CDK8 inhibitor | BI-1347

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Summary

BI-1347 is a selective nanomolar CDK8 inhibitor, suitable for testing biological hypotheses *in vitro* and also *in vivo*.

Chemical Structure

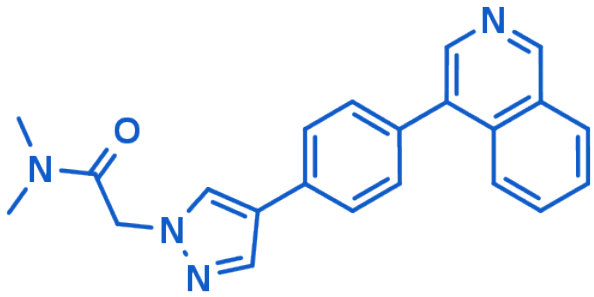

Figure 1: 2-D structure of BI-1347, an inhibitor of CDK8

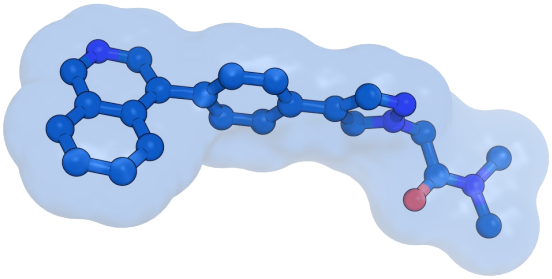

Figure 2: 3-D structure of BI-1347, 3D conformation as observed in the X-ray structure of the complex with CDK8 (see Figure 3)

Highlights

BI-1347 is a potent and selective Cyclin-dependent kinase 8 (CDK8) /cyclinC inhibitor with an IC_{50} of 1 nM. With its good DMPK profile, this compound is suitable for both *in vitro* and *in vivo* experiments and may be a useful tool to explore the role of CDK8 in human diseases such as cancer. In an *in vivo* xenograft model, BI-1347 treatment resulted in tumor growth inhibition.

Target information

CDK8 and its closely related paralog CDK19 are transcription-regulating cyclin C–dependent kinases. CDK8 and CDK19 are components of the Mediator complex, a multiprotein assembly containing up to 30 subunits organized in four modules: head, middle, tail and CDK/Cyclin. The Mediator complex serves as a hub for diverse signaling pathways and provides a link between transcriptional regulators and the RNA polymerase II (Pol II) transcription machinery to regulate gene expression[2].

CDK8 and CDK19 form the kinase module of the Mediator complex along with MED12 and MED13. Recently, several subunits have been implicated in a growing number of human diseases including developmental disorders and cancer. Most evidence has been gathered for the kinase module subunit CDK8, which has been linked to colon and pancreatic cancer and was also investigated as a potential target in cancer therapy.[2] CDK8 inhibition was shown to escalate the native activities of Natural Killer cells (NK cells), promoting their tumor surveillance and cytotoxicity.[3]

