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Design and synthesis of pyridin-2-yloxymethylpiperidin-1-ylbutyl amide CCR5 antagonists that are potent inhibitors of M-tropic (R5) HIV-1 replication

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ABSTRACT

A novel series of CCR5 antagonists were identified based on the redesign of Schering C. An SAR was established based on inhibition of CCR5 (RANTES) binding and these compounds exhibited potent inhibition of R5 HIV-1 replication in peripheral blood mononuclear cells.

The discovery of the chemokine receptors CXCR4 and CCR5 in 1996 as co-receptors[1] for HIV-1 entry into cells prompted a global research effort to discover novel antagonists of these receptors. Given that individuals harboring the homozygous form of the CCR5 delta 32 allele are highly resistant to macrophage-tropic (M-tropic), CCR5-tropic or R5 HIV-1 infection[2] and that the M-tropic strain is the most prevalent strain the chemokine receptor CCR5 was established as an important and novel target for potentially preventing HIV-1 infection. As a consequence there was a concerted effort by many of the large pharmaceutical companies to identify and develop a small molecule antagonist of CCR5.[3] Ultimately Pfizer was successful at obtaining FDA approval for maraviroc in 2007 for treatment experienced patients infected exclusively with CCR5-tropic HIV-1 virus and following further clinical trials maraviroc was approved for use in treatment-naïve patients with CCR5-tropic virus in 2009.[4]

We have had a longstanding research interest in developing small molecule antagonists of CXCR4 and have demonstrated that blocking CXCR4 with small molecule antagonists, AMD3100[5] and AMD070,[6] results in viral load reduction in T tropic (X4) HIV-1 infected patients.[7,8] Given the prevalence of M-tropic strains of HIV-1 we were also interested in developing a small molecule antagonist of CCR5 which could potentially be used in combination with a CXCR4 antagonist. In addition, the emergence of T-tropic or X4 HIV-1 variants in a minority of HIV-1 infected persons has been observed following treatment with maraviroc.[9] This development strongly suggests that a combination of CCR5 and CXCR4 antagonists for treatment of dual/mixed tropic HIV-1 infection will be required for complete viral suppression.

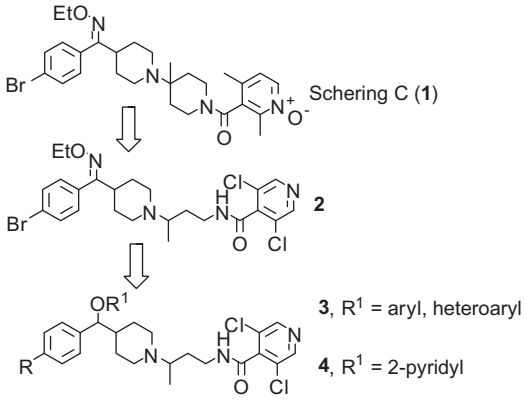

Figure 1. Structure of Schering C (**1**) and related analogs **2**–**4**.

Our medicinal chemistry strategy was to modify the lead compound in clinical development at the time, Schering C (**1**) or SCH

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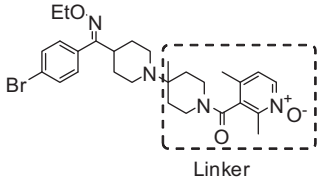
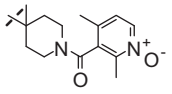
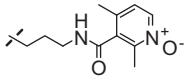
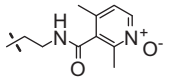
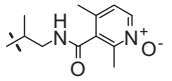
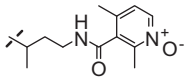
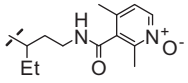
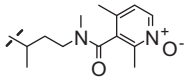
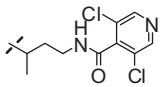
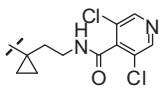
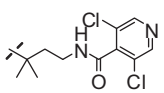
351125.[10] The tactic was to redesign **1** by first opening up the lower piperidine ring and then find a replacement for the oxime moiety to afford analogs **3** and **4** (Fig. 1). The ^{125}I RANTES competitive binding assay[11] was used to establish a structure activity relationship (SAR) and the anti-HIV-1 activity was assessed utilizing the R5 HIV-1 PBMC assay.[12]

