opnMe by Boehringer Ingelheim

PHGDH Inhibitor

BI-4924

Boehringer Ingelheim

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Summary

BI-4924 is a potent and selective inhibitor of PHGDH. We also provide the cell permeable prodrug BI-4916 and the negative control BI-5583.

Chemical Structure

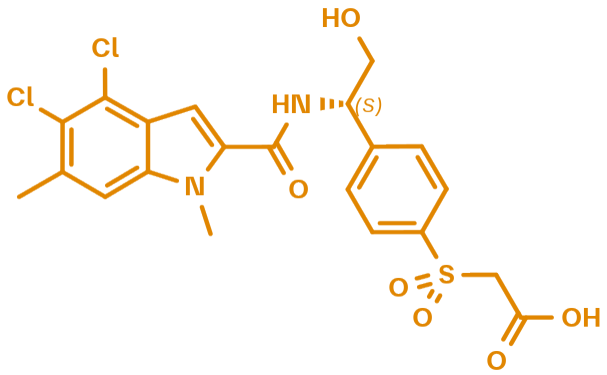

Figure 1: 2D structure of BI-4924, an inhibitor of PHGDH

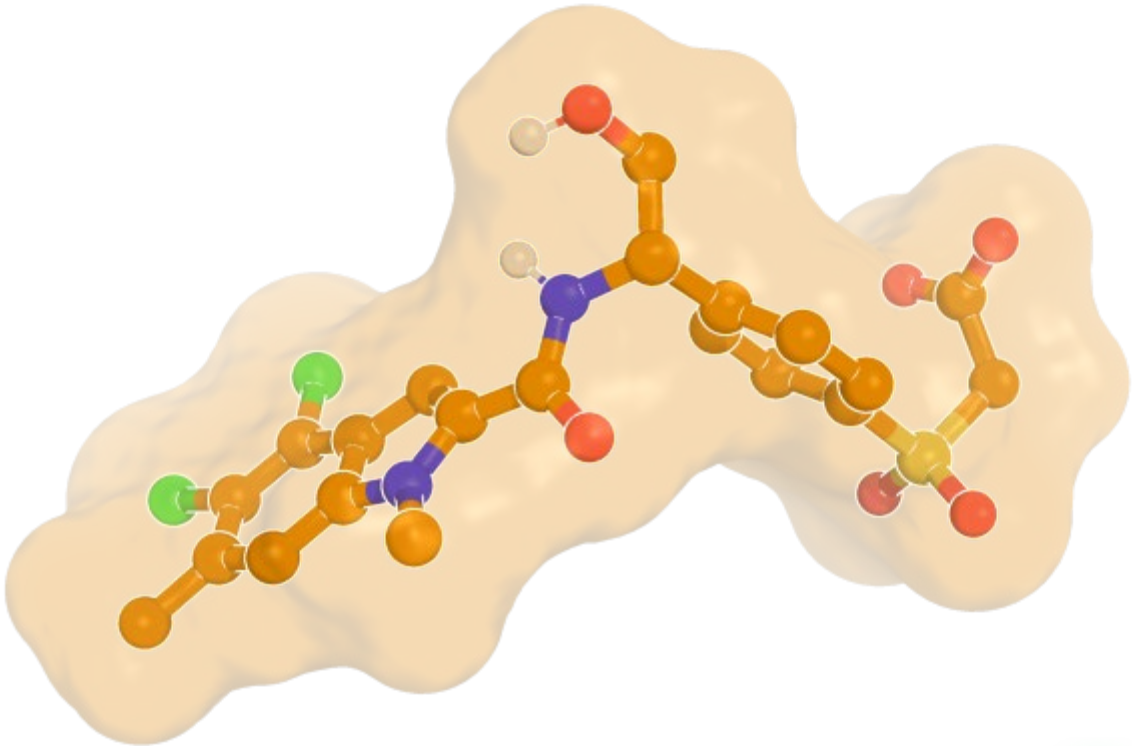

Figure 2: BI-4924, 3D conformation, as observed in complex 6RJ6 (PDB code).

Highlights

BI-4924 is a highly potent inhibitor of PHGDH with good selectivity. We also provide the cell permeable prodrug BI-4916 which is the ethyl ester of BI-4924 and was used to achieve intracellular enrichment of BI-4924. In addition, we provide the negative control BI-5583.

Target information

PHGDH (3-phosphoglycerate dehydrogenase) catalyzes the first step of de novo serine biosynthesis downstream of glycolysis and is the rate limiting enzyme for the pathway. PHGDH converts 3-phosphoglycerate (3-PG) to 3-phosphohydroxypyruvate (3-PHP) in a NAD-dependent manner. PHGDH is amplified or overexpressed in a subset of tumors, most frequently melanoma and triple-negative breast cancers. Cells with amplified or overexpressed PHGDH show an elevated serine synthesis and are relatively resistant to serine starvation while showing some dependency on PHGDH activity.

