Bioorganic & Medicinal Chemistry Letters 21 (2011) 4745–4749

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Special ergolines efficiently inhibit the chemokine receptor CXCR3 in blood

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ARTICLE INFO

Article history:
Received 30 May 2011
Revised 14 June 2011
Accepted 15 June 2011
Available online 29 June 2011

Keywords:
CXCR3
Ergoline
CXCL9
CXCL10
CXCL11

ABSTRACT

The structure–activity relationship of highly potent special ergolines which selectively block the chemokine receptor CXCR3 is reported. The most potent compounds showed IC_{50} values below 10 nM in both ligand binding and Ca^{2+}-mobilization assays. However, these compounds were poorly active in an assay that measures receptor occupancy in blood. Introduction of polar substituents led to derivatives with IC_{50} values below 10 nM in this assay. Among them was compound **11a** which showed both a favorable PK profile and cross reactivity with rodent CXCR3 making it a promising tool compound to further explore the role of CXCR3 in animal models.

Chemokines are a group of chemotactic peptides that bind to G-protein coupled receptors and regulate leukocyte trafficking to lymphoid organs and tissues under resting conditions as well as during inflammation.[1] The inflammatory chemokine receptor CXCR3 is predominantly expressed on activated inflammatory T helper 1 (Th1) T cells, but not on resting cells or on Th2 cells. CXCR3 binds with high affinities three different ligands, that is, Mig (CXCL9, monokine induced by IFN-γ), IP-10 (CXCL10, IFN-γ-induced protein-10), and ITAC (CXCL11, IFN inducible T cell alpha chemoattractant).[2] These ligands are produced by activated leukocytes (monocytes and macrophages), vascular endothelial cells and activated tissue cells. The main inducing factor is the cytokine, IFN-γ.[3] Because IFN-γ itself and activated monocytes and macrophages are present in most Th1-mediated inflammatory sites, high levels of CXCR3 ligand expression as well as high numbers of CXCR3 expressing cells are observed in inflamed joints of rheumatoid arthritis (RA) patients,[4] in MS lesions in the brain,[5] during pancreatitis in type 1 diabetes[6] and in human allograft recipients during episodes of acute rejection.[7] Further evidence for an involvement of CXCR3 and its ligands in allograft rejection stems from literature reports on transplantation experiments utilizing both KO mice and neutralizing principles such as anti CXCR3 monoclonal antibodies and antisense peptide nucleic acid.[8] However, these findings could not be confirmed by us and others.[9] Nevertheless, CXCR3 could be an attractive target for pharmaceutical intervention because prevention of ligand–receptor interactions may alleviate various inflammatory conditions.

Several reports on low molecular weight CXCR3 inhibitors have been published.[10] We have reported on the discovery of the lysergic acid-derived inhibitor **1a** (Table 1) which is a selective and potent antagonist of CXCR3.[11] Contrary to basic ergoline derivatives the neutral urea **1a** did not significantly inhibit Serotonin, Andrenergic and Dopamine receptors. Therefore, we call this compound 'special ergoline'. Here we describe the SAR of this promising lead series and disclose derivatives with IC_{50} values below 10 nM in ligand binding and Ca^{2+}-mobilization assays as well as in an assay that measures receptor occupancy in blood.

A variety of amides were prepared from 6-nor-lysergic acid derivative **2** (Scheme 1).[12] Reaction with phenyl isocyanate gave urea **3**. Saponification led to acid **4** which was transformed into the corresponding amides **1a**–**1w** (Table 1). The epimers were separated on silica gel. The desired 8*R*-epimers generally eluted first.[13]

