PHGDH Inhibitor | BI-4916

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Summary

BI-4916 is the ester prodrug of BI-4924, a highly potent inhibitor of PHGDH with good selectivity. We also provide the negative control BI-5583.

The ester prodrug BI-4916 should be used to perform cellular experiments.

Chemical Structure

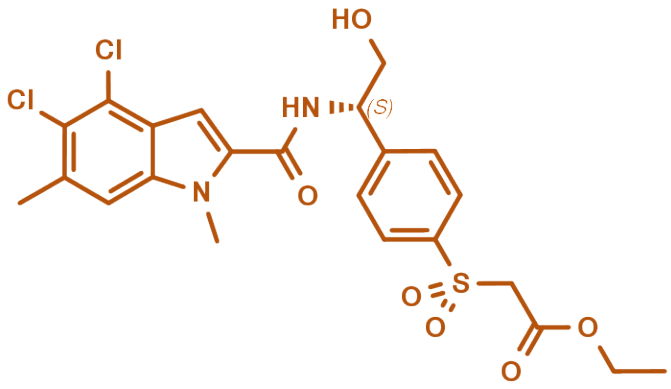

Figure 1: 2-D structure of BI-4916, an ester prodrug of the PHGDH inhibitor BI-4924

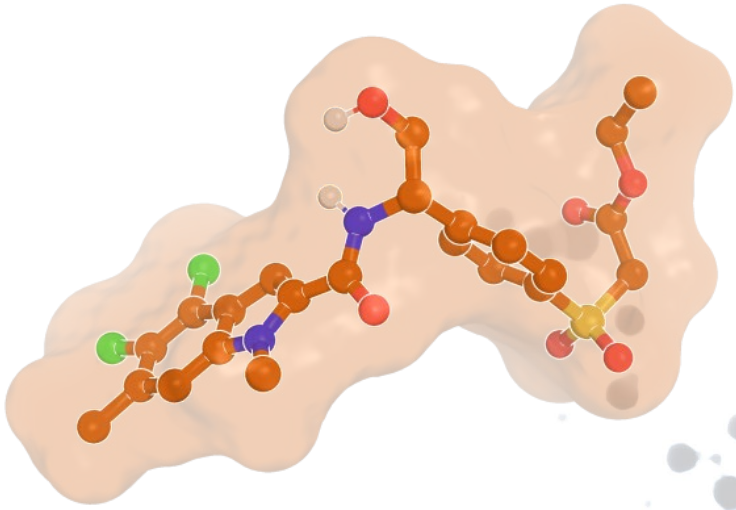

Figure 2: BI-4916, 3D conformation, as observed in complex 6RJ6 (PDB code).

Highlights

BI-4916 is an ester prodrug of the highly potent PHGDH inhibitor BI-4924. In contrast to BI-4924, BI-4916 is cell permeable, undergoing cellular uptake followed by hydrolysis to BI-4924. This allows for it to be used as intracellular enrichment of BI-4916. The negative control BI-5583 is also provided. Both compounds should be only used to perform cellular experiments.

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.

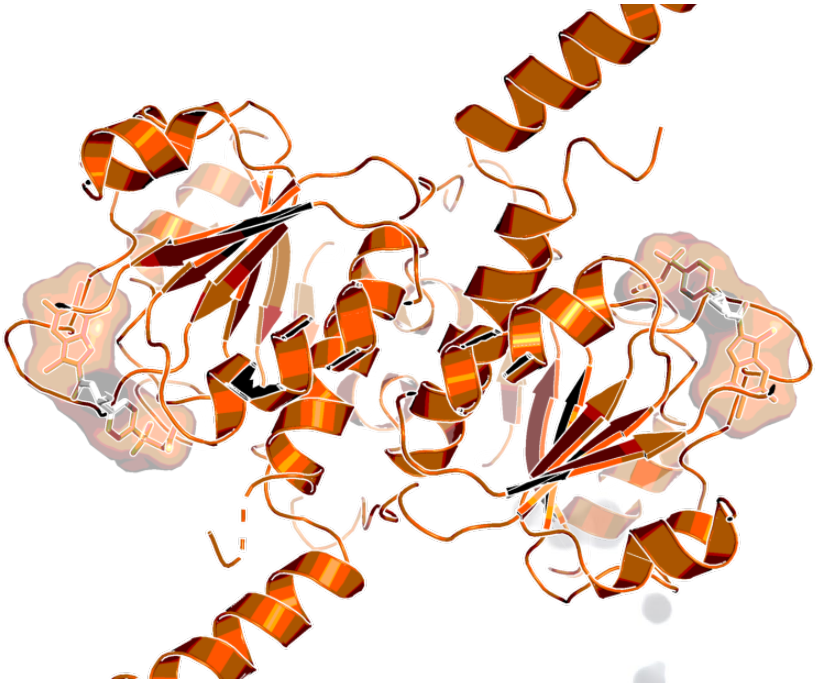

Figure 3: BI-4924 bound to PHGDH (PDB code: 6RJ6)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-4916	BI-5583
MW [Da]	527.4	372.8
NAD^+ high assay (250 µM) (IC_{50}) [nM][1]	169*	n.d.
PHGDH SPR [µM] [1]	n.a.	28.4
^{13}C-Serine; 72 h (IC_{50}) [nM][1]	2,032	n.a.

* The chemical stability of the tosyl acetate ester was found to be limited under the assay conditions – It is highly likely that all activity in the biochemical assay results from the formation of the carboxylic acid analog BI-4924 which is also available on opnMe.com.

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-4916	BI-5583
logP	5.6	n.a.
Solubility @ pH 6.8 [µg/ml]	<1	>87
CACO permeability @ pH 7.4 [$*10^{-6}$ cm/s]	n.d.	<1.8
CACO efflux ratio	n.d.	n.a.
Microsomal stability (human/mouse/rat) [% Q_H]	n.d.	24/-/<23
Hepatocyte stability (mouse) [% Q_H]	n.d.	n.a.
Plasma protein binding (10% FCS) [%]	98.8	Ongoing

CYP 3A4 (IC_{50}) [µM]	>50	>50
CYP 2C8 (IC_{50}) [µM]	39.0	>50
CYP 2C9 (IC_{50}) [µM]	>50	>50
CYP 2C19 (IC_{50}) [µM]	>50	>50
CYP 2D6 (IC_{50}) [µM]	>50	>50

Negative control

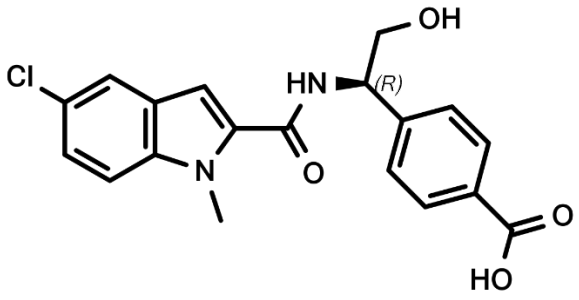

Figure 4: BI-5583 which serves as a negative control

Selectivity

The SafetyScreen44™ panel has been measured (@10 µM) for BI-4916, and for 3/44 proteins > 70% CTRL inhibition was found: CCKA (82%), 5HT2B (94%), ALPHA2A (101%).

SELECTIVITY DATA AVAILABLE	BI-4916	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 (active form of prodrug BI-4916) bound to PHGDH (PDB code: 6RJ6)

Reference molecule(s)

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

Supplementary data

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

References

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