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Synthesis and evaluation of 2-phenyl-1,4-butanediamine-based CCR5 antagonists for the treatment of HIV-1

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ABSTRACT

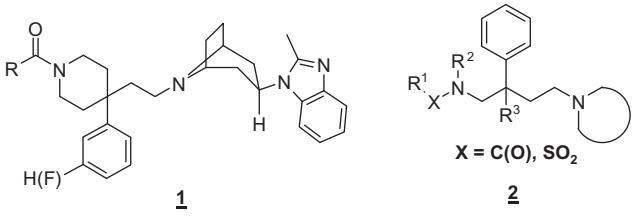
We describe the synthesis and potency of a novel series of N-substituted 2-phenyl- and 2-methyl-2-phenyl-1,4-diaminobutane- based CCR5 antagonists. Compounds **7a** and **12f** were found to be potent in anti-HIV assays and bioavailable in the low-dose rat PK model.

The Chemokine Receptor R5 (CCR5) is a member of the 7TM G-protein coupled receptor (GPCR) family and, with CD4, serves as a co-receptor for HIV-1 infection of host cells. CCR5 antagonism enabled a novel mechanism to inhibit HIV-1 infection and thus it became an attractive target pursued by the pharmaceutical industry.[1] Significant research and development efforts have led to several small molecule clinical candidates[2] and one FDA approved drug, Maraviroc.[3] Additional CCR5 antagonists with improved potency and pharmacokinetics suitable for daily dosing, are needed and offer promise as potential new components of the anti-HIV combination therapy.

Our laboratories have recently reported the synthesis and structure–activity relationship of a series of 4,4-disubstituted piperidine carboxamide CCR5 antagonists exemplified by **1**, which have demonstrated activity against HIV-1 (Fig. 1).[4] Herein, we wish to disclose further investigation of novel series 2-methyl-2-phenyl-1,4-diaminobutane (MDAB) and 2-phenyl-1,4-diaminobutane (DAB), represented by **2** (Fig. 1). Although the 1,4-diaminobutane scaffold has been previously explored in CCR5 and was demonstrated to potently displace MIP-1α in the CCR5 radioligand binding assay, compounds turned out to be only modest inhibitors of HIV in cellular assays.[5]

We first examined so far unreported influence of tropane moiety on compound antiviral potency in the 1,4-diaminobutane scaffold series.

The synthesis of racemic, 2-phenyl-DAB analogs **7a–i**, **11a–c**, **12a–f** and **14a–f** is described below. Analoging at either amine center was conveniently carried out using separate convergent syntheses from commercially available diethyl (phenylmethylidene)propanedioate. Analogs **7a–i** were prepared in six steps (Scheme 1) by conjugate addition of potassium cyanide in ethanol to afford the 3-cyano-3-phenylpropanoate ester (**3**) which was converted to the corresponding aldehyde (**4**) in a two-step procedure by reduction with lithium borohydride in refluxing THF followed by oxidation using Dess–Martin periodinane. The aldehyde was reacted with *endo*-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (**6**)[4] under reductive amination conditions and



1 **2**

Figure 1. 4,4-Disubstituted piperidine **1** and diaminobutane (DAB) scaffold **2**.