Diethylamide **1a** showed promising inhibition in binding and Ca^{2+}-mobilization assays.[14] Primary (**1b**) and secondary amides **1b** and **1c** were inactive and significantly less potent, respectively, whereas dimethylamide **1d** showed slightly improved inhibition. Introduction of polar groups led to decreased potency (**1e** and **1f**). Amides of cyclic amines were highly potent (**1g**–**1j**). Pyrrolidine-amide **1h** and piperidine-amide **1i** were optimal for CXCR3 inhibition with IC_{50} values below 10 nM in both binding and mobilization assays. Their unsaturated analogs **1k** and **1l** were similarly potent. Introduction of heteroatoms in the ring system (**1m**–**1r**) led to decreased potencies compared to **1h** and **1i**. The morpholine amide **1q** was the best compound in this sub-series. In a small series of hydroxylated cyclic amides (**1s**–**1w**) hydroxy-piperidine amide **1s** was found to be the most potent derivative. The high potencies of selected compounds (**1a**, **1h**, **1i**, **1q**) were confirmed in an ITAC-induced cell migration assays (74, 19, 13, 78 nM, respectively).[14] All

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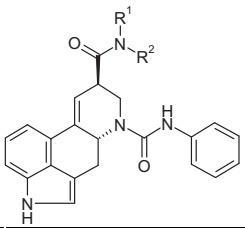
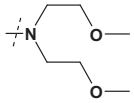
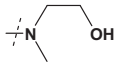
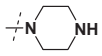
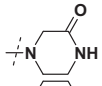
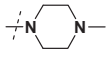
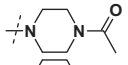
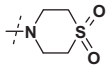
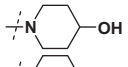
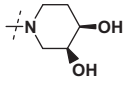
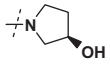
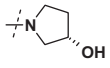
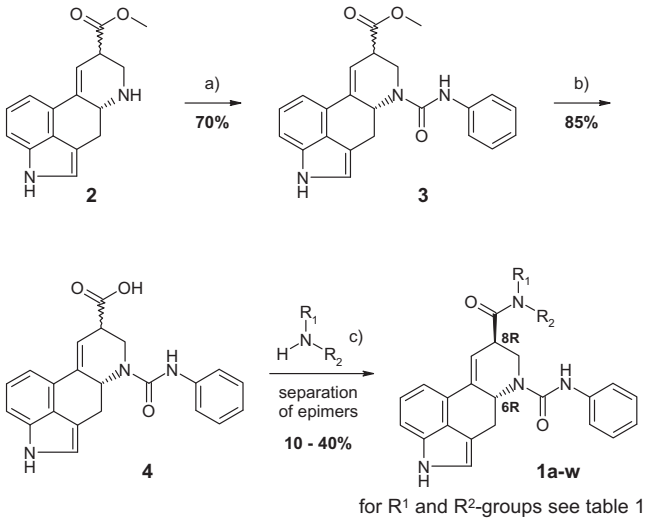
doi:10.1016/j.bmcl.2011.06.070

Table 1
Amide modifications



	–NR¹R²	Binding[14] IC_{50}* (nM)	Ca^{2+} mobil.[14] IC_{50} (nM)* hu (mouse)
1a		51	18 (30)
1b		>10,000	n.t.
1c		379	71 (90)
1d		28	10 (10)
1e		305	187 (437)
1f		66	12 (9)
1g		61	8 (14)
1h		5	4 (4)
1i		9	5 (6)
1j		81	14 (13)
1k		17	3 (3)
1l		12	4 (2)
1m		1010	457 (1730)
1n		255	74
1o		131	83 (112)
1p		825	286
1q		22	16 (12)
1r		1160	216
1s		400	67 (534)
1t		14	5 (8)
1u		50	200 (40)
1v		61	22
1w		47	12 (19)

* Mean values of at least two independent measurements.



