sEH inhibitor | BI-1935

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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

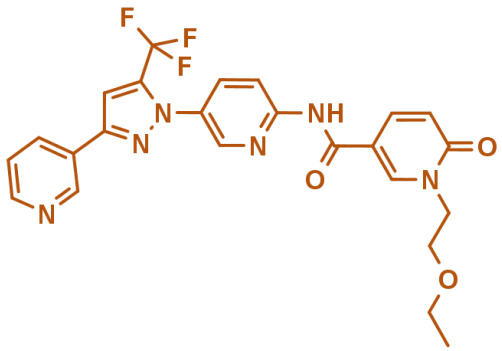

Figure 1: 2-D structure of BI-1935, an inhibitor of sEH

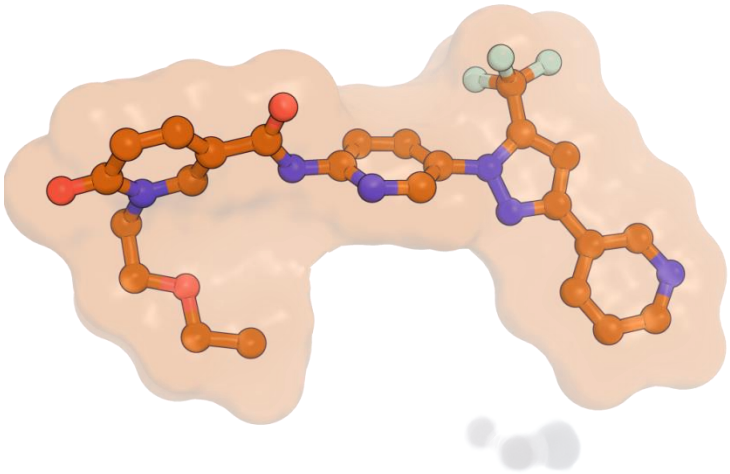

Figure 2: 3-D structure of BI-1935, an inhibitor of sEH

Highlights

BI-1935 is a potent and selective small molecule inhibitor of Soluble epoxide hydrolase (sEH). In a biochemical h-sEH binding assay it shows an IC_{50} of 7 nM and is also highly active in a cellular Hep G2-DHET assay format (IC_{50} < 1 nM). BI-1935 can also be used *in vivo* and showed a dose dependent effect on mean arterial pressure blood pressure in Dahl salt sensitive rats. It also shows good selectivity against hCYP epoxygenases 2J2/2C9/2C19 and IL-2.

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]

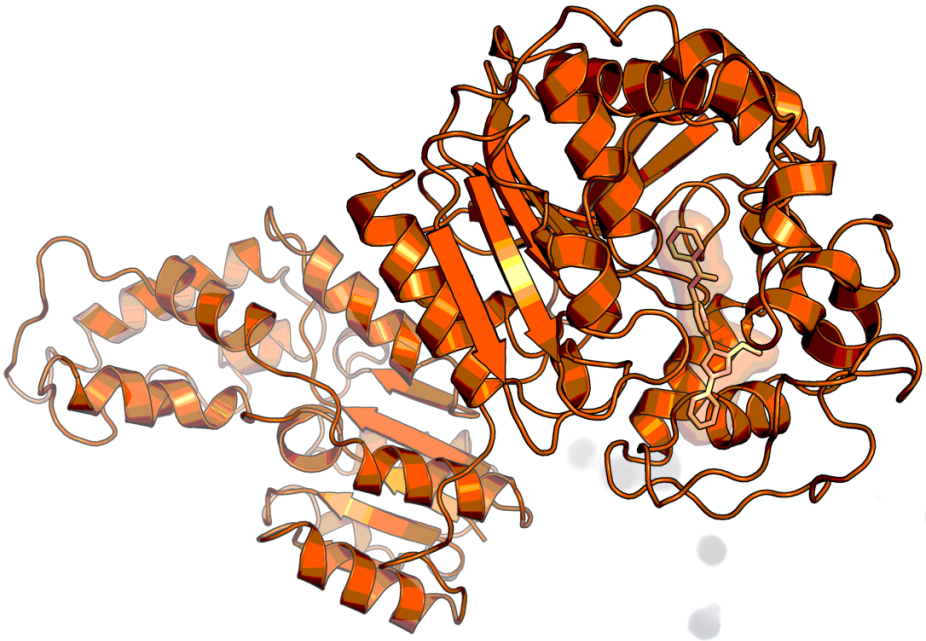

Figure 3: Human sEH in complex with a pyrazole agonist (PDB code: 3OTQ)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-1935	BI-64BS
MW [Da]	498.5	388.9
h-sEH (IC_{50}) [nM][a]	7	>100,000
r-sEH (IC_{50}) [nM][b]	7	-
sEH_HepG2 [nM][c]	<1	-
sEH_RAT FPDR[nM]	7.4	-
CYP 2J2 [µM]	3	-
CYP 2C9 [µM]	1	-
CYP 2C19 [µM]	10	-
CYP 3A4 [µM]	>50	-
CYP 2D6	>50	-
IL-2 [µM]		-

[a]Human and rat soluble epoxide hydrolase inhibition, [b]Rat soluble epoxide hydrolase inhibition; [c]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	
Aqueous solubility @ pH 6.8 [µg/ml]	37	
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	32	
CACO efflux ratio	1	
Hepatocyte clearance [% Q_H] human /rat	72	43
Plasma protein binding [%] human / rat	97.7	99.1

In vivo DMPK parameters

Pharmacokinetic parameters of BI-1935 in rats

PROBE NAME	BI 1935
t_{max} [h][b]	2.7
C_{max} [µM][b]	3.6
AUC_{0-inf} [nMh][b]	30582
F [%][b]	85
CL [ml/min/kg][a]	2.9
V_{ss} [l/kg][a]	0.5
MRT [h]	3
AUC_{0-inf} [nMh][a]	14463

[a] *iv* (1.2 mg/kg); [b] *po* fasted (3 mg/kg)

Negative control

The molecule BI-64BS can be used as *in vitro* negative control ($IC_{50\ h\text{-}sEH}$ = >100 µM)

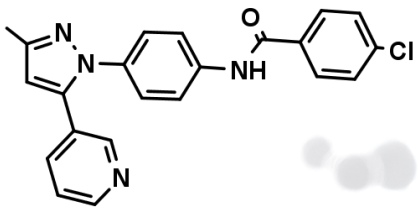

Figure 4: BI-64BS, negative control

Selectivity

A Boehringer Ingelheim in-house screen of BI-1935 against hCYP epoxygenases 2J2/2C9/2C19 and IL-2 showed >100fold 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).

BI-1935	SELECTIVITY DATA AVAILABLE
Cerep®	No
Panlabs®	Yes
Invitrogen®	No
DiscoverX®	No
Dundee	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

Summary

BI-1935 is a potent and selective small molecule inhibitor of Soluble epoxide hydrolase (sEH). In a biochemical binding assay h-sEH it shows an IC_{50} of 7 nM and is also highly active in a cellular Hep G2-DHET assay format (IC_{50} < 1 nM). BI-1935 can also be used *in vivo* and showed a dose dependent effect on mean arterial pressure blood pressure in Dahl salt sensitive rats. It also shows good selectivity against hCYP epoxygenases 2J2/2C9/2C19 and IL-2. A Eurofins-Panlabs panel was measured and is available. The compound is recommended to perform *in vitro* and *in vivo* research to explore sEH biology.

Supplementary data

Selectivity data can be downloaded free of charge from this site.

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