opnMe by Boehringer Ingelheim

Aurora B inhibitor

BI 831266

Boehringer Ingelheim

Table of contents

Summary

BI 831266 is a potent and selective Aurora B inhibitor that inhibits cell proliferation and could be used as a tool compound for testing biological hypotheses.

Chemical Structure

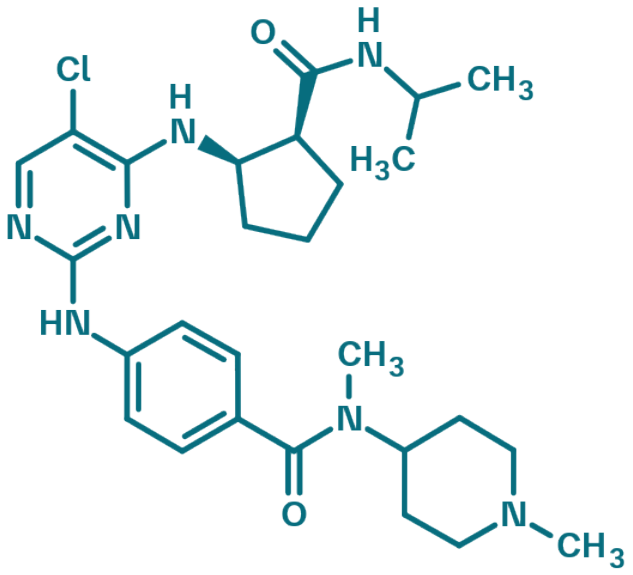

Figure 1: 2D structure of BI 831266, an inhibitor of Aurora B

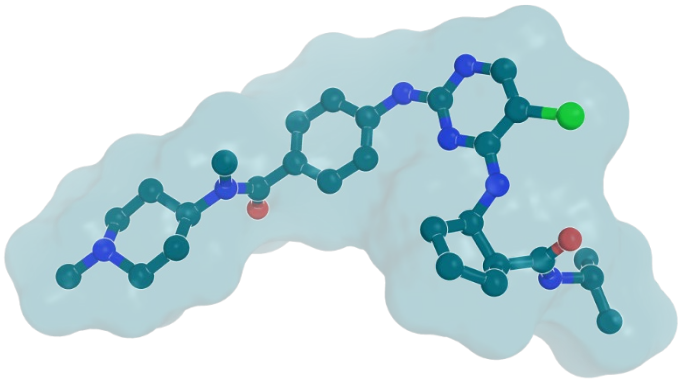

Figure 2: 3D structure of BI 831266, an inhibitor of Aurora B

Highlights

BI-831266 is a potent and selective Aurora B inhibitor (IC_{50} = 42 nM). This compound is suitable for both *in vitro* and *in vivo* experiments. It has been shown to inhibit cellular proliferation *in vitro* with an IC_{50} of around 10 nM. *In vivo*, it was tested in xenograft models and tumor growth inhibition was observed.

Target information

Aurora B belongs to the highly conserved Aurora family, a family of 3 nuclear serine-threonine kinases. Aurora A, B and C play important roles in maintaining genetic stability and fidelity of mitosis of cells[1].

The Aurora kinases share a highly conserved catalytic domain but different subcellular localizations. Aurora kinases contain mainly two domains: 1) NH2-terminal regulatory domain, 2) COOH-terminal catalytic domain. The three auroras A, B, and C share great homology in the catalytic domain.

Phosphorylation at threonine within the activation loop is necessary for kinase activity[2].

Aurora B regulates chromosomal orientation, chromosome condensation, spindle assembly, and cytokinesis[1]. It plays a direct role in histone H3 phosphorylation.

The overexpression of Aurora B has been observed in several tumor types and has been linked with a poor prognosis of cancer patients[3].

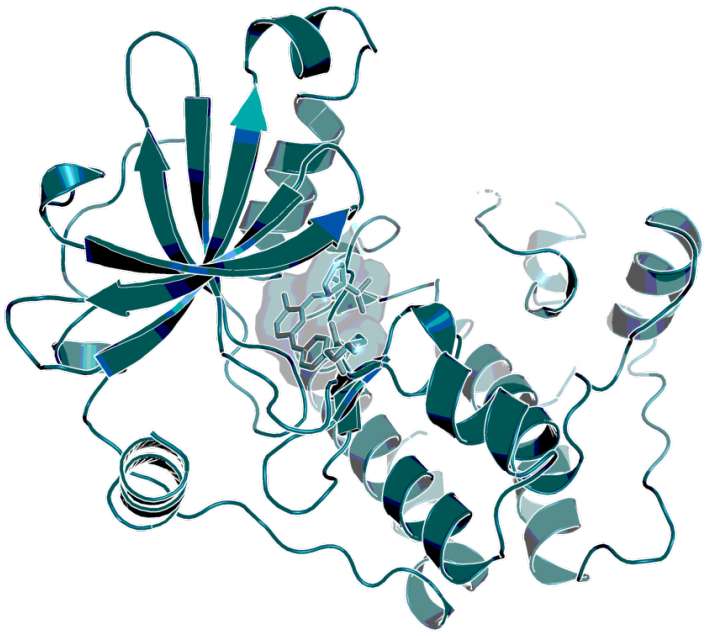

Figure 3: BI 831266 bound to Aurora B, as observed by X-ray (structure solved at Boehringer Ingelheim)

In vitro activity

BI 831266 is a potent Aurora B inhibitor with an IC_{50} of 42 nM.