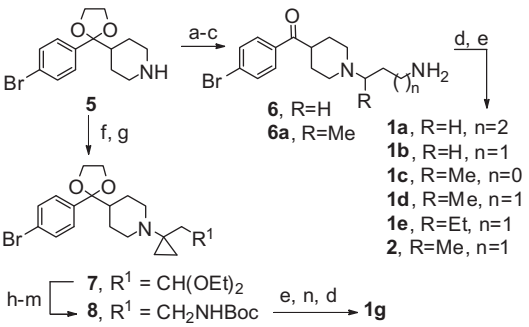
Modification of the lower piperidine ring was carried out to find a suitable ring replacement (Table 1) with a direct comparison to **1** which has an IC_{50} of 0.04 μM in the competitive binding assay and an IC_{50} of 0.160 μM in the HIV-1 PBMC assay. The compounds in Table 1 were all prepared as the *E*-isomer at the oxime similar to **1**. Simply disconnecting the C–C bond at the quaternary carbon atom afforded the isobutyl chain derivative **1d** that was sevenfold less potent in binding (IC_{50} of 0.29 μM) compared to **1** whilst still retaining antiviral activity but at a reduced level of 2.5 μM. The closely related propyl analog **1a** although comparable in potency to **1d** was cytotoxic and therefore not further evaluated. Interestingly replacement of the methyl group with the more sterically demanding ethyl **1e** resulted in a marked decrease in binding inhibition to CCR5. In addition, alkylation of the amide nitrogen with a methyl group **1f** rendered the compound inactive, in stark contrast to **1**. A preliminary effort was also expended on finding a replacement for the amide N-oxide, since in several cases rotamers were observed as was also reported for **1**,[13] and this resulted in the identification of the 3,5-dichloropyridine moiety as a suitable replacement. For example, the binding inhibition of compound **2** containing the 3,5-dichloropyridine moiety was comparable to **1a** and **1d**. The importance of the methyl stereocenter was confirmed by the gem dimethyl **1g** and cyclopropyl analogs **1h** which were 15-fold and 165-fold less potent in inhibitory binding compared to **1f**. Based on this data we concluded that the optimal replacement of the piperidine ring was the isobutyl chain attached to a secondary amide with a 3,5-dichloropyridine moiety as exemplified by compound **2**.

Table 1
CC-Chemokine RANTES binding inhibition, anti-HIV-1 (BaL) activity and cellular cytotoxicity of compound **1** analogs and compound **2**[a]



Compd	Linker	^{125}I RANTES binding IC_{50}[b] (μM)	HIV-1 PBMC IC_{50}[c] (μM)	PBMC CC_{50}[d] (μM)
1		0.04 (n = 9)	0.16 (n = 3)	>1.6
1a		0.18 (n = 2)	>1.5	7.5
1b		na	>39.17	195.8
1c		17.01	>36.41	182.1
1d		0.29	2.54	>177.9
1e		na	>32.76	>177.9
1f		5.62	>36.54	>182.7
2		0.13	>6.70	33.8
1g		21.37	>6.60	33.0
1h		1.76	>6.81	34.0

[a] Assays were performed in duplicate and values represent the mean with standard deviations <30% of the mean. Bracketed values represent the number of experiments.
[b] CCR5 competitive ligand binding assays were performed with ^{125}I-RANTES on membranes prepared from HEK293F cells transfected to express CCR5.
[c] Peripheral blood mononuclear cells (PBMC) were isolated from healthy volunteers and infected by R5 HIV-1 (BaL strain) as reported in Ref. 12. IC_{50} is the concentration of the compound required to inhibit viral replication by 50% as measured by p-24 HIV-1 specific Ag ELISA.
[d] CC_{50} is the concentration required to reduce the viability of PBMC by 50%.

