opnMe by Boehringer Ingelheim

Neutrophil Elastase inhibito

BI-5524

Boehringer Ingelheim

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Summary

BI-5524 is a highly potent and selective inhibitor of human neutrophil elastase with a favourable pharmacokinetic (PK) profile suited for *in vivo* studies. The distomer BI-5525 is available as a negative control.

Chemical Structure

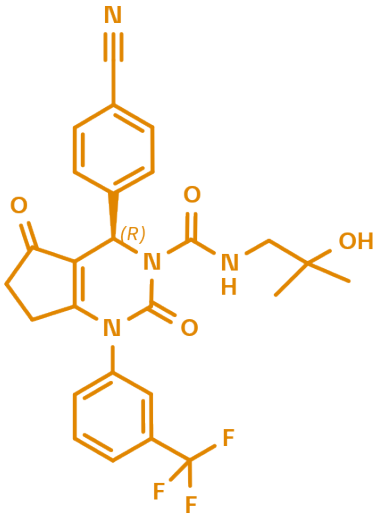

Figure 1: 2D structure of BI-5524

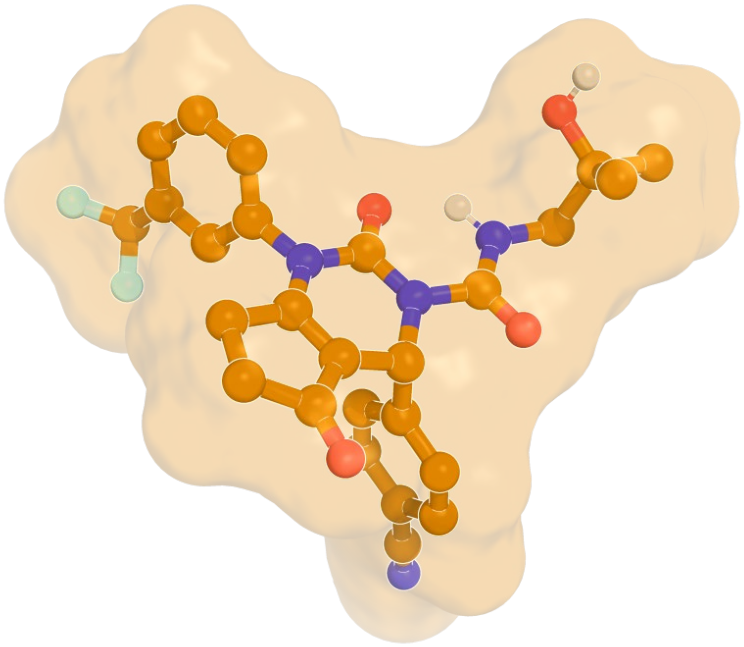

Figure 2: Low energy 3D conformation of BI-5524

Highlights

BI-5524 in an inhibitor of human neutrophil elastase (hNE), which dysregulation is associated with inflammatory and fibrotic diseases. It inhibits the neutrophil-derived serine protease elastase by binding to its catalytic site with high potency and selectivity. Its excellent PK properties allow for the investigation of suitable disease models in rodent species. The distomer BI-5525 can be used as negative control.

Target information

The serine protease neutrophil elastase (NE) is expressed in bone marrow precursor cells and is stored in the granules of peripheral blood neutrophils at high concentrations. Upon neutrophil activation, NE is secreted causing degradation of the extracellular matrix components, like elastin, fibronectin, laminin, collagen and proteoglycans[3]. In addition, NE activity is implicated in the activation of proinflammatory pathways[4].

While normal NE function is required for microbial clearance and an appropriate innate immune response, NE dysregulation is described to play a major role in a number of chronic inflammatory and fibrotic diseases in different organs[5]. As part of various research approaches NE Inhibitors have been associated with a potential role in several diseases such as idiopathic pulmonary fibrosis as well as other inflammatory and fibrotic diseases of the lung[2]. Significant protection or resistance against experimental lung emphysema[6], pulmonary hypersension[7], pulmonary fibrosis[8] and myocarditis[9] could also be shown in murine elastase knock-out models.

Figure 3: Structure of hNE in complex with dihydropyrimidone inhibitor BAY-678 (PDB ID 5A0A)[1]

In vitro activity

BI-5524 shows sub-nanomolar potency in representative *in vitro* assays.

