opnMe by Boehringer Ingelheim

PLK 1 inhibitor

BI-2536

Boehringer Ingelheim

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Summary

BI-2536 was the first potent and selective PLK1 inhibitor which entered clinical trials. It is a suitable *in vitro* and *in vivo* tool to study PLK function.

Chemical Structure

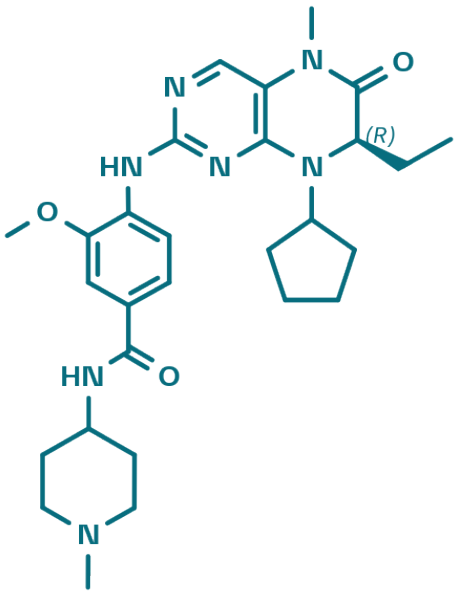

Figure 1: 2D structure of BI-2536, an inhibitor of PLK1

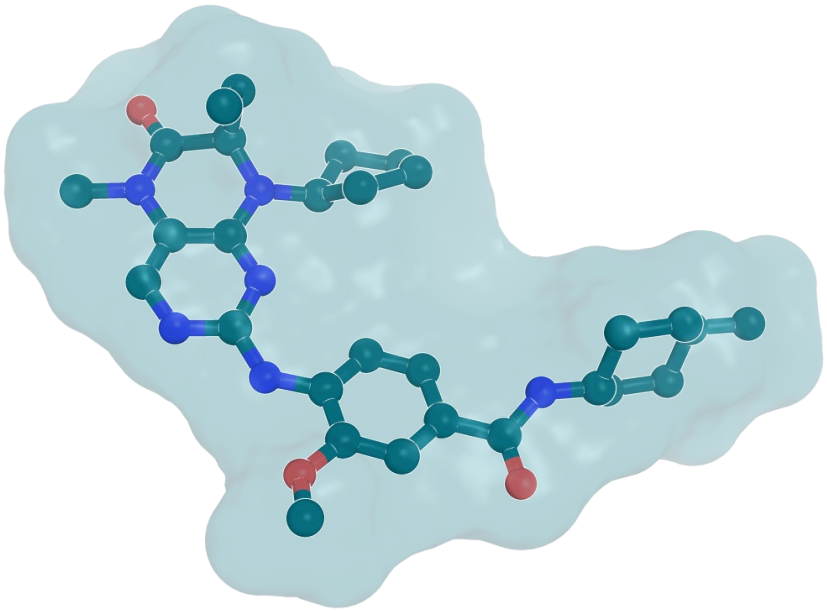

Figure 2: 3D structure of BI-2536, as observed in complex with PLK1 by X-ray crystallography

Highlights

BI-2536 is a potent and selective Polo-like kinase 1 (PLK1) inhibitor (IC_{50} = 0.8 nM). Its activity has been demonstrated in a large variety of human tumor cell lines, as well as in mouse xenograft models (*i.v.* administration). This compound is suitable for both *in vitro* and *in vivo* studies. BI-2536 was the first PLK1 inhibitor to enter clinical trials.

Target information

Polo-like kinase 1 (PLK1) is a key regulator of cell division in eukaryotic cells. PLK1 contributes to the activation of the cyclin B1/CDK1 complex and is involved in centrosome maturation and bipolar spindle formation at the onset of mitosis. Moreover, PLK1 controls mitotic exit by regulating the anaphase-promoting complex, and it is also involved in the temporal and spatial coordination of cytokinesis.

