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). 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).

**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. BCL6 is essential for the germinal center (GC) reaction. It represses a broad set of genes that are required to sustain mutagenic activity without activating the DNA damage response or apoptosis. 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 and frequently overexpressed in DLBCL.

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

I-3802 displays an IC$_{50}$ ≤ 3 nM in a BCL6::BCOR *ULight* TR-FRET assay and degrades BCL6 protein with a DC$_{50}$ of 20 nM (in SU-DHL-4 cell lines)\(^1\).

<table>
<thead>
<tr>
<th>PROBE NAME / NEGATIVE CONTROL</th>
<th>BI-3802</th>
<th>BI-5273</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW [Da]</td>
<td>485</td>
<td>500</td>
</tr>
<tr>
<td>BCL6::BCOR <em>ULight</em> TR-FRET (IC$_{50}$) [nM](^a)</td>
<td>≤ 3</td>
<td>10,162</td>
</tr>
<tr>
<td>BCL6::NCOR LUMIER (IC$_{50}$) [nM]</td>
<td>43</td>
<td>n.d.</td>
</tr>
<tr>
<td>BCL6 protein degradation (DC$_{50}$) [nM](^b)</td>
<td>20</td>
<td>inactive</td>
</tr>
</tbody>
</table>

\(^a\)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

\(^1\)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**

<table>
<thead>
<tr>
<th>PROBE NAME / NEGATIVE CONTROL</th>
<th>BI-3802</th>
<th>BI-5273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous solubility @ pH 6.8 [µg/ml]</td>
<td>&lt; 1</td>
<td>84</td>
</tr>
<tr>
<td>CACO permeability @ pH 7.4 [*10$^{-6}$ cm/s]</td>
<td>8.5</td>
<td>22</td>
</tr>
<tr>
<td>CACO efflux ratio</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Human hepatocyte clearance [% Q$_{H}$]</td>
<td>56</td>
<td>n.d.</td>
</tr>
<tr>
<td>Plasma protein binding human [%]</td>
<td>99.95</td>
<td>n.d.</td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th>PROBE NAME</th>
<th>BI-3802</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose [mg/kg]</td>
<td>10</td>
</tr>
<tr>
<td>AUD [nMh]</td>
<td>1,860</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; [nM]</td>
<td>193</td>
</tr>
</tbody>
</table>

**Negative control**

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

![Figure 4: BI-5273 which serves as a negative control](image)

**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.

BCL 6 degrader | BI-3802
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 \textit{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