PROBE NAME / NEGATIVE CONTROL	BI 831266	BI-1282
MW [Da, free base][a]	528.1	505.6
Aurora B binding (IC_{50}) [nM]	42	> 4,000
Aurora B binding Invitrogen Panel (IC_{50}) [nM]	25	-
Histone H3 phosphorylation modulation as biomarker (IC_{50}) [nM]	51	n.d.
H460 polyploide phenotype > 50% [nM]	14	n.d.
H460 tumor cell proliferation inhibition (IC_{50}) [nM]	11	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

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI 831266	BI-1282
log D @ pH 11	2.8	2.4
Solubility @ pH 7.4 [µg/mL]	875	n.d.
Caco-2 permeability AB @ pH 7.4 [$*10^{-6}$ cm/s]	6.1	n.d.
Caco-2 efflux ratio	6.0	n.d.
Human hepatocyte clearance [% Q_H]	12	n.d.
Plasma Protein Binding human [%]	48	n.d.

In vivo DMPK parameters

PROBE NAME	BI 831266		
Species	mouse[a]	rat[b]	dog[c]
Dose *i.v./p.o.* [mg/kg]	10 / 10	4 / 10	0.5 / 2
Clearance [% Q_H]	71	45	19
Mean residence time after *i.v.* dose [h]	0.6	1.4	1.0
F [%]	34	20	9
V_{ss} [L/kg]	2.6	3.6	1.1

[a] i.v. / p.o. dose: 10 mg/kg / 10 mg/kg
[b] i.v. / p.o. dose: 4 mg/kg / 10 mg/kg
[c] i.v. / p.o. dose: 0.5 mg/kg / 2 mg/kg

Negative control

The diaminopyrimidine BI-1282 with the N-methyl group to block kinase hinge-binding can be used as an *in vitro* negative control.

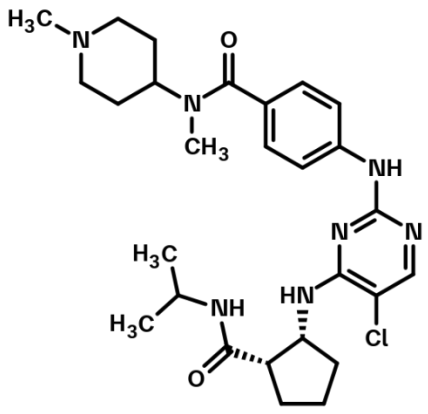

Figure 4: BI-1282 which serves as a negative control

Selectivity

Extensive external screens available (also see supplementary data):

Invitrogen® panel: 47 kinases screened @ 1 µM
Selected IC_{50} measured @ Invitrogen®:
AURKB IC_{50} = 25 nM; AURKC IC_{50} = 37 nM; RET IC_{50} = 169 nM; EPHA2 IC_{50} = 181 nM;
STK6 IC_{50} = 183 nM; AMPK A1B1G1 IC_{50} = 2.95 µM; AMPK A2B1G1 IC_{50} = 3.88 µM
Dundee panel: 87 kinases screened @ 1 and 3 µM
DiscoverX® panel: 468 kinases screened @ 1 µM
Eurofins Safety Panel 44™ External screen covering 68 targets: @ 10 µM

SELECTIVITY DATA AVAILABLE	BI 831266	BI-1282
SafetyScreen44™ with kind support of eurofins	No	Yes
Invitrogen®	Yes	No
DiscoverX®	Yes	No
Dundee	Yes	No

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

The Xray crystal structure of Aurora B/INCENP in complex with the -CF_3 analog of the probe (BI 811283) is available (PDB code: 5K3Y)[4].

Reference molecule(s)

AMG-900, AZD1152, AT9283, VX-680(MK-0457), PHA-680632, PHA-739358, CYC-116

Supplementary data

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

References

1. Tang A., Gao K., Chu L., Zhang R., Yang J., Zheng J. Aurora kinases: novel therapy targets in cancers *Oncotarget* **2017**, *Vol. 8*, (No. 14), 23937-23954. DOI:10.18632/oncotarget.14893, PubMed.

2. Bavetsias V., Linardopoulos S. Aurora Kinase inhibitors: Current Status and Outlook *Front. Oncol.* **2015**, *5:278*, 1-10. DOI:10.3389/fonc.2015.00278, PubMed.

3. Gavriilidisa P., Giakoustidis A., Giakoustidis D. Aurora Kinases and Potential Medical Applications of Aurora Kinase Inhibitors: A Review. *J Clin Med Res.* **2015**, *7(10)*, 742-751. DOI: http://dx.doi.org/10.14740/jocmr2295w, PubMed.

4. Sini P., Gürtler U., Zahn S. K., Baumann C., Rudolph D., Baumgartinger R., Strauss E., Haslinger C., Tontsch-Grunt U., Waizenegger I. C., Solca F., Bader G., Zoephel A., Treu M., Reiser U., Garin-Chesa P., Boehmelt G., Kraut N., Quant J., Adolf G. R. Pharmacological Profile of BI 847325, an Orally Bioavailable, ATP-Competitive Inhibitor of MEK and Aurora Kinases. *Mol. Cancer Ther.* **2016**, *15,* 2388-2398. DOI:10.1158/1535-7163.MCT-16-0066, PubMed.

5. Gollner A., Heine C., Hofbauer K. S. Kinase Degraders, Activators, and Inhibitors: Highlights and Synthesis Routes to the Chemical Probes on opnMe.com, Part 1 *ChemMedChem* **2023**, 18(10):e202300031. DOI: 10.1002/cmdc.202300031, PubMed.