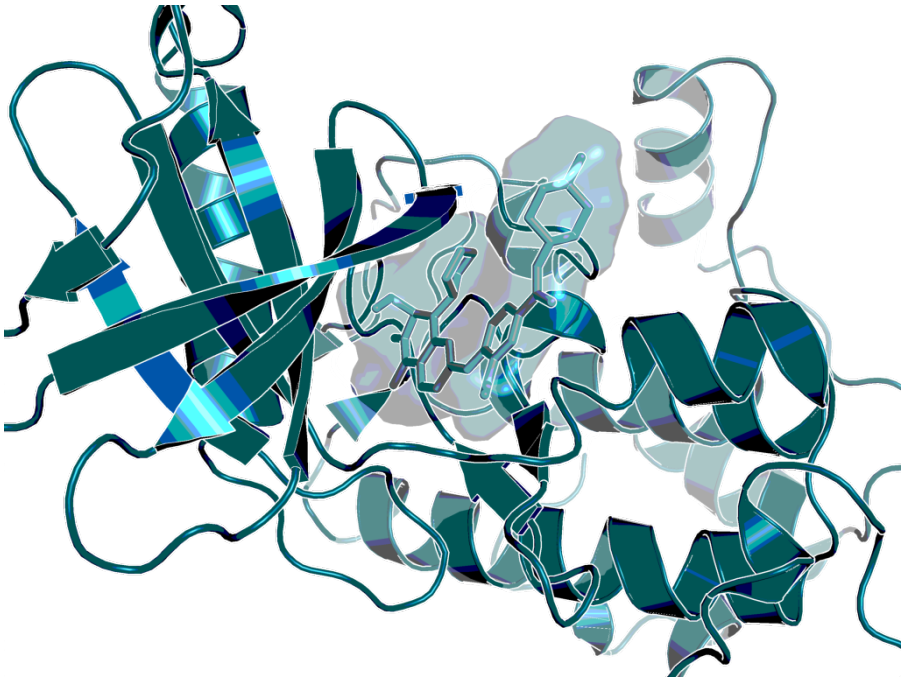

Figure 3: BI-2536 bound to PLK1 (X-ray structure solved at Boehringer-Ingelheim)

In vitro activity

BI-2536 shows EC_{50} values in a large panel of human tumor cell lines (carcinomas, sarcomas, melanomas and tumors derived from hematological malignancies) in the range of 2 to 25 nM[1].

PROBE NAME	BI-2536
MW [Da, free base][a]	521.7
PLK1 (IC_{50}) [nM]	0.83
NCI-H460 (EC_{50}) [nM]	12

[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-2536
logD @ pH 11	3.5
Solubility @ pH 5 (McIlvaine buffer) [µg/mL]	320
Microsomal stability (human) [% Q_H]	49
Hepatocyte stability (human) [% Q_H]	61
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	16.2
Caco-2 efflux ratio	3.0
Plasma Protein Binding (human/mouse/rat) [%]	91 / 95 / 95
CYP 3A4 (IC_{50}) [µM]	12.1
CYP 1A2 (IC_{50}) [µM]	>10

CYP 2C9 (IC_{50}) [µM]	2.0
CYP 2C19 (IC_{50}) [µM]	>10
CYP 2D6 (IC_{50}) [µM]	>50

In vivo DMPK parameters

BI-2536	MOUSE	RAT
Clearance [% Q_H][a]	116	56-200
Mean residence time after *i.v.* dose [h][a]	0.8	0-9-2.5
V_{ss} [L/kg][a]	5.6	4.8-55
F [%][b]	n.d.	14

[a] *i.v.* dose mouse: mg/kg; *i.v.* dose rat: mg/kg – to be checked
[b] *p.o.* dose mouse: mg/kg; *p.o.* dose rat: mg/kg – to be checked

In vivo pharmacology

BI-2536 is efficacious in mouse xenograft models in the range of 30-60 mg/kg (once or twice weekly *i.v.* administration)[1].

Selectivity

Low selectivity considering closest family members:
PLK2: IC_{50} = 3.5 nM
PLK3: IC_{50} = 9 nM
High overall kinase selectivity:
>1000-fold (panel of 63 protein kinases, supplemental data)[1]

SELECTIVITY DATA AVAILABLE	BI-2536
SafetyScreen44™ with kind support of eurofins	Yes
Invitrogen®	No
DiscoverX®	Yes[6]
Dundee	Yes

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

X-ray co-crystal structure available: PDB code: 2RKU

Reference molecule(s) – Inhibitors

Volasertib (BI 6727) shows similar *in vitro* profile, but *in vivo* longer half-life[7].

GSK-461364A is reported with PLK family selectivity[6].

Supplementary data

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

References

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8. The compound numbers mentioned herein are a reference to the numbering system employed in: 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: 36825440.