 | n.t. | n.t. | n.t. | 1.9 |

Table 10

| Analogue | | Ba-L-HOS $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | QTc (%) | RAT PO DNAUC [ng.h/mL] | MDCK Papp [nm/sec] |
|---|---|---|---|---|---|---|
| **67** |  | 7.48 | 5.22 | n.t. | 140 | 236 |
| **68** |  | 7.15 | 6.1 | 7.2 | 76 | 192 |
| **69** |  | 7.27 | 4.6 | n.t. | n.t. | 1.9 |
| **70** |  | 7.48 | 4.2 | n.t. | n.t. | 1 |


dx.doi.org/10.1021/jm200279v |J. Med. Chem. 2011, 54, 3756–3767

Table 11

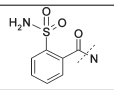
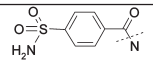
| Analogue | | Ba-L-HOS $pIC_{50}$ | Ba-L-PBL $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | QTc (%) | RAT PO DNAUC [ng.h/mL] |
|---|---|---|---|---|---|---|
| **71** |  | 7.04 | n.t. | n.t. | n.t. | n.t. |
| **72** |  | 7.79 | n.t. | 4.6 | n.t. | 0 |

Table 12

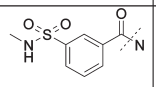
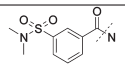
| Analogue | | Ba-L-HOS $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | Papp |
|---|---|---|---|---|
| **73** |  | 7.44 | 4.2 | 4.6 |
| **74** |  | 7.27 | 5.7 | 77.7 |

Table 13

| Analogue | | $pIC_{50}$ CCR5 binding [$^{125}$I-[MIP-1β] | Ba-L-HOS $pIC_{50}$ |
|---|---|---|---|
| **75** | Z=F | 6.75 | <6.0 |
| **76** | Y, Z= Cl, Cl | 7.80 | 6.37 |
| **77** | Y, Z= F, F | 7.50 | 5.91 |
| **78** | Y=Cl | 8.3 | 6.96 |
| **79** | Z=$CF_3$ | <5.50 | <6.00 |
| **80** | Y=O-Me | 7.75 | 6.42 |

**Acid Derivatives.** Compounds **51** and **52** were designed to probe whether affinity to hERG[21] could be decreased with carboxylic acid moieties in **2** and its *m*-F-phenyl analogue **50**. While the latter turned out to be a moderate hERG inhibitor, both **51** and **52** were inactive in hERG inhibition assay and maintained similar potency to **50** in the antiviral assay. However, we found out that **51** had poor MDCK permeability and **52** was not bioavailable, likely because of its low absorption and/or high rat in vivo clearance (Table 6).

Compounds **53** and **54**, analogues of benzoic acid derivative **1**, were also designed to probe whether adding the carboxylate moiety would be beneficial to optimizing both hERG and PK (Table 7). Similar to **51** and **52**, compounds **53** and **54** were not permeable in MDCK or bioavailable in the rat PK model.

Table 14

| Analogue | | | | | Ba-L-HOS $pIC_{50}$ |
|---|---|---|---|---|---|
| | X | Y | Z | W | |
| **81** | H | H | H | H | 8.51 |
| **82** | H | H | F | H | 7.35 |
| **83** | H | H | Cl | H | 7.35 |
| **84** | H | H | i-Pr | H | 6.81 |
| **85** | H | $CF_3$ | H | H | 7.45 |
| **86** | H | F | H | H | 7.96 |
| **87** | H | Cl | H | H | 7.54 |
| **88** | H | iPr | H | H | 6.69 |
| **89** | H | Me | H | H | 8.85 |
| **90** | Me | H | H | H | 6.21 |
| **91** | H | F | Me | H | 6.81 |
| **92** | H | Cl | Me | H | 7.14 |
| **93** | H | Cl | F | H | 6.34 |
| **94** | H | F | Cl | H | 6.38 |
| **95** | H | Cl | Cl | H | 7.44 |
| **96** | H | $CH_2OH$ | H | H | 5.36 |
| **97** | H | OH | H | H | 4.72 |
| **98** | H | OEt | H | H | 6.22 |
| **99** | H | O-iPr | H | H | 6.07 |
| **100** | H | H | $CF_3$ | H | 7.75 |
| **101** | H | Cl | H | Cl | 6.33 |
| **102** | H | F | H | F | 6.94 |
| **103** | H | H | S-Me | H | 6.65 |
| **104** | H | S-Me | H | H | 6.30 |
| **105** | H | F | H | Cl | 6.90 |

