SYK inhibitor | BI 1002494

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Summary

BI 1002494 inhibits SYK with high target potency, good cellular potency, and shows good kinase specificity. It is recommended as *in vitro* and *in vivo* tool.

Chemical Structure

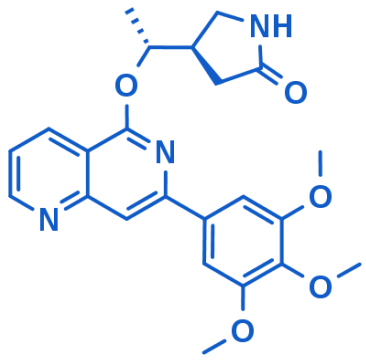

Figure 1: 2-D structure of BI 1002494, an inhibitor of SYK

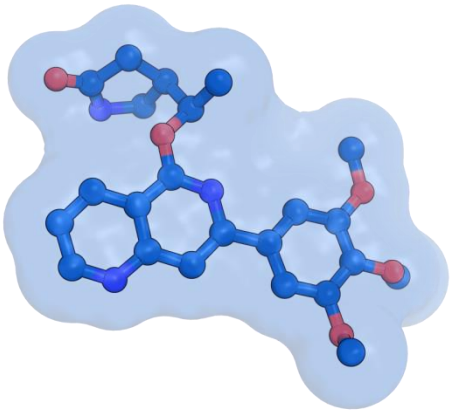

Figure 2: 3-D structure of BI 1002494, an inhibitor of SYK

Highlights

BI 1002494 is a potent inhibitor of SYK with an IC_{50} of 0.8 nM and inhibits in human whole blood the DNP/BSA (dinitroprusside / bovine serum albumine) induced expression of CD63 in basophils with an average IC_{50} of 115 nM (N=263) as well as in human B cells. BI 1002494, the goat anti-human IgD, induced secretion of CD69 with an IC_{50} of 810 nM (N=36). In addition to its excellent target inhibition, its high solubility and metabolic stability makes it a suitable tool for *in vivo* mouse and rat studies. For instance, it showed 90% reduction of BAL (bronchoalveolar lavage) eosinophils in a rat OVA model at 30 mg/kg (b.i.d.). No adverse events were observed in a 13-week mouse toxicology study up to 100 mg/kg (b.i.d.).

Target information

SYK propagates signal transduction for a number of immunoreceptor tyrosine-based activation motif–dependent proinflammatory pathways, including Fc receptor, B-cell receptor(BCR), and integrin signaling.

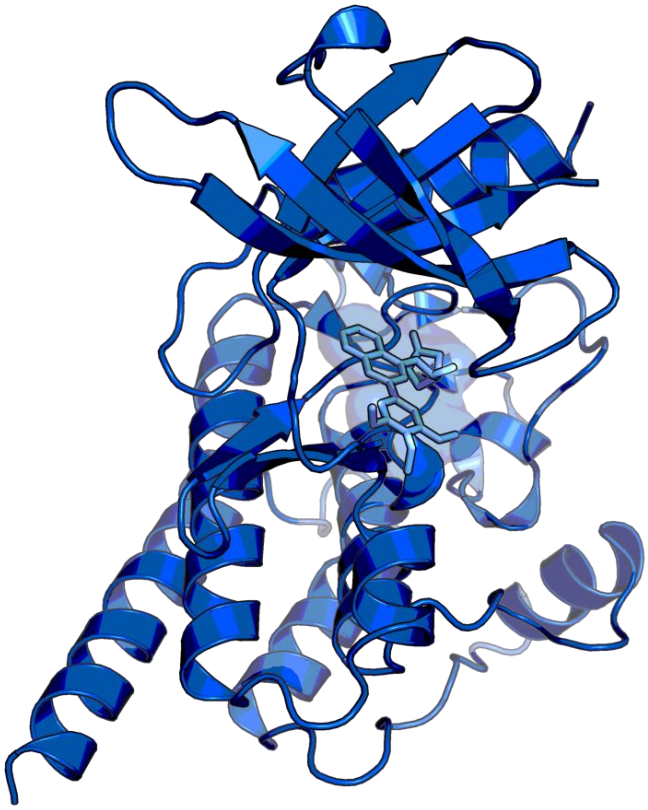

Figure 3: BI 1002494 in complex with SYK (X-ray structure solved at Boehringer Ingelheim)

