opnMe by Boehringer Ingelheim

ALK5 inhibitor I BI-4659

BI-4659

Boehringer Ingelheim

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Summary

BI-4659 inhibits ALK5 with an IC_{50} value of 19 nM and blocks the cellular phosphorylation of SMAD2/SMAD3 with an EC_{50} of 185 nM. BI-4659 is a suitable tool for testing biological hypotheses *in vitro*.

Chemical Structure

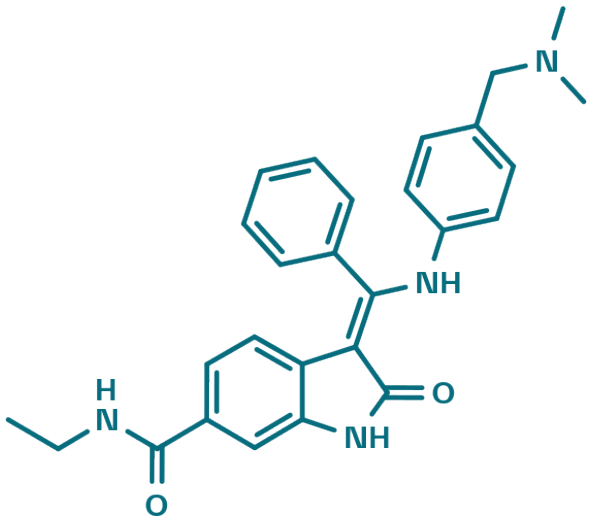

Figure 1: 2D structure of BI-4659, an ALK5 inhibitor

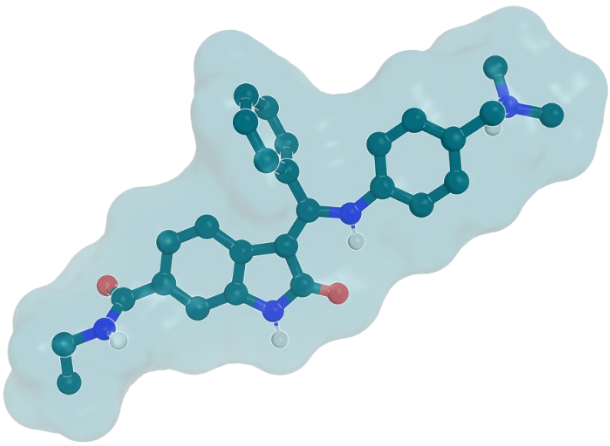

Figure 2: BI-4659, 3D conformation

Highlights

BI-4659 is a potent ALK5 (TGFßR1) inhibitor (IC_{50} = 19 nM). This compound showed good selectivity against a broad panel of other kinases. BI-4659 is able to block the phosphorylation of SMAD2 and SMAD3 in cells and is a suitable tool for in vitro studies[1]. However, it is not suited for in vivo experiments due to the very high clearance observed in rats.

Target information

Transforming growth factor β (TGFβ) is a pluripotent cytokine involved in the regulation of various biological processes such as cell proliferation, differentiation, migration, adhesion, apoptosis, and epithelial-to-mesenchymal transition (EMT). Therapeutic approaches to inhibit its signaling by targeting TGFβ receptor I (TGFβRI/ALK5) are discussed for the treatment of diseases such as Idiopathic Pulmonary Fibrosis (IPF) and cancer[2,3,4].

