opnMe by Boehringer Ingelheim

sEH Inhibitor

BI-1935

Boehringer Ingelheim

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Summary

BI-1935 is a potent and selective small molecule inhibitor of the enzyme soluble Epoxide Hydrolase (sEH) and can be used as *in vitro* or *in vivo* tool compound.

Chemical Structure

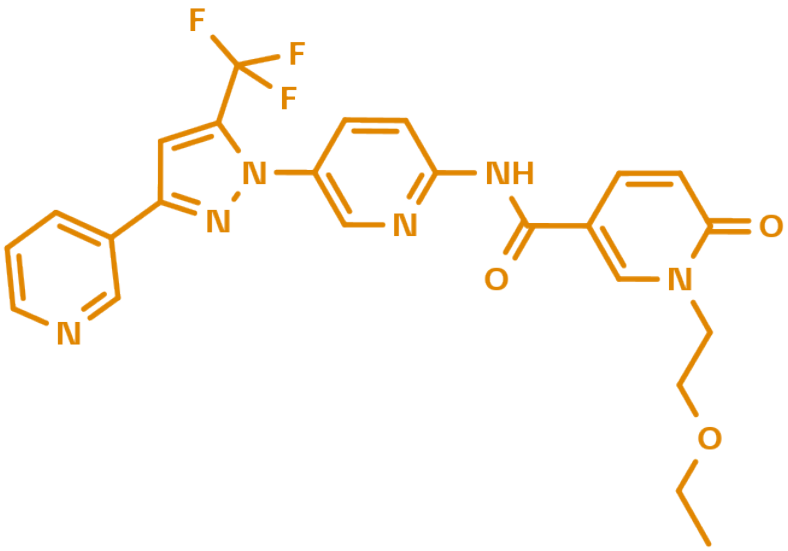

Figure 1: 2D structure of BI-1935, an inhibitor of sEH

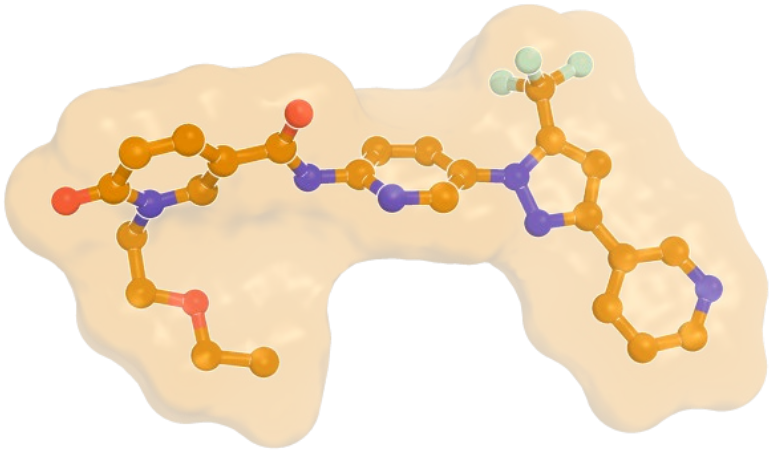

Figure 2: 3D structure of BI-1935, an inhibitor of sEH

Highlights

BI-1935 is a potent small molecule inhibitor of soluble Epoxide Hydrolase (sEH) (IC_{50} = 7 nM). It showed good selectivity against hCYP epoxygenases 2J2/2C9/2C19 and IL-2. In Dahl salt-sensitive rats, BI-1935 showed a dose-dependent effect on mean arterial pressure. This compound is suitable for both *in vitro* and *in vivo* experiments.

