opnMe by Boehringer Ingelheim

P38 MAPK Inhibitor

BIRB 796

Boehringer Ingelheim

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Summary

Doramapimod (BIRB 796) is an orally available, nanomolar inhibitor of p38 MAP kinase, showing a high selectivity compared to other proteins. It is a potent inhibitor of the p38 mitogen activated protein kinase (MAPK). The compound shows anti-inflammatory properties at nanomolar concentrations in cell cultures, which are based on the suppression of TNF-α production. Efficacy of the compound was also shown in animal models of endotoxin-stimulated TNF-α release and collagen-induced arthritis.

Chemical Structure

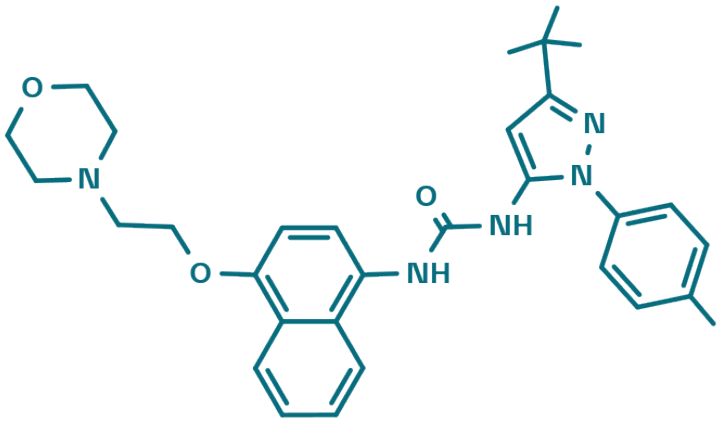

Figure 1: 2D structure of BIRB 796, a p38 MAP kinase inhibitor

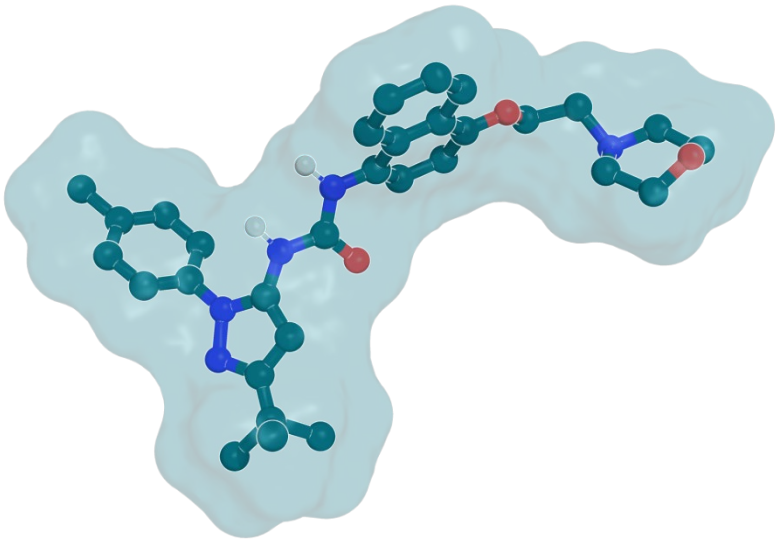

Figure 2: BIRB 3D conformation, as observed in complex (PDB Code: 1KV2)

Highlights

BIRB 796 (doramapimod) belongs to the diaryl urea class of inhibitors, binding to the allosteric site of human p38 mitogen activated protein kinase (MAPK). It can be used to study the regulation of proinflammatory cytokines, showing properties at nanomolar concentrations in cell cultures by suppressing the TNF-α production. The compound shows anti-inflammatory properties at nanomolar concentrations in cell cultures.

Target information

p38 MAPK plays a crucial role in regulating the production of proinflammatory cytokines, such as tumor necrosis factor and interleukin-1[1]. Blocking this kinase may represent an interesting concept for treating inflammatory diseases. Doramapimod is a Boehringer Ingelheim frontrunner compound of the diaryl urea class of inhibitors, which binds to an allosteric site of human p38 MAP kinase. The formation of this binding site requires a large conformational change not observed previously for other kinases, occurring in the Asp-Phe-Gly motif within the active site. Requirement for this change in conformation are slow binding kinetics, which could be demonstrated in solution studies of the compound.

