opnMe by Boehringer Ingelheim

CCR1 antagonist

BI 639667

Boehringer Ingelheim

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Summary

CCR1 is a key chemokine receptor for human monocyte/macrophage chemotaxis. BI 639667 blocks influx of pro-inflammatory cells to the site of inflammation.

Chemical Structure

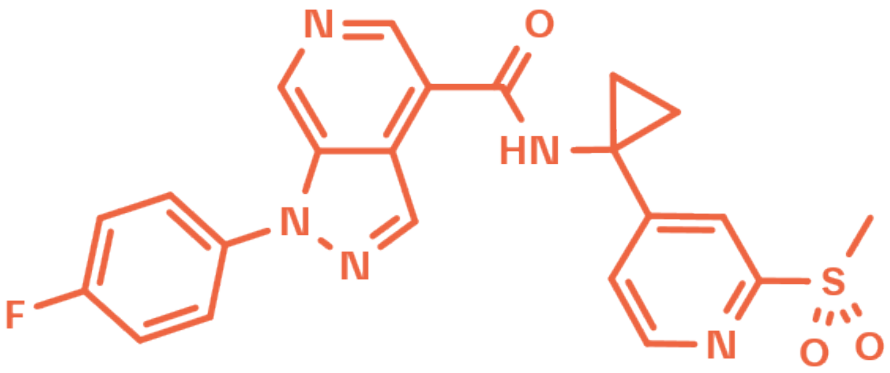

Figure 1: 2D structure of BI 639667, a CCR1 antagonist

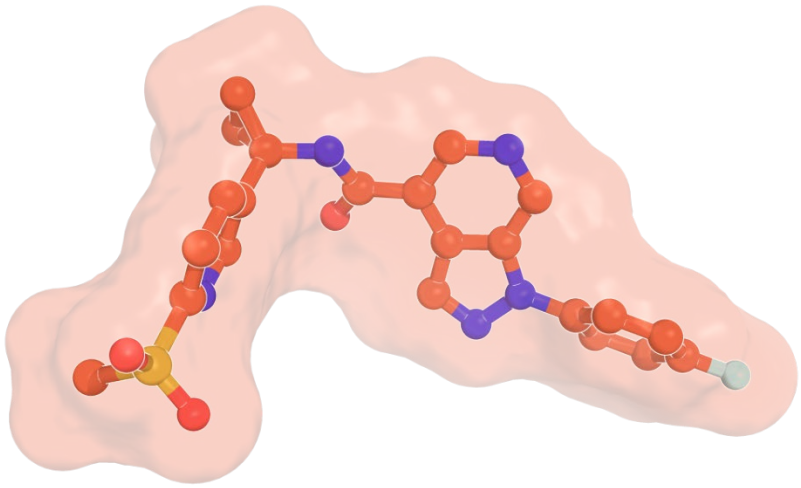

Figure 2: 3D structure of BI 639667

Highlights

BI 639667 is a potent and selective antagonist to the human chemokine receptor CCR1. It has been tested in the whole blood setting but not in *in vivo* disease models due to limited rodent cross-reactivity. The compound shows good physicochemical and PK properties, with a projected human half-life of 9-12 h. No pre-clinical safety liabilities have been identified (CV safety, drug-drug interaction potential, rodent toxicology). It was targeted once-a-day dosing to achieve IC_{50} coverage at trough levels of the human whole blood.

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). 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 regarded 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 639667 was halted also.

