LFA1 antagonist | BI-1950

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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

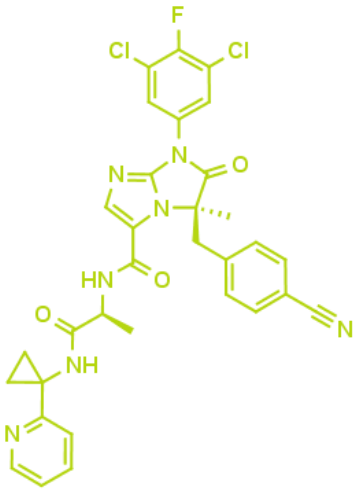

Figure 1: 2-D structure of BI-1950, a LFA1 antagonist

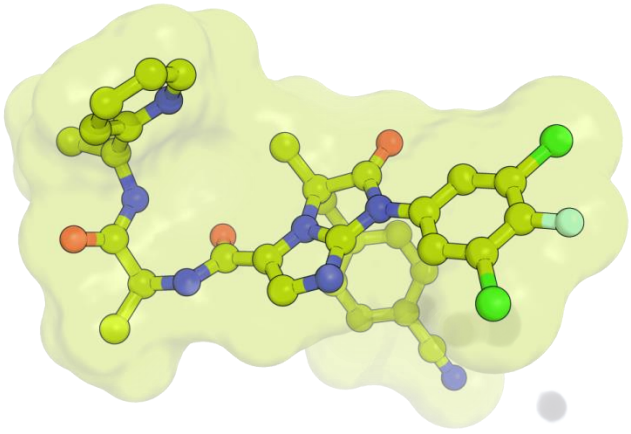

Figure 2: 3-D conformation of BI-1950

Highlights

BI-1950 potently inhibits the binding of LFA-1 to ICAM-1 (intercellular adhesion molecule 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. BI-1950 shows >1000 fold selectivity against the most closely related β2-integrin Mac-1 and β1-integrin function and has an attractive DMPK profile, making it a excellent molecule for testing pharmacological hypotheses *in vitro* and *in vivo*.

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]

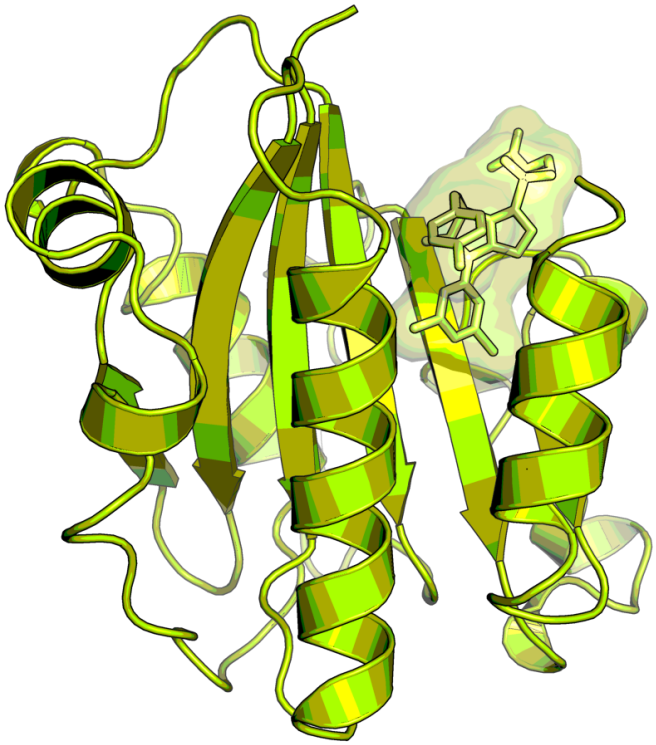

Figure 3: X-Ray structure of LFA-1 with an analogue of BI-1950 (solved at Boehringer Ingelheim)

In vitro activity

BI-1950 potently inhibits the binding of LFA-1 to ICAM-1 with a K_D value of 9 nM.

PROBE NAME / NEGATIVE CONTROL	BI-1950	BI-9446
MW [Da]	646.5	602.5
Inhibition of LFA-1 binding to ICAM-1 K_D [nM][a]	9	>1,000
Inhibition of SEB-induced production of IL-2 in human PBMC IC_{50} [nM][b]	3	>1,000
Inhibition of SEB-induced production of IL-2 in human whole blood IC_{50} [nM][b]	120	n.d.

[a]Binding assay; [b]SEB: staphylococcal enterotoxin B.

In vitro DMPK and CMC parameters

PROBE NAME	BI-1950	BI-9446
Solubility @ pH 6.8 [µg/ml]	0.9	0.1
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	13	n.d.
CACO efflux ratio	2	n.d.
Stability in liver microsomes (human/ mouse/rat) [% Q_H]	13 / 12 / 6	n.d.
Plasma protein binding (human/mouse/dog)	99.6 / 99.7 / 99.9	n.d.

In vivo DMPK parameters

PROBE NAME	BI-1950	
Species	mouse	rat
CL (*iv*) [% Q_H]	8	11
V_{ss} [l/kg]	3.3	2.7
MRT [h]	7.2	6.5
F [%]	154	21

In vivo pharmacology

BI-1950 shows an attractive DMPK profile and was tested in a proof-of-concept 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 PO.

Selectivity

In an external selectivity screen at Eurfins (Panlabs) BI-1950 hit 4/47 targets >50 % Inhibition @ 10 µM. See supplementary information for details.

BI-1950	SELECTIVITY DATA AVAILABLE
Cerep®	No
Eurofins-Panlabs®	Yes
Invitrogen®	No
DiscoverX®	No
Dundee	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).

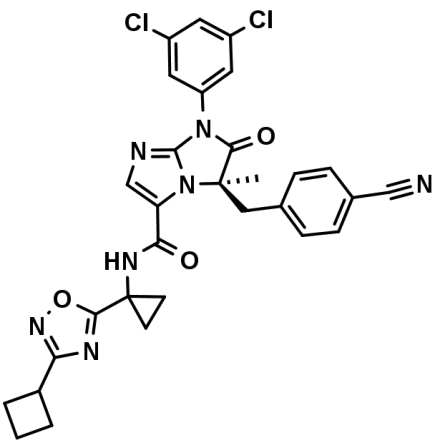

Figure 4: Chemical structure of the negative control BI-9446

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]

Summary

BI-1950 potently 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 IC50 value of 3 nM and 120 nM, respectively. BI-1950 is highly selective against related integrins and has an attractive DMPK profile. Providing this compound together with a negative probe should stimulate and support further research in this field.

Supplementary data

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

References

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