BLC6 degrader | BI-3802

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Summary

BI-3802 is a single digit nanomolar BCL6::Co-repressor inhibitor which induces efficacious BCL6 protein degradation in several DLBCL cell lines.

Chemical Structure

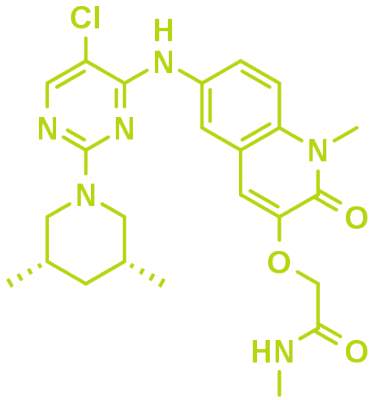

Figure 1: 2-D structure of BI-3802, a BCL6 degrader

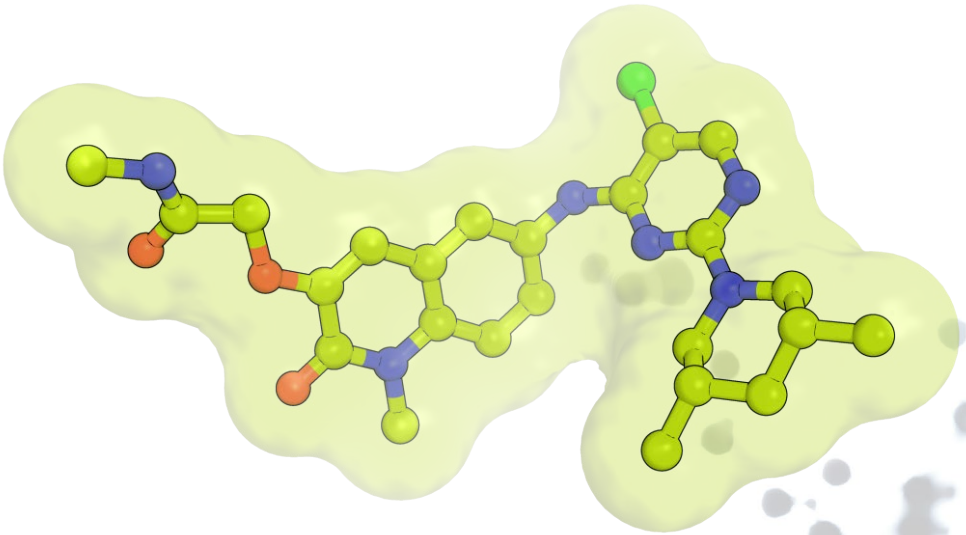

Figure 2: BI-3802, 3D conformation, as observed in complex with BCL6 by X-ray crystallography

Highlights

BI-3802 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* as well as in a cellular context. In addition, BI-3802 was found to be a potent and efficacious degrader of the BCL6 protein in many DLBCL cell lines[1]. Its good permeability and unprecedented protein degradation effects make this compound an ideal tool to study 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 DLBCL[5,6].

