# BCL6 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

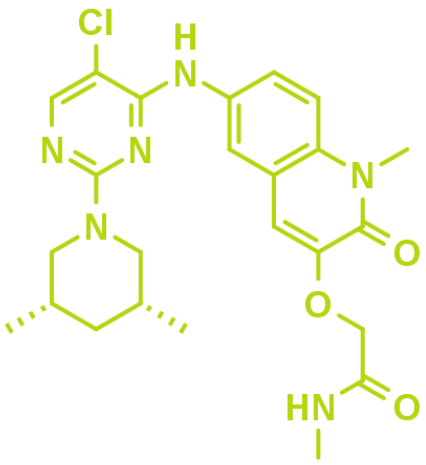


**Figure 1: 2-D structure of BI-3802, a BCL6 degrader**

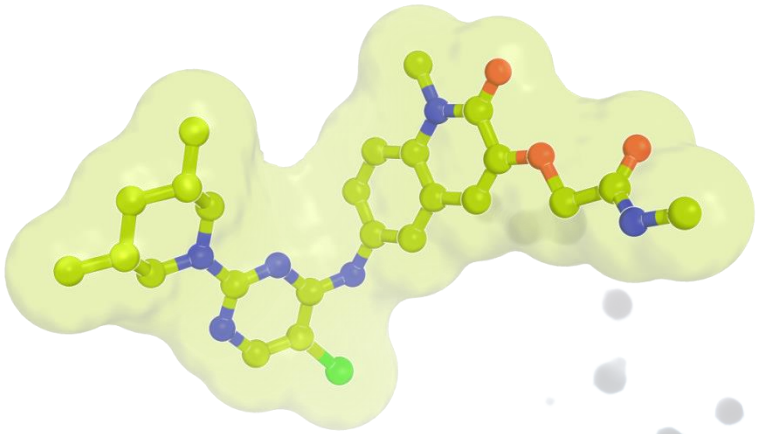

**Figure 2: BI-3802, 3D conformation, as observed in complex with BCL6 by X-ray crystallography**

# Highlights

B-cell lymphoma 6 (BCL6) is a known oncogenic driver and frequently overexpressed in many DLBCL. BI-3802 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-3802 inhibits the BCL6::Co-repressor complex formation with an $IC_{50}$ of 43 nM. Moreover, BI-3802 was found to be a potent and efficacious degrader of the BCL6 protein in many DLBCL cell lines ($DC_{50}$ = 20 nM in SU-DHL-4 cells)[1]. The good permeability properties of BI-3802 and the so far unprecedented BCL6 degradation effects make this molecule an ideal *in vitro* 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.

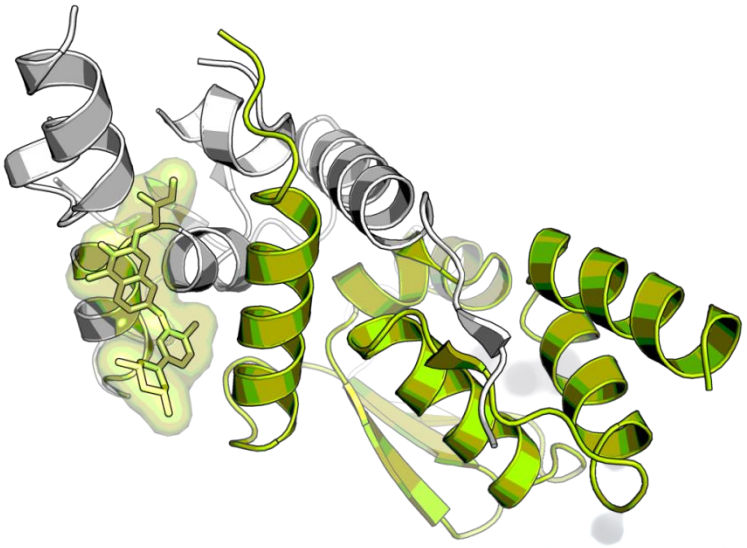

**Figure 3: BCL6-BTB dimer with BI-3802, as observed by X-ray.[1] BI-3802 binds at the interface of two monomers (monomers are shown in green and grey).**

## *In vitro* activity

I-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]..

| 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 ($DC_{50}$) [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

[b]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.

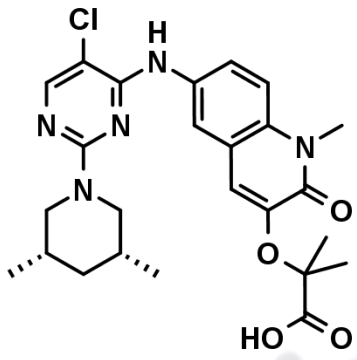


**Figure 4: BI-5273 which serves as a negative control**

## Selectivity

The intracellular selectivity profile of BI-3802 was determined in a chemoaffinity pulldown experiment with an immobilized BI-3802 analog. BCL6 was confirmed as the major target of this compound in DLBCL cells[1].

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

X-Ray Co-crystal structure of BI-3802 to become available in due course (submitted)[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.

## Summary

BI-3802 is a single digit nanomolar BCL6::Co-repressor inhibitor which induces efficacious BCL6 protein degradation in several DLBCL cell lines (e.g., $DC_{50}$ = 20 nM in SU-DHL-4 cells). BI-3802 is an ideal *in vitro* probe compound for testing hypotheses around BCL6 biology. With the close analogs BI-5273 as negative control and BI-3812 as classical non-degrading PPI inhibitor we also offer complementary tools.

## Supplementary data

Selectivity data can be downloaded free of charge from this site.

## References

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