Table 15

| analogue | RAT iv Cl [mL/(kg·min)] | RAT po DNAUC [ng·h/mL] |
|---|---|---|
| **81** | 31 | 12 |
| **86** | 26.8 | 59 |
| **89** | 28.3 | 27 |

These compounds were, however, inactive in the hERG patch-clamp assay. In addition, **54** caused no QTc prolongation in the guinea pig model.

Further efforts to modulate compound polarity and absorption were attempted with tetrazole and acylsulfonamide bioisosteres **55** and **56**. Both compounds maintained their antiviral potency with respect to other derivatives in this class but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continued to exhibit low permeability and high clearance in the rat in vivo PK model (Table 8).

The synthesis of **55** was accomplished by converting ethyl 2-cyano-2-methylpropanoate to ester **57**, followed by acylating **58**[13,23] with acid **59** (Figure 5).

Compounds **60**−**63** were designed as mimetics of acid **54**. These compounds had acceptable hERG properties, but permeability and/or bioavailability in rat PK was still an issue for this class, as exemplified by the tetrazolebenzoic acid derivative **60** (Table 9).

The synthesis of **62** can be accomplished by reacting **58** and acid **66**, which was obtained in several routine steps (Figure 6). Results in this group of compounds strongly suggest that while acids or acid bioisosteres maintain the antiviral potency and exhibit acceptable hERG/QTc profile, these compounds have poor membrane permeability and/or high in vivo clearance.

Amide, sulfonamide, alcohol, and ester derivatives in **67**−**70** were also examined as potential hERG and PK modulators (Table 10). The alcohol **67** and ester **68** were highly permeable and bioavailable in rat PK. However, both compounds were also moderately active in hERG. In addition, **68** was active (QTc = 7.2%) in the guinea pig model. On the other hand, sulfonamide **70** and to some degree amide **69** had low hERG $pIC_{50}$, leading to further efforts to optimize the sulfonamide series.

**Positional Isomers of the Primary Sulfonamide Motif.** A comparison of properties associated with *o*-, *m*-, and *p*-sulfonamide isomers **71**, **70**, and **72** reveals that **70** has the best overall profile, with **71** being relatively less potent and **72** found not to be bioavailable in the rat PK model (Table 11). We further explored the sulfonamide motif **70** by synthesizing the secondary and tertiary sulfonamide analogues **73** and **74** (Table 12). While the MDCK permeability was improved in secondary and tertiary sulfonamides, **74** was also moderately potent in the hERG patch-clamp assay, leading to discontinuation of the tertiary sulfonamide motif-containing series. On the other hand, we decided to further pursue the secondary sulfonamide motif in **73** because of its promising properties.

**Central Aromatic Ring Substitutions.** We next attempted to optimize the aromatic ring substitution pattern by synthesizing **75**−**80** (Table 13) and **81**−**105** (Table 14, Figure 7).[24,25] Most substitutions were found to be deleterious to anti-HIV potency with the exception of several meta substituents, such as *m*-F (**86**), *m*-Cl (**87**), and *m*-$CH_3$ (**89**). In particular, compound **86** was more bioavailable and had lower hERG potency ($IC_{50}$= 63 $\mu$M) compared to **1** (Table 15, Table 1). In contrast, potent methyl derivative **89** was less bioavailable than **86**, thus favoring further use of the 3-F phenyl substitution (**86**) in subsequent optimization efforts.

**Sulfonamide Substitution Pattern.** On the basis of **86**, we optimized the halogen substitution pattern in the sulfonamide-substituted aromatic ring (Table 16).

