

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

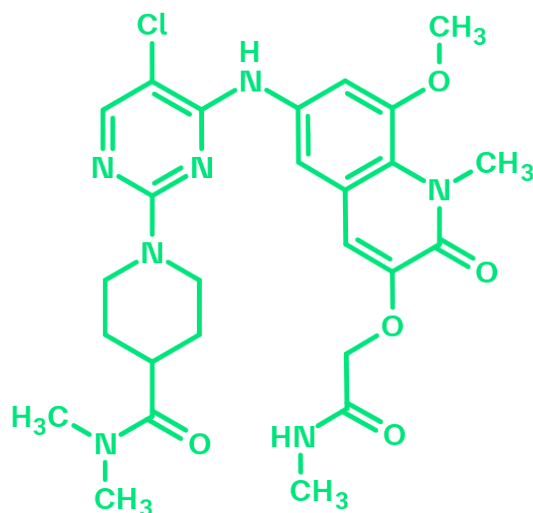


Figure 1: 2D structure of BI-3812, a BCL6 inhibitor

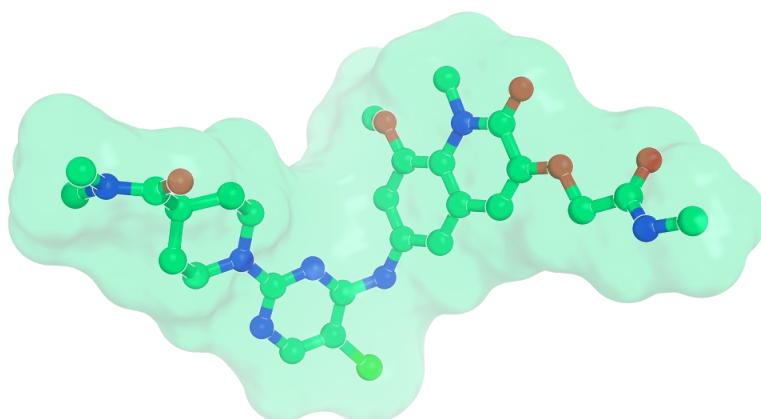


Figure 2: BI-3812, 3D conformation, based on X-ray structure with BI-3802

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 domain². BCL6 is essential for the germinal center (GC) reaction³. It represses a broad set of genes that are required to sustain mutagenic activity without activating the DNA damage response or apoptosis⁴. 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}.

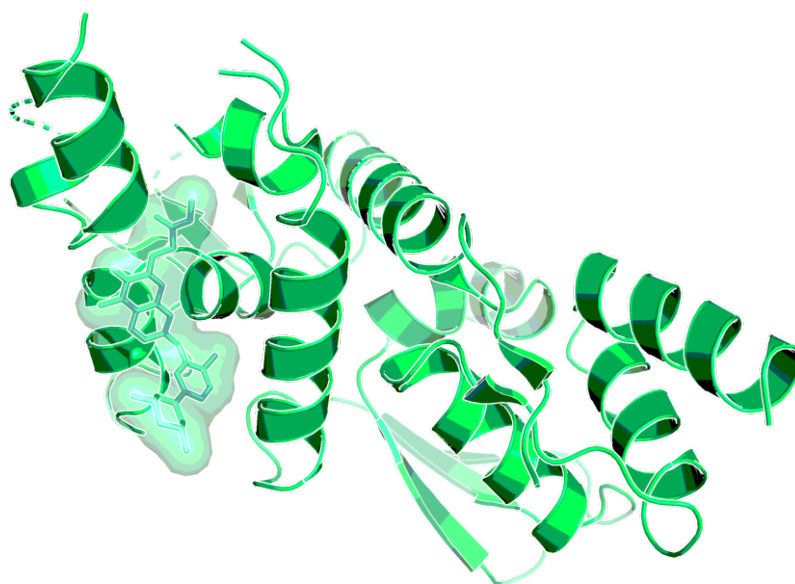


Figure 3: BCL6-BTB dimer with BI-3802, as observed by X-ray¹. BI-3802, a close analog of BI-3812, binds at the interface of two monomers (monomers are shown in green and grey).

In vitro activity

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

PROBE NAME / NEGATIVE CONTROL	BI-3812	BI-5273
MW [Da, free base] ^a	558.0	500.0
BCL6::BCOR ULight TR-FRET (IC_{50}) [nM] ^b	≤ 3	10,162
BCL6::NCOR LUMIER (IC_{50}) [nM]	40	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 With affinities of approximately 3 nM, the assay wall of this assay is reached, limiting the accuracy of the biochemical assay.

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-3812	BI-5273
log D @ pH 11	2.2	1.6
Solubility @ pH 6.8 [μ g/mL]	< 1	84
Caco-2 permeability AB @ pH 7.4 [$\times 10^{-6}$ cm/s]	2.8	22
Caco-2 efflux ratio	14	0.6
Plasma Protein Binding human [%]	96.9	n.d.

Negative control

BI-5273 is a close analog of BI-3812 which binds only very weakly to the BCL6 BTB domain ($IC_{50} \sim 10$ μ M).

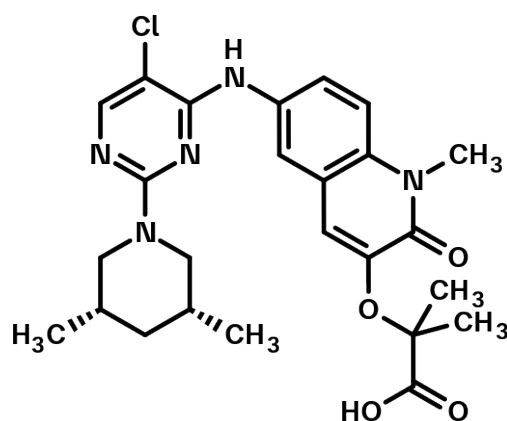


Figure 4: BI-5273 which serves as a negative control

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 cells¹.

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}.

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