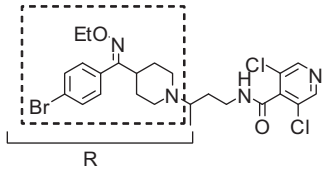


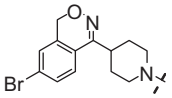
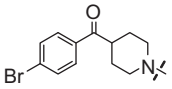
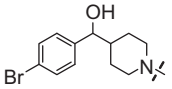
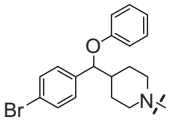
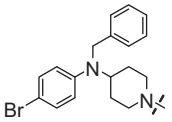
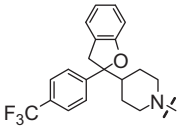
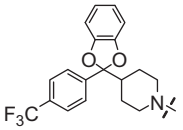
Scheme 1. Reagents and conditions: (a) RCH=CHCN, MeOH, 59–66%; or *t*-butyl (3-oxopentyl)carbamate, or *t*-butyl (2-oxopropyl)carbamate, $NaBH_3CN$, MeOH, 60 °C, 20–56%; (b) $BH_3{\cdot}Me_2S$, THF; (c) HCl/H_2O or 6 N HCl, EtOAc, 40–60% over two steps; (d) HOBt, EDCI/$ArCO_2H$, 59–89%; (e) $EtONH_2{\cdot}HCl$, MeOH, 32–78%; (f) 3,3-diethoxypropanoic acid, EDCI, HOBt, 66%; (g) EtMgBr, $Ti(OiPr)_4$, Et_2O/THF, 22%; (h) TFA, $CHCl_3$, 0 °C; (i) $NaBH_4$, MeOH, 83% over two steps; (j) MsCl, TEA, CH_2Cl_2; (k) NaN_3, DMF, 67% over two steps; (l) Ph_3P, THF, H_2O, 76%; (m) Boc_2O, THF, 84%; (n) TFA, CH_2Cl_2, 100%.

The compounds in Table 1 were synthesized using the advanced intermediate **5**[10] (Scheme 1) which underwent either reductive amination (**1c**, **1e**) or N-alkylation with a Michael acceptor (**1a-b**, **1d**, **1f**, **2**) to install the linker moiety. For example, in the synthesis of compound **2** the isobutyl amine **6a**, was prepared by Michael addition of the amine **5** to but-2-enenitrile followed by reduction of the nitrile to the primary amine using $BH_3{\cdot}Me_2S$ and finally hydrolysis of the ketal to the ketone using aqueous HCl. To complete the synthesis of **2** the amide and (*E*)-oxime were installed as reported by Palani et al.[10] In contrast, for compounds **1c** and **1e** the linker was added by reductive amination of **5** with *t*-butyl (2-oxopropyl)carbamate[14] or *t*-butyl (3-oxopentyl)carbamate[15] in the presence of $NaBH_3CN$. For compound **1g**, the cyclopropyl moiety of **7** was synthesized by cyclopropanation of the corresponding amide which was obtained by reaction of **5** with 3,3-diethoxypropanoic acid. Functional group manipulation converted the acetal of **7** to the Boc protected amine **8** which was subsequently converted to **1h** after formation of the oxime and amide.

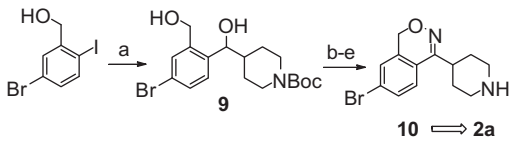
We next turned our attention to finding an appropriate replacement for the oxime moiety of compound **2** (Table 2). Locking the oxime into a six-membered ring (**2a**) resulted in a substantial loss in activity compared to **2**. In addition replacing the oxime with a ketone **2b** or hydroxyl group **2c** also had a deleterious effect on activity. However, we were encouraged to find that the *O*-aryl analog **2d** resulted in a comparable binding inhibition to **2**, with an

