BRD7/BRD9 inhibitor | BI-7273

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Summary

BI-7273 is a dual BRD7/BRD9 inhibitor (IC_{50}, BRD7 = 117 nM, IC_{50}, BRD9 = 19 nM (Alpha assay)) and shows excellent selectivity versus the BET family.

Chemical Structure

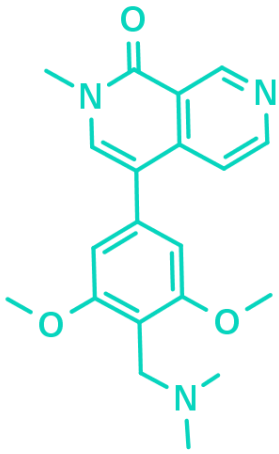

Figure 1: 2-D structure of BI-7273, a dual inhibitor of BRD7 and BRD9

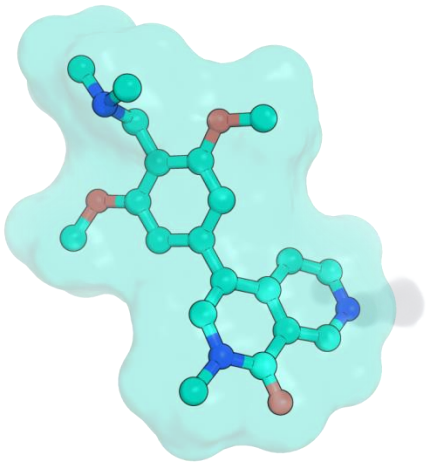

Figure 2: BI-7273, 3D conformation, as observed in complex with BRD9 by X-ray crystallography

Highlights

BI-7273 was developed in collaboration with the Structural Genomics Consortium (SGC). The potent dual BRD7/BRD9 inhibitor shows 30-fold better potency in the BRD7 AlphaScreen assay compared to our more selective BRD9 inhibitor BI-9564.
BI-7273 binds with high affinity to BRD9 and BRD7 (IC_{50}(BRD9, AlphaScreen) = 19 nM; IC_{50}(BRD7, AlphaScreen) = 117 nM) and is selective versus other BET family members (> 100 µM AlphaScreen). Binding affinity to CECR2 as the only off-target (IC_{50} (ITC) = 187 nM).
It shows good ADME parameters which make it a suitable probe compound for *in vitro* and *in vivo* experiments.[1] The negative control BI-6354 is recommended for *in vitro* experiments.

Target information

The mammalian switch/sucrose nonfermentable (SWI/SNF) complex is one of four mammalian chromatin remodelling complexes. Recurrent inactivating mutations in certain subunits of this complex have been identified in different cancers. Despite its known roles in tumor suppression, the mammalian SWI/SNF complex has recently received attention as a potential target for therapeutic inhibition.[2]

The human bromodomain family encompasses 61 domains, found on 46 proteins and BRD9 and BRD7 proteins containing a single acetyl-lysine reader bromodomain are components of the chromatin remodelling SWI/SNF BAF complex. A recent study highlighted a role of another SWI/SNF subunit, BRD9, in leukemia growth. The BRD9 bromodomain (BD) was shown to be required for the proliferation of acute myeloid leukemia (AML) cells.[3]

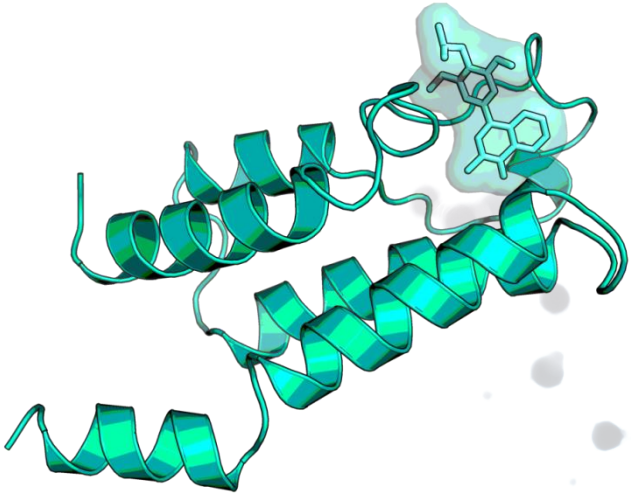

Figure 3: BRD9 with BI-7273, as observed by X-ray.[1]

