opnMe by Boehringer Ingelheim

IKKβ-Inhibitor

BI-605906

Boehringer Ingelheim

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Summary

BI 605906 is a highly potent and selective inhibitor of IKKb with an IC_{50} of 50 nM, that effectively blocks the phosphorylation of IkBα (EC_{50} 0.9 µM) and the expression of ICAM-1 (EC_{50} 0.7 µM) in HeLA cells. Together with the negative control BI-5026, BI 605906 is an excellent tool compound to explore IKKβ related pharmacology *in vitro* and *in vivo*.

Chemical Structure

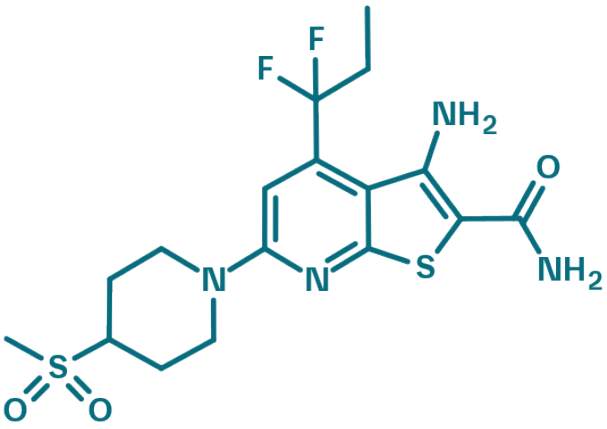

Figure 1: 2D structure of the IKKβ-Inhibitor BI 605906

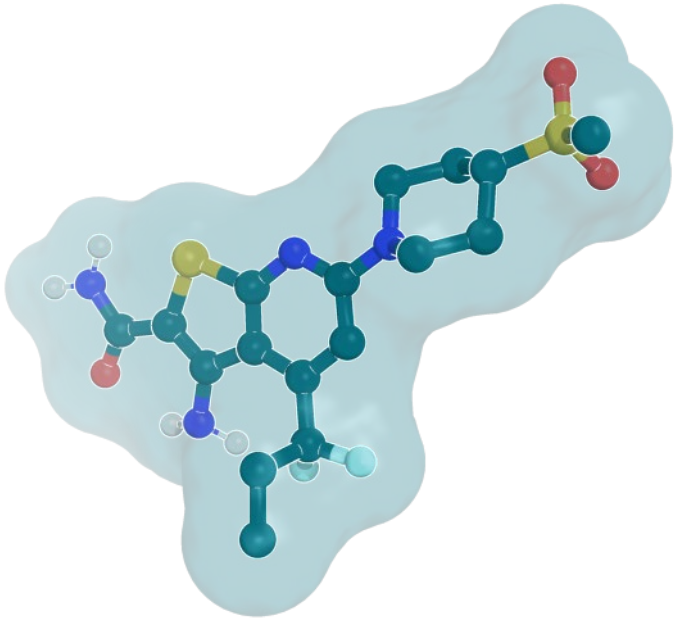

Figure 2: 3D structure of the IKKβ-Inhibitor BI 605906

Highlights

BI-605906 is a potent and highly selective IKKβ inhibitor (IC_{50} = 50 nM). *In vitro*, it has demonstrated effective and consistent inhibition of the phosphorylation of IkBα as well as the expression of ICAM-1. *In vivo*, BI-605906 has shown dose responsive efficacy in a rat model of collagen-induced arthritis. This compound may be a valuable tool to explore IKKβ-related pharmacology in numerous disease models.

Target information

The serine/threonine kinase IKKβ (inhibitor of I kappa kinase beta, also known as IKK2), serves as the immediate upstream activator of NF-kB mediated transcription and represents as such a key point of convergence for multiple inflammatory pathways induced by cytokines, viral and bacterial infections, antigens, oxidative stress and DNA-damaging agents. Biochemical inhibition of IKKβ has proven efficacious in numerous pharmacology disease models including models of arthritis, inflammatory bowel disease, asthma and tumor metastasis.