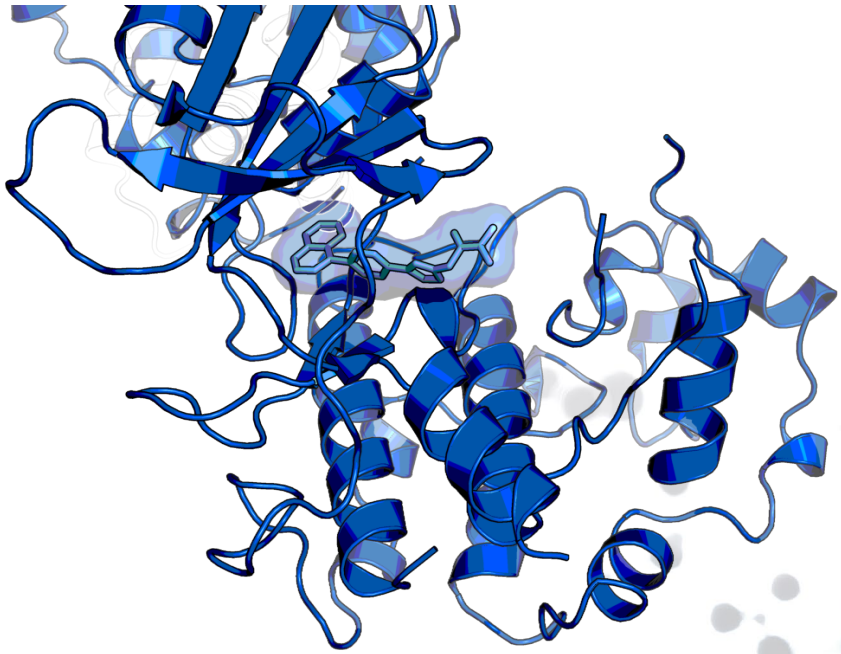

Figure 3: CDK8 in complex with inhibitor BI-1374 (X-ray structure solved at Boehringer-Ingelheim)

In vitro activity

BI-1347 is a potent and selective CDK8 inhibitor with an IC_{50} of 1 nM.

PROBE NAME / NEGATIVE CONTROL	BI-1347	BI-1374
MW [Da]	356	346
CDK8/cyclinC inhibition (IC_{50}) [nM]	1	671
Inhibition of pSTAT S727 in NK-92 cells (IC_{50}) [nM]	3	>10,000
Secretion of Perforin in NK-92 cells (EC_{50}) [nM]	10	n.d.
Inhibition of proliferation in MV-4-11b cells (IC_{50}) [nM]	7	n.d.
Inhibition of proliferation in NK-92 cells (IC_{50}) [nM]	>10,000	n.d.

In vitro DMPK and CMC parameters

PROBE NAME	BI-1347	BI-1374
Solubility FaSSIF / FeSSIF [µg/ml]	11 / 280	n.d.
Caco permeability @ pH 7.4 [$*10^{-6}$ cm/s]	95	n.d.
Caco efflux ratio	1.1	n.d.
Human hepatocyte clearance [% Q_H]	17	n.d.
Plasma protein binding 10% FCS [%]	64	n.d.
Plasma protein binding human [% Q_H]	98	n.d.

In vivo DMPK parameters

PROBE NAME	BI-1347	
Species	mouse	rat
Dose *i.v.* / *p.o.* [mg/kg]	1 / 10	1 / 3
CL [% Q_H]	15	14
Mean residence time after *iv* dose (l/kg)	0.6	0.7
F [%]	93	69
V_{ss} [l/kg]	0.5	0.4

Negative control

The compound BI-1374 can be used as an *in vitro* negative control (CDK8 IC_{50} = 671 nM)

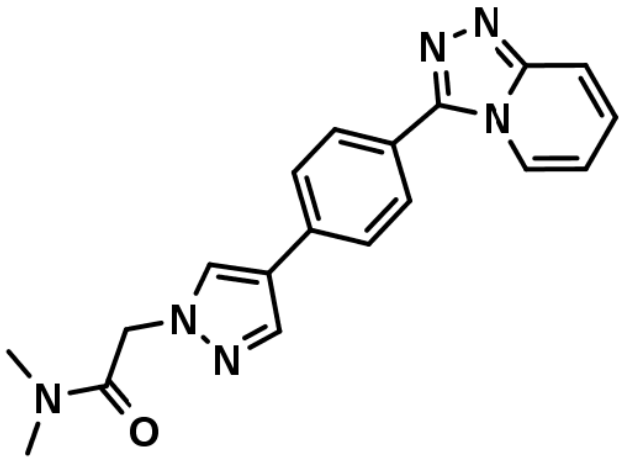

Figure 4: Chemical structure of the negative control BI-1374

Selectivity

Extensive external screens available (also see supplementary data):
Invitrogen® panel: 369 kinases screened @ 10 µM
Selected IC_{50} measured @ Invitrogen®:
CDK8 IC_{50} = 1.5 nM; CDK11 IC_{50} = 1.7 nM; MLCK IC_{50} = 531 nM; AURKB IC_{50} = 809 nM; FLT3 IC_{50} = 1360 nM; ICK IC_{50} = 2390 nM; STK16 IC_{50} = 3550 nM
Eurofins Safety Panel 44™ External screen covering 44 targets: @ 10 µM

SELECTIVITY DATA AVAILABLE	BI-1347	BI-1374
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	Yes	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

CCT251545, SEL120-34A

Supplementary data

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

References

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