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II. SAR studies of pyridyl–piperazinyl-piperidine derivatives as CXCR3 chemokine antagonists

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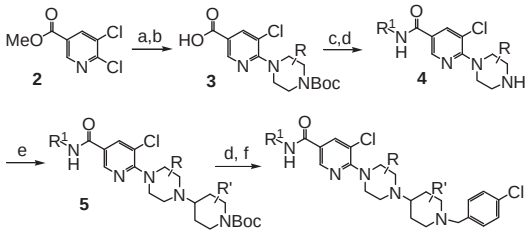
ABSTRACT

The structure–human CXCR3 binding affinity relationship of a series of pyridyl–piperazinyl-piperidine derivatives was explored. The optimization campaign highlighted the pronounced effect of 2′-piperazine substitution on CXCR3 receptor affinity. Analog **18j**, harboring a 2′(*S*)-ethylpiperazine moiety, exhibited a human CXCR3 IC_{50} of 0.2 nM.

CXCR3 is a G-protein coupled chemokine receptor which is predominantly expressed in activated T helper 1 (Th1) cells.[1] CXCR3 interacts with three endogenous interferon-inducible chemokines (CXCL9, CXCL10, and CXCL11) and has been demonstrated to play an important role in the Th1 inflammatory response.[2] A search for CXCR3 antagonists has been ignited by the potential that potent antagonists may have therapeutic benefit in the treatment of multiple sclerosis,[3] rheumatoid arthritis,[4] allograft rejection,[5] psoriasis,[6] and tumor metathesis.[7] Small molecule CXCR3 antagonists reported to date contain diverse scaffolds;[8] including the recently disclosed imidazo-pyrazines,[9] ergolines,[10] and camphor sulfonamides.[11]

We have reported the discovery of a class of CXCR3 antagonists (**1**) that contain a piperazinyl-piperidine core flanked by a left side (as drawn) nicotinamide and a right-side 4-chlorobenzyl group.[12] Herein, we report the results of the optimization campaign which highlights the dramatic effect of the 2′-piperazine substitution to the affinity of this series of CXCR3 antagonists. Furthermore, SAR exploration of the pendant regions indicates that the hydrogen bond donor of the alkyl nicotinamide and a one carbon linked aryl residue to the piperidine are essential for high CXCR3 receptor affinity in this series.

Synthesis of the analogs generally followed a solution-phase version of the previously disclosed solid-phase route as outlined in Scheme 1.[12] Nucleophilic aromatic substitution of **2** with an appropriately substituted Boc-protected piperazine derivative followed by ester hydrolysis led to carboxylic acids of structure **3**. HATU-mediated amide formation followed by acid promoted removal of the Boc group, generated intermediates of type **4**, which were converted to general structure **5** via reductive alkylation with the appropriate Boc-piperidinone derivative. Deprotection of the piperidine nitrogen and subsequent derivatization afforded the title analogs (**6a–6q**, **7a–7n**, **17a–17p**, **18a–18l**).



Scheme 1. General synthesis of analogs. Reagents and conditions: (a) Boc-piperazine derivative, K_2CO_3, DMF, 90 °C; (b) LiOH, MeOH, H_2O, rt; (c) amine, HATU, DIEA, DMF, rt; (d) TFA, DCM, rt; (e) Boc-piperidinone derivative, $Na(OAc)_3BH$, DCE, rt; (f) 4-chlorobenzaldehyde, $Na(OAc)_3BH$, DCE, rt.

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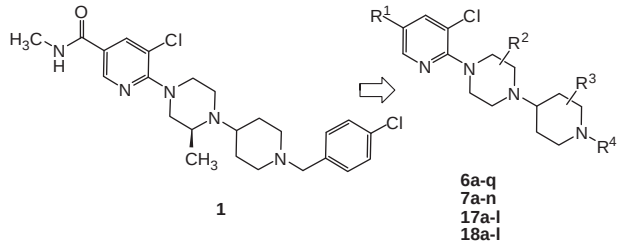
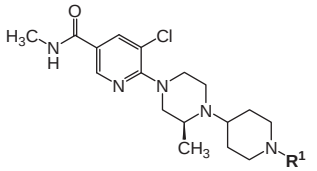


