BCL6 inhibitor | BI-3812

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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

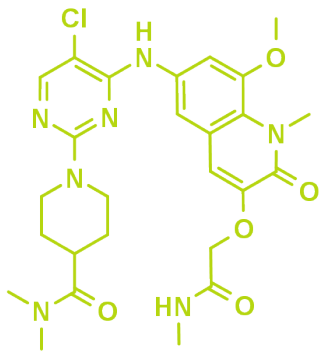

Figure 1: 2-D structure of BI-3812, a BCL6 inhibitor

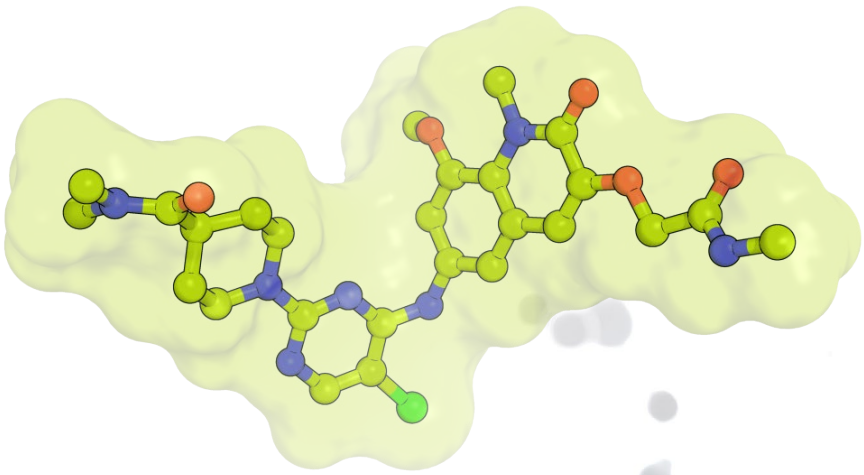

Figure 2: BI-3812, 3D conformation, based on X-ray structure with BI-3802

Highlights

B-cell lymphoma 6 (BCL6) is a known oncogenic driver and frequently overexpressed in many DLBCL. BI-3812 potently inhibits the interaction of the BTB/POZ domain of BCL6 with several co-repressors *in vitro* ($IC_{50} \leq 3$ nM). In a cellular context, BI-3812 inhibits the BCL6::Co-repressor complex formation with an IC_{50} of 40 nM[1]. The high potency and good permeability properties of BI-3812 make this molecule a very good cellular probe compound for testing hypotheses around BCL6 biology. With BI-5273 we also offer a structurally close analog which can be used as a negative control for *in vitro* experiments (IC_{50} ~ 10 µM).[1]

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 of DLBCL[5,6] and frequently overexpressed in DLBCL.

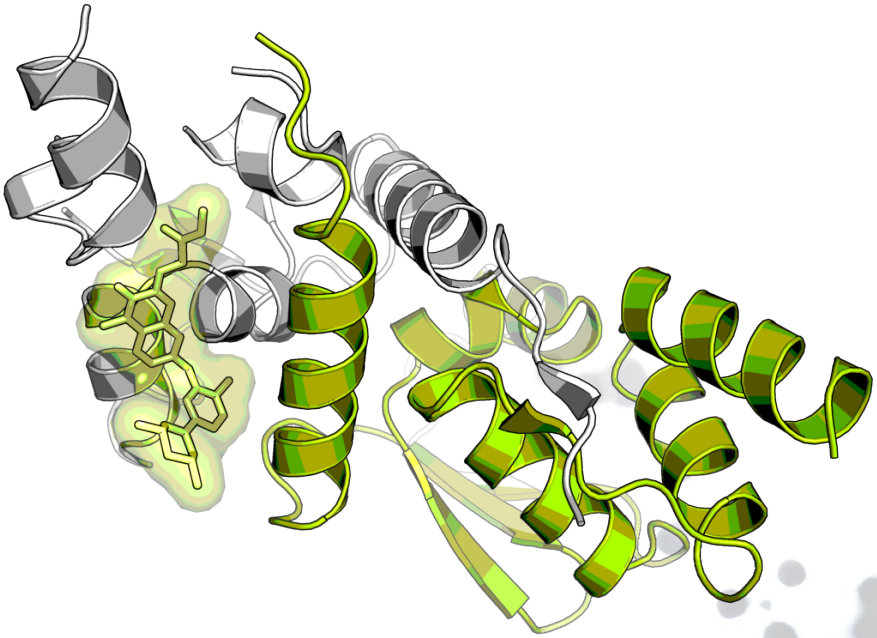

Figure 3: BCL6-BTB dimer with BI-3802, as observed by X-ray.[1] BI-3802, a close analog of BI-3812, binds at the interface of two monomers (monomers are shown in green and grey).

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 to store and use 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).

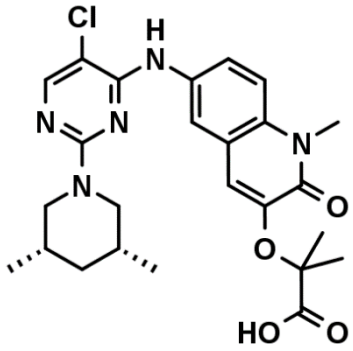

Figure 4: BI-5273 which serves as a negative control

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 of 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]

Summary

BI-3812 is a single digit nanomolar BCL6::Co-repressor inhibitor which also inhibits the BCL6::Co-repressor complex formation in cells (IC50 = 40 nM). BI-3812 is a classical PPI inhibitor probe compound for testing hypotheses around BCL6 biology in vitro.

References

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