FLAP antagonist | BI 665915

Table of contents

Summary

BI 665915 demonstrates nanomolar FLAP binding potency and is a molecule suitable for testing biological hypotheses *in vitro* and also *in vivo*.

Chemical Structure

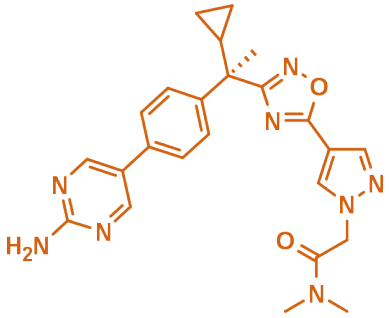

Figure 1: 2-D structure of BI 665915, an inhibitor of FLAP

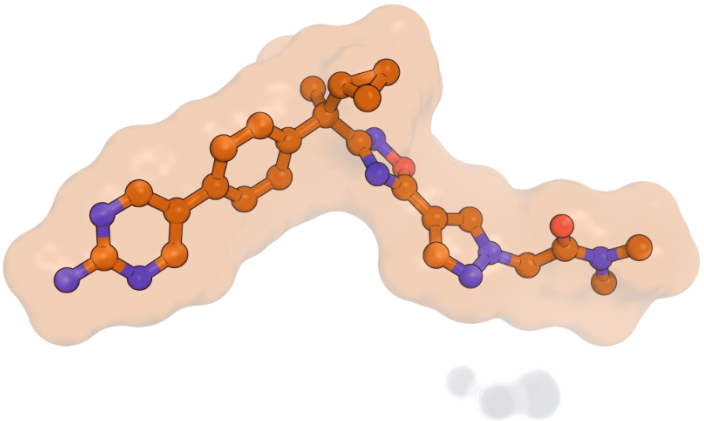

Figure 2: 3-D structure of BI 665915, an inhibitor of FLAP

Highlights

BI-665915 is a selective and highly potent 5-Lipoxygenase Activating Protein (FLAP) antagonist (IC_{50} = 1.7 nM). A favorable cross-species drug metabolism and attractive DMPK profile, with low i.v. plasma clearance and good oral bioavailability, make it an excellent tool for studying the LT pathway both *in vitro* and *in vivo*. BI-665915 has been shown to potently inhibit LTB4 production in mouse and human whole blood.

Target information

5-Lipoxygenase Activating Protein (FLAP) is an important protein in the Leukotriene (LT) pathway which acts as a partner of 5-lipoxygenase (5-LO) in the metabolism of arachidonic acid.[3]

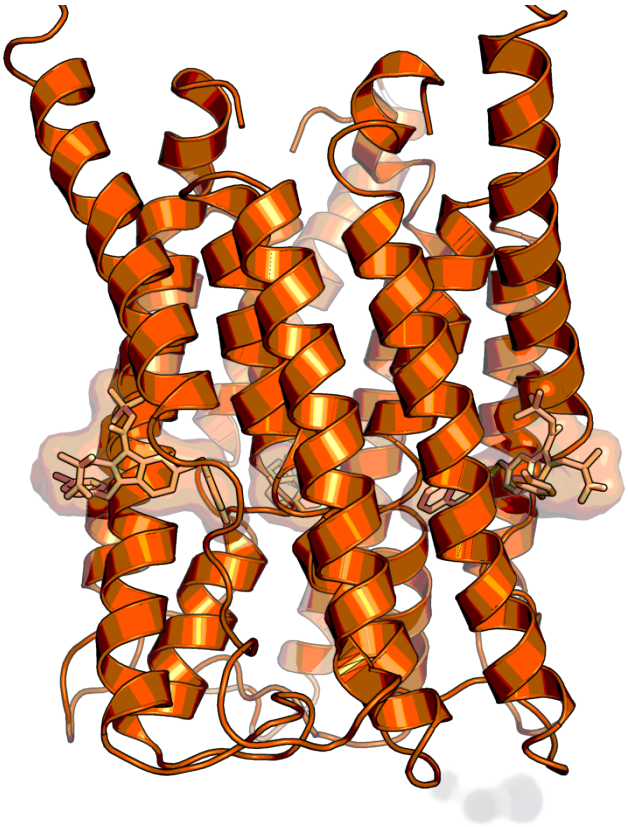

Figure 3: Human FLAP in complex with leukotriene synthesis inhibitors (PDB code: 2q7r)

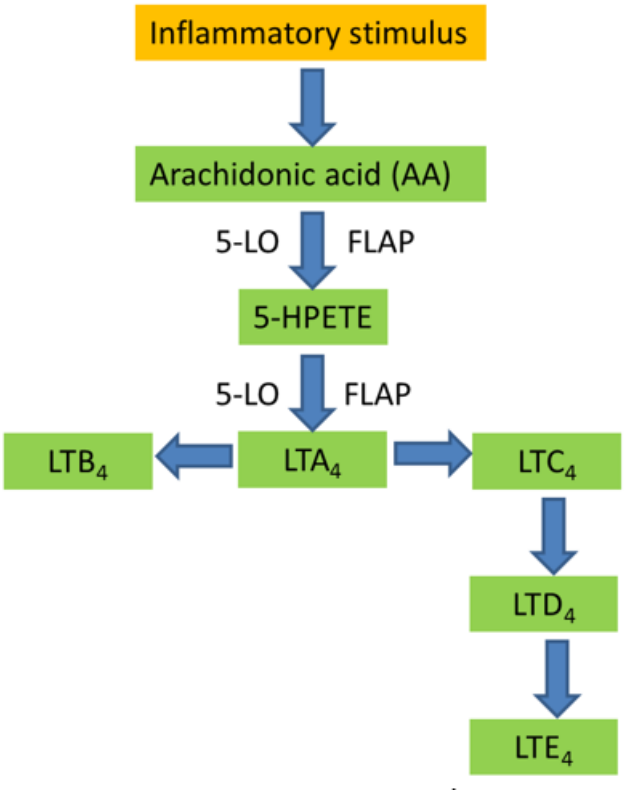

Figure 4: Leukotriene (LT) Pathway[1]