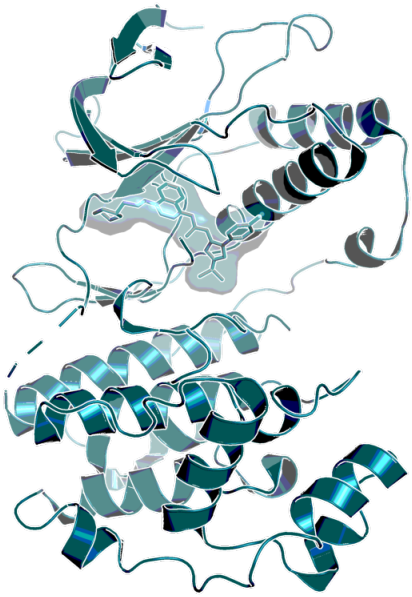

Figure 3: BIRB 796 in complex with p38 MAP kinase (PDB Code: 1KV2)

In vitro activity

BIRB 796 inhibits the isoforms α-δ of p38 MAPK with IC_{50} values of 38-520 nM[a].

PROBE NAME / NEGATIVE CONTROL	BIRB 796
MW [Da, free base][b]	527.7
p38α (IC_{50}) [nM]	38
p38β (IC_{50}) [nM]	65
p38γ (IC_{50}) [nM]	200
p38δ (IC_{50}) [nM]	520
B-Raf (IC_{50}) [nM]	83.4

[a]Assay conditions found in the reference 2
[b]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

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BIRB 796
logP @ pH 11	4.30
Solubility @ pH 6.8 [µg/mL]	<1
Caco-2 permeability AB @ pH7.4 [*10^{-6} cm/s]	33
Caco-2 efflux ratio	1.27
MDCK permeability P_{appAB}@ 1µM [10^{-6} cm/s]	16
MDCK efflux ratio	1.88
Microsomal stability (human/mouse/rat) [% Q_H]	88 / 82 / >88
Hepatocyte stability (human/mouse/rat) [% Q_H]	55 / - / 20

Plasma protein binding (human/mouse/rat) [%]	99.9 / >99.96 / >99.8
hERG [inh. % @ 0.1 µM]	14.8
CYP 3A4 (IC_{50}) [µM]	>50
CYP 2C8 (IC_{50}) [µM]	1.4
CYP 2C9 (IC_{50}) [µM]	5.0
CYP 2C19 (IC_{50}) [µM]	8.9
CYP 2D6 (IC_{50}) [µM]	>10
CYP 1A2 (IC_{50}) [µM]	>10

In vivo DMPK parameters

DMPK parameters were shared in the reference[2].

BIRB 796	MOUSE	RAT
Clearance[a]	0.33 [mL/min/kg]	4 [% Q_H]
t_{max} [h] [b]	1.0	n/A
C_{max} [ng/mL] [b]	27,000	5,500
F [%] [b]	23	80
V_{ss} [L/kg] [a]	0.07	0.2

[a] *i.v.* dose: 1 mg/kg
[b] *p.o.* dose: 10 mg/kg

In vivo pharmacology

The ability of BIRB 796 to inhibit production of TNFa was tested in rat by suppression of local edema after carrageenan injection into the paw[6]. Additionally, the efficacy could be shown in humans by dose dependant reduction of cytokine production after oral administration[8].

Selectivity

The SafetyScreen44™ panel has been measured (@10 mM) for BIRB 796, and for 0/44 proteins >70% inhibition was found. Highest inhibition was found for NA+/SITE2/R (65%), 5HT2AH_AGON (60%) and COX-2@CE (55%), respectively. Although it was found that BIRB 796 binds JNK2 in the nanomolar range, comparable to the p38 isoforms, the inhibition of the downstream pathway of JNK2 only occurs after treatment with micromolar doses.

SELECTIVITY DATA AVAILABLE	BIRB 796
SafetyScreen44™ with kind support of eurofins	Yes
Invitrogen®	Yes
DiscoverX®	Yes
Dundee	No

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

The X-ray crystal structure of target in complex with BIRB 796 is available (PDB Code: 1KV2)[1].

Reference molecule(s)

Other p38 MAPK inhibitors have been described in the literature[2,3].

Supplementary data

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

References

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