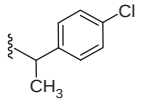
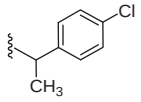
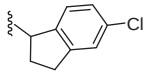
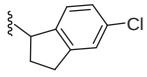
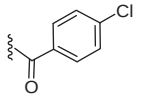
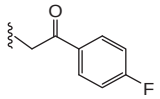
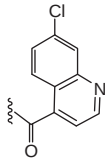
The SAR of the benzyl group was further explored with aromatic and heteroaromatic substitutions (Table 1). Replacement of the phenyl with unsubstituted aromatic heterocycles reduced binding affinity (**6a**–**6d**). Focus was therefore shifted to substitutions around the aromatic portion of the benzyl group. Replacement of the 4-chlorine atom in the lead (**1**) with a highly polar group such as 4-methanesulfonyl (**6e**) substantially reduced affinity. This result coupled with the poor tolerability of heterocycles, suggested that the lipophilic right-side interacted with a lipophilic region of the CXCR3 receptor, and thus further non-polar substitution patterns were explored. Lipophilic substituents such as 4-methyl (**6f**) or 4-trifluoromethyl (**6g**), however, were worse relative to the initial lead. On the other hand, 2,4-dihalo substitution of the benzyl group was well tolerated (**6h**–**6j**), with the additional 2-halo substitution adding slightly to the overall affinity. Substitution of the benzylic methylene was investigated to block this potential metabolic site and moderate the basicity of the piperidine nitrogen for increased absorption. Interestingly, methyl substitution of the benzylic methylene was stereo-sensitive (**6k**–**6l**). Cyclization from the benzylic carbon to the pendent phenyl ring (**6m**–**6n**) was also tolerated, but did not offer any obvious advantage compared with simple methyl substitution. Benzamide **6o** resulted in a seven-fold reduction in affinity compared to compound **1**. In general, 4-chlorobenzyl (**1**) or 2,4-dihalobenzyl (**6h–6i**) substitution of the piperidine nitrogen was most preferred. The 4-chlorobenzyl group was fixed as the benchmark right-hand side and attention was concentrated on optimizing other regions of the molecule.

We previously reported that that *S*-methyl substitution at the 2′-position of the piperazine ring resulted in a sufficient affinity enhancement which then enabled truncation of the high molecular weight carboxamide tail of the initial screening hit (Table 2; compare unsubstituted **7a** and **7c** with 2*(S)*-methyl-substituted **7b** and **1**).[12] This observation prompted an exploration of additional substitutions of the piperazine and piperidine rings in an attempt to increase the CXCR3 binding affinity while maintaining the truncated amide.

Synthesis of the core-modified analogs followed the previously disclosed route as outlined in Scheme 1.[12] The required substituted piperidine or piperazine intermediates (except those in **7l** and **7n**) were available from commercial sources or synthesized according to known procedures.[13] Synthesis of analog **7l** is outlined in Scheme 2. Reaction between Boc-piperazine and 4-chlorobenzylpiperidinone in the presence of diethylaluminum cyanide produced 4-cyano substituted intermediate **8**, which was transformed into 4-methyl substituted compound **9** by reaction with methyl Grignard.[14] After removal of the Boc group, fragment **10** was attached to nicotinamide **11** using Buchwald coupling conditions to produce analog **7l**. Analog **7n** was synthesized from a piperidine-2,4-dione intermediate as illustrated in Scheme 3. 4-Chlorobenzylamine was treated with methyl acrylate to produce secondary amine **12**, followed by stirring with diketene to afford ketone **13**. Ring cyclization was achieved by treatment of **13** with sodium methoxide in methanol and the resultant trione **14** was heated under acidic conditions to remove the acetyl group. The dione **15** was then coupled with an appropriately substituted intermediate **4** through reductive amination to produce analog **7n**.