**Table 16. SAR of Halogen Substitution Pattern in the Unsubstituted Sulfonamide Class**

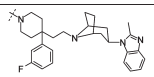
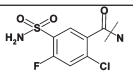
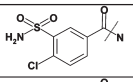
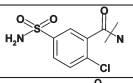
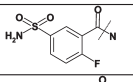
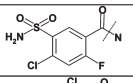
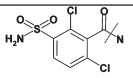
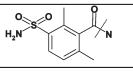
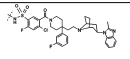
| Analogue |  | Ba-L-PBL pIC50 | hERG patch clamp pIC50 | QTc (%) | RAT PO DNAUC [ng.h/mL] |
|---|---|---|---|---|---|
| **108** |  | 8.36 | <4.50 | 1.1 | 50 |
| **109** |  | 8.20 | 4.2 | 2.8 | 56 |
| **110** |  | 8.04 | <4.3 | n/a | 0 |
| **111** |  | 7.62 | 4.38 | 2.0 | 55 |
| **112** |  | 7.37 | <4.3 | 3.1 | 202 |
| **113** |  | 7.77 | 4.28 | n/a | 35 |
| **114** |  | 7.18 | n/a | n/a | 15 |

**Table 17. SAR for Alkylsulfonamides in the 2-Cl, 4-F Series**

| Analogue |  | Ba-L-HOS $pIC_{50}$ | Ba-L-PBL $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | QTc (%) | RAT PO DNAUC [ng.h/mL] | Dog PO DNAUC [ng.h/mL] |
|---|---|---|---|---|---|---|---|
| **116** |  | 8.16 | 8.65 | 4.51 | n.t. | 19 | n.t. |
| **117** |  | 8.12 | 9.07 | 4.52 | 5.8 | 108 | n.t. |
| **118** |  | 8.40 | 8.80 | 4.89 | n.t. | 139 | n.t. |
| **119** |  | 8.60 | 8.82 | 4.92 | n.t. | 41 | 309 |
| **120** |  | 8.53 | 8.72 | 5.10 | 0.6 | 192 | 139 |
| **121** |  | 7.81 | 8.17 | 5.05 | n.t | 20 | 58 |
| **122** GSK163929 |  | 8.37 | 8.46 | 4.72 | 1.2 | 272 | 170 |


