BCL6 inhibitor | BI-3812

Table of contents

Summary

BI-3812 is a single digit nanomolar BCL6::Co-repressor inhibitor which also inhibits the BCL6::Co-repressor complex formation in cells.

Chemical Structure

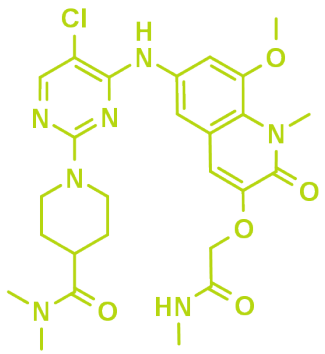

Figure 1: 2-D structure of BI-3812, a BCL6 inhibitor

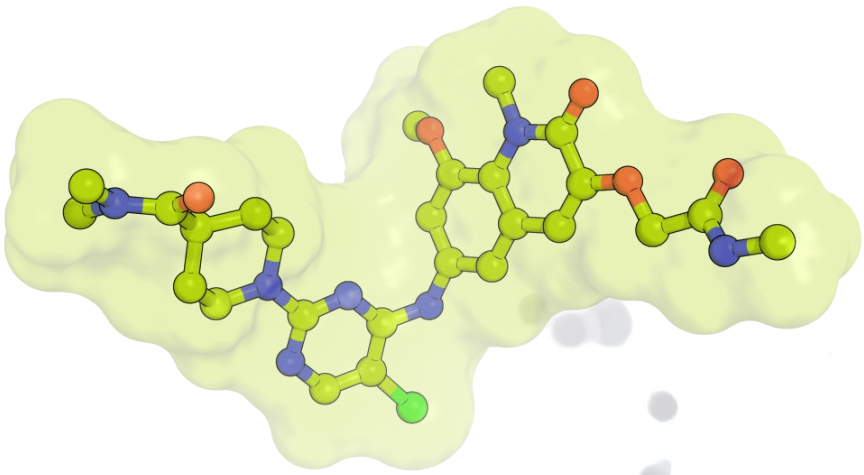

Figure 2: BI-3812, 3D conformation, based on X-ray structure with BI-3802

Highlights

BI-3812 is a highly potent B-cell lymphoma 6 (BCL6) inhibitor. It inhibits the interaction of the BTB/POZ domain of BCL6 with several co-repressors *in vitro* ($IC_{50} \leq 3$ nM), as well as the formation of BCL6::Co-repressor complexes in a cellular context ($IC_{50} = 40$ nM)[1]. Its high potency and good permeability make it an attractive tool for testing hypotheses around BCL6 biology *in vitro*.

Target information

B-cell lymphoma 6 (BCL6) functions as a transcriptional repressor that binds specific DNA sequences *via* its Zn-fingers and recruits transcriptional co-repressors (e.g. BCOR, SMRT, NCOR) by its BTB/POZ domain.[2] BCL6 is essential for the germinal center (GC) reaction.[3] It represses a broad set of genes that are required to sustain mutagenic activity without activating the DNA damage response or apoptosis.[4] BCL6 also prevents maturation to plasma or memory cells and helps to maintain a de-differentiated state. Its expression must be switched off to allow the B-cell to exit the GC cycle and differentiate. BCL6 is a known oncogenic driver and frequently overexpressed in Diffuse large B-cell lymphoma (DLBCL)[5,6].