Table 2
CC-Chemokine RANTES binding inhibition, anti-HIV-1 (BaL) activity and cellular cytotoxicity of compound **2** analogs[a]



Compd	R	^{125}I RANTES binding IC_{50} (μM)	HIV-1 PBMC IC_{50} (μM)	PBMC CC_{50} (μM)
2a		12.25 (*n* = 2)	>7.4	185.1
2b		na	32.6	188.6
2c		3.39	>39.6	198.3
2d		0.13	>1.3	31.7
2e		0.03	0.22	4.28
2f		0.04 (*n* = 2)	0.22	33.8
2g		0.03	0.01 (*n* = 3)	7.8

[a] See footnotes in Table 1.



Scheme 2. Reagents and conditions: (a) *n*-BuLi, THF, *N*-Boc-4-formylpiperidine, TMEDA, 50%; (b) *N*-hydroxy phthalimide, DIAD, PPh_3, THF, 60%; (c) PCC, SiO_2, CH_2Cl_2, 90%; (d) hydrazine, EtOH; (e) TFA, CH_2Cl_2, 80% over two steps.

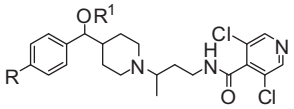
IC_{50} of 0.13 μM and an antiviral activity in the low μM range. Interestingly, the aniline analog **2e** resulted in approximately a 10-fold increase in both binding inhibition and anti-HIV-1 activity compared to **2**. A further modification that appeared promising was the spiro benzopyran analog **2f** and the spiro benzoketal **2g** both of which potently inhibited CCR5 ligand (RANTES) binding with an IC_{50} of 0.04 μM and 0.03 μM, respectively. More importantly, the antiviral activity of **2f** was comparable to the aniline analog, whereas the benzoketal **2g** was 10-fold more potent with an IC_{50} of 0.01 μM. However, the spiro benzopyrans were discounted early on due to synthetic challenges and although the spiro benzoketals had exceptional pharmacokinetic properties the series was not further pursued due to muscarinic receptor cross-reactivity.[16] However, both the *O*-aryl series and the aniline series were further advanced and the *O*-aryl series are the subject of this Letter.

The benzo oximine **2a** was prepared from commercially available 5-bromo-(2-iodophenyl)methanol (Scheme 2) by regioselective lithiation using *n*-BuLi followed by reaction with *N*-Boc-4-formylpiperidine to afford the diol **9** in 50% yield. The oximine ring was formed by Mitsunobu reaction of the primary alcohol with *N*-hydroxy phthalimide to afford the alkoxy phthalimide. Oxidation of the secondary alcohol to the ketone followed by treatment with hydrazine liberated the amine which underwent an intramolecular cyclization to afford the oximine. Boc cleavage under acidic conditions gave **10** which was then converted to **2a** using conditions from Scheme 1.

The intermediate **11** is illustrative of the methodology used to prepare many of the compounds in Tables 2–4 (Scheme 3). Compounds containing other substituents in the place of the CF_3 group were synthesized in a similar manner. Compound **11** was simply prepared by the addition of lithiated 2-bromo-4-(trifluoromethyl)benzene to *N*-Boc-2-formylpiperidine followed by oxidation of the alcohol to the ketone. The benzoketal **12**, the precursor to **2g**, was readily prepared by reaction of **11** with catechol in the presence of *p*-TsOH in refluxing xylene. In contrast, the spiro benzofuran **2f** was prepared from the intermediate **15**. Reaction of **11** with the Grignard of 1-bromo-(2-bromomethyl)benzene afforded the tertiary alcohol **14** which underwent an intramolecular Pd(0) catalyzed coupling[17] with the bromobenzene moiety followed by Boc deprotection to afford **15**. Reduction of **11** to the alcohol provided ready access to the *O*-aryl compounds (Table 3) which were prepared using Mitsunobu chemistry. The *O*-pyridyl compounds (Table 4) were prepared either by O-alkylation of the corresponding alkoxide or by Mitsunobu chemistry. For example, reaction of the alkoxide with 2-chloro-6-cyanopyridine gave the *O*-pyridyl intermediate which afforded **4p**[18] using the methodology described in Scheme 1.

