opnMe by Boehringer Ingelheim

BCL6 degrader

BI-1136

Boehringer Ingelheim

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Summary

BI-1136 is an unprecedented, potent and selective orally bioavailable BCL6 degrader with rodent *in vivo* activity. A negative control (BI-1135) is available.

Chemical Structure

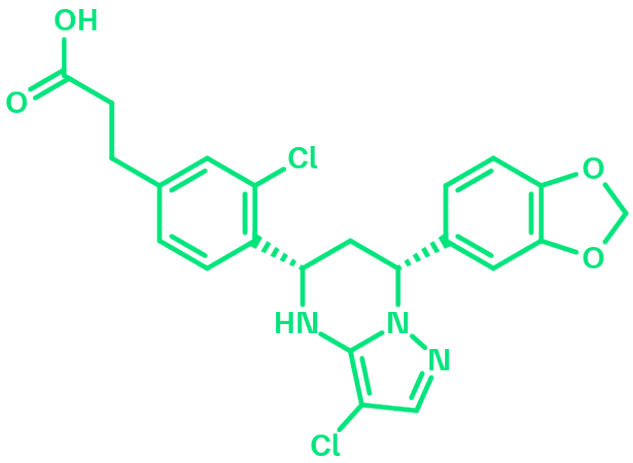

Figure 1: 2D structure of BI-1136, an orally bioavailable BCL6 degrader

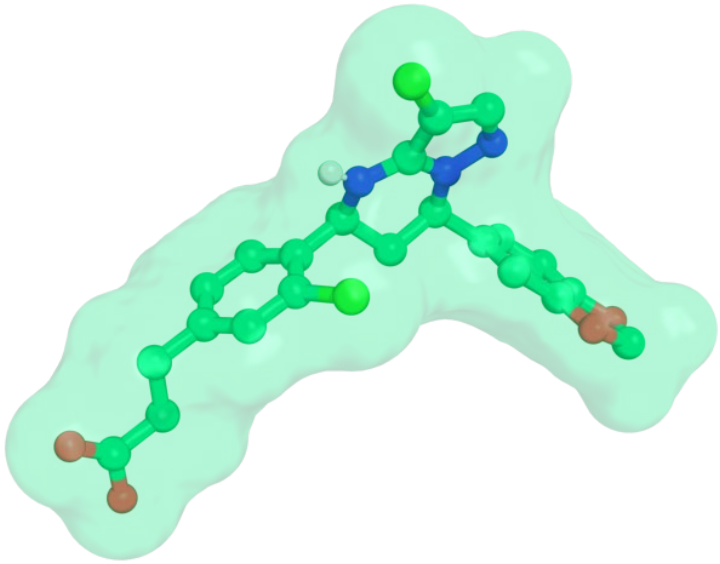

Figure 2: BI-1136, 3D conformation.

Highlights

With BI-1136, we share a selective orally bioavailable BCL6 degrader with high potency. The molecule is suitable for *in vivo* testing in rodents. Mechanistically, the molecule acts as a BCL6 specific protein degrader and displays a strong induction of expression of BCL6-repressed genes. Having been previously offered as a molecule for collaboration, we now share BI-1136 with the entire research community.

Target information

The transcriptional regulator BCL6 represses genes required for the differentiation of B-cells in germinal centers (GC)[2]. Errors in the GC reaction can give rise to mutated B cells that maintain an elevated proliferation and fail to differentiate, contributing to the genesis of DLBCL[3]. BCL6 is an oncogenic driver for DLBCL[4,5,6,7] and its expression is frequently elevated by mutations in DLBCL. However, despite significant research efforts, the clinical relevance of targeting BCL6 in DLBCL remains to be proven.

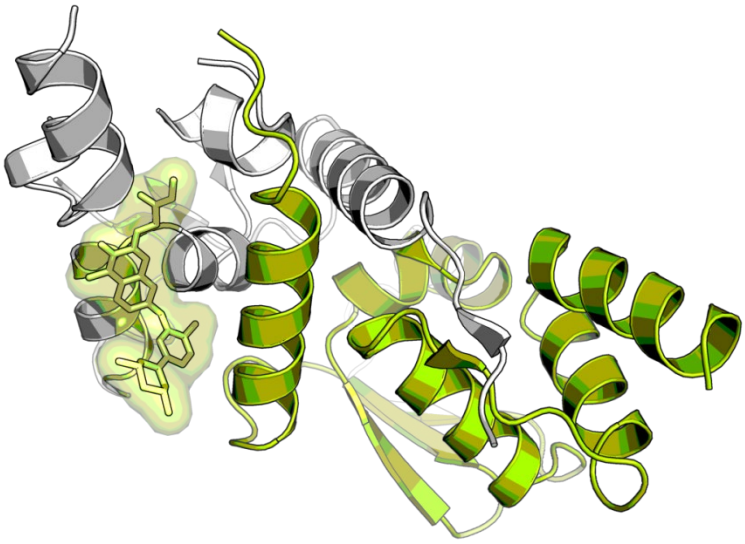

Figure 3: BCL6-BTB dimer with BI-3802, as observed by X-ray[1]. BI-3802 binds at the interface of two monomers (monomers are shown in green and grey).

