



CCR1 antagonist | BI-9667

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Summary

CCR1 is a key chemokine receptor for human monocyte/macrophage chemotaxis. BI-9667 blocks influx of pro-inflammatory cells to the site of inflammation.

Chemical Structure

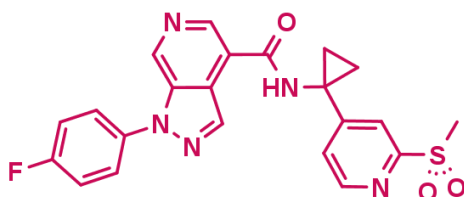


Figure 1: 2-D structure of BI-9667, a CCR1 antagonist

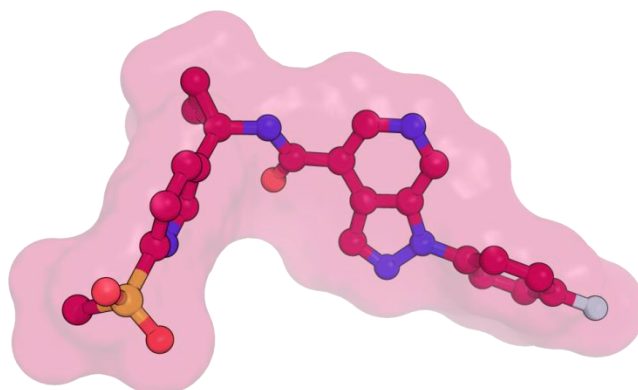


Figure 2: 3-D structure of BI-9667

Highlights

BI-9667 is a potent and selective antagonist to human CCR1, including in the whole blood setting. Its rodent cross-reactivity is limited. The compound shows good physical-chemical and pharmacokinetic properties. It is projected to have a human half-life of 9-12 h. It was targeted to be dosed once-a-day to achieve IC₉₀ coverage at trough levels of the human whole blood IC₅₀. No

pre-clinical safety liabilities have been identified (CV safety, drug-drug interaction potential, rodent and dog toxicology).

Target information

Chemotactic cytokine receptor-1 (CCR1) is a G protein-coupled receptor that belongs to a family of more than 20 chemokine receptors that have emerged as attractive targets for drug discovery. There are various chemokines that interact with these chemokine receptors and are well known to mediate basal and inflammatory leukocyte trafficking. CCR1 is expressed on immune cell types including monocytes, macrophages, T-lymphocytes, neutrophils, basophils, eosinophils, NK cells, mast cells and dendritic cells. The binding of the chemokine MIP-1 alpha (CCL3), MCP3 (CCL7) and RANTES (CCL5) to CCR1 is reported to play a role in the trafficking of monocytes, macrophages and Th1 cells to inflamed tissues in rheumatoid arthritis (RA) and multiple sclerosis (MS) new. Macrophages and Th1 cells in the synovia of RA patients are also major producers of MIP-1 alpha and RANTES, and they continuously recruit leukocytes to the synovial tissues of RA patients resulting in chronic inflammation. Thus, CCR1 has been regards as a potential target for treating inflammatory disease. Antagonists that block the interactions between CCR1 and its chemokine ligands could block chemotaxis of monocytes, macrophages and Th1 cells to inflamed tissues ameliorating the chronic inflammation associated with autoimmune diseases such as RA and MS. However, in 2013, it was demonstrated by BMS that with sufficiently target coverage no significant efficacy was achieved in a Phase IIa RA trial. Consequently, development of BI-9667 was halted also.



Figure 3: Complex of human CCR2 with orthosteric and allosteric antagonists (PDB code: 5t1a)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-9667	BI-9307
MW [Da]	451.5	547.5
CCR1 binding affinity (IC ₅₀) [nM] (SPA binding)	5.4	n.d.
CCR1 molecular potency (IC ₅₀) [nM] (Ca flux)	24	>3000
CCR1 cellular potency (IC ₅₀) [nM] (chemotaxis)	2.4	n.d.
Whole blood potency (IC ₅₀) [nM] (Receptor internalization)	9	n.d.

In vitro DMPK and CMC parameters

PROBE NAME	BI-9667	BI-9307
Aqueous solubility @ pH 6.8 [µg/ml]	8	>65 (unknown crystallinity)
CACO permeability @ pH 7.4 [*10 ⁻⁶ cm/s]	2.9	n.d.
CACO efflux ratio	7.3	n.d.
Human hepatocyte clearance [% Q _H]	<5	33 (HLM)
Plasma protein binding human [% Q _H]	66%	n.d.

In vivo DMPK parameters

PROBE NAME	BI-9667		
Species	Rat	Dog	Cyno
CL [% Q _H]	13	5.8	17

MRT [h]	1.9	6.9	4.4
V _{ss} [l/kg]	1.1	0.7	1.9
F [%]	10	29	35

In vivo pharmacology

Due to reduced mouse rodent potency this compound was not tested in in vivo disease models. However, efficacy in models such as collagen induced arthritis (CIA) in mouse has been demonstrated with cross-reactive tool compound in house

Selectivity

Good selectivity. PanLabs receptor screen on 69 targets @ 10 µM: 67 targets < 45% inhibition, A2A/HU: 69%, DATRANS 71%; neither reproduced in dose response

BI-9667	SELECTIVITY DATA AVAILABLE
Cerep [®]	No
Eurofins-Panlabs [®]	Yes
Invitrogen [®]	No
DiscoverX [®]	No
Dundee	No

Negative control

A structurally closely related inactive analogue, BI-9307, is available

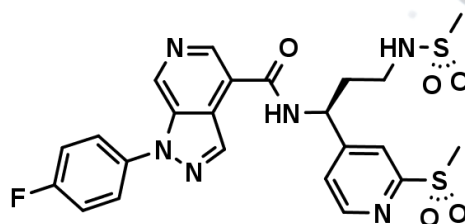


Figure 4: Chemical structure of the negative control BI-9307

Co-crystal structure of the BI probe compound and the target protein

Not available

Reference molecule(s)

CCX-354, BMS-817399

Summary

BI-9667 is a potent, selective human CCR1 antagonist with optimized drug-like properties.

Supplementary data

Selectivity data can be downloaded free of charge from this site.

References

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2. Tak, P. P.; Balanescu, A.; Tseluyko, V.; Bojin, S.; Drescher, E.; Dairaghi, D.; Miao, S.; Marchesin, V.; Jaen, J.; Schall, T. J.; Bekker, P. Chemokine Receptor CCR1 antagonist CCX-354-C treatment for Rheumatoid Arthritis: CARAT-2, a Randomised, Placebo controlled Clinical Trial. *Ann. Rheum. Dis.* **2013**, *72*, 337-344 [DOI: 10.1136/annrheumdis-2011-201605](https://doi.org/10.1136/annrheumdis-2011-201605), [PubMed](#).
3. Kivitz, A.; Maciag, P.; Gulati, P.; Shuyan, D.; Connolly, S. E.; Davies, P.; Li, X.; Repsher, T.; Haggerty, H. G.; Londei, M. THU0109 Lack of Efficacy of CCR1 Antagonist BMS-817399 in Patients with Moderate to Severe Rheumatoid Arthritis: Results of 12-Week Proof-of-Concept Study EULAR 2014 Poster, [DOI: 10.1136/annrheumdis-2014-eular.3871](https://doi.org/10.1136/annrheumdis-2014-eular.3871).