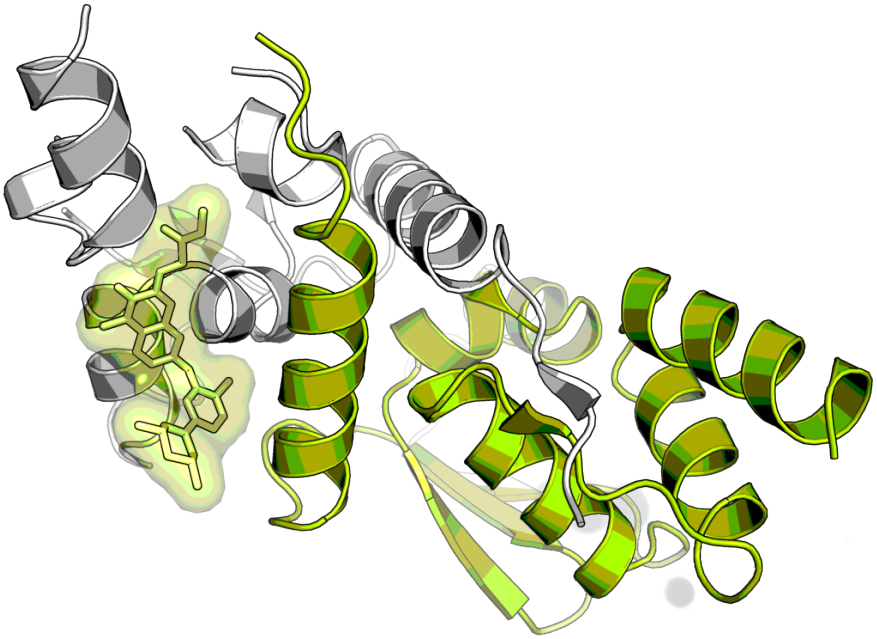

Figure 3: BCL6-BTB dimer with BI-3802, as observed by X-ray.[1] BI-3802, a close analog of BI-3812, binds at the interface of two monomers (monomers are shown in green and grey).

In vitro activity

BI-3812 displays an $IC_{50} \leq 3$ nM in a BCL6::BCOR U*Light* TR-FRET assay.

PROBE NAME / NEGATIVE CONTROL	BI-3812	BI-5273
MW [Da]	558	500
BCL6::BCOR UL*ight* TR-FRET (IC_{50}) [nM][a]	≤3	10,162
BCL6::NCOR LUMIER (IC_{50}) [nM]	40	n.d.

[a] With affinities of approximately 3 nM, the assay wall of this assay is reached, limiting the accuracy of the biochemical assay.

We recommend storing and using 1 mM DMSO stock solutions of BI-3812 for all *in vitro* experiments.

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-3812	BI-5273
Aqueous solubility @ pH 6.8 [µg/ml]	<1	84
CACO permeability @ pH 7.4 [$*10^{-6}$ cm/s]	2.8	22
CACO efflux ratio	14	0.6
Human hepatocyte clearance [% Q_H]	n.d.	n.d.
Plasma protein binding human [%]	96.89	n.d.

Negative control

BI-5273 is a close analog of BI-3812 which binds only very weakly to the BCL6 BTB domain (IC_{50} ~ 10 µM).

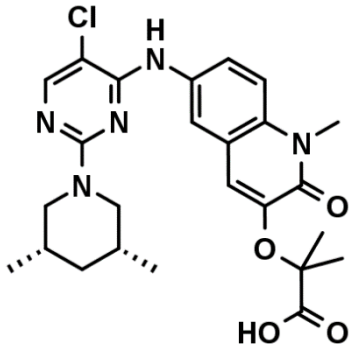

Figure 4: BI-5273 which serves as a negative control

Selectivity

The intracellular selectivity profile was determined for the close analog BI-3802. For BI-3802, BCL6 was confirmed as the major target of this compound in DLBCL cells.[1]

SELECTIVITY DATA AVAILABLE	BI-3812	BI-5273
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	Yes	No
DiscoverX®	No	No
Dundee	No	No

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

Not available. However, the X-ray structure with the close analog BI-3802 was solved at Boehringer Ingelheim.

Reference molecule(s)

Several small molecule BCL6 inhibitors have been published recently.[7,8,9,10]

