PHGDH Inhibitor | BI-4924

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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

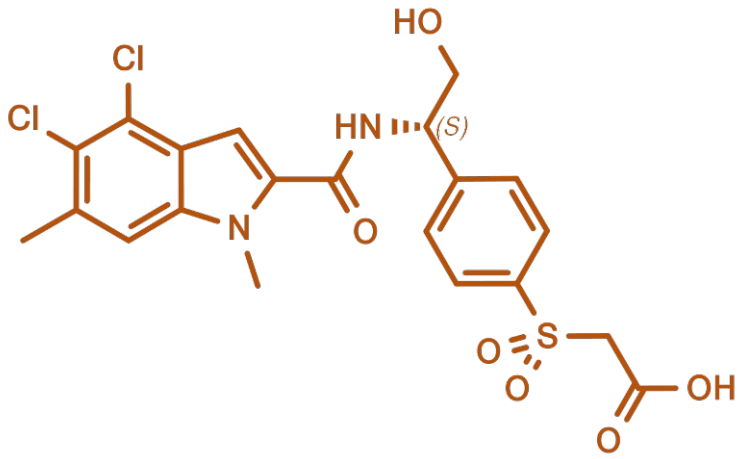

Figure 1: 2-D structure of BI-4924, an inhibitor of PHGDH

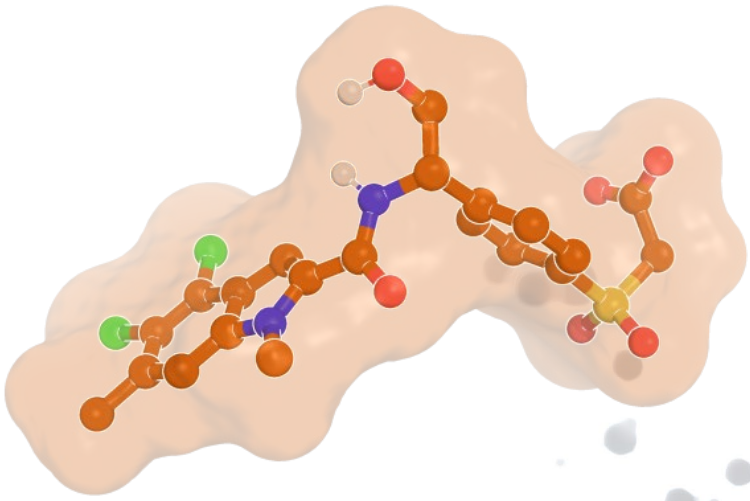

Figure 2: BI-4924, 3D conformation, as observed in complex 6RJ6 (PDB code).

Highlights

BI-4924 is a highly potent inhibitor of PHGDH. It has high selectivity against most other dehydrogenase targets and has high microsomal as well as hepatocytic stability. We also provide the cell permeable ester prodrug BI-4916, a highly selective molecule used to achieve intracellular enrichment of BI-4924. The negative control is BI-5583. These compounds are for *in vitro* 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.

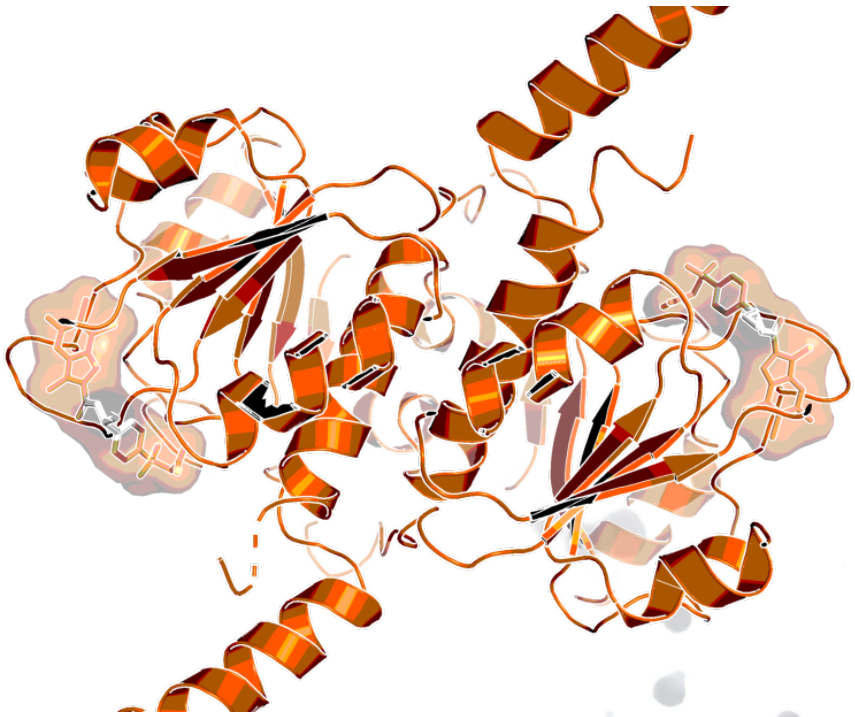

Figure 3: BI-4924 bound to PHGDH (PDB code: 6RJ6)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-4924	BI-5583
MW [Da]	499.4	372.8
NAD^+ high assay (250 µM) (IC_{50}) [nM][1]	3	n.d.
PHGDH SPR [nM] [1]	26	28,400
^{13}C-Serine; 72 h (IC_{50}) [nM][1]	2,200	n.a.

