

BCL6 degrader | BI-1136

(*in vivo*, orally bioavailable molecule)

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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

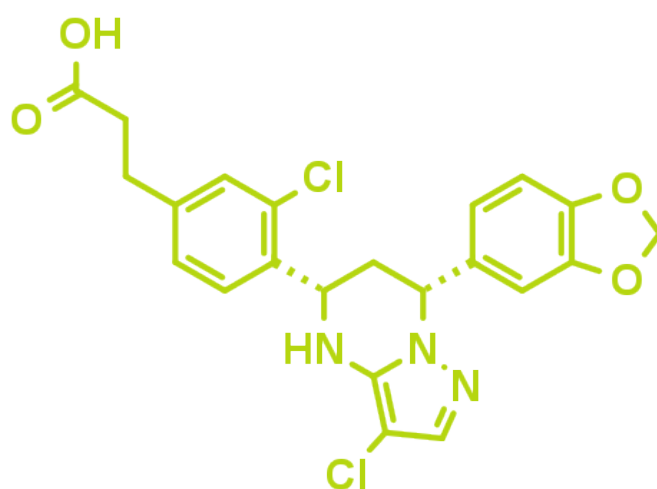


Figure 1: 2-D structure of BI-1136, an orally bioavailable BCL6 degrader

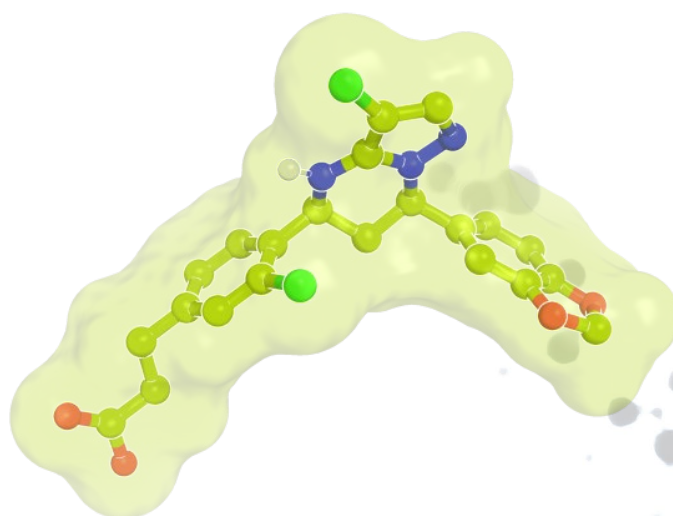


Figure 2: BI-1136, 3D conformation.

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 previously been offered as a molecule for collaboration, we now share BI-1136 with the entire research community and take over all shipment costs.

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 diffuse large B-cell lymphoma (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.

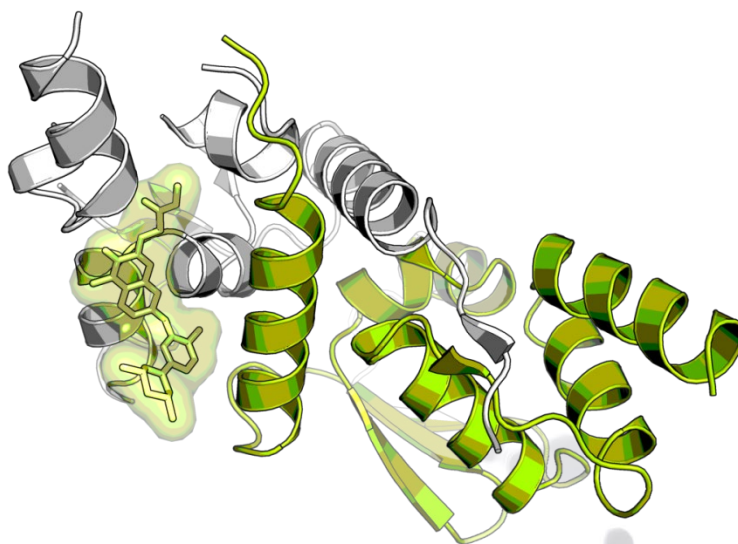


Figure 3: BCL6-BTB dimer with BI-3802, as observed by X-ray.¹ BI-3802 binds at the interface of two monomers (monomers are shown in green and grey).

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 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 60-200 nM. Interestingly we found that the BCL6 degrader BI-1136 displays 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]	460.3	460.3
BCL6::BCOR ULight TR-FRET (IC_{50}) [nM] ^a	44	17,625
BCL6::NCOR LUMIER (IC_{50}) [nM] ^a	210	>10,000
BCL6 protein degradation (DC_{50}) [nM] ^{a, b}	63	N/A

^a for assay conditions see ref. 1

^b 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 mouse liver microsomes.

PROBE NAME / NEGATIVE CONTROL	BI-1136	BI-1135
logP (pH 2.0)	5.5	N/A
logD (pH 2.0)	N/A	3.31
Solubility @ pH 6.8 [$\mu\text{g/ml}$]	>93	90
CACO permeability @ pH 7.4 [$*10^{-6}$ cm/s]	19.8	23
CACO efflux ratio	0.6	1.1
MDCK permeability $P_{\text{app}a-b/b-a}$ @ $1\mu\text{M}$ [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. % @ $10\mu\text{M}$]	17.4	N/A
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 iv 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. (2 [mg/kg])

^b p.o. (20 [mg/kg])

In vivo pharmacology

The PK properties of BI-1136 in several animal species render it 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.

Negative control

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

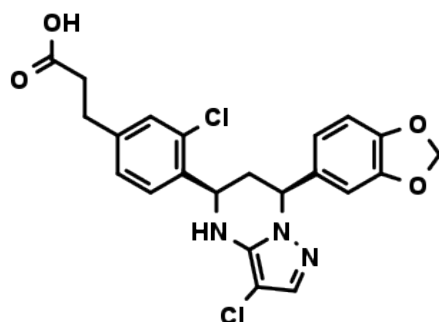



Figure 4: BI-1135 which serves as a negative control

Selectivity

BI-1136 shows high selectivity at 10 μM concentration versus a panel of 44 receptors (no inhibition), Kinase panel (38 kinases, no hit at 10 μM). The compound is well tolerated in mice in doses up to 1g/kg daily. The negative control BI-1135 showed inhibition with more than 50% @10 μM in 1 out of 44 targets. 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 support of  eurofins	Yes	Yes
Invitrogen®	Yes	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

BI-1136 is complementary to BI-3802, a potent BCL6 degrader with *in vitro* activity. For more information see references 8,9,10,11.

Supplementary data

2-D structure files can be downloaded free of charge from [openMe](#).

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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