Aurora B inhibitor | BI 831266

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Summary

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

Chemical Structure

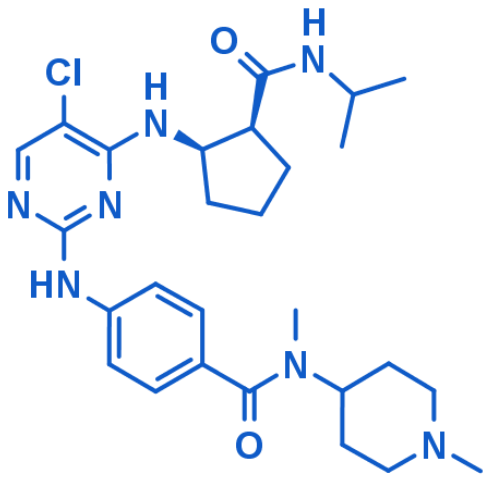

Figure 1: 2-D structure of BI 831266, an inhibitor of Aurora B

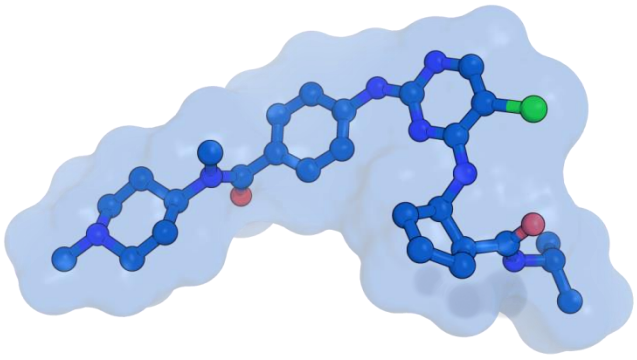

Figure 2: 3-D structure of BI 831266, an inhibitor of Aurora B

Highlights

The serine-threonine kinase Aurora B belongs to the highly conserved Aurora family. As a chromosomal passenger protein Aurora B is involved in chromosome segregation, spindle-checkpoint, and cytokinesis.[1] BI 831266 demonstrates good Aurora B binding potency within the nanomolar range and inhibits cellular proliferation in vitro with an IC_{50} of around 10 nM. The BI 831266 Aurora B inhibitor with its DMPK profile showed tumor growth inhibition in *in vivo* xenograft models. Together with the also available structurally similar compound BI-1282, which can be used as negative control due to much weaker potency, BI 831266 can serve as an excellent small molecule inhibitor for testing biological hypotheses *in vitro* and *in vivo*.

Target information

The 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.

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. 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]

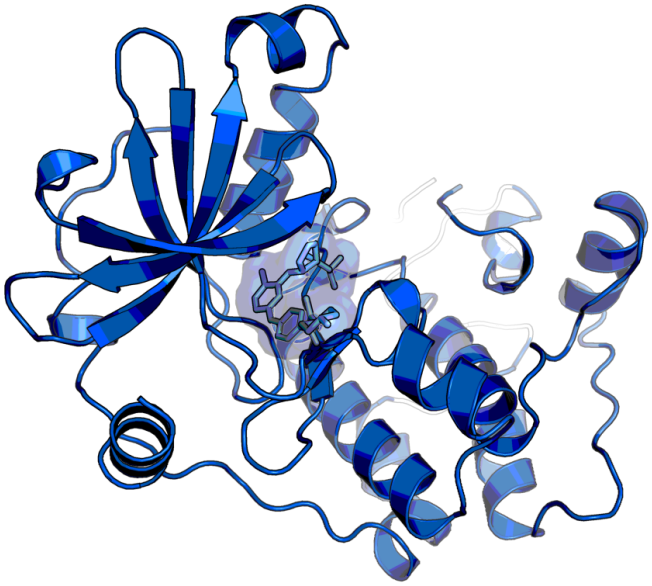

Figure 3: BI 831266 bound to Aurora B, as observed by X-ray (structure solved at Boehringer-Ingelheim)

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[e]
MW [Da]	565	542
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.

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI 831266	BI-1282
Aqueous solubility @ pH 7.4 [µg/ml]	875	n.d.
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	6.1	n.d.
CACO efflux ratio	6.0	n.d.
Human hepatocyte clearance [% Q_H]	12	n.d.
Plasma protein binding human [% Q_H]	48	n.d.

In vivo DMPK parameters

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

Negative control

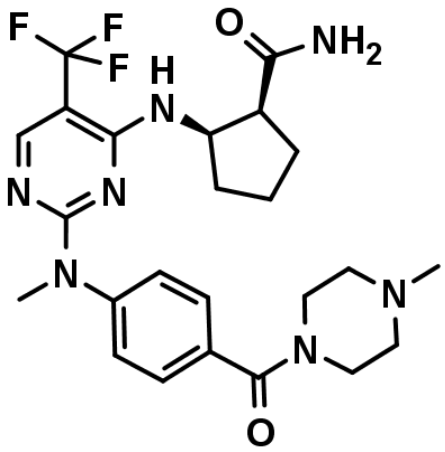

Figure 4: BI-1282 which serves as a negative control

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

Selectivity

Extensive external screens available (also see supplementary data):

Invitrogen panel: 47 kinases screened @ 1 µM

Selected IC_{50}s 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

Panlabs External screen covering 68 targets: @ 10 µM

BI 831266	SELECTIVITY DATA AVAILABLE
Cerep®	No
Eurofins-Panlabs®	Yes
Invitrogen®	Yes
DiscoverX®	Yes
Dundee	Yes

Co-crystal structure of the BI 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

Summary

The Aurora family of serine/threonine kinases plays an important role in chromosome alignment, segregation and cytokinesis during mitosis. Recent studies have found aberrant expression of Aurora kinases in a variety of human solid tumors and hematological malignancies, suggesting they have a role in carcinogenesis.

BI 831266 demonstrates excellent Aurora B binding potency with an IC_{50} of 42 nM and cellular proliferation inhibition in a number of cancer cell lines with IC_{50}'s below 10 nM (eg. HCT116, H460, COLO357 and BxPC-3 of 4, 11, 6 and 5 nM respectively).

An acceptable cross-species drug metabolism and DMPK profile and good selectivity make it an excellent molecule for testing biological hypotheses *in vitro* and *in vivo*. With BI-1282 we also can offer a structurally similar molecule as a negative control for *in vitro* experiments due to its significant weaker potency of > 4000 nM. By providing this set of molecules we hope to further simulate research in the field.

Supplementary data

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

References

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

3. Paschalis Gavriilidisa, Alexandros Giakoustidis, Dimitrios Giakoustidis *J Clin Med Res.* **2015**, *7(10)*, 742-751. DOI: http://dx.doi.org/10.14740/jocmr2295w, PubMed

4. Sini P, Gurtler U, Zahn SK, Baumann C, Rudolph D, Baumgartinger R, Strauss E, Haslinger C, Tontsch-Grunt U, Waizenegger IC, Solca F, Bader G, Zoephel A, Treu M, Reiser U, Garin-Chesa P, Boehmelt G, Kraut N, Quant J, Adolf GR 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