dx.doi.org/10.1021/jm200279v |*J. Med. Chem.* 2011, 54, 3756–3767

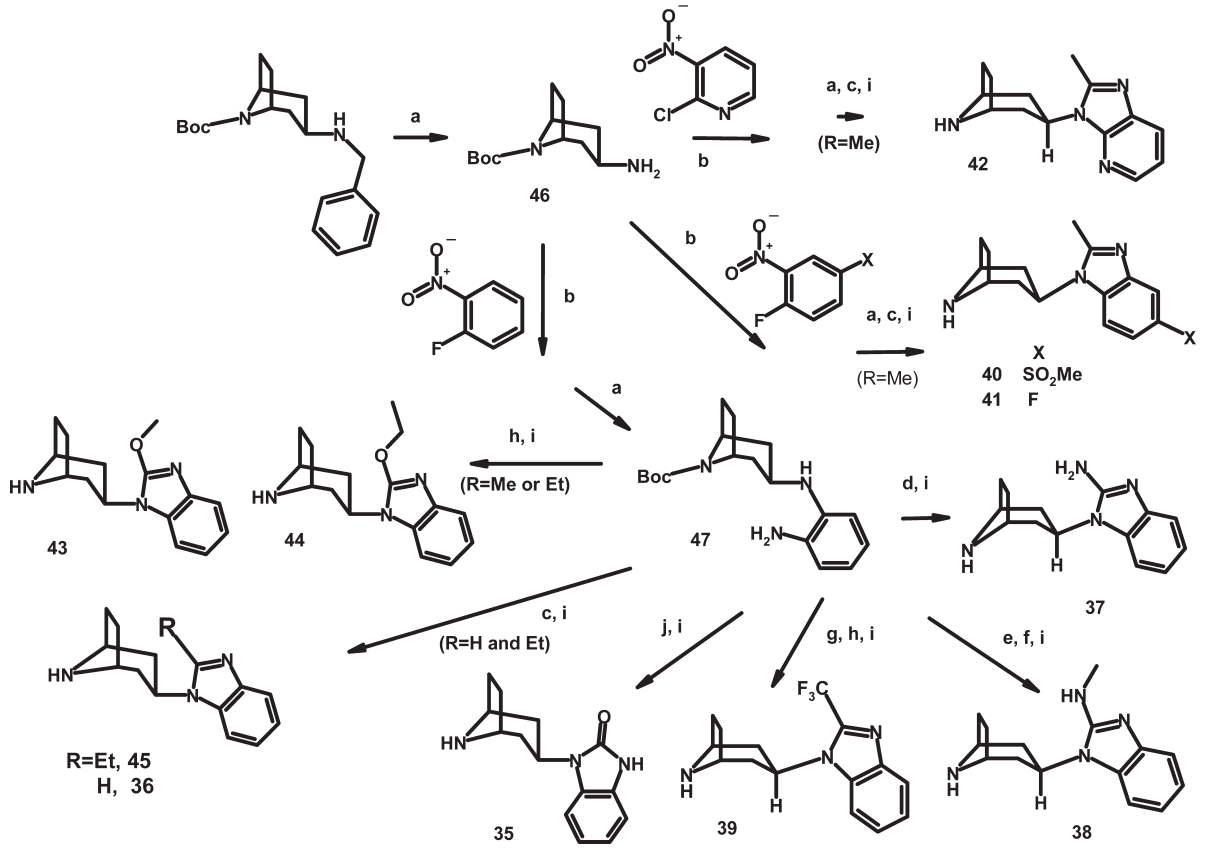



**Figure 3.** Reagents and conditions: (a) $H_2$, Pd/C, methanol; (b) 1-methyl-2-pyrrolidinone, DIEA, 70 °C, 16 h; (c) $RCH(OEt)_3$, reflux; (d) BrCN, methanol, reflux; (e) $CH_3NCS$, THF; (f) EDC, DMF; (g) trifluoroacetic acid, CDI, DMF, room temp; (h) $C(OR)_4$, reflux; (i) 4 N HCl/dioxane, free-base; (j) triphosgene, toluene, TEA, 80 °C, 1 h.

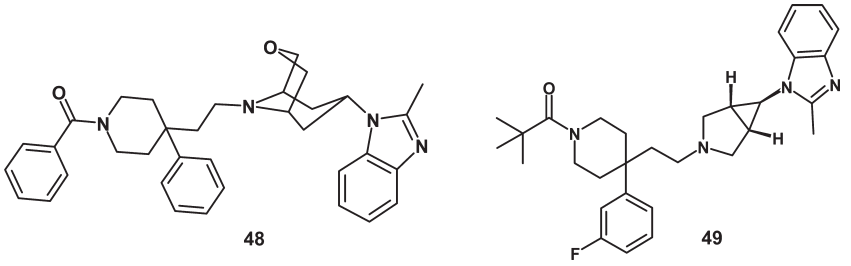



**Figure 4.** Modified piperidine analogues **48** and **49**.

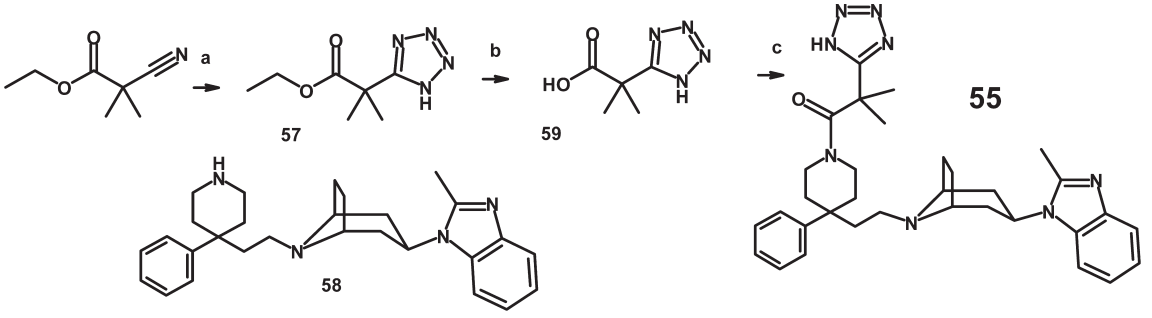



**Figure 5.** Reagents and condtions: (a) dibutyl(oxo)stannane trimethylsilyl azide, toluene (80%); (b) NaOH (equiv), ethanol/water; (c) HATU, **58**, DIEA, DMF.