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-7273	BI-6354
MW [Da]	353.4	279.3
ITC(BRD9) (K_D) [nM][a]	15	n.d.
AlphaScreen(BRD9) (IC_{50}) [nM][a]	19	27192
AlphaScreen(BRD7) (IC_{50}) [nM][a]	117	81896
AlphaScreen(BRD4-BD1) (IC_{50}) [nM][a]	>100000	>100000

[a]for detailed assay conditions see Ref. 1

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-7273			BI-6354		
logP	2.0			n.d.		
Solubility @ pH 6.8 [µg/ml]	>91			>59		
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	1.4			n.d.		
CACO efflux ratio	26			n.d.		
Microsomal stability (human/mouse/ rat) [% Q_H]	<24	56	<23	<24	n.d.	<23
Hepatocyte stability (human/mouse/ rat) [% Q_H]	17	58	7	n.d.		

Plasma protein binding (human/mouse/ rat) [%]	31	44	33	n.d.
CYP 3A4 (IC_{50}) [µM]	>50			n.d.
CYP 2C8 (IC_{50}) [µM]	>50			n.d.
CYP 2C9 (IC_{50}) [µM]	>50			n.d.
CYP 2C19 (IC_{50}) [µM]	>50			n.d.
CYP 2D6 (IC_{50}) [µM]	>50			n.d.

In vivo DMPK parameters

BI-7273 showed moderate to high absorptive permeability and moderate in vivo plasma clearances upon i.v. dosing. BI-7273 displayed good oral bioavailability.

BI-7273	MOUSE
Clearance [% Q_H]	57[a]
Mean residence time after iv dose [l/kg]	0.5[a]
t_{max} [h]	1.7[b]
C_{max} [nM]	2970[b]
F [%]	39[b]
V_{ss} [l/kg]	1.6[a]

[a] *i.v. 5* mg/kg
[b] *p.o.* 20 mg/kg

In vivo pharmacology

No *in vivo* pharmacological studies have been performed with BI-7273.

Negative control

BI-6354 is available as an *in vitro* negative control. It shows only very weak potency on BRD9 and BRD7 and no potency on BRD4. Also see the “In vitro activity” section.

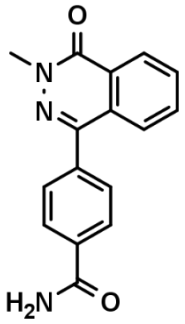

Figure 4: BI-6354 which serves as an *in vitro* negative control

Selectivity

BI-7273 was screened on 48 bromodomains and 31 kinases. Beside BRD9 (K_D = <1 nM) and BRD7 (KD = <1 nM) only CECR2 (88 nM) and FALZ (K_D = 850 nM) showed a K_D < 1 µM in the DiscoverX assay (48 bromodomains). BI-7273 showed a K_D of 187 nM in the CECR2 ITC assay, but no cellular effect at 1 µM in FRAP assay. From the 31 kinases only 3 kinases (ACVR1, TGFBR1, ACVR2B) showing an % inhibition of > 43% @10 µM, for which the measured IC_{50} values were all > 3.5 µM.

BI-7273	SELECTIVITY DATA AVAILABLE
Cerep®	No
Panlabs®	No
Invitrogen®	Yes
DiscoverX®	Yes
Dundee	No

Co-crystal structure of the Boehringer Ingelheim probe compound and the target protein.

The Xray crystal structure of target in complex with BI-9564 is available (PDB code: 5EU1)[1].

Reference molecule(s)

LP99[4], I-BRD9[5], 'compound 28'[6], BI-9564[1,7].

Summary

BI-7273 is a potent dual BRD7/BRD9 inhibitor with 30 fold better potency in the BRD7 AlphaScreen assay compared to our more selective BRD9 inhibitor BI-9564.
BI-7273 binds with high affinity to BRD9 and BRD7 (IC_{50}(BRD9, AlphaScreen) = 19 nM; IC_{50}(BRD7, AlphaScreen) = 117 nM) and is selective versus other BET family members (> 100 µM AlphaScreen). Binding affinity to CECR2 as the only off-target (IC_{50} (ITC) = 187 nM).
It shows good ADME parameters which make it a suitable probe compound for *in vitro* and *in vivo* experiments to test the biology of BRD7 and BRD9.[1,7] The negative control BI-6354 is recommended for *in vitro* experiments.

Supplementary data

Selectivity data and 2-D structure files can be downloaded free of charge from opnMe.

References

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