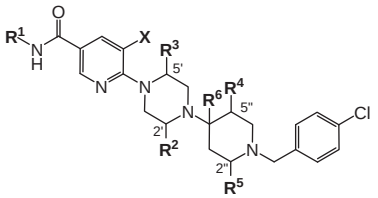
Table 1
Variation of the right-hand benzyl group



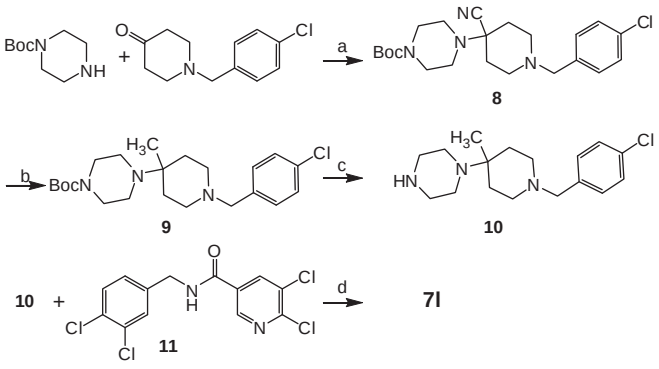
Compds	R^1	hCXCR3 binding IC_{50} (nM)
1	4-Chlorobenzyl	32
6a	Furan-2-ylmethyl	8100
6b	Thiophen-2-ylmethyl	1980
6c	Pyrrol-2-ylmethyl	8060
6d	Pyridin-2-ylmethyl	7990
6e	4-(Methylsulfonyl)benzyl	>10,000
6f	4-Methylbenzyl	87
6g	4-Trifluoromethyl	63
6h	4-Chloro-2-fluorobenzyl	18
6i	2,4-Dichlorobenzyl	17
6j	4-Fluoro-2-chlorobenzyl	58
6k	 (isomer 1)	5
6l	 (isomer 2)	110
6m	 (isomer 1)	29
6n	 (isomer 2)	35
6o		210
6p		>10,000
6q		>10,000

The beneficial effect of 2′-methyl piperizine substitution, prompted further exploration of methyl substitution throughout the piperazinyl-piperidine core. While *S*-methyl substitution on the 5′-position of the piperizine ring was tolerated (Table 2; compare **7g** with unsubstituted **7e**), 5′-methyl substitution with an *R* configuration decreased binding affinity six-fold (**7h**) relative to the *S* configuration (**7g**). The possibility that the conformational effect of 5′-methyl piperazine substitution could be equivalent to the 5-chloro pyridyl was disproven by the weak activity of 5-des-chloropyridyl racemic compound **7i**. Substitution on the core piperidine ring was next investigated. Methyl substitution in the

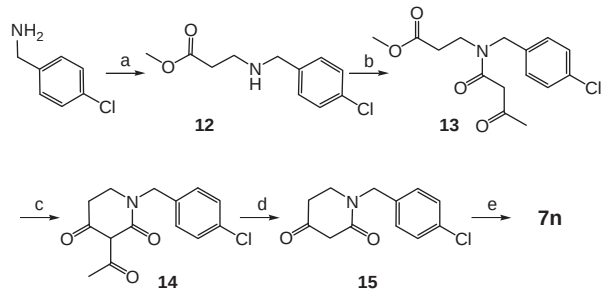
Table 2
Effect of substitution on piperazinyl-piperidine core



Compds	R^1	R^2	R^3	R^4	R^5	R^6	X	hCXCR3 binding IC_{50} (nM)
7a	3,4-Difluorobenzyl	H	H	H	H	H	Cl	40
7b	3,4-Difluorobenzyl	*S*-Me	H	H	H	H	Cl	6
7c	Methyl	H	H	H	H	H	Cl	560
1	Methyl	*S*-Me	H	H	H	H	Cl	32
7e	3,4-Dichlorobenzyl	H	H	H	H	H	Cl	35
7f	3,4-Dichlorobenzyl	*S*-Me	H	H	H	H	Cl	16
7g	3,4-Dichlorobenzyl	H	*S*-Me	H	H	H	Cl	39
7h	3,4-Dichlorobenzyl	H	R-Me	H	H	H	Cl	220
7i	3,4-Difluorobenzyl	H	R,*S*-Me	H	H	H	H	2700
7j	Methyl	H	H	R,*S*-Me	H	H	Cl	64
7k	Methyl	*S*-Me	H	H	R,*S*-Me	H	Cl	31
7l	3,4-Dichlorobenzyl	H	H	H	H	Me	Cl	27
7m	3,4-Difluorobenzyl	Carbonyl	H	H	H	H	Cl	1400
7n	Methyl	*S*-Me	H	H	Carbonyl	H	Cl	7000