dx.doi.org/10.1021/jm200279v |*J. Med. Chem.* 2011, 54, 3756–3767

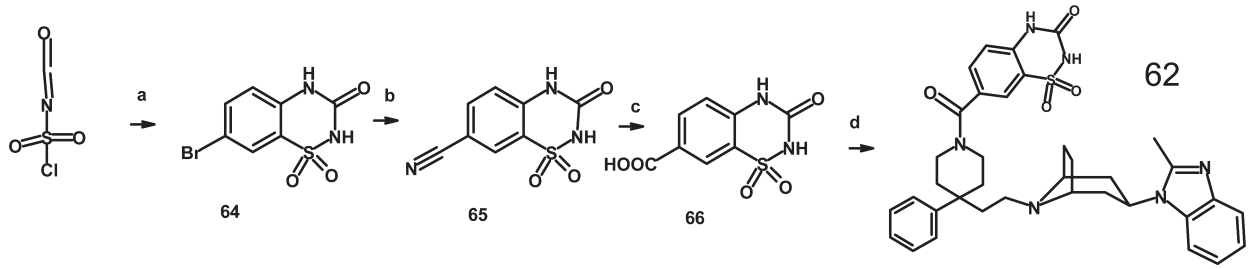



**Figure 6.** Reagents and conditions: (a) 4-Br-aniline, nitromethane, $AlCl_3$, reflux 30 min; (b) dimethylformamide, $Pd(PPh_3)_4$, $Bu_3SnCN$, 120 °C; (c) 1 N $NaOH_{aq}$ reflux, 20 min; (d) HATU, DIEA, DMF, **58**.