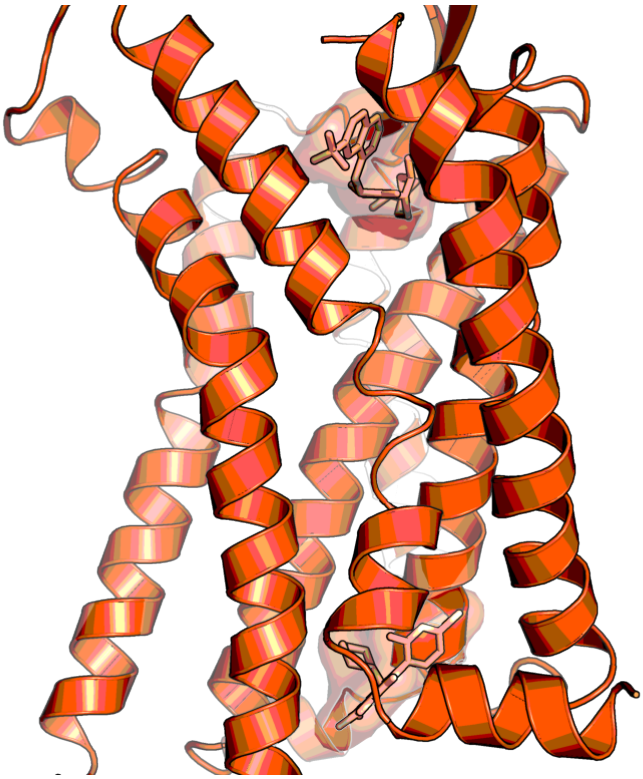

Figure 3: Complex of human CCR2 with orthosteric and allosteric antagonists (PDB code: 5t1a)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI 639667	BI-9307
MW [Da, free base][a]	451.5	546.6
CCR1 binding affinity (IC_{50}) [nM] (SPA binding)	5.4	n.a.
CCR1 molecular potency (IC_{50}) [nM] (Caflux)	24	>3,000
CCR1 cellular potency (IC_{50}) [nM] (chemotaxis)	2.4	n.a.
Whole blood potency (IC_{50}) [nM] (Receptor internalization)	9	n.a.

[a] For the salt form you will get, please refer to the label on the vial and for the molecular weight of the salt, please refer to the FAQs

In vitro DMPK and CMC parameters

PROBE NAME	BI 639667	BI-9307
logD @ pH 11	2.0	1.5
Solubility @ pH 6.8 [µg/mL]	15.9	>65
Microsomal stability (human/rat) [% Q_H]	<30 / 17	n.a.
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	2.9	n.a.
Caco-2 efflux ratio	18	n.a.
Human heptocyte clearance [% Q_H]	<21	33 (HLM)
Plasma Protein Binding human [%]	66	n.a.

In vivo DMPK parameters

PROBE NAME	BI 639667		
Species[a]	Rat	Dog	Cyno
Clearance [% Q_H]	13	5.8	17
Mean residence time after *i.v.* dose [h]	1.9	6.9	4.4
V_{ss} [L/kg]	1.1	0.7	1.9
F [%]	10	29	35

[a] *i.v.* dose: 1 mg/kg

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.

Negative control

A structurally closely related inactive analogue BI-9307 is available as negative control.

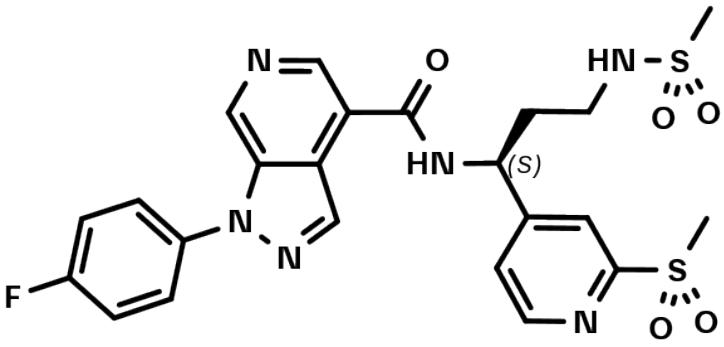

Figure 4: BI-9307, negative control

Selectivity

BI 639667 shows good off-target selectivity. Eurofins Safety Panel 44™ receptor screen on 69 targets @ 10 µM: 67 targets < 45% inhibition, A2A/HU: 69%, DATRANS 71%; neither reproduced in dose response.

SELECTIVITY DATA AVAILABLE	BI 639667	BI-9307
SafetyScreen44™ with kind support of eurofins	Yes	Yes
PDSP[4]	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

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

Not available

Reference molecule(s)

CCX-354, BMS-817399

Supplementary data

2D structure files can be downloaded free of charge from opnMe.

References

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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 *Annals of the Rheumatic Diseases* **2014**, 73, 215-215. DOI:10.1136/annrheumdis-2014-eular.3871.

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