In vitro activity

BI-1136 is an unprecedented molecule that potently inhibits the interaction of the BTB/POZ domain of BCL6 with several co-repressors *in vitro* ($IC_{50} \leq 50$ nM). In a cellular context, the BCL6 degrader inhibits the BCL6::co-repressor complex formation with an IC_{50} of 210 nM. Moreover, our BCL6 degrader was found to be a potent and efficacious degrader of the BCL6 protein in mouse and human diffuse large B-cell lymphoma (DLBCL) cell lines (DC_{50} = 63 nM in SU-DHL-4 cells) as well as in other BCL6 expressing cells tested (macrophages, NSCLC, Burkitt and breast cancer cell lines). It induces BCL6 target genes in SU-DHL-4 cells with an EC_{50} of 60-200nM. Interestingly we found that the BCL-6 degrader BI-1136 display significantly stronger induction of expression of BCL6-repressed genes than compounds that merely inhibit co-repressor interactions. The BCL6 degrader is mouse cross reactive and highly selective for BCL6.

PROBE NAME / NEGATIVE CONTROL	BI-1136	BI-1135
MW [Da, free base][a]	460.3	460.3
BCL6::BCOR ULight TR-FRET (IC_{50}) [nM][b]	44	17,625
BCL6::NCOR LUMIER (IC_{50}) [nM][b]	210	>10,000
BCL6 protein degradation (DC_{50}) [nM][b, c]	63	nA

[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] For assay conditions see ref.1
[c] In SU-DHL-4 cells

In vitro DMPK and CMC parameters

BI-1136 has acceptable solubility in water at neutral pH, high permeability in Caco-2 and MDCK assays and medium plasma protein binding and stability in moue liver microsomes.

PROBE NAME / NEGATIVE CONTROL	BI-1136	BI-1135
logP @ pH 2.0	5.5	nA
logD @ pH 2.0	nA	3.31
Solubility @ pH 6.8 [µg/mL]	>93	90
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	19.8	23
Caco-2 efflux ratio	0.6	1.1
MDCK permeability P_{appAB} @ 1µM [10^{-6} cm/s]	5.9	6.2
MDCK efflux ratio	2.4	2.6
Microsomal stability (human/mouse/rat) [% Q_H]	53 / 32 / <23	43 / 51 / 43
Hepatocyte stability (human/mouse/rat) [% Q_H]	18 / 23 / 8	11 / 35 / 22
Plasma Protein Binding (human/mouse/rat) [%]	99.2 / 96.8 / 97.9	99.8 / 99.4 / >99.6
hERG [inh. % @ 10 µM]	17.4	nA
CYP 3A4 (IC_{50}) [µM]	13	>50
CYP 2C8 (IC_{50}) [µM]	5	12.5
CYP 2C9 (IC_{50}) [µM]	>50	>50
CYP 2C19 (IC_{50}) [µM]	>50	>50
CYP 2D6 (IC_{50}) [µM]	>50	>50

In vivo DMPK parameters

The BCL6 degrader shows pharmacokinetic (PK) properties that are suitable for *in vivo* testing in several animal species and is well tolerated.

BI-1136	MOUSE	RAT
Clearance [% Q_H][a]	78	27
Mean residence time after *i.v.* dose [h][a]	0.44	1.5
t_{max} [h][b]	0.25	1.5
C_{max} [nM/µmol/kg][b]	59	155
F [%][b]	27	56
V_{ss} [L/kg][a]	1.8	1.7

[a] *i.v.* dose: 2 mg/kg
[b] *p.o.* dose: 20 mg/kg

In vivo pharmacology

PK properties in several animal species are suitable for once or twice daily oral dosing in acute or sub-chronic *in vivo* experiments, resulting in significant but not complete degradation of BCL6 in SU-DHL-4 xenografts. It is well tolerated.

Negative control

We encourage to order a BI-1135 as a negative control which is the inactive enantiomer of BI-1136 and displays a differentiated pharmacological profile.

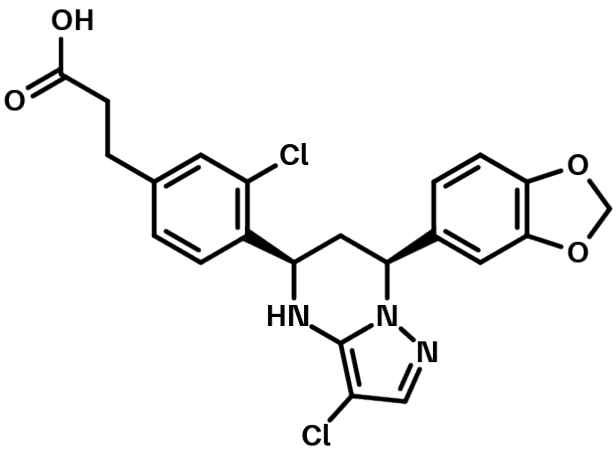

Figure 4: BI-1135 which serves as a negative control

Selectivity

BI-1136 shows high selectivity at 10 µM concentration versus a panel of 44 receptors (no binding), Kinase panel (38 kinases, no hit at 10 µM). The compound is well tolerated in mice up to 1 g/kg daily dose in mice. The negative control BI-1135 showed in 1 out of 44 targets inhibition with more than 50% @10 µM. It showed binding in the endothelin (ETA/H) assay with an inhibition of 54% @10 µM.

SELECTIVITY DATA AVAILABLE	BI-1136	BI-1135
SafetyScreen44™ with kind of support of eurofins	Yes	Yes
Invitrogen®	Yes	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

Recent publications using BI-3802, a potent BCL6 degrader[8,9,10,11].

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

BI-1136 and its negative control BI-1135 have been designed as part of a collaboration with Forma Therapeutics. Forma is now a fully owned subsidiary of Novo Nordisk A/S.

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