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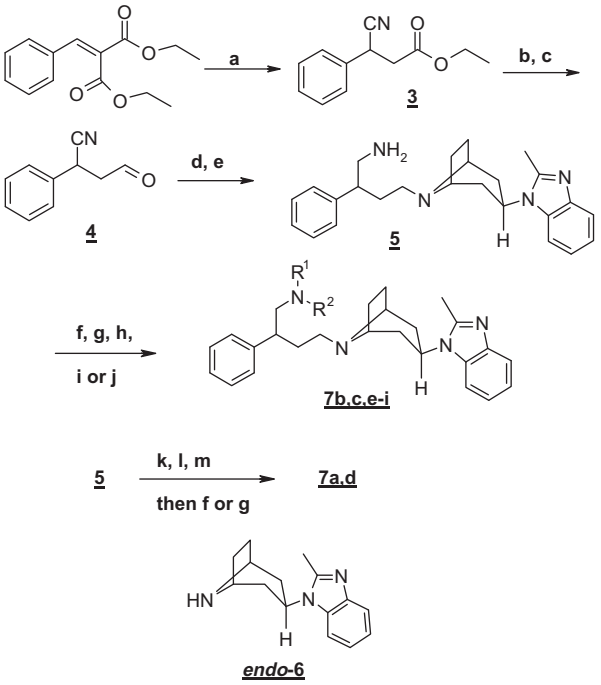
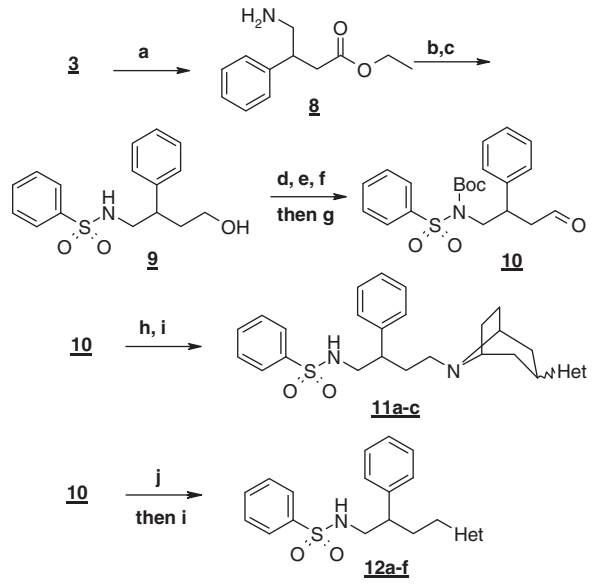
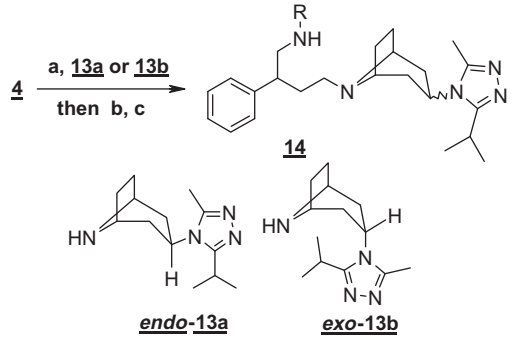


Scheme 1. Reagents and conditions: (a) KCN, EtOH–H_2O, 70 °C, overnight, 73%; (b) $LiBH_4$, THF, reflux, 2 h, 59%; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 89%; (d) $NaBH(OAc)_3$, *endo*-**6**, CH_2Cl_2, rt, 18 h, 70%; (e) Raney-Ni, H_2 (50 psi), EtOH/concd NH_4OH (6:1), rt, 18 h, 99%; (f) 4,4-difluorocyclohexanecarboxylic acid, HATU, iPr_2NEt, CH_2Cl_2, rt, 2 h, 56%; (g) RSO_2Cl, iPr_2NEt, CH_2Cl_2, rt, 37–74%; (h) morpholine-4-sulfonyl chloride, ACN, iPr_2NEt, 5 h, 80 °C, 70–72%; (i) Ac_2O, iPr_2NEt, CH_2Cl_2, rt, 83%; (j) iPr_2NEt, $P(O)(OMe)_2Cl$, CH_2Cl_2, rt, 43%; (k) *o*-NosCl, iPr_2NEt, CH_2Cl_2, 74%; (l) (i) NaH, THF, rt; (ii) MeI, 80%; (m) LiOH, $HSCH_2CO_2H$, DMF, rt, 2 h, 100%.



Scheme 2. Reagents and conditions: (a) Pd/C, H_2 (60 psi), EtOH, concd HCl, rt, overnight, 45%; (b) $PhSO_2Cl$, iPr_2NEt, CH_2Cl_2, rt, 18 h, 92%; (c) $LiBH_4$, THF, 65 °C, 2 h, 100%; (d) TBSCl, DMAP, ImH, CH_2Cl_2, 30 min rt, 88%; (e) (i) DMF, NaH; (ii) Boc_2O, rt, 1 h, 55%; (f) THF, TBAF, AcOH, rt, 18 h, 100%; (g) DMP, CH_2Cl_2, 2 h, rt, 82%; (h) tropanes corresponding to entries **11a–c** in Table 2, $NaBH(OAc)_3$, CH_2Cl_2, rt; (i) TFA, CH_2Cl_2, rt, 3 h; (j) amines corresponding to entries **12a–f** in Table 2, $NaBH(OAc)_3$, CH_2Cl_2, rt.

the nitrile hydrogenated over Raney-Nickel catalyst in the presence of concentrated ammonia to afford the 2-phenyl-1,4-diaminobutane (**5**) in good overall yield. The primary amine was then



Scheme 3. Reagents and conditions: (a) $NaBH(OAc)_3$, CH_2Cl_2, rt, 18 h, 93%; (b) Raney-Ni, H_2 (60 psi), EtOH, concd NH_4OH, rt, 18 h, 95%; (c) RCO_2H/HATU/iPr_2NEt/CH_2Cl_2 or RSO_2Cl/iPr_2NEt/CH_2Cl_2, rt, 1–2 h.

