BPTF inhibitor | BI-7190

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Summary

BI-7190 is a probe to study the impact of BPTF bromodomain inhibition *in vitro* and *in vivo*. It binds with high affinity to the bromodomain of BPTF K_D (BPTF, DiscoveRx) = 3.5 nM, displays good cellular potency EC_{50} (BPTF, nanoBRET) = 58, and selectivity to bromodomain family members.

Chemical Structure

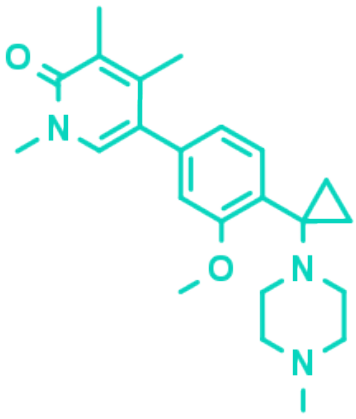

Figure 1: 2-D structure of BI-7190 an inhibitor of the BPTF bromodomain

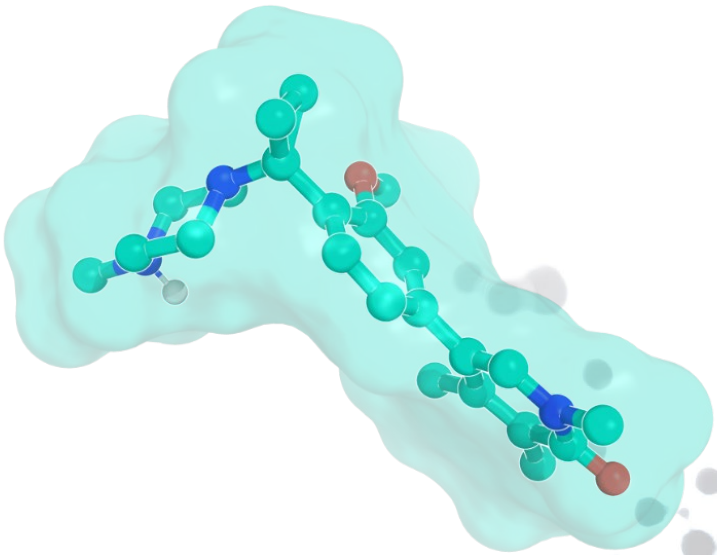

Figure 2: BI-7190, 3D conformation, as observed in complex with the BPTF bromodomain

Highlights

BI-7190 was discovered by screening of selected analogues of the BRD9 bromodomain probe BI-9564.[1] The combination of potency, selectivity, and good ADME parameters make it ideal to study the impact of the inhibition mediated by the bromodomain of the epigenetic reader function of BPTF (*in vitro* and *in vivo*). BI-4827 is used as negative control *in vitro*.

Target information

BPTF (Bromodomain PHD Finger Transcription Factor) is a core component of the nucleosome remodeling factor (NURF) complex, an essential component of chromatin biology. Knowledge of its function is required to fully understand how the genome is regulated. This protein is a histone-binding component of the NURF complex.[2] It recognizes acetylated lysines on histone H4, through its bromodomain, as well as di- and tri-methylated lysine 4 on histone H3, through its PHD fingers.[3-5] The NURF complex catalyzes ATP-dependent nucleosome sliding and facilitates transcription of chromatin. The potential pro-tumorigenic role of BPTF has been reported across several indications over the last few years.[6]

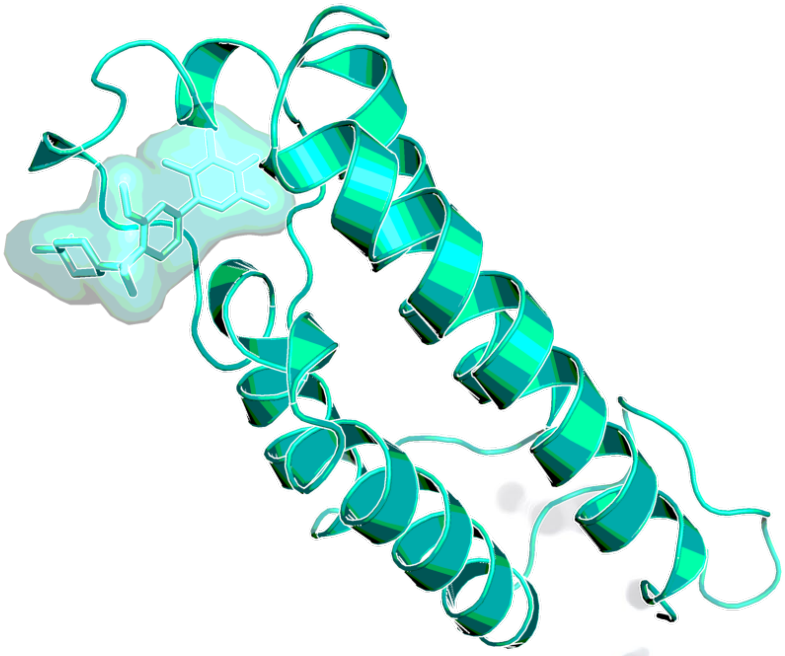

Figure 3: Bromodomain of BPTF with BI-7190, as observed by x-ray.