Scheme 2. Synthesis of analog **7l**. Reagents and conditions: (a) $Al(Et)_2CN$, $Ti(OiPr)_4$, DCM, rt, 20 h, 41%; (b) CH_3MgBr, THF, 60 °C, 2 h, 67%; (c) 6 M aq HCl, EtOAc, rt, 2 h, 93%; (d) $Pd(OAc)_2$, DBBP, Cs_2CO_3, dioxane, 90 °C, 16 h.



Scheme 3. Synthesis of analog **7n**. Reagents and conditions: (a) methyl acrylate, MeOH, 0 °C to rt, 16 h, 98%; (b) diketene, MeOH, 0 °C to rt, 2 h, 100%; (c) NaOMe, MeOH, rt, 5 h, 96%; (d) 10% aq HCl, EtOH, reflux, 16 h, 85%; (e) **4**, $Na(OAc)_3BH$, HOAc, 1,2-dichloroethane, rt, 16 h, 31%.

5″-position of the piperidine ring (**7j**) increased affinity compared to the unsubstituted analog **7c**. This piperidine substitution, however, increased the stereochemical complexity of the molecule by the introduction of two new chiral centers which was deemed undesirable. Methylation of the piperidine's 2″-position was also tolerated (**7k**) but this modification also increased the stereochemical complexity without providing any significant benefit. Finally, methylation of the 4″-piperidine carbon was tolerated, but without a significant change in affinity (**7l** vs **7e**). Hence, methyl substitution was tolerated in various positions throughout the heterocyclic core rings but the 2′-piperazine position provided the largest augmentation of affinity without a significant increase in the structural complexity of the targets.

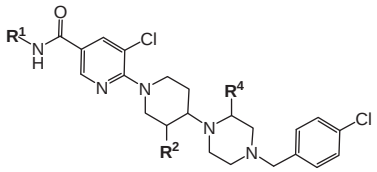
The role of the two basic nitrogens in the core was next explored with piperazin-2-one **7m** and piperidinone **7n**. Both lactam analogs exhibited a substantial drop in activity in relation to their respective cyclic amine analogs. This observation is consistent with the lack of activity exhibited by the inverted piperidinyl-piperazine analog **16a**. Attempts were made to revive activity in the 'reversed' series by methyl substitution (Table 3; **16b**–**16d**). Interestingly, the best analog in this series (**16d**) was substituted with a methyl at the site analogous to the 2′-position of the piperazine in lead structure **1**.

Isosteric replacements for the 5-pyridyl carboxamide (R^1, Table 4) were next explored. The methyl ester (**17a**) and acyclic amidines (**17b**, **17c**) exhibited weaker activity. A set of 'reverse' amides were prepared.[15] Small alkyl amides, such methyl (**17d**) and cyclopropyl (**17e**) amides were equal to or better than the initial lead, but due to the embedded aminopyridine substructure this series was deprioritized.

The parent amide (**17f**) exhibited similar binding affinity to lead compound **1**. Interestingly, an increase in the size and lipophilicity of the alkyl group improved the affinity (**17g–17i**). The aromatic 3,4-difluorophenyl amide **17j**, however, was equal in affinity to the methyl amide lead **1**. To examine the contribution of the amide NH group, secondary amides **17k** and **17l** were prepared. The drop in affinity of these two derivatives in conjunction with the weak binding of previously discussed ester **17a** confirmed the critical nature of the proton donor of the amide moiety. In general, simple alkyl secondary amides displayed the best activity in this series. Thus, we decided to maintain a small alkyl secondary amide in this region for the next SAR exploration.