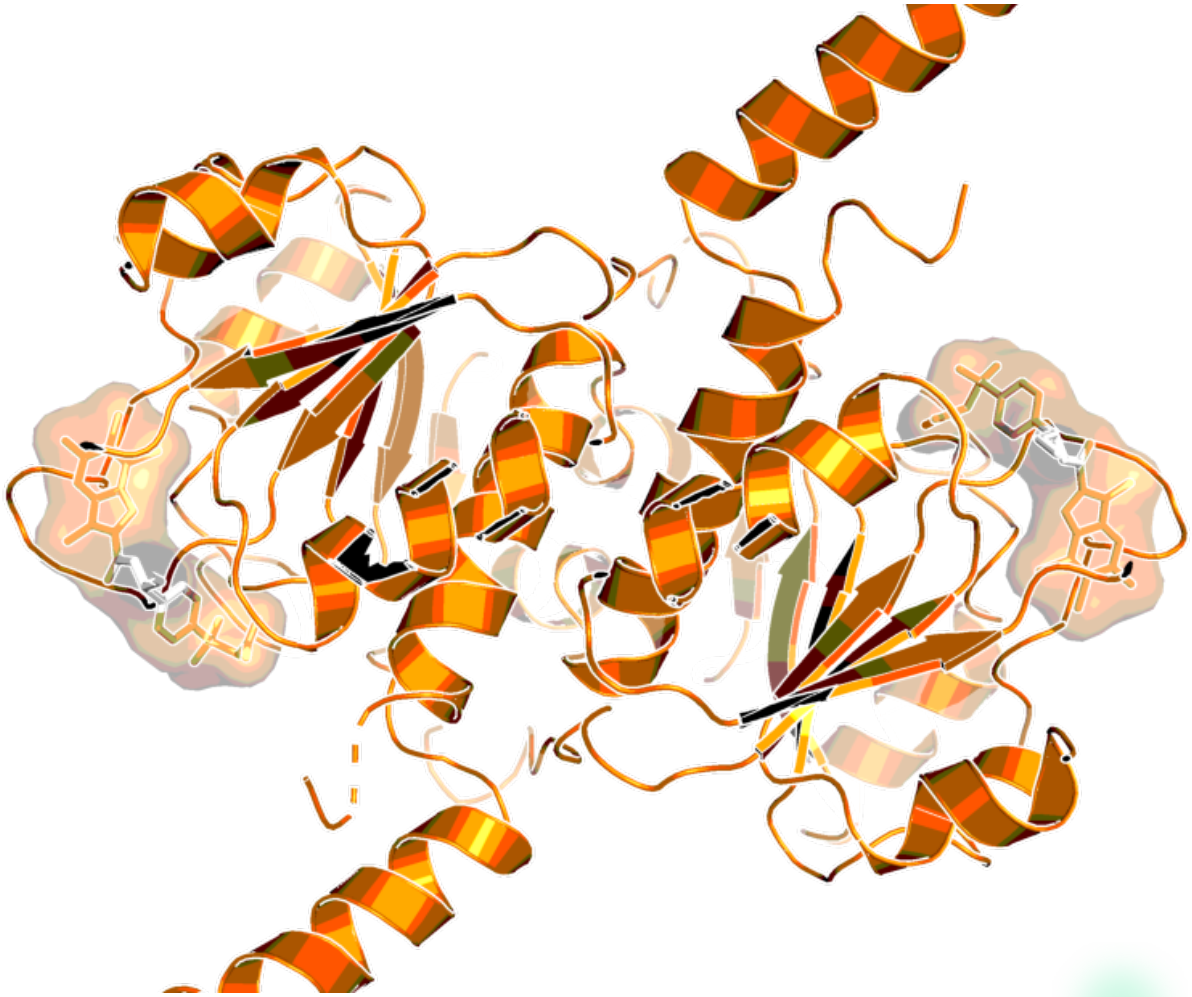

Figure 3: BI-4924 bound to PHGDH (PDB code: 6RJ6)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-4924	BI-5583
MW [Da, free base][a]	499.4	372.8
NAD^+ high assay (250 µM) (IC_{50}) [nM][b]	3	n.d.
PHGDH SPR [nM][b]	26	28,400
^{13}C-Serine; 72 h (IC_{50}) [nM][b]	2,200	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
[b] To be checked

In vitro DMPK and CMC parameters

To perform cellular experiments, we suggest using BI-4916 which is the ester prodrug of BI-4924 since it shows better permeability and leads to intracellular enrichment of BI-4924.

PROBE NAME / NEGATIVE CONTROL	BI-4924	BI-5583
logD @ pH 11	0.62	-0.36
Solubility @ pH 7 [µg/mL]	59	>87
Caco-2 permeability AB @ pH 7.4 [$*10^{-6}$ cm/s]	0.21	<1.8
Caco-2 efflux ratio	10.8	n.a.
Microsomal stability (human/mouse/rat) [% Q_H]	<24 / <24 / <23	24 / - / <23
Hepatocyte stability (mouse) [% Q_H]	32	n.a.
Plasma Protein Binding (mouse) [%]	99.6	Ongoing
CYP 3A4 (IC_{50}) [µM]	>50	>50
CYP 2C8 (IC_{50}) [µM]	31	>50
CYP 2C9 (IC_{50}) [µM]	>50	>50
CYP 2C19 (IC_{50}) [µM]	>50	>50
CYP 2D6 (IC_{50}) [µM]	>50	>50

Negative control

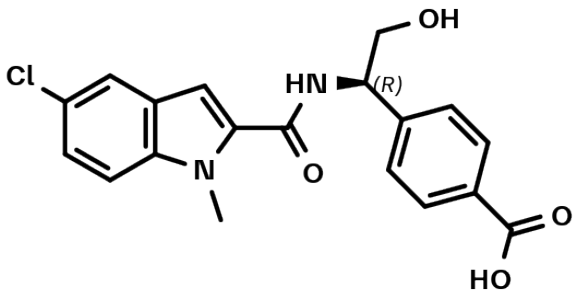

Figure 4: BI-5583 which serves as a negative control

Selectivity

The SafetyScreen44™ panel has been measured for BI-4924, and for 2/44 proteins > 70% CTRL inhibition was found: 5HT2B (78%), PDE3A (86%).

SELECTIVITY DATA AVAILABLE	BI-4924	BI-5583
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	No	Yes
DiscoverX®	No	No
Dundee	No	No

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

BI-4924 bound to PHGDH (PDB code: 6RJ6)

Reference molecule(s)

Other PHGDH inhibitors have been described in literature[2].

Supplementary data

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

References

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