Target information

The enzyme soluble Epoxide Hydrolase (sEH) is involved in the metabolism of chemical mediators originated from arachidonic acid[2,3]. sEH catalyzes the hydrolysis of epoxyeicosatrienoic acids (EETs) which is derived from oxidation of arachidonic acid by CYP2J & CYP2C to the corresponding dihydroxyeicosatrienoic acids (DHETs). Inhibition of sEH is expected to increase EETs levels and thereby potentiating *in vivo* pharmacological effects which include anti-inflammatory and vasodilatory properties. Selective inhibition of Soluble epoxide hydrolase has been invoked to account for the antihypertensive effect of dicyclohexyl urea in the spontaneously hypertensive rat[4,5]. EETs elicit a vasodilatory response by acting as an endothelium derived hyperpolarizing factor that mediates vasodilatation through the stimulation of calcium-activated potassium channels in smooth muscle cells[6,7,8]. Selective sEH inhibitors have also shown beneficial effects in an angiotensin II-dependent model of hypertension in the Sprague–Dawley rat[9], and protective action in models of hypertension induced renal damage and failure[10]. An sEH inhibitor significantly decreased the total bronchoalveolar lavage cell number in tobacco smoke-exposed rats, with significant reductions noted in neutrophils, alveolar macrophages, and lymphocytes in a rat model of airway inflammation[11]. These reports suggest that inhibition of sEH represents a potentially method for the treatment of inflammatory and cardiovascular diseases[1].

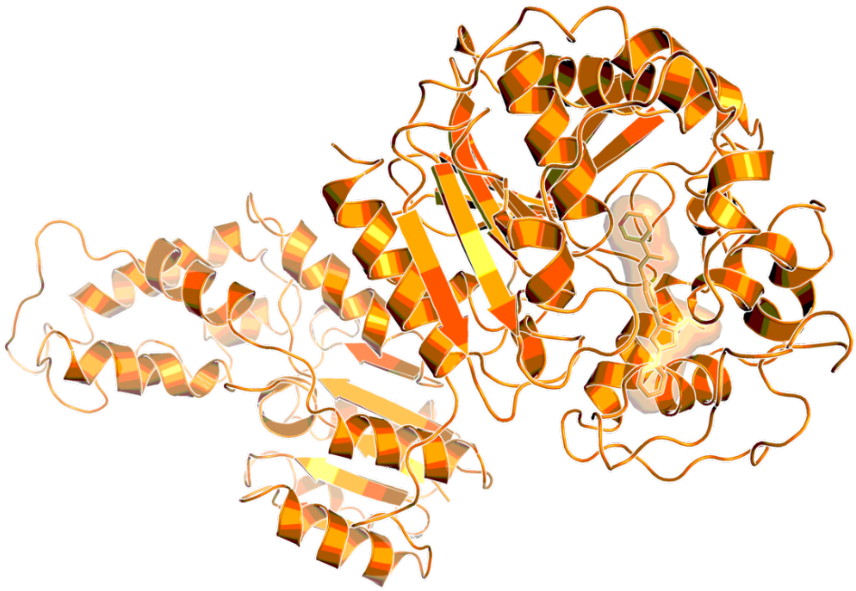

Figure 3: Human sEH in complex with a pyrazole agonist (PDB code: 3OTQ).

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-1935	BI-2049
MW [Da, free base][a]	498.5	503.5
h-seh (IC_{50}) [nM][b]	7	>100,000
r-sEH (IC_{50}) [nM][c]	7	-
sEH_HepG2 [nM][d]	<1	-
sEH_RAT FPDR [nM]	7.4	-
IL-2 [µM]		-

[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] Human and rat soluble Epoxide Hydrolase inhibition
[c] Rat soluble Epoxide Hydrolase inhibition
[d] Cellular assay for inhibition of sEH in human Hep G2 Cells, ELISA readout

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-1935	BI-2049
logD @ pH 11	3	5.5
Solubility @ pH 7 [µg/mL]	20.7	Not fully soluble
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	32	n.d.
Caco-2 efflux ratio	1	n.d.
Microsomal stability (human/mouse/rat) [% Q_H]	48 / 50 / 45	34 / - / 33
Hepatocyte stability (human/mouse/rat) [% Q_H]	28 / 95 / 84	n.d.
Plasma Protein Binding (human / rat) [%]	97.7 / 99.1	>99 / n.d.
CYP 2J2 [µM]	3	n.d.
CYP 2C9 [µM]	4.1	n.d.
CYP 3A4 [µM]	>50	n.d.
CYP 2D6	>50	n.d.