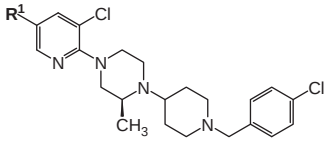
Since 2′(*S*)-methyl substitution of the piperazine in **1** enhanced binding activity, we further explored the SAR at this position (Table 5). Analogs **18a**–**18d** and **18k–18l** were prepared from readily available substituted piperazines[13a] through the method outlined in Scheme 1. Analogs **18e**–**18h** were directly derived from compound **18d** (Scheme 4). Reduction of the ester functional group of **18d** with sodium borohydride afforded alcohol analog **18e**,

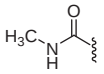
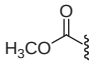
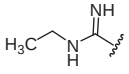
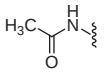
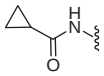
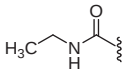
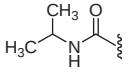
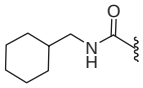
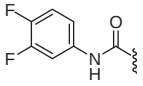
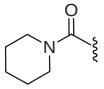
Table 3
Effect of methyl substitution on 'reversed' piperidinyl-piperazine analogs



Compds	R^1	R^2	R^4	hCXCR3 binding IC_{50} (nM)
16a	3,4-Dichlorobenzyl	H	H	4500
16b	Methyl	H	*S*-Me	12,500
16c	Methyl	H	R-Me	7350
16d	Methyl	R,*S*-Me	H	280

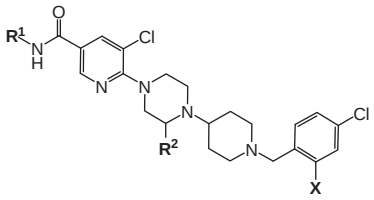
Table 4
Human CXCR3 binding IC_{50} of analogs **17a–17l**



Compds	R^1	IC_{50}[9] (nM)
1		32
17a		520
17b		80
17c		83
17d		8
17e		20
17f		39
17g		2.3
17h		5
17i		2.4
17j		22
17k		900
17l		630

which was subsequently transformed into the methyl ether analog **18f** by $TMSCHN_2$ treatment. Hydrolysis of ester **18d** resulted in the acid analog **18g**, which was used to prepare the carboxamide analog **18h** via HATU mediated coupling.

Table 5
Effect of 2'-substitution on piperazine ring

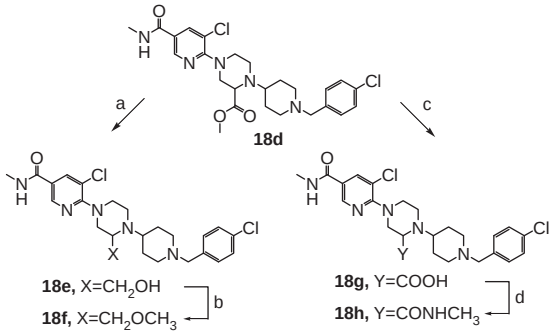


Compds	R^1	R^2	X	hCXCR3 binding IC_{50} (nM)
7c	Me	H	H	560
1	Me	(*S*)-Methyl	H	32
18a	Me	(*S*)-Ethyl	H	3
18b	Me	(*S*)-Isobutyl	H	260
18c	Me	(*S*)-Phenyl	H	830
18d	Me	(*R,S*)-COOMe	H	140
18e	Me	(*R,S*)-CH_2OH	H	910
18f	Me	(*R,S*)-CH_2OMe	H	3100
18g	Me	(*R,S*)-COOH	H	>50,000
18h	Me	*R,S*-COONHMe	H	8900
18i	Et	(*S*)-Ethyl	H	0.3
18j	Et	(*S*)-Ethyl	F	0.2
18k	Et	(*S*)-Isopropyl	H	23
18l	Et	(*R,S*)-Cyclopropyl	F	32