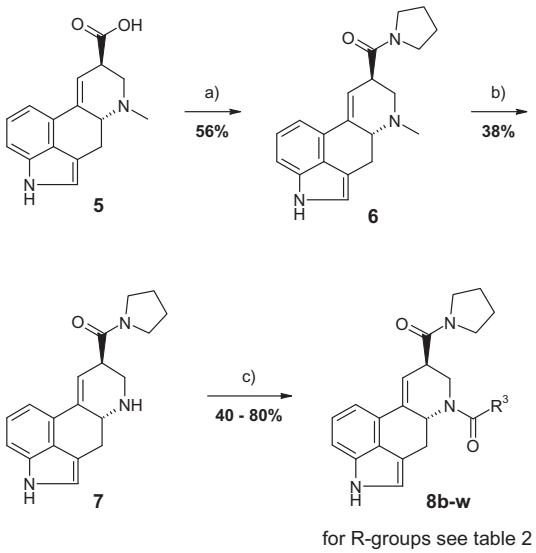
Scheme 1. Reagents and conditions: (a) Ph-NCO, CH_2Cl_2, 20 °C, 16 h; (b) LiOH, $CH_3OH/THF/H_2O$ (1:2:1), 20 °C, 2 h; (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP), NEt_3, CH_2Cl_2, 20 °C, 4 h or propanphosphonic acid anhydride, NEt_3, CH_2Cl_2, 0–5 °C, 1 h.

compounds were found similarly active on murine CXCR3 in an assay monitoring I-TAC induced Ca^{2+} mobilization.

Based on the highly active compound **1h** a series of ureas were prepared starting from lysergic acid (**5**). Transformation into pyrrolidine amide **6** was followed by N-demethylation which was achieved applying the non-classical Polonovski protocol,[15] a superior method when compared to the von Braun de-methylation involving highly toxic and hazardous cyanogen bromide.[16] Reaction of **6** with perbenzoic acid led to the formation of the corresponding N-oxide intermediate which was treated with Fe^{2+} to give compound **7**. Compounds **8b–8w** were obtained from **7** (see Scheme 2 and Table 2). Amides **8v** and **8w** were obtained from **7** by reaction with the corresponding acid chlorides (see Scheme 2).

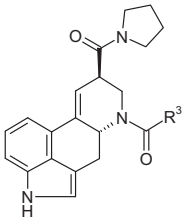
The 2-fluorophenyl derivative **8b** was less potent than **1h** whereas the 3- and 4-fluorophenyl ureas **8c** and **8d** showed comparable inhibition. Methoxy substituents resulted in a significant drop of activity (**8e**–**8g**). Amino groups were not tolerated (**8h**–**8j**). Thiophenyl ureas **8k** and **8l** showed only slightly reduced potencies compared to **1h** whereas pyrrole derivative **8m** was found to be completely inactive. In a small series of aliphatic derivatives (**8n**–**8s**) only the cyclohexyl and cycloheptyl ureas **8l** and **8m** showed promising activities. Both the benzyl derivative **8t** and furanyl methyl derivative **8u** were poorly active. Introduction of amides instead of the urea led to poorly active derivatives **8v** and **8w**. Thus the phenyl urea seems to be optimal for CXCR3 inhibition.

Several of our more potent CXCR3 antagonists were tested in assays that measure receptor occupancy in blood. The assay principle was based on the attribute that staining of blood lymphocytes with anti-CXCR3 antibodies is prevented when I-TAC is added to the blood samples and that the anti-CXCR3 staining was dose-dependently restored when the samples were pre-incubated with inhibitors before the addition of I-TAC.[17] Very disappointingly, compound **1h** which showed IC_{50} values of 5 and 4 nM in binding an mobilization assays, respectively, only modestly inhibited ITAC binding to CXCR3 in both rat blood (IC_{50} = 3300 nM) and human blood (IC_{50} = 700 nM). Related piperidine amide **1i** showed an IC_{50} value of 840 nM in human blood. Interestingly, the less potent derivative **1t** ($c \log P$ = 1.2) which is more polar than **1h** ($c \log P$ = 2.7) and **1i** ($c \log P$ = 3.2) showed improved inhibition in blood (rat: 410 nM; hu: 200 nM). Thus, we aimed at compounds



