

BI 605906: A Chemical Probe for IKKB

Version 1.0 (25th June 2021)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/chemProbes#!specificprobeoverview/BI%20605906>

Overview

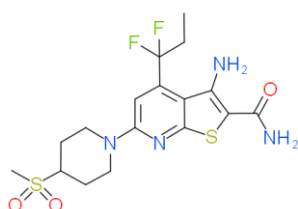
The serine/threonine kinase **IKKB** serves as the immediate upstream activator of NF κB mediated transcription and is therefore a key point of convergence for multiple inflammatory pathways induced by cytokines, viral and bacterial infections, antigens, oxidative stress and DNA damaging agents. Biochemical inhibition of IKKB has proven to be efficacious in numerous disease models such as arthritis, inflammatory bowel disease, asthma and tumor metastasis.

Summary

Chemical Probe Name	BI 605906
Negative control compound	BI-5026
Target(s) (synonyms)	IKKB (inhibitor of nuclear factor kappa B kinase subunit beta, IKK2, NFKB1KB, IKK-beta, IKKB)
Recommended cell assay concentration	Use at concentration up to 5 μM for BI 605906 and BI-5026; use with inactive control and SGC-GAK-1 and SGC-AAK1-1 probes for best interpretation of data.
Suitability for <i>in vivo</i> use and recommended dose	Tested in mouse, rat, dog and cynomolgus monkey (IV: 1 mg/kg; PO: 10 mg/kg). An effect was shown in the rat collagen induced arthritis model at a dose of 60 mg/kg.
Publications	None at time of writing
Orthogonal chemical probes	
<i>In vitro</i> assay(s) used to characterise	Inhibition of IKKB
Cellular assay(s) for target-engagement	Inhibition of phospho-IκBα and ICAM1 in HeLa cells

Chemical Probe & Negative Control Structures and Use

BI 605906 Chemical Probe



SMILES: CCC(c1cc(nc2c1c(c(N)=O)s2)N)N1CCC(CC1)S(C)(=O)=O(F)F

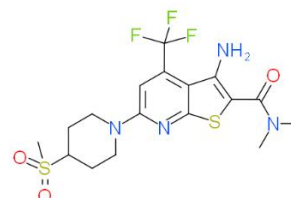
InChiKey: IYHHRZBKXXKDDY-UHFFFAOYSA-N

Molecular weight: 432.11

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

BI-5026 Negative Control



SMILES: CN(C)C(c1c(c2c(cc(nc2s1)N)1CCC(CC1)S(C)(=O)=O)C(F)(F)N)=O

InChiKey: HHYGVXHXNNIDJF-UHFFFAOYSA-N

Molecular weight: 450.1

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

In vitro Potency & Selectivity:

BI 605906 shows potent activity on IKKB (IC₅₀ = 49 nM). 3 hits found out of 397 kinases tested (IC₅₀ [nM] from dose response measurements): GAK (188), AAK1 (272), IRAK3 (921). Clean Panlabs panel except for PDE3A with 31 % Ctrl at 10 μM. BI-5026 exhibits no activity with IC₅₀ > 10 μM.

Potency in Cells and Cellular Target Engagement:

BI 605906 effectively blocks the phosphorylation of I κ B α ($EC_{50} = 0.9 \mu\text{M}$) and the expression of ICAM-1 ($EC_{50} = 0.7 \mu\text{M}$).
NanoBRET results (IC_{50} [μM]): GAK (6.5), AAK1 (7.0), IRAK3 (> 20).