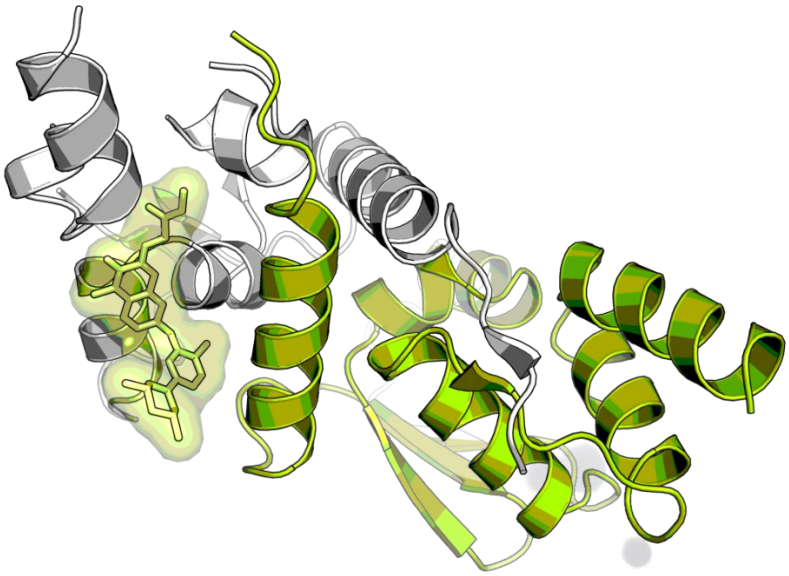

Figure 3: BCL6-BTB dimer with BI-3802, as observed by X-ray.[1] BI-3802 binds at the interface of two monomers (monomers are shown in green and grey).

In vitro activity

BI-3802 displays an $IC_{50} \leq 3$ nM in a BCL6::BCOR U*Light* TR-FRET assay and degrades BCL6 protein with a DC_{50} of 20 nM (in SU-DHL-4 cell lines).[1]

It also inhibits the BCL6::Co-repressor complex formation with an IC_{50} of 43 nM.

PROBE NAME / NEGATIVE CONTROL	BI-3802	BI-5273
MW [Da]	485	500
BCL6::BCOR U*light* TR-FRET (IC_{50}) [nM][a]	≤3	10,162
BCL6::NCOR LUMIER (IC_{50}) [nM]	43	n.d.
BCL6 protein degradation (IC_{50}) [nM][b]	20	*Inactive*

[a] With affinities of approximately 3 nM, the assay wall of this assay is reached, limiting the accuracy of the biochemical assay.
[b] in SU-DHL-4 cells

It is recommended to store and use 1 mM DMSO stock solutions of BI-3802 for all *in vitro* experiments.

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-3802	BI-5273
Aqueous solubility @ pH 6.8 [µg/ml]	<1	84
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	8.5	22
CACO efflux ratio	0.4	0.6
Human hepatocyte clearance [% Q_H]	56	n.d.
Plasma protein binding human [%]	99.95	n.d.

In vivo DMPK parameters

BI-3802 showed poor bioavailability after *p.o.* administration in mice (see table). PK profile of BI-3802 after *p.o.* dosing in mice

PROBE NAME	BI-3802	
Dose [mg/kg]	10	100
AUD [nMh]	1,860	4,650
C_{max} [nM]	193	599

Negative control

BI-5273 is a close analog of BI-3802 which binds only very weakly to the BCL6 BTB domain (IC_{50} ~ 10 µM) and does not induce protein degradation.

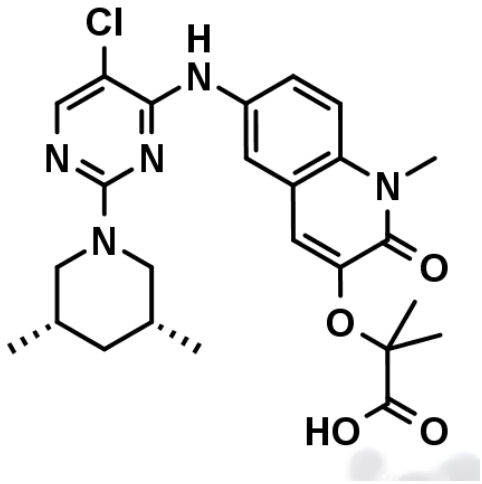

Figure 4: BI-5273 which serves as a negative control

Selectivity

SELECTIVITY DATA AVAILABLE	BI-3802	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

The X-ray crystal structure of BCL6 in complex with BI-3802 is available (PDB code: 5MW2).[1]

Reference molecule(s)

Several small molecule BCL6 inhibitors have been published recently.[7,8,9,10] None of those is described as a BCL6 protein degrader.

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

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