In vitro activity

BI 1002494 inhibits SYK with an IC_{50} of 0.8 nM

PROBE NAME	BI 1002494
MW [Da]	423.46
SYK (IC_{50}) [nM]	0.8
CD63 (EC_{50}) [nM] human whole blood	115*
CD63 (EC_{50}) [nM] human whole blood	810**

*N=263, **N= 36

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI 1002494	
Aqueous solubility @ pH 7.4 [µg/ml]	500	
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	30	
CACO efflux ratio	2.8	
Rat hepatocyte clearance [% Q_H]	51	
Plasma protein binding [%] mouse / rat	93	95

In vivo DMPK parameters

BI 1002494	MOUSE	RAT
CL [% Q_H]	58	41
MRT [h]	0.4	0.9
V_{ss} [L/kg]	0.8	1.5
F[%]	58	41

Negative control

With BI-2492 a structurally very similar molecule (diastereoisomer) with an SYK IC_{50} = 625 nM (780-fold less potent than BI 1002494) is offered which can be used as a negative control.

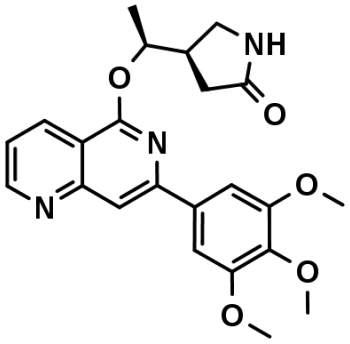

Figure 4: BI-2492, negative control

In vivo pharmacology

BI 1002494 showed 90% reduction of BAL (bronchoalveolar lavage) eosinophils in rat OVA (ovalbumin) model at 30 mg/kg. Rat passive anaphylaxis pulmonary model IC_{50},unbound = 50 nM.[1]

Selectivity

Invitrogen 23/239 kinases hit > 50% INH @ 1 µM
Cerep: 3/56 targets > 50% INH @ 10 µM (M_1 (h): 70%, A_1 (h): 63%, A_{2A} (h): 59. [1]

BI 1002494	SELECTIVITY DATA AVAILABLE
Cerep®	Yes
Panlabs®	No
Invitrogen®	Yes
DiscoverX®	No
Dundee	No

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

X-ray co-crystal structure solved at Boehringer Ingelheim (unpublished)

Reference molecule(s)

Fostamatinib, Entospletenib

Summary

BI 1002494 is due to its high potency, good physicochemical properties, suitable selectivity profile and low toxicity an excellent tool to explore SYK functions *in vitro* and *in vivo*.

Supplementary data

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

References

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2. Tabeling C., Herbert J., Hocke A.C., Lamb D.J., Wollin S.L., Erb K.J., Boiarina E., Movassagh H., Scheffel J., Doehn J.M., Hippenstiel S., Maurer M., Gounni A.S., Kuebler W.M., Suttorp N., Witzenrath M. Spleen tyrosine kinase inhibition blocks airway constriction and protects from Th2-induced airway inflammation and remodelling. *Allergy* **2017**, *72*, 1061-1072 DOI: 10.1111/all.13101, PubMed

3. van Eeuwijk J.M., Stegner D., Lamb D.J., Kraft P., Beck S., Thielmann I., Kiefer F., Walzog B., Stoll G., Nieswandt B.The Novel Oral Syk Inhibitor, BI1002494, Protects Mice From Arterial Thrombosis and Thromboinflammatory Brain Infarction. *Arterioscler Thromb Vasc Biol.* **2016**, *36*, 1247-1253. DOI: 10.1161/ATVBAHA.115.306883, PubMed.