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
logP	5.3	n.a.
Solubility @ pH 6.8 [µg/ml]	59	>87
CACO permeability @ pH 7.4 [$*10^{-6}$ cm/s]	0.21	<1.8
CACO 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

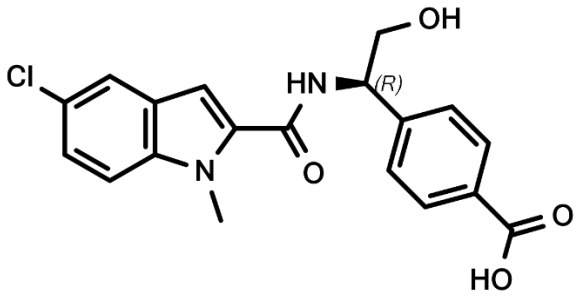

Figure 4: BI-5583 which serves as a negative control

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

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

References

1. Weinstabl, H., Treu, M., Rinnenthal, J., Zahn, S. K., Ettmayer, P., Bader, G., Dahmann, G., Kessler, D., Rumpel, K., Mischerikow, N., Savarese, F., Gerstberger, T., Mayer, M., Zoephel, A., Schnitzer, R., Sommergruber, W., Martinelli, P., Arnhof, H., Peric-Simov, B., Hofbauer, K. S., Garavel, G., Scherbantin, Y., Mitzner, S., Fett, T. N., Scholz, G., Bruchhaus, J., Burkard, M., Kousek, R., Ciftci, T., Sharps, B., Schrenk, A., Harrer, C., Haering, D., Wolkerstorfer, B., Zhang, X., Lv, X., Du, A., Li, D., Li, Y., Quant, J., Pearson, M., McConnell, D. B. Intracellular trapping of the selective phosphoglycerate dehydrogenase (PHGDH) inhibitor BI-4924 disrupts serine biosynthesis *J. Med. Chem.* **2019**, *62*, 7976−7997. DOI: 10.1021/acs.jmedchem.9b00718, PubMed.

2. Li, M., Wu, C., Yang, Y., Zheng, M., Yu, S., Wang, J., Chen, L., Li, H. 3-Phosphoglycerate dehydrogenase: a potential target for cancer treatment *Cell Oncol.* **2021**. DOI: 10.1007/s13402-021-00599-9, PubMed.

3. Zogg, C. K. Phosphoglycerate Dehydrogenase: Potential Therapeutic Target and Putative Metabolic Oncogene *J. Oncol.* **2014**, *2014*, 524101. DOI: 10.1155/2014/524101, PubMed.

4. Possemato, R., Marks, K. M., Shaul, Y. D., Pacold, M. E., Kim, D., Birsoy, K., Sethumadhavan, S., Woo, H.-K., Jang, H. G., Jha, A. K., Chen, W. W., Barrett, F. G., Stransky, N., Tsun, Z.-Y., Cowley, G. S., Barretina, J., Kalaany, N. Y., Hsu, P. P., Ottina, K., Chan, A. M., Yuan, B., Garraway, L. A., Root, D. E., Mino-Kenudson, M., Brachtel, E. F., Driggers, E. M., Sabatini, D. M. Functional Genomics Reveal that the Serine Synthesis Pathway is Essential in Breast Cancer. *Nature* **2011**, *476*, 346. DOI: 10.1038/nature10350, PubMed.

5. Locasale, J. W., Grassian, A. R., Melman, T., Lyssiotis, C. A., Mattaini, K. R., Bass, A. J., Heffron, G., Metallo, C. M., Muranen, T., Sharfi, H., Sasaki, A. T., Anastasiou, D., Mullarky, E., Vokes, N. I., Sasaki, M., Beroukhim, R., Stephanopoulos, G., Ligon, A. H., Meyerson, M., Richardson, A. L., Chin, L., Wagner, G., Asara, J. M., Brugge, J. S., Cantley, L. C., Vander Heiden, M. G. Phosphoglycerate Dehydrogenase Diverts Glycolytic Flux and Contributes to Oncogenesis. *Nat. Genet.* **2011**, *43*, 869. DOI: 10.1038/ng.890, PubMed.

6. Mullarky, E., Mattaini, K. R., Vander Heiden, M. G., Cantley, L. C., Locasale, J. W. PHGDH Amplification and Altered Glucose Metabolism in Human Melanoma: PHGDH Amplification and Altered Glucose Metabolism *Pigm. Cell Melanoma Res.* **2011**, *24*, 1112–1115.