References

1. Kerres N., Steurer S., Schlager S., Bader G., Berger H., Caligiuri M., Dank C., Engen J. R., Ettmayer P., Fischerauer B., Flotzinger G., Gerlach D., Gerstberger T., Gmaschitz T., Greb P., Han B., Heyes E., Iacob R. E., Kessler D., Kölle H., Lamarre L., Lancia D. R., Lucas S., Mayer M., Mayr K., Mischerikow N., Mück K., Peinsipp C., Petermann O., Reiser U., Rudolph D., Rumpel K., Salomon C., Scharn D., Schnitzer R., Schrenk A., Schweifer N., Thompson D., Traxler E., Varecka R., Voss T., Weiss-Puxbaum A., Winkler S., Zheng X., Zoephel A., Kraut N., McConnell D., Pearson M., Koegl M. Chemically induced degradation of the oncogenic transcription factor BCL6 *Cell Rep.* **2017**, 20(12), 2860-2875. DOI: 10.1016/j.celrep.2017.08.081, PubMed.
2. Zollman S., Godt D., Privé G. G., Couderc J. L., Laski F. A. The BTB domain, found primarily in zinc finger proteins, defines an evolutionarily conserved family that includes several developmentally regulated genes in Drosophila *Proc. Natl. Acad. Sci. U S A* **1994**, 91, 10717-10721. PMC, PubMed.
3. Dent A. L., Shaffer A. L., Yu X., Allman D., Staudt L. M. Control of inflammation, cytokine expression, and germinal center formation by BCL-6, *Science* **1997**, *276*, 589-592. DOI: 10.1126/science.276.5312.589, PubMed.
4. Basso K., Saito M., Sumazin P., Margolin A. A., Wang K., Lim W. K., Kitagawa Y., Schneider C., Alvarez M. J., Califano A., Dalla-Favera R. Integrated biochemical and computational approach identifies BCL6 direct target genes controlling multiple pathways in normal germinal center B cells *Blood* **2010**, *115*, 975-984. DOI: 10.1182/blood-2009-06-227017, PubMed.
5. KBasso K., Dalla-Favera R. Roles of BCL6 in normal and transformed germinal center B cells *Immunol. Rev.* **2012**, *247*, 172-183. DOI: 10.1111/j.1600-065X.2012.01112.x, PubMed.
6. Hatzi K., Melnick A. Breaking bad in the germinal center: how deregulation of BCL6 contributes to lymphomagenesis *Trends Mol. Med.* **2014**, *20*, 343-352. DOI: 10.1016/j.molmed.2014.03.001, PubMed.
7. Cardenas M. G., Yu W., Beguelin W., Teater M. R., Geng H., Goldstein R. L., Oswald E., Hatzi K., Yang S. N., Cohen J., Shaknovich R., Vanommeslaeghe K., Cheng H., Liang D., Cho H. J., Abbott J., Tam W., Du W., Leonard J. P., Elemento O., Cerchietti L., Cierpicki T., Xue F., MacKerell A. D. Jr., Melnick A. M. Rationally designed BCL6 inhibitors target activated B cell diffuse large B cell lymphoma *J. Clin. Invest.* **2016**, *126*, 3351-3362. DOI: 10.1172/JCI85795, PubMed.

8. McCoull W., Abrams R. D., Anderson E., Blades K., Barton P., Box M., Burgess J., Byth K., Cao Q., Chuaqui C., Carbajo R. J., Cheung T., Code E., Ferguson A. D., Fillery S., Fuller N. O., Gangl E., Gao N., Grist M., Hargreaves D., Howard M. R., Hu J., Kemmitt P. D., Nelson J. E., O'Connell N., Prince D. B., Raubo P., Rawlins P. B., Robb G. R., Shi J., Waring M. J., Whittaker D., Wylot M., Zhu X. Discovery of Pyrazolo[1,5-a]pyrimidine B-Cell Lymphoma 6 (BCL6) Binders and Optimization to High Affinity Macrocyclic Inhibitors, *J. Med. Chem.* **2017**, *60*, 4386-4402. DOI: 10.1021/acs.jmedchem.7b00359, PubMed.

9. Kamada Y., Sakai N., Sogabe S., Ida K., Oki H., Sakamoto K., Lane W., Snell G., Iida M., Imaeda Y., Sakamoto J., Matsui J. Discovery of a B-cell lymphoma 6 Protein–Protein Interaction Inhibitor by a Biophysics-driven Fragment-based Approach, *J. Med. Chem.* **2017**, *60*, 4358-4368. DOI: 10.1021/acs.jmedchem.7b00313, PubMed.

10. Yasui T., Yamamoto T., Sakai N., Asano K., Takai T., Yoshitomi Y., Davis M., Takagi T., Sakamoto K., Sogabe S., Kamada Y., Lane W., Snell G., Iwata M., Goto M., Inooka H., Sakamoto J. I., Nakada Y., Imaeda Y. Discovery of a novel B-cell lymphoma 6 (BCL6)-corepressor interaction inhibitor by utilizing structure-based drug design, *Bioorg. Med. Chem.* **2017**, *25*, 4876-4886. DOI: 10.1016/j.bmc.2017.07.037, PubMed.