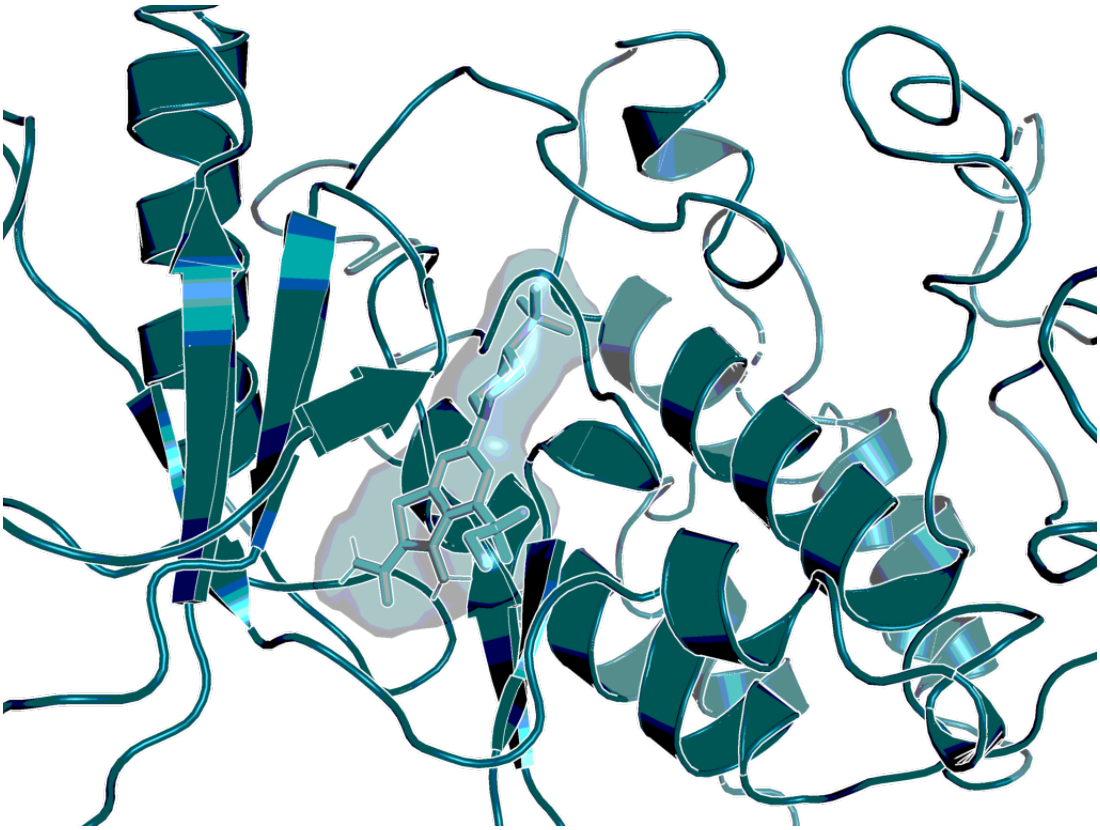

Figure 3: Model of BI 605906 bound to IKKβ, based on PDB code: 3RZF[9]

In vitro activity

BI 605906 is a highly selective reversible ATP competitive inhibitor of IKKβ with an IC_{50} value of 50 nM. BI 605906 has demonstrated mechanistically consistent cell-based inhibition of the phosphorylation of IkBα, the immediate substrate of IKKβ (EC_{50} 0.9 µM) and the expression of downstream NF-kB transcriptional products such as ICAM-1 (EC_{50} 0.7 µM).

PROBE NAME / NEGATIVE CONTROL	BI 605906	BI-5026
MW [Da, free base][a]	432.5	450.5
Inhibition of IKKβ (IC_{50}) [nM]	50	>10,000
Inhibition of phospho-IκBα in HeLa cells (EC_{50}) [µM]	0.9	n.a.
Inhibition of expression of ICAM-1 in HeLa cells (EC_{50}) [µM]	0.7	n.a.

