PLK 1 inhibitor | BI - 2536

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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

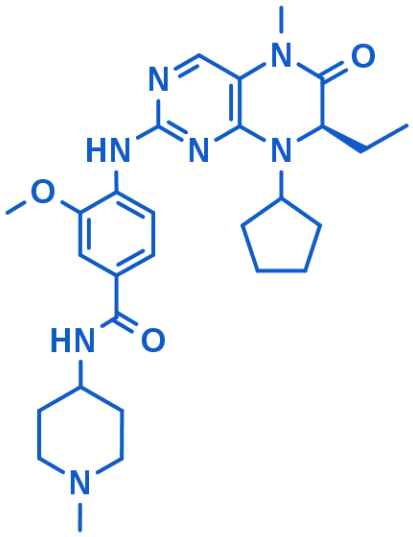

Figure 1: 2-D structure of BI-2536, an inhibitor of PLK1

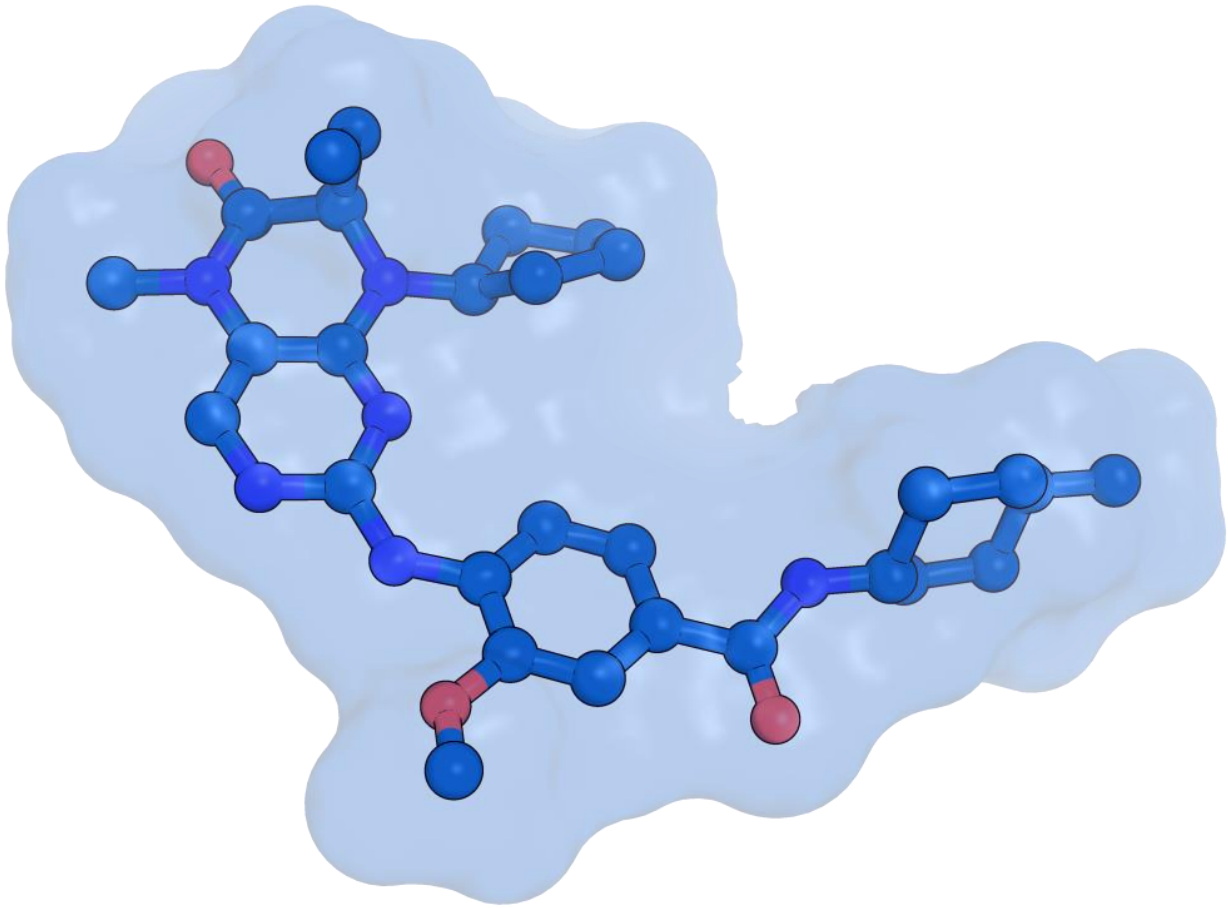

Figure 2: 3-D structure of BI-2536, as observed in complex with PLK1 by X-ray crystallography

Highlights

BI-2536 inhibits the PLK1 enzyme with an IC_{50} of 0.8 nM and is active in a large variety of human tumor cell lines in the range of EC_{50} = 2-25 nM. In vivo, BI-2536 is efficacious in mouse xenograft models in the range of 30-60 mg/kg (once or twice weekly *i.v.* administration).

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.

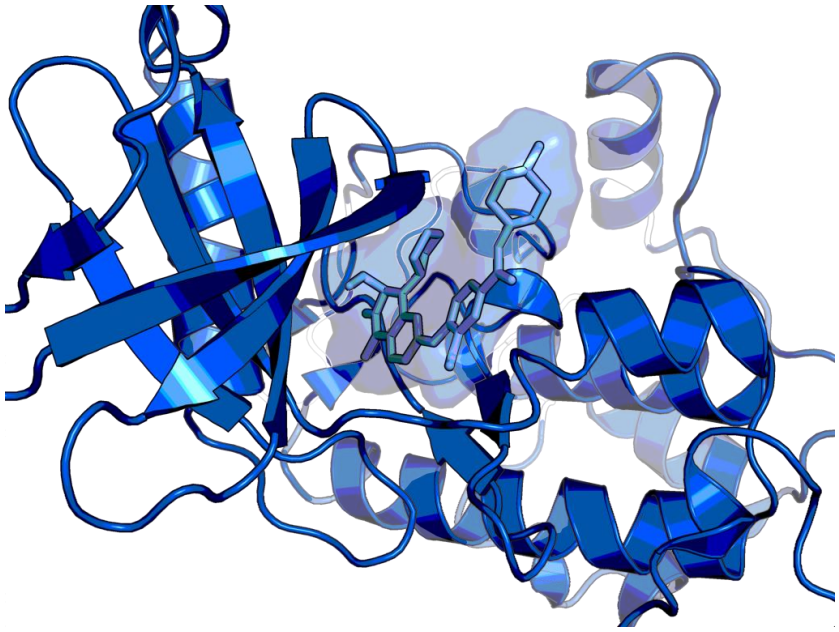

Figure 3: BI-2536 bound to PLK1 (Xray structure solved at Boehringer-Ingelheim)

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 / NEGATIVE CONTROL	BI-2536
PLK1 (IC50) [nM]	0.83
NCI-H460 (EC_{50}) [nM]	12

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-2536		
MW [Da]	521.7		
Solubility @ pH 5, McIlvaine buffer [µg/ml]	320		
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	16		
CACO efflux ratio	3		
Plasma protein binding human / mouse / rat [%]	91	95	95

In vivo DMPK parameters

BI-2536	MOUSE	RAT
CL [% Q_H]	116	56-200
MRT [h]	0.8	0-9-2.5
V_{ss} [l/kg]	5.6	4.8-55
F [%]	n.d.	14

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]

PROBE NAME	BI-2536
Cerep®	No
Eurofins-Panlabs®	No
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]

Summary

BI-2536 is a very well-studied tool for PLK1 function *in vitro* and *in vivo*. In house experimentsdo not provide evidence for BRD4 involvement at doses relevant *for in vivo* efficacy.

Supplementary data

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

References

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