Scheme 2. Reagents and conditions: (a) pyrrolidine (2 equiv), propanphosphonic acid anhydride (1.5 equiv), NEt_3 (2 equiv), CH_2Cl_2, 0–5 °C, 30 min; (b) (1) *meta*-chlor-perbenzoic acid (1.25 equiv), 0 °C, 10 min, (2) $FeSO_4 \cdot 7\ H_2O$ (0.5 equiv) CH_3OH, 20 °C, 2 h; (c) R^3-NCO, THF, 20 °C, 10 min; or diphosgene (1.5 equiv), NEt_3, CH_2Cl_2, 20 °C, 20 min; then H_2N–R^3 (5 equiv), 20 °C, 2 h; or R^3–COCl, NEt_3, CH_2Cl_2, 20 °C, 30 min.

Table 2
Urea modifications



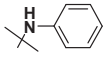
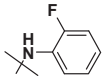
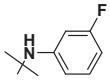
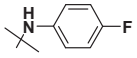
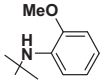
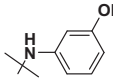
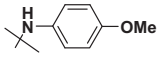
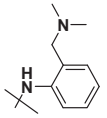
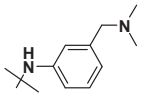
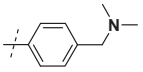
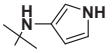
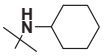
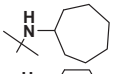
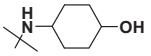
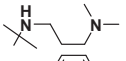
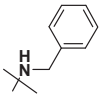
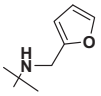
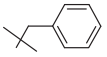
	–R^3	Binding[14] IC_{50}* (nM)	Ca^{2+} mobil.[14] IC_{50}* (nM) hu (mouse)
1h		5	4 (4)
8b		43	20 (16)
8c		4	3 (2)
8d		7	4 (4)
8e		523	60
8f		278	27 (74)
8g		393	89
8h		n.t.	>10,000
8i		n.t.	6200

Table 2 (*continued*)

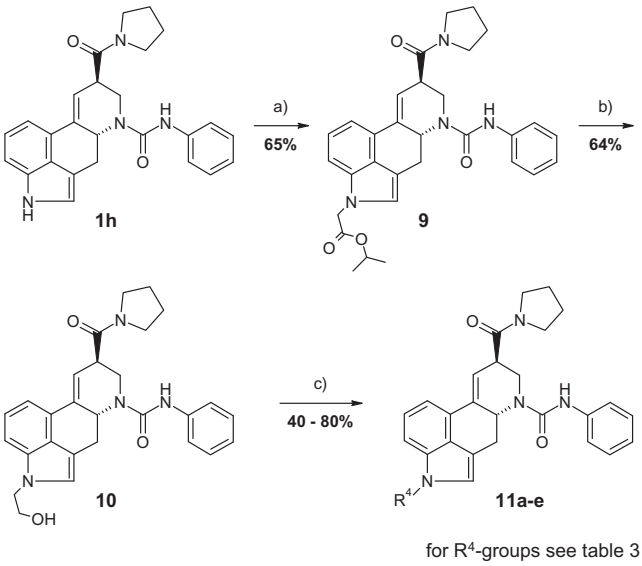
	–R^3	Binding[14] IC_{50}* (nM)	Ca^{2+} mobil.[14] IC_{50}* (nM) hu (mouse)
8j		n.t.	5400
8k		26	7 (11)
8l		37	8 (10)
8m		>10,000	>10,000
8n		160	73 (81)
8o		24	11(31)
8p		28	14 (16)
8q		>10,000	9475
8r		>10,000	>10,000
8s		n.t.	>10,000
8t		2200	2200
8u		2600	10,000
8v		>10,000	6120
8w		427	170

