ATX (Autotaxin) inhibitor | BI-2545

Table of contents

Summary

BI-2545 is highly potent inhibitor of Autotaxin (ATX) which can be used to test hypotheses *in vitro* and *in vivo*. We also offer BI-3017 as inactive control.

Chemical Structure

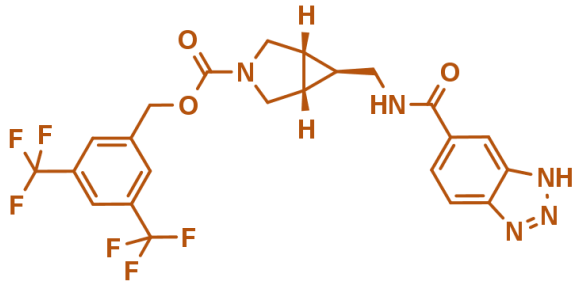

Figure 1: 2-D structure of BI-2545, an inhibitor of Autotaxin (ATX)

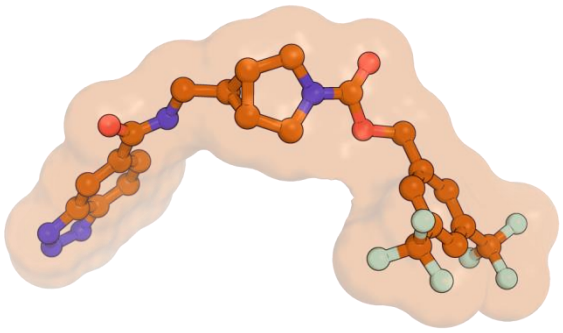

Figure 2: 3-D structure of BI-2445, 3D conformation as observed in the X-ray structure of the complex with ATX (see Figure 3)

Highlights

BI-2545 inhibits human ATX with an IC_{50} of 2.2 nM. In human whole blood BI-2545 inhibits Autotaxin with an IC_{50} of 29 nM and in rat whole blood with an IC50 of 96 nM. *In vivo* BI-2545 demonstrated after a single oral dose to rats at 10 mg/kg a LPA reduction of up to 90%. We also offer BI-3017 as inactive control.

Target information

Autotaxin (ATX) is a secreted phosphodiesterase that hydrolyzes the abundant phospholipid lysophosphatidylcholine (LPC) to produce lysophosphatidic acid (LPA). Recent studies suggest that the ATX-LPA axis is highly implicated in a number of pathophysiological diseases including inflammation, cancer and idiopathic pulmonary fibrosis.

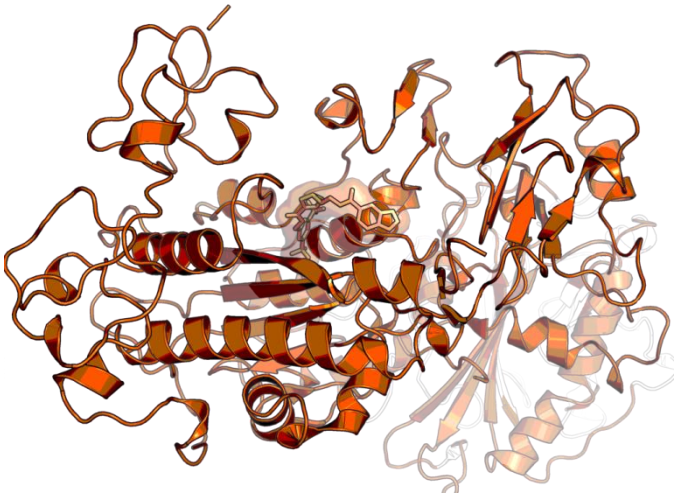

Figure 3: BI-2545 bound to ATX (X-ray structure solved at Boehringer Ingelheim)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-2545	BI-3017
MW [Da]	527.4	407.4
hATX LPA IC_{50} [nM]	2.2	8,900
rat whole blood IC_{50} [nM]	96	n.d.
human whole blood IC_{50}) [nM]	29	n.d.

In vitro DMPK and CMC parameters

PROBE NAME	BI-2545
Aqueous solubility @ pH 6.8 [µg/ml]	<1
CACO permeability @pH7.4 [*10^{-6} cm/s]	9.32
CACO efflux ratio	1.41
Human hepatocyte clearance [% Q_H]	22
Plasma protein binding human [% Q_H]	n.d.

In vivo DMPK parameters

PROBE NAME	BI-2545
Rat PK (*i.v.*)	
CL [mL/(min*kg)]	7
CL [% Q_H)]	10
MRT [h]	2.1
V_{ss} [l/kg]	0.9
Rat PK (*p.o.*)	
C_{max} [nM]	92
t_{max} [h]	1.7
MRT [h]	4.5
F [%]	30

Selectivity

BI-2545	SELECTIVITY DATA AVAILABLE
Cerep	Yes
Eurofins-Panlabs	No
Invitrogen	No
DiscoverX	No
Dundee	No

Negative control

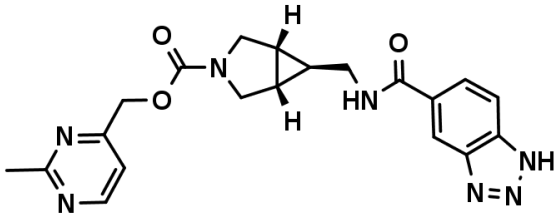

Figure 4: Chemical structure of the negative control BI-3017

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

The X-ray co-crystal structure of ATX with BI-2545 will be published (paper submitted).

Reference molecule(s)

See reference 1

Summary

BI-2545 inhibits human ATX with an IC_{50} of 2.2 nM. In human whole blood BI-2545 inhibits Autotaxin with an IC_{50} of 29 nM and in rat whole blood with an IC_{50} of 96 nM. *In vivo* BI-2545

demonstrated after a single oral dose to rats at 10 mg/kg a LPA reduction of up to 90%. We also offer BI-3017 as inactive control.

Supplementary data

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

References

1. Agnès Joncour *et al.* Discovery, Structure-Activity Relationship, and Binding Mode of an Imidazo[1,2-a]pyridine Series of Autotaxin Inhibitors, *J. Med. Chem.* **2017**, *60*, 6480-6515. DOI: 10.1021/acs.jmedchem.7b00647, PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28731719
2. Diana Castagna *et al.* Development of Autotaxin Inhibitors: An Overview of the Patent and Primary Literature, *J. Med. Chem.* **2016**, *59*, 5604-5621. DOI: 10.1021/acs.jmedchem.5b01599, PubMed.
3. Matthew G.K. Benesch, Yi M. Ko, Todd P.W. McMullen, David N. Brindley Autotaxin in the crosshairs: Taking aim at cancer and other inflammatory conditions*, FEBS Letters*, **2014**, *588*, 2712-2727. DOI: 10.1016/j.febslet.2014.02.009, PubMed.
4. Spencer B. Jones *et al.* Novel Autotaxin Inhibitors for the Treatment of Osteoarthritis Pain: Lead Optimization via Structure-Based Drug Design, *ACS Med. Chem. Lett.* **2016**, *7*, 857-861. DOI: 10.1021/acsmedchemlett.6b00207, PubMed.
5. Anastassis Perrakis, Wouter H. Moolenaar Autotaxin: structure-function and signalling, *J. Lipid Res.* **2014**, *55*, 1010-1018. DOI: 10.1194/jlr.R046391, PubMed
6. Boehringer Ingelheim paper, submitted