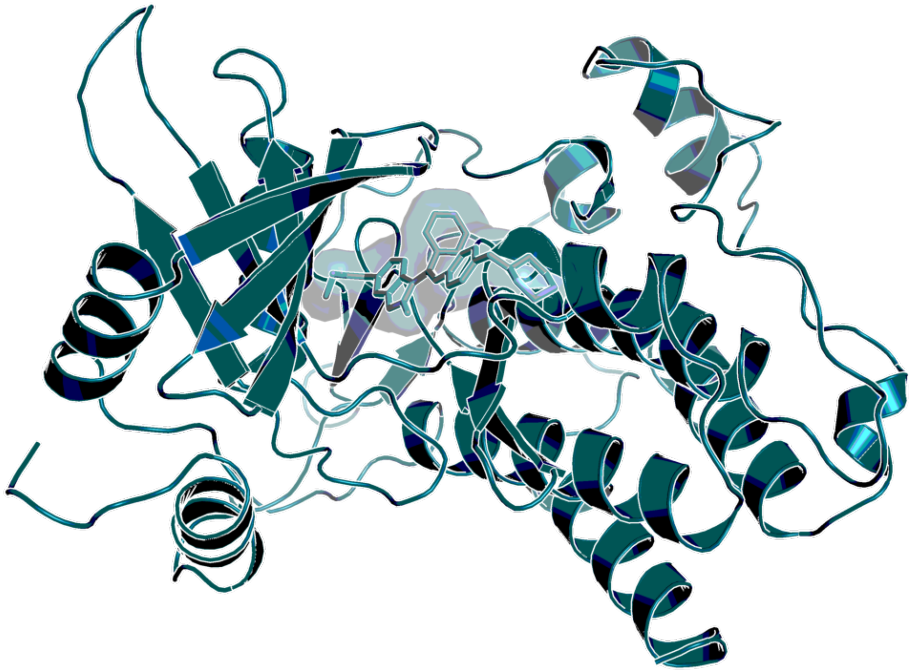

Figure 3: Crystal structure of ALK5 complexed with a close analog of BI-4659 (PDB code 2X7O)[1]

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-4659	BI-4101
MW [Da, free base][a]	440.5	418.5
Inhibition of ALK5 (Kinase Glow assay, IC_{50}) [nM][b]	19	>50000
Inhibition of phosphorylation of SMAD2 and SMA3 in HaCaT cells (EC_{50}) [nM]	185	n.d.

[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] For detailed assay conditions see reference 1

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-4659			BI-4101
logD @ pH 2/ 11	0.7 / 3.1			n.d.
Solubility @ pH 6.8 [µg/mL]	2			n.d.
Solubility @ pH 4 [µg/mL]	84			n.d.
Solubility @ pH 2 [µg/mL]	71			n.d.
Caco-2 permeability AB @ pH 7.4 [$*10^{-6}$ cm/s]	8			n.d.
Caco-2 efflux ratio	6			n.d.
Microsomal stability (human/mouse/rat) [% QH]	26	23	<22	n.d.
hERG [inh. % @ 10 µM]	38.5			n.d.
hERG IC_{50} [µM]	>10			n.d.

CYP 3A4 (IC_{50}) [µM]	>50	n.d.
CYP 2C8 (IC_{50}) [µM]	>50	n.d.
CYP 2C9 (IC_{50}) [µM]	>50	n.d.
CYP 2C19 (IC_{50}) [µM]	>50	n.d.
CYP 2D6 (IC_{50}) [µM]	>50	n.d.

In vivo DMPK parameters

BI-4659 showed very high clearance in rat and therefore is not suited if *in vivo* studies

BI-4659	RAT
Clearance [$\%Q_H$][a]	123
Mean residence time after *i.v.* dose [h][a]	1.7
t_{max} [h][b]	3.3
C_{max} [nM][b]	27.7
F [%][b]	50
Vss [L/kg][a]	9

[a] *i.v. dose:* 4.5 mg/kg
[b] *p.o.* dose: 45 mg/kg

Negative control

BI-4101 shows no inhibition of ALK5 in the Kinase Glow assay (IC_{50} > 50 µM) and therefore is a suitable negative control for *in vitro* experiments (BI-4101 = Compound **48** [1])

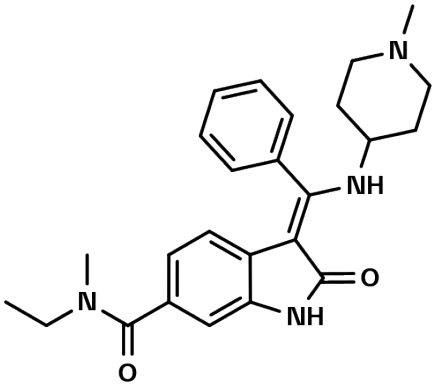

Figure 4: BI-4101 which serves as a negative control

Selectivity

BI-4659 shows good selectivity in kinase panels. The compound shows no inhibition of 218/232 kinases tested at 2 µM. Cross-reactive kinases (%inhibition data at 0.2 µM): ABL1 (67), BLK (85), CSF1R (FMS) (82), FGR (91), FLT3 (66), FYN (74), LCK (100), LYN A (79), LYN (78), MAP4K5 (KHS1) (77), MELK (80), NTRK3 (TRKC) (78), RET (79), SNF1LK2 (96), YES1 (90).

Selectivity data is available on opnMe.com for download free of charge.

SELECTIVITY DATA AVAILABLE	BI-4659	BI-4101
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	Yes	No
DiscoverX®	Yes	No
Dundee	Yes	No

Co-crystal structure of the Boehringer Ingelheim probe compound and the target protein

No in-house structure is available for BI-4659, but for related compound (PDB code 2x7o).

Reference molecule(s)

SB-505124, SB-525334, GK6604, SD-208, LY-2157299, EW-7197, GW788388 and others. For a review on ALK5 kinase inhibitors in oncology[5].

Supplementary data

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

References

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