* Mean values of at least two independent measurements.

equipotent to **1h** with significantly increased polarity. As polar groups in both the amide portion (**1m**–**1w**) and the urea portion (**8h**–**8j**, **8m**, **8q**, and **8s**) generally led to less potent derivatives we decided to explore the indole nitrogen as a potential attachment point. Starting from compound **1h** a small series of derivatives was prepared (Scheme 3). Isopropyl acetate was introduced applying phase transfer conditions. The resulting ester **9** was reduced with lithium borohydride to give alcohol **10** which was tosylated and transformed into amines **11a**–**11e**.

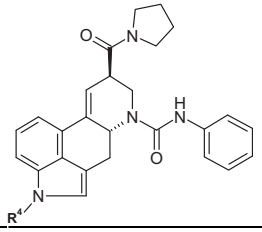
Introduction of a relatively large lipophilic residue (compound **9**, Table 3) led to reduced potency compared to **1h** but did not completely abolish inhibition of CXCR3. However, introduction of a neutral, hydrophilic residue (compound **10**, Table 3) did not significantly affect inhibition in both binding and Ca^{2+}-mobilization assays but significantly improved potency in blood. The same trend was observed for compounds **11a**[18]–**11e** containing basic amino functions (Table 3). It is worthwhile to note that the improved activities of compounds **10** and **11a**–**11e** in the presence of blood compared to **1h** can not be explained by reduced protein binding as the free fractions in rat and human serum for these compounds were similar (**1h**: rat 4%, hu 3%; **10:** rat 7, hu 8%; **11a** rat 4, hu 7%;).

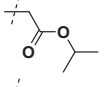
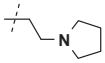
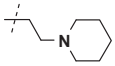
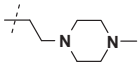
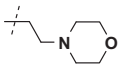
The in vivo PK properties of **11a** were assessed in Sprague–Dawley rats after intravenous and oral administration of the compound (Table 4). The oral bioavailability was 97% and blood levels (AUC normalized to a dose of 1 mg/kg was 2658 nM h), clearance and half life ($T_{1/2}$ = 8.9 h) were found to be favorable. The maximal concentration (C_{max}) normalized to a dose of 1 mg/kg was 137 nM. In contrast to many basic ergoline derivatives lacking the urea



Scheme 3. Reagents and conditions: (a) $BrCH_2CO_2iPr$ (4.0 equiv), $BnNEt_3Cl$, CH_2Cl_2, NaOH (40%), 0–5 °C, 1 h; (b) $LiBH_4$ (4.0 equiv), THF, 0–5 °C, 5 h; (c) (1) TsCl (1.5 equiv), DMAP (1.5 equiv), CH_2Cl_2, 25 °C, 2 h, (2) amine (20 equiv), CH_3CN, 25–55 °C, 1–5 h.

Table 3
Indole modifications



	–R^4	Binding[14] IC_{50}* (nM)	Ca^{2+} mobil. [14] IC_{50}* (nM) hu (mouse)	Rat blood IC_{50} (nM)
1h		5	4 (4)	3300
9		145	53 (53)	n.t.
10		6	5 (4)	7
11a		2	2 (2)	5
11b		3	3 (2)	14
11c		2	5 (3)	16
11d		5	5 (3)	23
11e		24	8 (5)	40

* Mean values of at least three independent measurements.

moiety which do not block CXCR3 but are highly active against various Serotonin, Andrenergic and Dopamine receptors,[11] the 'special ergoline' **11a** did not inhibit these receptors with IC_{50} values below 2500 nM. Furthermore, all animals treated in PK studies showed normal behavior indicating the absence of a metabolic conversion into a basic ergoline. Compound **11a** is highly soluble (>1 mM at pH 6.8) and did not inhibit the hERG channel (IC_{50} >30 μM in an automated patch clamp assay).