In vitro activity

The compound binds with high affinity to BPTF (DiscoveRx K_D = 3.5 nM). Cellular target engagement was confirmed by nanoBRET (BPTF EC_{50} = 58 nM) and a more than 19-fold selectivity window towards the bromodomain family off-targets was observed (e.g., nanoBRET (BRD9) EC_{50} = 1,100nM).

PROBE NAME / NEGATIVE CONTROL	BI-7190	BI-4827
MW [Da]	381.51	393.40
DiscoveRx (BPTF) (K_D) [nM]	3.5	> 10,000
ITC (BPTF) (K_D) [nM][a]	85	> 50,000
nanoBRET (BPTF) EC_{50} [nM]	58	> 50,000
nanoBRET (BRD9) EC_{50} [nM]	1,100	> 50,000

[a] 20 mM HEPES pH 7.5, 150 mM NaCl, 1 mM TCEP and 5% (w/v) glycerol.

In vitro DMPK and CMC parameters

BI-7190 has good solubility in water at neutral pH, high absorptive permeability and a low efflux ratio in the Caco-2 assay, relatively low plasma protein binding and species-dependent *in vitro* metabolic stability in liver microsomes (low in mouse, moderate to high in rat and human).

PROBE NAME / NEGATIVE CONTROL	BI-7190	BI-4827
clogP	2.9	2.6
Solubility @ pH 6.8 [µg/ml]	> 84	> 100
CACO permeability $P_{app, a-b}$ @ 10 µM [$*10^{-6}$ cm/s]	21	39
CACO efflux ratio	1.7	0.97
MDCK permeability $P_{app, a-b}$ @ 10 µM [10^{-6} cm/s]	7.2	6.4

MDCK efflux ratio	10	7.7
Microsomal stability (human/mouse/rat) [% Q_H]	28 / 78 / <23	<24 / - / <23
Hepatocyte stability (human/mouse/rat) [% Q_H]	12 / 91 / 40	≤ 6 / 69 / 48
Plasma protein binding (human/mouse/rat) [% bound]	72 / 67 / 59	43 / 33 / 35
hERG [inh. % @ 10 µM]	15	7.9
CYP 3A4 (IC_{50}) [µM]	≥ 38	> 50
CYP 2C8 (IC_{50}) [µM]	> 50	> 50
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

BI-7190 was profiled in mice in an i.v. bolus single dose pharmacokinetic study, resulting in a moderate to high plasma clearance and high volume of distribution. With an oral dose of 30 mg/kg in mice the compound demonstrated efficient intestinal absorption with high plasma exposure and excellent oral bioavailability of 145 % due to non-linear PK.

BI-7190	MOUSE
Plasma clearance 5 mg/kg i.v. (% Q_H)	64
Vss 5 mg/kg i.v. [l/kg]	2.1
Mean residence time 5 mg/kg i.v. [h]	0.6

AUC(0-inf) 30 mg/kg p.o. [nM·h]	33,200
t_{max} 30 mg/kg p.o. [h]	1.0
C_{max} 30 mg/kg p.o. [nM]	7,900
F 5 mg/kg p.o. (%)	145

In vivo pharmacology

n.a

Negative control

BI-4827 (BPTF K_D (BPTF, DiscoveRx) > 10µM) is an inactive analog of BI-7190 and can be used as negative control for *in vitro* experiments.

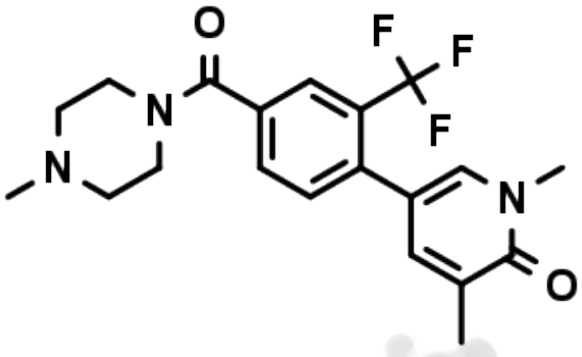

Figure 4: BI-4827 which serves as a negative control

Selectivity

No significant hits were observed in Kinase and Cerep panels. BI-7190 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 negative control BI-4827 shows high selectivity hitting 0/44 targets inhibition with more than 50% @10 µM.

SELECTIVITY DATA AVAILABLE	BI-7190	BI-4827
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	Yes	No
DiscoverX®	Yes	Yes
Dundee	No	No

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

The Xray crystal structure of the BPTF bromodomain in complex with BI-7190 is available (PDB code: 8AG2)[1].

Reference molecule(s)

NVS-BPTF-1[7], TP-238[8]

Supplementary data

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

References

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