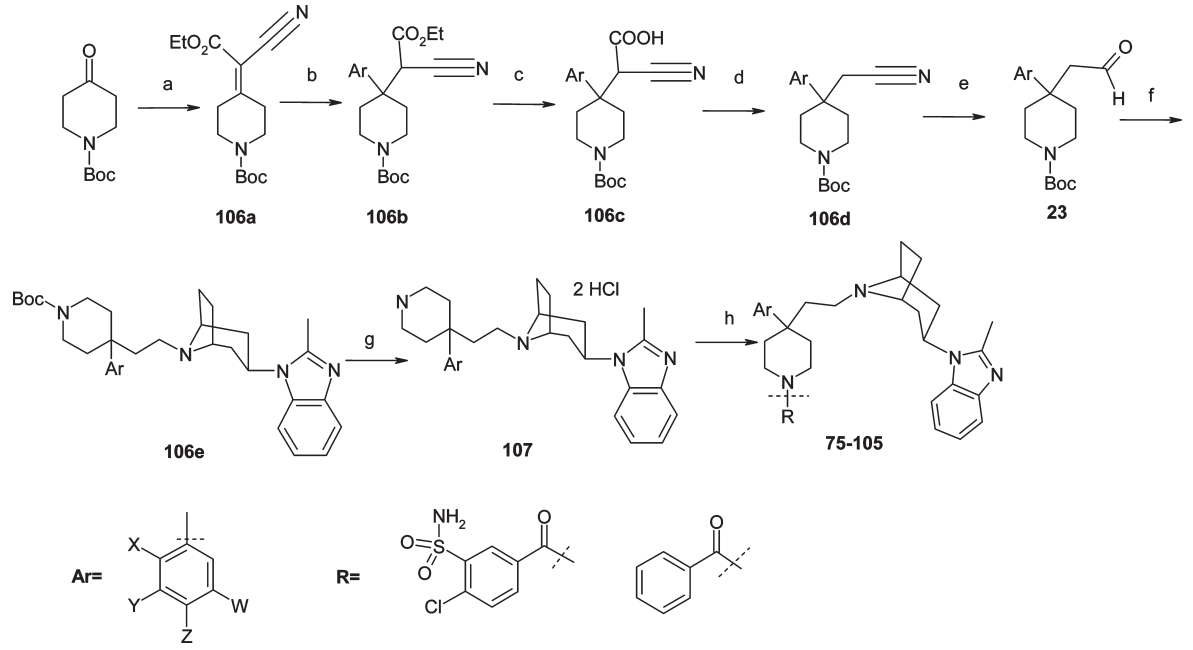



**Figure 7.** Reagents and conditions: (a) ethyl cyanoacetate, $NH_4OAc$, AcOH, benzene; (b) ArMgBr, CuI,THF, 2 h; (c) 2 M NaOH, room temp, 2 h; (d) $Cu_2O$/MeCN, reflux 30 min; (e) DIBAL-H, DCM, −40 °C, 1 h; (f) DCE, 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole, sodium triacetoxyborohydride; (g) 4 M HCl in dioxane, room temp, 1 h; (h) dichloromethane, benzoic acid derivative, HATU, Hunig base.

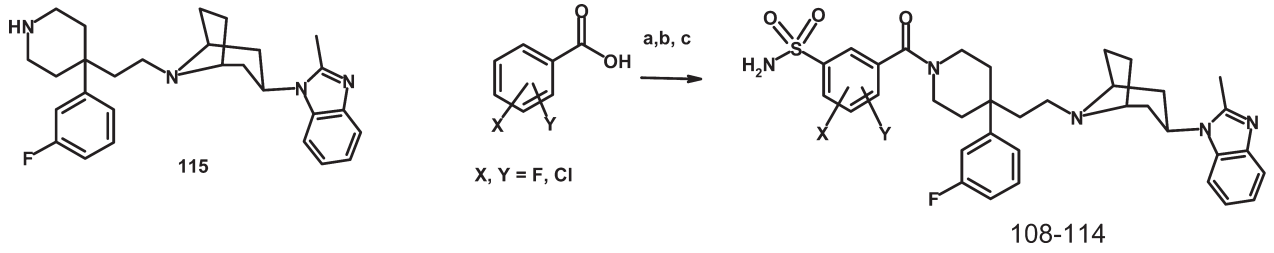



**Figure 8.** Reagents and condtions: (a) $ClSO_3H$, 150 °C; (b) dioxane/water, conc aq $NH_4OH$, 0 °C; (c) DMF, DIEA, HATU, **120**.

Compounds **108**−**114** were synthesized from commercially available mono- and dihalogen-substituted benzoic acids and converted to sulfonamides as described in Figure 8. Inhibitor **112** was highly bioavailable in the rat PK model, but its antiviral potency was substantially lower than that of **108**. On the other hand, compounds **108** and **109** were the most potent and bioavailable analogues in this subseries. Owing to superior QTc data, the halogen motif in **108** was explored further with *N*-sulfonamide substituents (Table 17).

Ethyl derivatve **117** had borderline QTc property, while cycloalkyl and propyl derivatives **116**, **119**, and **121** had low to

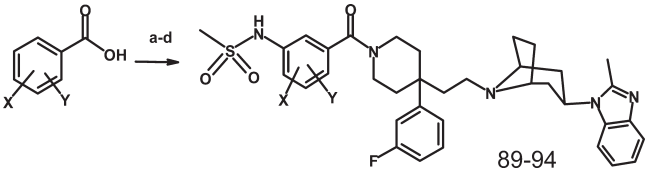



**Figure 9.** Reagents and conditions: (a) $HNO_3$, $H_2SO_4$; (b) MeOH, Pd/C, $H_2$ or $SnCl_2$, conc HCl; (c) (i) dichloromethane, pyridine, TMSCl; (ii) pyridine, MsCl; (iii) 10 N $NaOH_{aq}$, neutralize with 1 N HCl aq; (d) *N*-Me-morpholine, cyanuric chloride, **115**.