The membrane-attached 5-lipoxygenase activating protein (FLAP) binds to arachidonic acid (AA) and selectively transfers AA to 5-lipoxygenase (5-LO), which oxidizes AA to 5-hydroperoxyeicosatetraenoic acid (5-HpETE) followed by a dehydration to LTA_4.[1,3]

Leukotrienes (LTs) are a family of eicosanoid proinflammatory mediators that are biosynthesized from arachidonic acid (AA) *via* oxidative metabolism.[3] The leukotriene pathway constitutes a series of events underlying the inflammatory components of several diseases such as asthma, allergy, and atherosclerosis.[3,5,6]

More information about the target can be found in the following J. Med. Chem publication[1] by Hidenori Takahashi *et al.* and references cited therein.

In vitro activity

BI 665915 shows a high potency (IC_{50} = 1.7 nM in the FLAP binding assay).

PROBE NAME / NEGATIVE CONTROL	BI 665915	BI-0153[e]
MW [Da]	465	430
FLAP binding (IC_{50}) [nM][a]	1.7	670
FLAP Functional inhibition in human whole blood(IC_{50}) [nM][b]	45	>5,000
FLAP Functional inhibition in mouse whole blood (IC_{50}) [nM][c]	4,800	n.d.

[a] Binding assay; geometric mean values ($n \geq 3$), each determined from duplicate 10-point concentration–response curves;

[b] Human whole blood assays; geometric mean values ($n \geq 3$), each determined from duplicate 10-point concentration–response curves;

[c] Mouse whole blood assays performed using the same protocol as that for the hWB assay; geometric mean values ($n \geq 3$), each determined from duplicate 8-point concentration–response curves

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-665915	BI-0153[e]
Aqueous solubility @ pH 6.8 [µg/ml]	48	>43
CACO permeability @ pH 7.4 [$*10^{-6}$ cm/s]	34	n.d.
CACO efflux ratio	1.9	n.d.

Human hepatocyte clearance [% Q_H]	4.1	n.d.
Plasma protein binding human [% Q_H]	95.3	n.d.

[a] Please refer to the section negative control

In vivo DMPK parameters

BI 665915 was evaluated in rats, dogs, and cynomolgus monkeys (see table). The compound showed low *i.v.* plasma clearance over the three species and a good bioavailability of 45 to 63%.

In mice high exposures were observed at a dose of 100 mg/kg ($AUC_{0\text{-}inf}$ = 436,000 nM*h).

In vivo DMPK parameters of BI 665915 in the rat, dog, and cynomolgus monkey[a]

BI-665915	RAT	DOG	MONKEY
CL [% Q_H][b,c]	7.0	2.8	3.6
Mean residence time after *i.v.* dose (l/kg)[b]	3.1	23	4.8
F [%]	63	58	45.
V_{ss} [l/kg][b]	0.9	1.2	0.5

[a] Dose = *i.v.*, 1 mg/kg; dosing vehicle, 70% PEG; *p.o.*, 10 mg/kg; dosing suspension vehicle, 0.5% methyl cellulose/0.015% Tween; all DMPK parameters were determined after 11-time point blood sampling (0, 5, 15, 30 min, 1, 2, 4, 6, 8, 12, and 24h) per *i.v.* or *p.o.* dose.

[b] Mean values (n = 3).

[c] Value represents the percentage of hepatic blood flow.

In vivo pharmacology

BI 665915 shows an attractive DMPK profile and therefore was tested in a mouse *ex vivo* model of mechanism engagement. Blood samples were stimulated with calcimycin, and the levels of LTB_4

were measured. BI 665915 demonstrated dose-dependent LTB_4 production inhibition in mouse whole blood, 2h after a single oral dose.[1]

Negative control

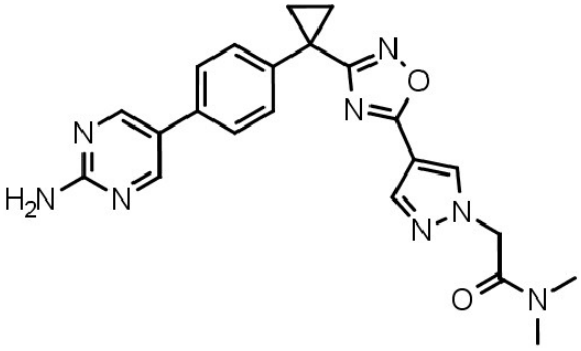

Figure 5: The closely related analogue BI-0153 can be used as an *in vitro* negative control

Selectivity

Extensive external screens covering 751 targets did not give strong hits (see supplementary data section)

Invitrogen® panel: 546 kinases < 30% inhibition @ 3µM

Eurofins Safety Panel 44™ External screen covering 68 targets: @ 10µM

Eurofins Safety Panel 44™ External screen covering 137 targets: @ 20µM

SELECTIVITY DATA AVAILABLE	BI 665915	BI-0153
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	Yes	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 recent review on FLAP inhibitors see Reference 2

Supplementary data

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

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