Table 4
PK parameters of compound **11a**

Parameter	**11a**
CL (mL min^{-1} kg^{-1})	13 ± 3
V_{SS} (L kg^{-1})	8.3 ± 1.6
$t_{1/2term}$ (h)	8.9 ± 0.9
AUC iv d.n. (nM h)	2′729 ± 877
AUC po d.n. (nM h)	2′658 ± 447
F (%)	97 ± 16
C_{max} d.n. (nM)	137 ± 30
T_{max} (h)	3.1 ± 1.8

Formulations: iv 1 mg/kg, solution in NMP: PEG200 (30:70), volume 0.5 mL kg^{-1}; po 3 mg/kg, suspension in CMC/water/Tween (0.5:99:0.5), volume 2.5 mL kg^{-1}. CL (total blood clearance), V_{SS} (apparent volume of distribution at steady state), $t_{1/2term}$ (terminal half-life for elimination, AUC (area under the curve extrapolated to infinity), F (oral bioavailability), C_{max} (maximal blood concentration after po administration), T_{max} (time of peak blood concentration after po administration, d.n. (dose-normalized, i.e., calculated to a dose of 1 mg kg^{-1}).

Starting from the promising lead compound **1a** we have discovered highly potent, selective special ergolines such as **1h** that inhibit CXCR3 with IC_{50} values as low as 5 nM in both binding and mobilization assays. However, **1h** and related compounds showed only modest potency in an assay that measures receptor occupancy in blood. Introduction of polar, solubilizing residues led to derivatives such as **10** and **11a** with comparable potencies in binding and mobilization assays but with highly promising activities in blood. Favorable PK properties of **11a** in rats make it a promising tool compound to explore the role of CXCR3 in various disease models.

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17. ITAC binding assay in blood: EDTA anti-coagulated blood samples were incubated with or without (controls) serial dilutions of low molecular weight inhibitors for 1 h at 37 °C. ITAC was directly added to the samples followed by a further incubation for 1 h at 37 °C. Subsequently the samples were stained with fluorescence labeled anti-CXCR3 antibodies and the fluorescence signals of lymphocytes measured by flow cytometry. We measured the degree of restoration of the anti-CXCR3 stain by the inhibitors compared to the samples that were not incubated with I-TAC. The calculated IC_{50} values for each compound indicated at which concentration 50% of I-TAC binding to CXCR3 was inhibited.
18. *Analytical data of compound* ***11a***: ^{1}H NMR (400 MHz, DMSO) δ = 1.75–2.03 (4H, m, pyrrolidine–CH_2–CH_2–CH_2–CH_2–), 2.18 (6 H, s, N(CH_3)$_2$), 2.60 (2 H, t, J = 6.0 Hz, N–CH_2–CH_2–N(CH_3)$_2$), 2.93 (1H, t (br), J = 12.5 Hz, H-7$_{ax}$), 3.18–3.28 (2 H, m), 3.28–3.38 (including H_2O signal, m), 3.62–3.81 (3 H, m, H-8, pyrrolidine–CH_2–CH_2–CH_2–CH_2–), 4.20 (2H, t, J = 6.0 Hz, N–CH_2–CH_2–N(CH_3)$_2$), 4.41 (1H, t (br), J = 12.5 Hz, H-7$_{eq}$), 4.75 (1H, m, H-5), 6.52 (1H, d, J = 5.5 Hz, H-9), 6.91 (1H, t, J = 7.5 Hz, Ar-H-9), 7.07–7.11 (3H, m, Ar-H), 7.22 (3H, m, Ar-H), 7.28 (1 H, dd, J = 6.0 Hz, J = 1.5 Hz), 7.38 (2 H, d, J = 7.0 Hz), 9.12 (1H, s, NH_{urea}); MS/HR HRMS: m/z calcd for $C_{30}H_{35}N_5O_2$ [M+H]$^+$: 498.2864; found: 498.2864.