[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

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI 605906	BI-5026
logD @ pH 11	1.93	2.4
Solubility @ pH 7 [µg/mL]	41.6	n.a.
Caco-2 permeability AB @ pH 7.4 [$*10^{-6}$ cm/s]	19.7	n.a.
Caco-2 efflux ratio	1.6	n.a.
Microsomal stability (human/mouse/rat/dog/cyno) [% Q_H]	26 / 69 / 28 / 26 / 28	n.a.
Hepatocyte stability (human/rat/dog/cyno) [% Q_H]	18 / 52 / 64 / 39	n.a.
Plasma Protein Binding (human/mouse/rat/dog/cyno) [%]	92 / 92 / 97 / 94 / 94	n.a.
hERG (IC_{50}) [µM]	25	n.a.
CYP 3A4 (IC_{50}) [µM]	18	n.a.
CYP 2C8 (IC_{50}) [µM]	n.a.	n.a.
CYP 2C9 (IC_{50}) [µM]	17	n.a.
CYP 2C19 (IC_{50}) [µM]	>30	n.a.
CYP 2D6 (IC_{50}) [µM]	>30	n.a.

In vivo DMPK parameters

BI 605906	MOUSE	RAT	DOG	CYNO
Clearance [% Q_H][a]	33	38	27	18
Mean residence time after *i.v.* dose [h][a]	0.8	0.9	2.4	3.4
t_{max} [h][b]	0.5	2.3	2.3	12
C_{max} [nM][b]	2,000	490	800	240
F [%][b]	38	38	24	16
V_{ss} [L/kg][a]	1.5	1.5	1.2	1.6

[a] *i.v.* dose: mg/kg, [b] *p.o.* dose: mg/kg – to be checked

In vivo pharmacology

BI 605906 shows dose responsive effects in the rat collagen induced arthritis model demonstrating comparable efficacy to anti-TNFa standard etanercept at a dose of 60 mg/kg.

Negative control

BI-5026 is a close analog of BI 605906 that is inactive on IKKβ and its isoforms IKKα/γ (IC_{50} > 10 µM).

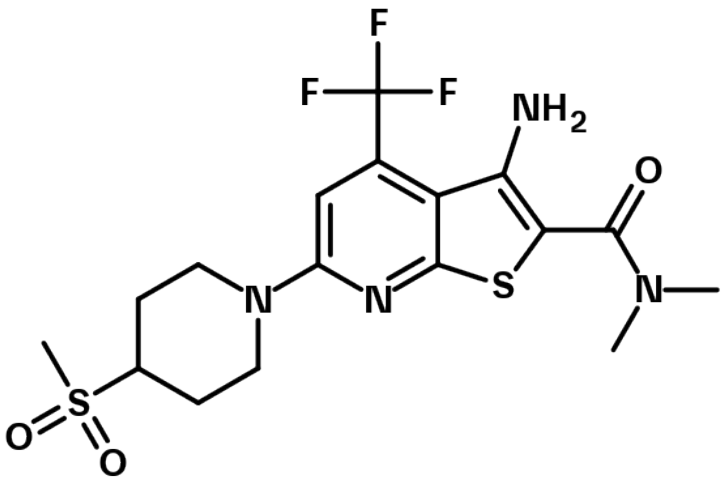

Figure 4: BI-5026 which serves as a negative control

Selectivity

BI 605906 is a highly selective inhibitor of IKKβ and hits only 3/397 other kinases >50% inhibition at 10 µM: GAK (93%), AAK1 (87%) and IRAK3 (76%).

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)[9]. Significant inhibition (modulation) observed for 3 of the 315 GPCRs tested @ 10 µM (D3 52%Inh, GABA/PBR 52%Inh, D2 70%Inh).

SELECTIVITY DATA AVAILABLE	BI-605906	BI-5026
SafetyScreen44™ with kind support of eurofins	Yes	Yes
PRESTO-TANGO (PDSP)	Yes	Yes
Invitrogen®	Yes	No
DiscoverX®	No	No
Dundee	Yes	No

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

No X-ray crystal structures available.

Reference molecule(s)

Please see reference 7.

Supplementary data

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

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