The SAR of the 2′-position on the piperazine ring is outlined in Table 5. The 2′(*S*)-ethyl analog **18a** afforded a 10-fold improvement in affinity (IC_{50} = 3 nM). Larger alkyl, such as isobutyl (**18b**) and phenyl (**18c**) substitution led to a dramatic drop in binding affinity. Substitution at the 2′-position with a polar substituent such as an ester, alcohol, ether, carboxylic acid, or carboxamide also significantly led to decreased binding affinity (**18d–18h**). Combination of the optimized 2′-(*S*)-ethyl-piperazinyl-piperidine core with a slightly larger ethyl carboxamide R^1 substituent produced analogs **18i** and **18j** which achieved sub-nanomolar CXCR3 receptor binding affinity. Pairing of a slightly larger 2′-(*S*)-isopropyl- or 2′-(*R,S*)-cyclopropyl-piperazine with the same ethyl carboxamide R^1 substituent (**18k**, **18l**) resulted in a drop in receptor affinity, confirming that the 2′-(*S*)-ethyl piperazinyl-piperidine core was fully optimized.

Representative compounds in all of the series were profiled for rodent CXCR3 receptor affinity and functional assays.[16] Select mouse and rat CXCR3 affinity data (Table 6) illustrates the nearly 100-fold gain in intrinsic receptor affinity observed for the 2′-substituted compounds **18i** and **18j** compared with the larger, unsubstituted structure **7a**.

With the SAR for receptor affinity established, attention was turned to the pharmacokinetics of the lead series. Initial analogs **7a** and **7b** demonstrated moderate exposure in a rat when orally dosed (AUC = 920 nM h and 500 nM h, respectively; 10 mpk, 6 h,



Scheme 4. Synthesis of analogs **18e–18h**. Reagents and conditions: (a) $NaBH_4$, EtOH, 80 °C, 3 h, 85%; (b) $TMSCHN_2$, HBF_4, THF, 0 °C, 30 min, 72%; (c) LiOH, H_2O/THF/MeOH, rt, 5 h, 100%; (d) $MeNH_2$, HATU, DIEA, DMF, rt, 16 h, 76%.

Table 6
PK profile of lead CXCR3 antagonists

Compds	Mouse CXCR3 binding IC_{50} (nM)	Rat CXCR3 binding IC_{50} (nM)	Rat AUC[a] (nM h)
7a	84	97	920
7b	6.7	9.9	500
18i	0.5	1.2	410
18j	1.1	1.6	950

[a] PO, 10 mpk, 6 h, 0.4% MC.

MC).[17] The smaller, more active analogs **18i** and **18j** maintained comparable exposure levels (AUC = 410 nM h and 950 nM h, respectively). Hence, truncation of the R^1 carboxamide substituent was not sufficient to enhance the rat PK profile of this series of CXCR3 antagonists.

In summary, modifications were made throughout the piperazinyl-piperidine core of the CXCR3 antagonist **1**. While tolerated, most of the pyridyl carboxamide or benzyl substitutions did not enhance binding affinity toward the CXCR3 receptor. In contrast, changes to the 2′-position of the piperazine had a strong influence on receptor binding. A modest increase in the size of the alkyl group at the 2′-position of the piperazine ring from methyl to ethyl, improved binding affinity significantly, resulting in the first reported sub-nanomolar (IC_{50}) CXCR3 receptor antagonists. Hence, the 2′-position of the piperazine ring is an important pharmacophore element in the interaction of the current lead molecules **18i** and **18j** with the CXCR3 receptor. Further optimization efforts in this series will be reported in separate publications.

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15. Analogs **17e**–**17i** were synthesized as previously described.[12]
16. Representative compounds **6k**, **6l**, **7b**, **17h** and **17i** showed functional anatagonism in CXCR3 mediated chemotaxis assays. For example compound **7b** showed IC_{50} of 23 nM in IP-10 induced hCXCR3 chemotaxis.
17. Sprague–Dawly rat PK of compound **7b** was determined: AUC (PO, 5 mpk, 24 h) = 1100 nM h, $T_{1/2}$ = 6.8 h, Vd[ss] = 17.6 L/kg, and CL = 32.6 mL/min/kg. Additionally, CYP 2D6, 3A4 and 2C19 inhibition (IC_{50}) was >10 μM.