The SAR that was developed for the *O*-aryl series is shown in Table 3. Although the molecules contain two stereocenters the SAR was based on the diastereoisomeric mixtures. In an effort to find a replacement for the bromide it was found that the CF_3 group provided the best overall enhancement in binding inhibition, for example, the IC_{50} for RANTES binding inhibition of **3a** was 0.05 μM vs 0.13 μM for **2e**. Substitution of electron withdrawing cyano or chloro groups at the 3-position resulted in improved potencies compared to the 2-substituted analogs. For example, the 3-cyano analog **3c** resulted in a twofold improvement in binding inhibition (IC_{50} of 0.05 μM) and a fivefold improvement in antiviral activity (IC_{50} of 0.48 μM) compared to the 2-cyano analog **3b**. Similarly, the 3-chloro analog **3e** gave a comparable improvement in binding inhibition (IC_{50} of 0.06 μM) and a 15-fold improvement in antiviral activity (IC_{50} of 0.075 μM) compared to the 2-chloro analog **3d**. The most potent antiviral analog in this series was the 3-CF_3 analog **3g** with an antiviral IC_{50} of 0.03 μM, fivefold more potent then **1**. Interestingly the methyl ester **3j** resulted in a dramatic loss in antiviral activity. Further evidence that electron withdrawing groups provide a benefit in antiviral potency was the fivefold enhancement gained with the 3-F analog **3i** compared to the phenyl group **3a**, IC_{50} of 0.23 μM versus 1.27 μM. Although the potency of this series was promising the lipophilicity as measured by *c* Log *P* exceeded 5 very likely contributing to poor oral absorption and as a consequence the more hydrophilic pyridyl analogs **3k**–**m** were synthesized. We were pleased to find that the 2-pyridyl analog **3k** had acceptable binding and viral inhibitory activity to warrant further investigation.

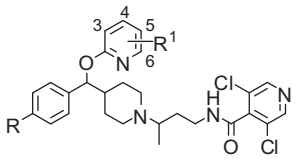
Table 3
CC-Chemokine RANTES binding inhibition, anti-HIV-1 (BaL) activity and cellular cytotoxicity of compounds 3[a]



Compd	R	R^1	^{125}I RANTES binding IC_{50} (μM)	HIV-1 PBMC IC_{50} (μM)	PBMC CC_{50} (μM)
3a	CF_3	Ph	0.05	1.27	6.8
3b	CF_3	2-CNPh	0.10	2.87	17.0
3c	CF_3	3-CNPh	0.05	0.48	15.7
3d	CF_3	2-ClPh	0.12	>1.27	4.4
3e	CF_3	3-ClPh	0.06	0.07	8.1
3f	CF_3	2-CF_3Ph	na	0.10	12.5
3g	CF_3	3-CF_3Ph	na	0.03	7.0
3h	CF_3	4-CF_3Ph	na	>1.23	3.1
3i	CF_3	3-FPh	0.04	0.23	5.4
3j	CF_3	3-CO_2MePh	na	>6.26	15.2
3k	Br	2-Pyridyl	0.14 (n = 4)	3.76	33.7
3l	Br	3-Pyridyl	0.97	3.30	32.5
3m	Br	4-Pyridyl	na	>0.24	31.2

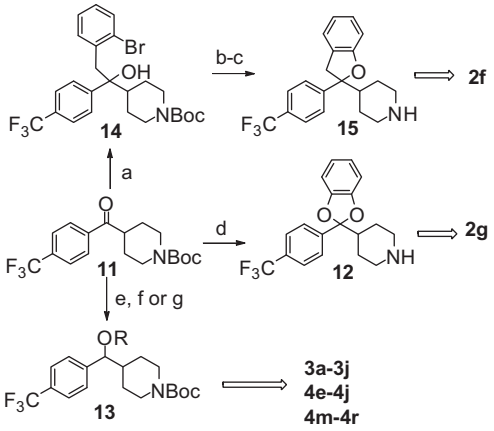
[a] See footnotes in Table 1.