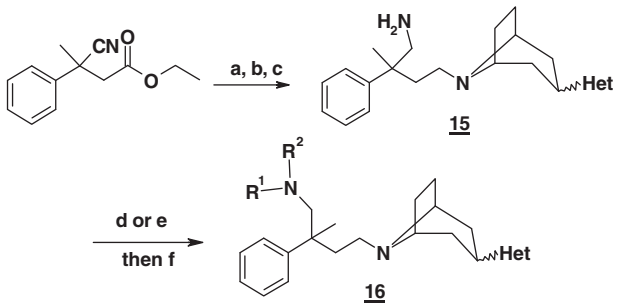
subjected to standard acylating conditions to afford the corresponding amides, sulfonamides and sulfonyl ureas **7a–i**.

The synthesis of analogs **11a–c** (Scheme 2) began with the hydrogenation of 3-cyano-3-phenylpropanoate (**3**) over palladium on carbon in ethanol and aqueous HCl to give 3-phenyl-4-amino ester (**8**) which was then treated with phenylsulfonyl chloride and Hunig's base at ambient temperature. The resulting ethyl 3-phenyl-4-[(phenylsulfonyl)amino]butanoate was reduced to the corresponding alcohol (**9**) with lithium borohydride. Upon oxidation of the alcohol, it was discovered that the resulting aldehyde undergoes spontaneous intramolecular cyclization with the sulfonamide to give the five-membered N,O-aminal which was highly unreactive to reductive amination conditions. Hence, we fashioned an orthogonally-protected synthesis in which alcohol (**9**) is first protected as the *O*-*tert*-butyldimethylsilyl ether and subsequently treated with sodium hydride and di-*tert*-butyldicarbonate in DMF at room temperature which converted the 1-phenylsulfonamide into its *N*-Boc derivative. Silyl deprotection was achieved with TBAF in THF and the primary alcohol oxidized to the aldehyde (**10**) in 40% yield over four steps. Intermediate **10** was subjected to standard reductive amination conditions with tropane imidazoles,[6] to give the corresponding 2-phenyl-DAB analogs **11a–c** after Boc-deprotection with TFA in dichloromethane. Additionally, 4-substituted piperdines and 2-substituted octahydropyrrolo[3,4-*c*]pyrroles were also condensed with (**10**) to give analogs (**12a–f**).

Analogs **14a–f** were prepared in a similar fashion to **7a–f** (Scheme 3). Hence, aldehyde (**4**) was treated with *endo*- and *exo*-tropane-1,2,4-triazoles (**13a**) and (**13b**)[7] in the presence of sodium triacetoxyborohydride followed by Raney-Nickel reduction of the nitrile. The resulting amine was then converted to amides and sulfonamides **14a–f** using standard chemistry.

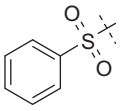
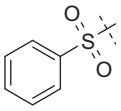
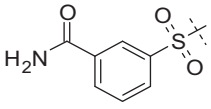
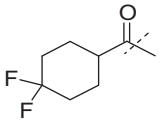
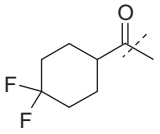
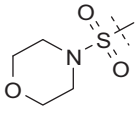
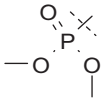
Finally, 2-methyl-2-phenyl-1,4-diaminobutanes **16a–f** were prepared as racemates in five steps from ethyl 3-cyano-3-phenylbutanoate[8] (Scheme 4). Low-temperature, DIBAL reduction of the ethyl ester afforded the aldehyde which was subsequently treated with either *endo*-tropane (**6**) or *exo*-tropane (**13b**) under the standard reductive amination conditions. Due to the hindered nature of the nitrile, hydrogenation required elevated temperature (50 °C) but proceeded in high yield and gave MDAB intermediate **15**. Treatment of the primary amine with phenylsulfonyl chloride/Hunig's base or 4,4-difluorocyclohexanecarboxylic acid/HATU afforded the corresponding sulfonamides and amides (**16a–f**), respectively. These, in turn, could be N-methylated with NaH/MeI with variable yield.