In vivo DMPK parameters

Pharmacokinetic parameters of BI-1935 in rats

BI-1935	RAT
Clearance [mL/min/kg][a]	4.1
Mean residence time after *i.v.* dose [h][a]	3
t_{max} [h][b]	2.7
V_{ss} [L/kg][a]	0.5
C_{max} [µM][b]	10670
F [%]	100

[a] *i.v.* dose: 0.6 mg/kg
[b] *p.o.* dose: fasted 1.5 mg/kg

Negative control

The molecule BI-2049 can be used as *in vitro* negative control ($IC_{50\ h\text{-}sEH}$ > 3 µM)
Until 21.03.2018, the compound BI-64BS was offered on opnMe.com as *in vitro* negative control ($IC_{50\ h\text{-}sEH}$ ≥ 100 µM) which was replaced by BI-2049 which is structurally more similar to BI-1935.

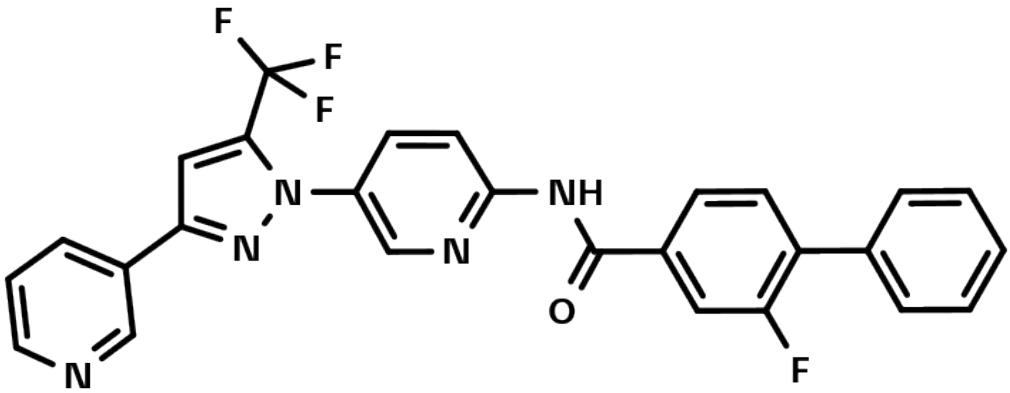

Figure 4: BI-2049, negative control

Selectivity

A Boehringer Ingelheim in-house screen of BI-1935 against hCYP epoxygenases 2J2/2C9/2C19 and IL-2 showed >100-fold selectivity (> 1µM for all). A Eurofins-Panlabs panel was measured against 67 targets (please refer to supplementary data). 61 / 67 < 20% Inhibition @ 10 µM, 5 / 67 < 80% Inhibition @ 10 µM, Thromboxane Synthase 96% inhibition @ 10 µM (IC_{50} = 0.132 µM). 5LO (5-Lipoxygenase) 66% inhibition @ 10 µM (IC_{50} = 5.92 µM).

The selectivity of the compound against a selection of 315 GPCR targets was also tested simultaneously and in parallel using the PRESTO-TANGO selectivity screen provided by the Psychoactive Drug Screening Program (PDSP)[13]. Significant inhibition (modulation) observed for 2 of the 315 GPCRs tested @ 10 µM (DAT 82%Inh, Sigma 1 50%Inh).

SELECTIVITY DATA AVAILABLE	BI-1935	BI-2049
SafetyScreen44™ with kind support of eurofins	Yes	Yes
PRESTO-TANGO (PDSP)	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

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

No X-ray co-crystal structure available

Reference molecule(s)

For a review on sEH inhibitors please refer to reference 12

Supplementary data

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

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