opnMe by Boehringer Ingelheim

LFA-1

BI-1950

Boehringer Ingelheim

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Summary

BI-1950 is a highly potent inhibitor of LFA-1 and an excellent molecule for testing biological hypotheses *in vitro* and *in vivo*.

Chemical Structure

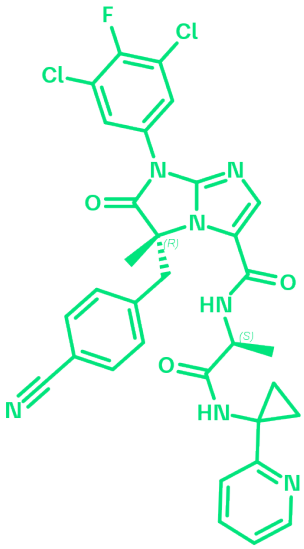

Figure 1: 2D structure of BI-1950, a LFA1 antagonist

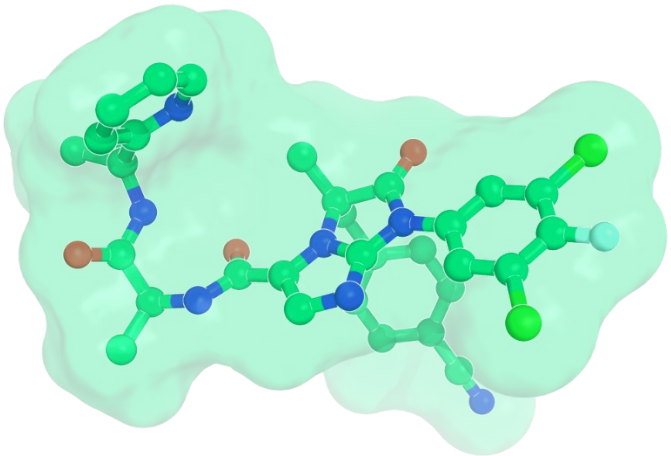

Figure 2: 3D conformation of BI-1950

Highlights

BI-1950 is a highly potent and selective lymphocyte function-associated antigen-1 (LFA-1) inhibitor. It prevents the binding of ICAM-1 to LFA-1 and, as a result, inhibits the production of IL-2 as demonstrated in human whole blood and PBMCs. BI-1950 shows an attractive DMPK profile and was tested *in vivo* in a proof-of-concept mouse model for delayed-type hypersensitivity, where it inhibited swelling in a dose-dependent manner and showed full efficacy at an oral dose of 3 mg/kg.

Target information

The integrin LFA-1 (lymphocyte function-associated antigen-1) is a receptor present on lymphocytes that plays, together with its major ligand ICAM-1 (intercellular adhesion molecule 1), an important role in immune cell function[1,3,4].

Figure 3: X-Ray structure of LFA-1 with an analogue of BI-1950 (solved at Boehringer Ingelheim)

In vitro activity

It inhibits the binding of LFA-1 to ICAM-1 with a K_D value of 9 nM and the production of IL-2 in human PBMC and whole blood with an IC_{50} value of 3 nM and 120 nM, respectively.

PROBE NAME / NEGATIVE CONTROL	BI-1950	BI-9446
MW [Da, free base][a]	646.5	602.5
Inhibition of LFA-1 binding to ICAM-1 K_D [nM][b]	9	>1,000
Inhibition of SEB-induced production of IL-2 in human PBMC IC_{50} [nM][c]	3	>1,000
Inhibition of SEB-induced production of IL-2 in human whole blood IC_{50} [nM][c]	120	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
[b] Binding assay
[c] SEB: staphylococcal enterotoxin B

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-1950	BI-9446
logD @ pH 11	4.7	5.9
Solubility @ pH 6.8 [µg/mL]	1.2	0.1
Caco-2 permeability AB @ pH 7.4 [$*10^{-6}$ cm/s]	13	n.a.
Caco-2 efflux ratio	2	n.a.
Microsomal stability (human/mouse/rat) [% Q_H]	13 / 12 / 6	n.a.
Plasma Protein Binding (human/mouse/dog) [%]	99.6 / 99.7 / 99.9	n.a.
hERG [inh. % @ 1 µM]	6.7	n.a.

In vivo DMPK parameters

PROBE NAME / NEGATIVE CONTROL	BI-1950	
Species	mouse	rat
Clearance [% Q_H][a]	5	1.1
V_{ss} [L/kg][a]	1.3	2.7
Mean residence time after *i.v.* dose [h][a]	5	6.5
F [%][b]	84	21

[a] *i.v.* dose: 1 mg/kg
[b] *p.o.* dose: 10 mg/kg

In vivo pharmacology

BI-1950 shows an attractive DMPK profile and was tested in a proof-of-concept LFA-1 model *in vivo*. As BI-1950 demonstrates greater than 250-fold selectivity for human over mouse LFA-1 as assessed in paired assays that measure the inhibition of IL-2 production in SEB-stimulated human PBMC and mouse splenocytes (SEB: staphylococcal enterotoxin B), a *trans vivo* model for delayed type hypersensitivity (DTH) in SCID mice was used[5]. After injection of human PBMCs into the footpad of SCID mice and stimulation with a specific antigen (tetanus toxoid, TT), the DTH response is quantified by measuring the footpad swelling. BI-1950 inhibited swelling in a dose dependent manner and showed full efficacy at a dose of 3 mg/kg *p.o.*.

Selectivity

In an external selectivity screen at Eurofins SafetyScreen44™ BI-1950 hit 4/47 targets >50 % Inhibition @ 10 µM. See supplementary information for details.

BI-1950 shows > 1,000-fold selectivity against the most closely related b2-integrin Mac-1 and b1-integrin function.

SELECTIVITY DATA AVAILABLE	BI-1950	BI-9446
SafetyScreen44™ with kind support of eurofins	Yes	Yes
PDSP[9]	Yes	Yes
Invitrogen®	No	No

DiscoverX®	No	No
Dundee	No	No

Negative control

The close analog BI-9446 can be used as negative control for *in vitro* studies with much weaker affinity to LFA-1 (> 1µM).

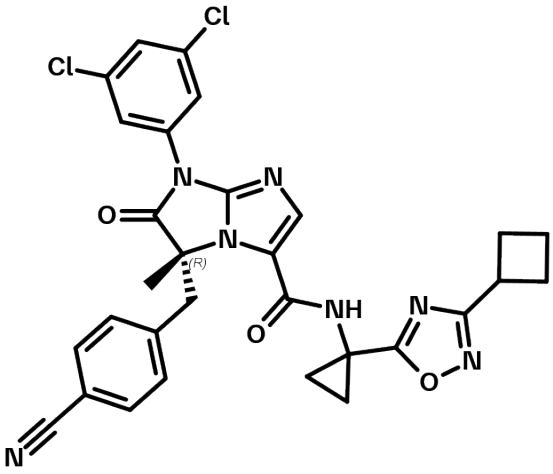

Figure 4: Chemical structure of the negative control BI-9446

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

No Xray structure is available for BI-1950 but for the structurally related compound (**17d** in *J. Med. Chem.* **2004**, *47*, 5356)[2].

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

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