All synthesized compounds were tested for antiviral activity in the HOS cell assay and selected compounds were tested in the PBL cell assay against the Ba-L strain.[9] Structure–activity relationship of analogs **7a–i** is shown in Table 1. Amine functionalization of



Scheme 4. Reagents and conditions: (a) DIBAL-H, THF, −78 °C, 1 h, 19%; (b)$NaBH(OAc)_3$, **6** or **13b**, CH_2Cl_2, rt, 18 h; 85%; (c) Raney-Ni, H_2 (50 psi), EtOH, concd NH_4OH, 50 °C, 18 h, 90%; (d) HATU, difluorocyclohexylcarboxylic acid, iPr_2NEt, CH_2Cl_2, rt, 18 h, 72%; (e) $PhSO_2Cl$, iPr_2NEt, CH_2Cl_2, rt, 18 h, 73%; (f) NaH, THF or DMF then MeI, 7–75%.

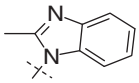
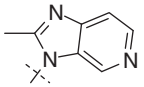
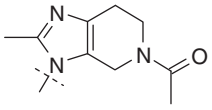
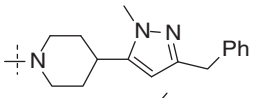
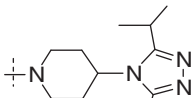
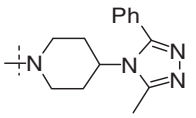
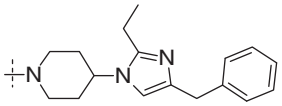
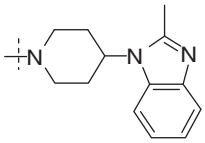
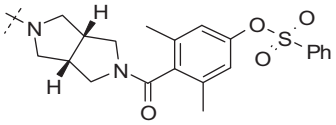
Table 1
Inhibitory potencies of 2-phenyl DAB analogues **7a–i** (synthesized according to Scheme 1) in the HOS and PBL cell assays

Compds[a]	R^1	R^2	HOS[b] IC_{50}[c] (μM)	PBL[b] IC_{50}[c] (μM)
7a		Me	0.008	0.06
7b		H	0.065	0.112
7c		H	0.016	0.161
7d		Me	0.520	ND[d]
7e		H	0.411	ND
7f		H	0.023	0.099
7g		H	0.013	ND
7h		H	0.866	ND
7i		H	0.077	ND

[a] All values refer to racemic compounds.
[b] For a description of the HOS and PBL antiviral assays, see Ref. 9.
[c] IC_{50} values ($n \geqslant 2$ for HOS and $n \geqslant 3$ for PBL) have a standard error usually less than 20%, with assay-to-assay variability usually less than ±25% for the standard compound (aplaviroc).
[d] Not determined.

the N-terminal of the 2-phenyl-DAB series reveals three trends. First, sulfonamide, sulfonyl urea and phosphoramide-based inhibitors are more potent than respective carboxamides. Secondly, as can be seen by a comparison of **7b–f** and **7e–h** the size of the terminal substituent has relatively little effect on potency within each series, the values were observed to be within 2–3-fold between the sulfonamide and carboxamide series. Another noteworthy observation is the effect of *N*-methyl substitution. In the sulfonamide series, a significant improvement in potency is seen in N-methylated 7a compared to non-methylated **7b**. However, a comparison of **7d** and **7e** shows that methylation has no discernable effect in the carboxamide series.

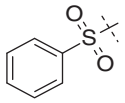
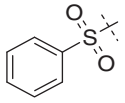
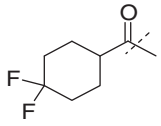
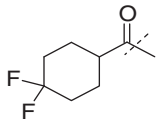
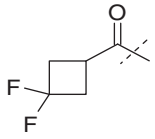
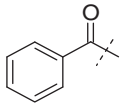
Table 2
Inhibitory potencies of **11a–c** and **12a–f** (synthesized according to Scheme 2) in the HOS and PBL cell assays

Compds[a]	Heterocycle	HOS[b] IC_{50}[c] (μM)	PBL[b] IC_{50}[c] (μM)
exo-**11a**		0.117	ND[d]
endo-**11b**		0.038	ND
endo-**11c**		0.003	0.001
12a		0.088	ND
12b		0.989	ND
12c		5.025	ND
12d		0.045	0.043
12e		0.362	ND
12f		0.008	0.001

[a] All values refer to racemic compounds.
[b] For a description of the HOS and PBL antiviral assays, see Ref. 9.
[c] IC_{50} values ($n \geqslant 2$ for HOS and $n \geqslant 3$ for PBL) have a standard error usually less than 20%, with assay-to-assay variability usually less than ±25% for the standard compound (aplaviroc).
[d] Not determined.