Table 4
CC-Chemokine RANTES binding inhibition, anti-HIV-1 (BaL) activity and cellular cytotoxicity for compounds **4**[a]



Compd	R	R^1	^{125}I RANTES binding IC_{50} (μM)	HIV-1 PBMC IC_{50} (μM)	PBMC CC_{50} (μM)
4a	Br	3-Me	0.19	0.34	32.1
4b	Br	4-Me	0.14	1.96 (n = 2)	32.5
4c	Br	5-Me	3.80	>1.29	32.2
4d	Br	6-Me	0.22	1.55	6.5
4e	CF_3	3-Me	0.06	2.95	33.0
4f	CF_3	4-Me	0.05	>6.72	33.6
4g	CF_3	6-Me	0.04	0.17 (n = 5)	6.7
4h	CF_3	3-Cl	0.14	0.08	16.7
4i	CF_3	4-Cl	0.07	0.43	4.26
4j	CF_3	6-Cl	0.02 (n = 2)	0.009 (n = 7)	>32.5
4k	OCF_3	6-Cl	0.03	0.002 (n = 3)	6.0
4l	SO_2Me	6-Cl	0.01	0.004 (n = 2)	>29.5
4m	CF_3	H	0.03	0.13 (n = 2)	34.1
4n	CF_3	6-OMe	na	>1.30	32.7
4o	CF_3	6-CF_3	0.13	0.060	13.5
4p	CF_3	6-CN	0.04	0.009	15.7
4q	CF_3	6-CO_2Me	1.05	0.52	14.6
4r	CF_3	6-CO_2H	na	>28.70	28.7

[a] See footnotes in Table 1.



Scheme 3. Reagents and conditions: (a) 1-bromo-2-(bromomethyl)benzene, Mg, I_2, Et_2O; then THF/Et_2O, 90%; (b) $Pd(OAc)_2$, BINAP, K_2CO_3, toluene, 75%; (c) TFA, CH_2Cl_2; (d) catechol, TsOH, xylene, reflux, 47 h, 47% over two steps; (e) $NaBH_4$, MeOH, 87%; (f) NaH, substituted halopyridine, DMF, 90 °C, 44–95%; (g) substituted hydroxypyridine or substituted phenol, Ph_3P, DIAD, THF, 48–82%.

Having recognized that a substituent on the ring in the *O*-aryl series provided an enhancement in both binding inhibition and antiviral potency we sought to determine the optimal point of substitution of the *O*-pyridine ring (Table 4). With the R substituent equal to bromine we walked the methyl group around the ring and determined that the 5-Me analog **4c** was substantially less potent in binding inhibition compared to the 3-, 4- and 6-Me analogs, **4a**, **4b** and **4d** which had a comparable binding inhibition in the range of 0.14–0.22 μM. In addition the anti-HIV-1 activity for these three compounds ranged from 0.34 to 1.96 μM. However, as was observed for the *O*-aryl series (Table 3) when the bromine atom was replaced with a CF_3 group the binding inhibition for compounds **4e**–**4g** was enhanced with the IC_{50} in the range of 0.04–0.06 μM. Interestingly, although the binding inhibition was similar for all three compounds only the 6-Me substituent **4g** displayed moderate antiviral activity with an IC_{50} of 0.17 μM. However, substitution of an electron withdrawing chloro or cyano substituent at the 6-postion, **4j** and **4p**, provided a 19-fold enhancement in antiviral potency to an IC_{50} of 0.009 μM compared to the 6-Me analog **4g**. In contrast, the effect of electron donating substituents on the pyridine ring such as the methoxy group **4n** and carboxylic acid group **4q** were detrimental to antiviral activity. Replacing the R group with a $-OCF_3$ group **4k** or a $-SO_2Me$ group **4l** resulted in an additional enhancement in binding inhibition (IC_{50} 0.03 and 0.01 μM) and antiviral potency, IC_{50} of 0.002 and 0.004 μM, respectively. These compounds were 18–80-fold more potent then **1** in the inhibition of HIV-1 replication.