PROBE NAME / NEGATIVE CONTROL	BI-5524	BI-5525
MW [Da, free base][a]	512.5	512.5
hNE inhibitor assay (IC_{50}) [nM][b]	0.5	>30.0
Mouse NE inhibitor assay (IC_{50}) [nM]	12	n.a.
Zymosan assay plasma (EC_{50}) [nM][c]	0.4	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

[b] Inhibition of hNE was tested in a biochemical assay using purified commercial hNE and a fluorescent peptide substrate[10]
[c] Inhibition of zymosan-stimulated NE activity in human plasma[10,11]

In vitro DMPK and CMC parameters

BI-5524 shows good solubility and permeability as well as metabolic stability *in vitro*.

PROBE NAME / NEGATIVE CONTROL	BI-5524	BI-5525
logP @ pH 11	2.7	2.7
Solubility @ pH 6.8 [µg/mL]	79.0	47
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	11.1	17.0
Caco-2 efflux ratio	6.8	3.2
Microsomal stability (human/mouse/rat) [% Q_H]	<23 / <23 / 37	n.a.
Hepatocyte stability (human/mouse/rat) [% Q_H]	0 / 0 / 50	n.a.
Plasma Protein Binding (human/mouse/rat) [%]	73 / 75 / 58	n.a.
hERG [inh. % @ 10 µM]	27.4	n.a.
CYP 3A4 (IC_{50}) [µM]	>50	>50
CYP 2C8 (IC_{50}) [µM]	>50	>50
CYP 2C9 (IC_{50}) [µM]	>50	>50
CYP 2C19 (IC_{50}) [µM]	>50	>50
CYP 2D6 (IC_{50}) [µM]	>50	>50

In vivo DMPK parameter

BI-5524 shows excellent PK properties in rodent species and is suited for *in vivo* studies.

BI-5524	MOUSE	RAT
Clearance [% Q_H][a]	19	52
Mean residence time after *i.v.* dose [h][a]	2.0	1.4

t_{max} [h]	1.0[b]	2.0[c]
C_{max} [nM]	2,278[b]	24,696[c]
F [%]	100[b]	100[c]
V_{ss} [L/kg]a	2.0	3.1

[a] mouse *i.v. dose:* 0.5 mg/kg, rat *i.v. dose:* 0.5 mg/kg
[b] mouse *p.o.* dose: 5 mg/kg
[c] mouse *p.o.* dose: 100 mg/kg

Negative control

BI-5525 is the distomer of the active probe BI-5524. It has an at least 75-fold lower activity in hNE inhibitor assays and it is virtually inactive.

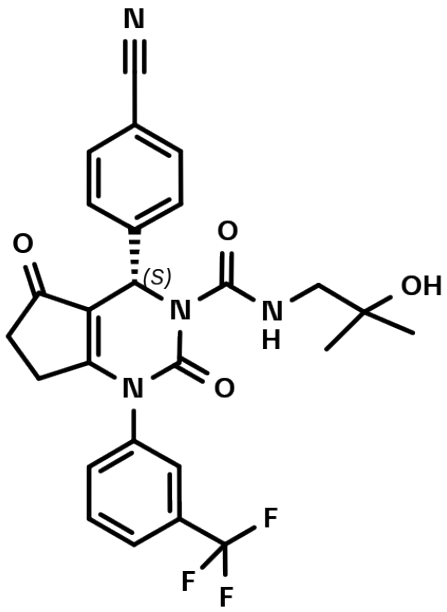

Figure 4: BI-5525 which serves as a negative control

Selectivity

BI-5524 displays a high selectivity for hNE (Inhibition of closely related proteases, like proteinase 3 and cathepsin G @ >100 nM and >10 mM, respectively). BI-5524 was also tested on 96 targets in a selectivity panel and showed ≥1000-fold selectivity for all targets (≤ 50% inhibition @ 10 µM).
BI-5525 was tested in 44 targets in SafetyScreen44™ and showed for all targets <50% inhibition @10 µM.

SELECTIVITY DATA AVAILABLE	BI-5524	BI-5525
SafetyScreen44™ with kind of support of eurofins	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule

BAY-678

Supplementary data

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

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