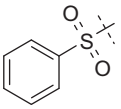
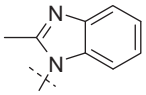
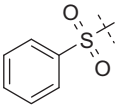
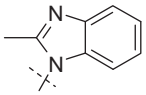
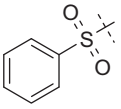
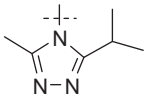
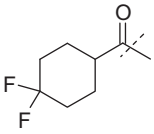
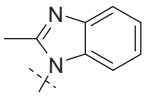
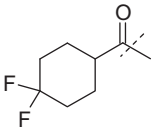
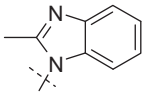
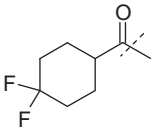
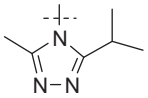
Table 2 shows selected, representative results of the effect of various changes to the right side N-terminal of the 2-phenyl DAB series. Replacement of the *endo*-tropane benzimidazole with its *exo*-tropane counterpart (example **11a**) gives only a modest decrease in potency (~2-fold). 3-Imidazolopyridine in **11b** is also tolerated. Particularly noteworthy is the high potency of **11c**, obtained when benzimidazole is replaced with 5-acetyl-2-methyl-4,5,6,7-tetrahydro-imidazo[4,5-*c*]pyridine. In general,

Table 3
Inhibitory potenciesof **14a–f** (synthesized according to Scheme 3) in the HOS cell assay

Compds[a]	R	*endo/exo*	HOS[b] IC_{50}[c] (μM)
14a		*endo*	0.480
14b		*exo*	0.146
14c		*endo*	0.866
14d		*exo*	9.735
14e		*endo*	>20
14f		*endo*	>20

[a] All values refer to racemic compounds.
[b] For a description of the HOS antiviral assay, see Ref. 9.
[c] IC_{50} values ($n \geqslant 2$) have a standard error usually less than 20%, with assay-to-assay variability usually less than ±25% for the standard compound (aplaviroc).

Table 4
Inhibitory potencies of **16a–f** (synthesized according to Scheme 4) in HOS and PBL cell assays

Compds[a]	R^1	R^2	Heterocycle	HOS[b] IC_{50}[c] (μM)	PBL[b] IC_{50}[c] (μM)
endo-**16a**		Me		0.009	0.001
endo-**16b**		H		0.124	ND[d]
exo-**16c**		H		0.578	ND
endo-**16d**		Me		0.235	ND
endo-**16e**		H		0.249	ND
exo-**16f**		H		0.583	ND

[a] All values refer to racemic compounds.
[b] For a description of the HOS and PBL antiviral assays, see Ref. 9.
[c] IC_{50} values ($n \geqslant 2$ for HOS and $n \geqslant 3$ for PBL) have a standard error usually less than 20%, with assay-to-assay variability usually less than ±25% for the standard compound (aplaviroc).
[d] Not determined.

replacement of the tropane ring with piperdine was poorly tolerated, as can be seen from a comparison of **7b** to **12e**. However, potency comparable to the tropane series of Table 1 was seen from the 2-ethyl-4-(phenylmethyl)-imidazole (**12d**) and 1-methyl-3-(phenylmethyl)-pyrazole (**12a**) substituents. The bicyclic octahydropyrrolo[3,4-*c*]pyrrole ring also shows promise as can be seen by example **12f** which gave 8 nM in the HOS assay. Piperdine is presumed to be inferior to tropane due to the lack of rigidity of the central ring system which imparts a degree of conformational restraint to the molecule. Table 3 details the results observed when the tropane benzimidazole is replaced with 3-methyl-5-isopropyl-1,2,4-triazole. In all cases, the triazole was found to be suboptimal for the 2-phenyl DAB series. Despite the poor results for these analogs, some of the same trends are observed between the tropane benzimidazole series (table 1) and the tropane-1,2,4-triazole series. Sulfonamides **14a** and **14b** show that there was not a significant difference between *endo* and *exo* isomers.

However, carboxamides **14c** and **14d** do not obey this general rule. Also noteworthy was that the use of the Maraviroc amine and acyl motif in analogues **14c** and **14d** resulted in a significantly lower potency than that of Maraviroc itself (IC_{50} HOS = 1.5 nM, IC_{50} PBL = 2.6 nM). This suggests a substantially different binding mode of the DAB and Maraviroc scaffolds to CCR5, which may potentially result in a different resistance profile of compounds in this series from that of MVC.