Although the *O*-pyridyl compounds exhibited potent anti-viral activity the pharmacokinetic properties in rat and dog for a representative example, compound **4j**, was poor (*F*% of 20 and 6, respectively) when compared to **1** (Table 5). The poor pharmacokinetic properties of **4j** and related compounds can most likely be attributed to the high molecular weight (MW 662) and high lipophilicity (*c* Log *P* 6.6) and as a consequence these compounds were not fur-

Table 5
Pharmacokinetics of **1** and **4j** in rat and dog[a]

Compound	Species	C_{max} (μM)	AUC_{0-inf} (h μM)	CL (ml/min/kg)	V (L/kg)	$T_{1/2}$ (h)	F (%)
1	Rat	1.6	4.3	31.7	7.2	2.7	48
4j	Rat	0.2	2.4	141.7	15.2	1.2	20
4j	Dog	0.1	0.5	31.7	20.8	7.7	6

[a] Clearance (CL), volume of distribution (V_{dss}) and half life ($T_{1/2}$) calculated following a 10 μmol/kg iv dose in rat and 5 μmol/kg iv dose in dog. Oral bioavailability (F) calculated following solution doses of 100 μmol/kg in rat and 12.5 μmol/kg in dog.

ther assessed for potential drug-drug interactions (CYP P450 inhibition) or cardiovascular safety (hERG). However, the selectivity of **4j** and related analogs was evaluated in Ca^{2+} flux assays against a series of other closely related G-protein-coupled receptors (GPCRs), which included CCR1, CCR2b, CCR4, CXCR1, CXCR2 and CXCR4, and were found to be non-inhibitory. In addition **4j** and analogs were not cross reactive to the M2 muscarinic receptor.

In conclusion we designed a novel series of antagonists of the chemokine receptor CCR5 based on inhibition of CCR5 ligand (RANTES) binding that exhibited potent inhibition of R5 HIV-1 (BaL) replication in PBMC. Given that these compounds had poor pharmacokinetic properties and two stereogenic centers they were not further pursued, but the SAR was used to optimize the aniline series (**2e**, Table 2), and these results will be reported shortly.

References and notes

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18. *3,5-Dichloro-N-(3-(4-((6-cyanopyridin-2-yloxy)(4-trifluoromethyl phenyl)methyl)piperidin-1-yl)butyl)isonicotinamide*: White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47–0.78 (m, 3H), 0.92 (m, 7H), 1.19 (m, 2H), 1.51 (m, 2H), 1.69–2.04 (m, 8H), 2.38 (m, 2H), 2.65 (m, 1H), 2.73–2.88 (m, 5H), 3.33 (m, 2H), 3.86 (m, 2H), 5.41 (m, 2H), 6.93 (d, 2H, J = 8.4 Hz), 7.26 (m, 2H), 7.35 (m, 4H), 7.56 (d, 4H, J = 4.5 Hz), 7.65 (m, 2H), 8.59 (s, 2H), 8.61 (s, 2H), 9.03 (d, 1H, J = 4.8 Hz), 9.12 (d, 1H, J = 4.5 Hz). ^{13}C NMR ($CDCl_3$) δ 13.26, 28.52, 28.68, 29.44, 30.09, 20.30, 40.16, 40.23, 41.41, 43.71, 43.80, 51.72, 60.41, 60.48, 80.58, 116.09, 117.09, 122.23, 125.33, 127.57, 129.08, 130.28, 139.50, 143.16, 143.25, 147.66, 147.70, 161.49, 161.56, 162.99. ES-MS m/z 628 (M+Na). Anal. Calcd. for $C_{29}H_{28}N_5Cl_2F_3O_2$: C, 57.43; H, 4.65; N, 11.55; Cl, 11.69; F, 9.40. Found: C, 57.20; H, 4.65; N, 11.54; Cl, 11.50; F, 9.20.