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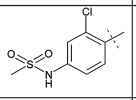
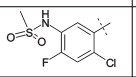
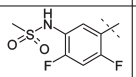
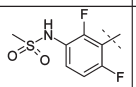
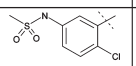
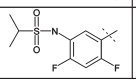
Table 18. Reverse Sulfonamide SAR

| Analogue | | Ba-L-HOS $pIC_{50}$ | Ba-L-PBL $pIC_{50}$ | hERG patch clamp $pIC_{50}$ | QTc (%) | RAT PO DNAUC [ng.h/mL] | Dog PO DNAUC [ng.h/mL] | Cyno PO DNAUC [ng.h/mL] |
|---|---|---|---|---|---|---|---|---|
| **123** |  | 8.38 | 7.74 | 5.0 | 2.4 | 59 | 217 | 48 |
| **124** |  | 8.70 | 8.13 | <4.50 | n.t. | 76 | 157 | 59 |
| **125** |  | 8.21 | 8.14 | 4.00 | 1.2 | 338 | 287 | 43.8 |
| **126** |  | 8.47 | 8.58 | 4.44 | 1.5 | 109 | 247 | 19.9 |
| **127** |  | 8.44 | 8.81 | n.t. | n.t. | 13 | n.t. | n.t. |
| **128** |  | 8.37 | 7.15 | 5.05 | n.t. | 125 | n.t. | n.t. |

moderate rat and/or dog bioavailabilities, excluding these compounds from further consideration. On the other hand, trifluoroethyl and methyl derivatives **120** and **122** had acceptable rat and/or dog bioavailability. Compound **122** also demonstrated some bioavailability in cyno PK (DNAUC = 38 ng·h/mL at 10 mg/kg po dose) and thus had the most balanced profile of the desired antiviral, hERG/QTc, and cross-species pharmacokinetic properties.

**Reverse Sulfonamides.** While exploring additional compound space, we applied the SAR learned in the forward sulfonamide series (Tables 16 and 17) to design the reverse sulfonamides (Table 18, Figure 9). The reverse sulfonamides were somewhat less hydrophobic than the forward sulfonamides and were found to be very potent in anti-HIV assays.[27,28] Among compounds examined, **125** had the most balanced PK properties across several animal species and was found inactive in the QTc assay. While **122** and **125** were in many respects comparable, compound **122** was favored because of potential aniline metabolite formation from reverse sulfonamide **125**.

**Preclinical Characterization of Compound 122.** The allometric scaling of plasma rat, dog, and monkey iv PK data for **122** predicted the human therapeutic dose at 900 mg/day (13 (mg/kg)/day) q.d.[29−31] Compound **122** underwent a 7-day safety assessment in rats and dogs. No adverse effects were observed in rats at the maximum 2000 (mg/kg)/day dose, which yielded AUC = 77 000 ng·h/mL for male and 160 000 ng·h/mL for female rats and resulted in a range of 36- to 74-fold safety cover in rats. No adverse effects were observed in a 7-day dog safety assessment at a 250 (mg/kg)/day dose, which yielded AUC = 34 900 ng·h/mL in female dogs and 17 200 ng·h/mL in male dogs and resulted in a range of 8- to 16-fold safety cover in dogs. Combined virology, PK, and safety data supported further progression of **122** to the clinic.

## CONCLUSIONS

We present extensive potency, hERG, and pharmacokinetics SAR resulting in a conversion of the lead compound **1** into a clinical molecule **122**. Both compounds share significant structural similarities. Remarkably minor, nonintuitive modifications, such as *m*-F substitution in the central ring and halogen and sulfonamide substitutions in the benzylic acid, resulted in a major differentiation of potency, PK, and hERG inhibition between these compounds. Compound **122** was more potent in HOS and PBL assays ($pIC_{50}$ = 8.37 and 8.46) than compound **1** (7.80 and 7.12). It also had an improved bioavailability in rat (AUC = 272 ng·h/mL for **122** and 16 ng·h/mL for **1**) as well as improved hERG and QTc properties (hERG $pIC_{50}$ = 4.7, QTc = 1.2% for **122** and hERG $pIC_{50}$ = 5.7, QTc = 9.4% for **1**). On the basis of our work and reports published in the meantime,[21] we believe that the SAR converting lead **1** to druglike **122** described herein may have more general utility to other leads suffering from poor PK and hERG properties.

Further synthetic details can be found in the Supporting Information.

## ASSOCIATED CONTENT

**Supporting Information.** Synthesis details and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ABBREVIATIONS USED

hERG, human ether-a-go-go related gene; CCR5, C−C chemokine receptor type 5; HAART, highly active antiretroviral therapy; SAR, atructure−activity relationship

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