Somewhat inexplicable is the large potency discrepancy between 3,3-difluorocyclobutyl carboxamide **14e** (>20 μM) and 4,4-difluorocyclohexyl carboxamide **14c** (866 nM) despite their similar size and properties. However, the sulfonamide moiety was again demonstrated to be superior to the carboxamide.

Finke and co-workers[5] have described the structure–activity relationship of a series of 4-(piperidin-1-yl)-2-phenyl-1-(phenylsulfonylamino)butane CCR5 antagonists in which only modest antiviral activity ($IC_{95} \geqslant 200$ nM) was achieved. It has also been disclosed that installing a quaternary methyl group at C-2 offers a considerable improvement in potency (up to $IC_{90} = 3$ nM). It was our hope that this phenomenon could also be observed in our novel series of tropane-incorporating inhibitors. Table 4 shows the results for the 2-methyl-2-phenyl DAB series (Scheme 4). A direct comparison of compounds **16a–f** with their non- quaternary counterparts in Tables 1 and 2 shows that the quaternary methyl group offers little improvement in potency in the HOS assay, with values generally agreeing within twofold. However, in the case of examples **7a** and **16a**, the PBL assay values differ considerably. The same trends observed in Table 1 are seen in Table 4, with the N-methylated sulfonamide outperforming non-N-methylated (**16a** vs **16b**) but having no effect in the carboxamide series (**16d** vs **16e**).

In general, this series displayed hERG activity (dofetilide binding assay) which showed a dependence on structural features. For example, triazoles **14a–f** as a class showed less affinity ($IC_{50} \geqslant 10$ μM) while the benzimidazoles **7a–i** and **11a–c** gave low-micromolar to sub-micromolar IC_{50}s and the 4-piperdine series **12a–e** gave sub-micromolar IC_{50}s with the exception of **12b**.

The pharmacokinetic properties of **7a**, **11c**, **12f** and **16a** are shown in Table 5. While compounds were characterized by a moderate to high clearance, **7a** and **12f** exhibited low, but measurable

Table 5
Rat pharmacokinetics for selected analogs at 1 mg/kg IV and PO[a]

Compds	Cl (mL/min/kg)	%*F*	AUC (ng/mL)
7a	21	5	40
11c	62	<1	0
12f	32	2	10
16a	35	<1	0

[a] Evaluated in Sprague Dawley rats using 5% mannitol with 0.05% acetic acid as dose vehicle.

bioavailabilities at this low-dose.[10] Metabolite ID experiment on analog **7b** indicate oxidative attack on multiple sites including the tropane, benzimidazole and 2-phenyl rings, but interestingly not on the methylene group in SO_2–N–CH_2-moiety. This would suggest that the additional methylene group does not pose an inherent metabolic liability. Furthermore, analog **16a** was found to be moderately permeable in the MDCK cells (P_{app} = 70 nM/s), suggesting that the bioavailability is not absorption-limited. Human and rat hepatocyte data determined that analogs **7a**, **11c**, **12f** and **16a** are all rapidly metabolized ($t_{1/2} \leqslant 20$ min). We thus believe that oral bioavailability observed in this series is primarily determined by first-pass metabolism and could potentially be addressed with further analoging.

In conclusion, we discovered that in the MDAB series the use of *N*-methyl-sulfonamide and *endo*-tropane motifs leads to very high level of PBL cellular potency (e.g., for compound **16a**). Interestingly, the use of the same motifs in the DAB series was insufficient to secure high PBL potency (cf. compound **7a**). On the other hand, the use of *endo*-tropane substituted with the imidazole moiety in **11c** and the bicyclic-pyrrolidine in the DAB series in **12f**, again resulted in high antiviral PBL potency (IC_{50} = 1 nM). Similar antiviral potency level could not be accomplished in previously described class of DAB analogues, which were reported to be potent CCR5 binders, but had only modest antiviral potency in infected cells.[5] In addition, **7a** and **12f** had moderate clearance value in rat in PK and low, but measurable bioavailability from oral dosing at 1 mg/kg. The SAR described herein enables additional explorations towards improving the antiviral potency and PK in this novel series.

References and notes

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10. Maraviroc bioavailability was reported to be 6% at 10 mg/kg PO dose (*Drug Metab. Dispos.* **2005**, 587–595). However, under conditions employed to evaluate PK of analogues in Table 5, MVC plasma concentration after oral dosing was undetectable.