opnMe by Boehringer Ingelheim

ATX (Autotaxin) inhibitor

BI-2545

Boehringer Ingelheim

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

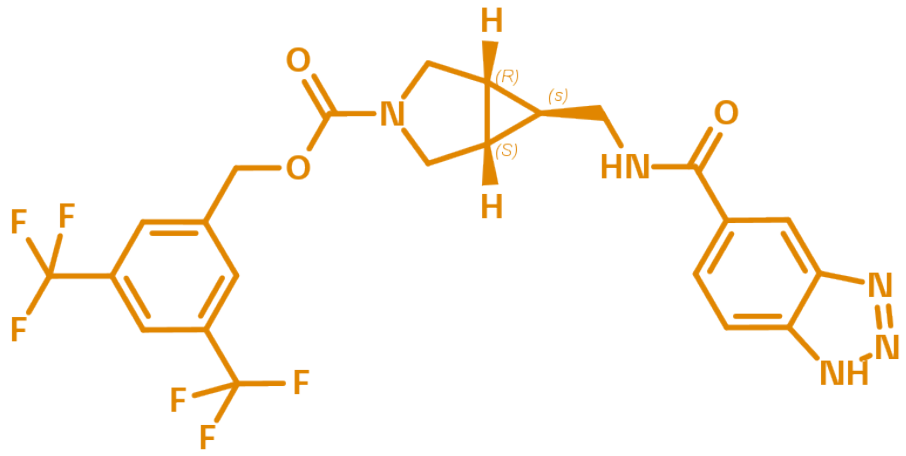

Figure 1: 2D structure of BI-2545, an inhibitor of Autotaxin (ATX)

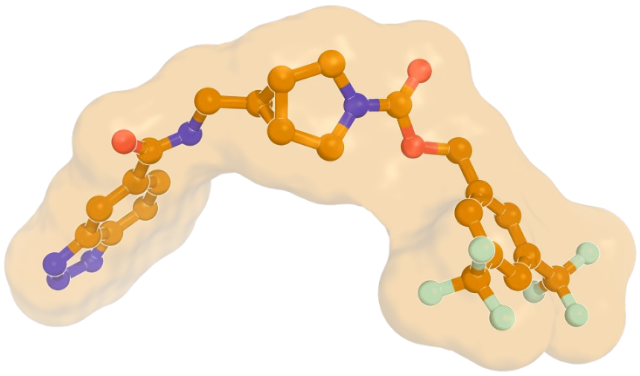

Figure 2: 3D structure of BI-2545, 3D conformation as observed in the X-ray structure of the complex with ATX (see Figure 3)

Highlights

BI-2545 is a highly potent human ATX inhibitor. This compound is suitable for both *in vitro* and *in vivo* studies. In human whole blood, BI-2545 inhibited ATX with an IC_{50} of 29 nM, while in rat whole blood the IC_{50} was 96 nM. In rats, an LPA reduction of up to 90% was observed after a single oral dose at 10 mg/kg.

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.

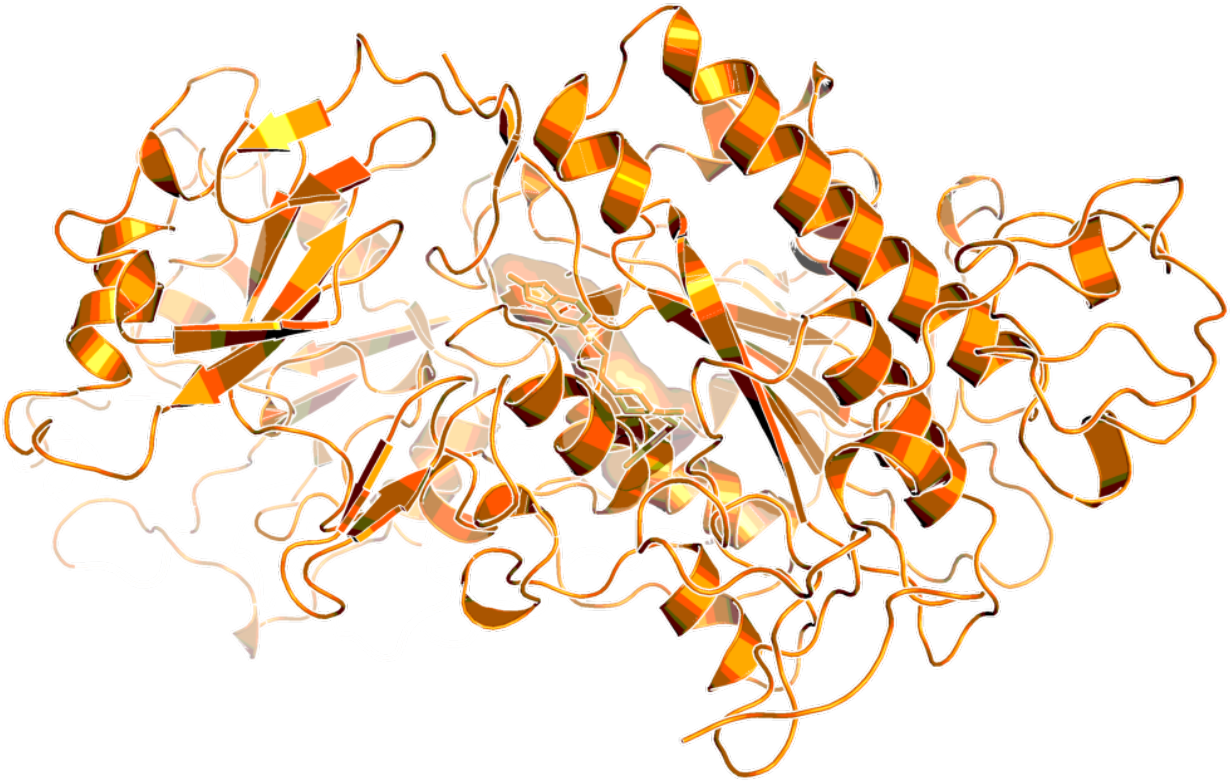

Figure 3: BI-2545 bound to ATX (PDB code: 5OHI, X-ray structure solved at Boehringer Ingelheim)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-2545	BI-3017
MW [Da, free base][a]	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.

[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-2545
logD @ pH 11	1.1
Solubility @ pH 6.8 [µg/mL]	< 1
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	9.3
Caco-2 efflux ratio	1.4
Human hepatocyte clearance [% Q_H]	22

In vivo DMPK parameters

PROBE NAME	BI-2545
Rat PK[a]	
Clearance [% Q_H)]	10
Mean residence time after *i.v.* dose [h]	2.1
V_{ss} [L/kg]	0.9
Rat PK[b]	
C_{max} [nM]	918
t_{max} [h]	1.7
F [%]	30

[a] *i.v.* dose: 0.52 mg/kg
[b] *p.o.* dose: 52 mg/kg

Negative control

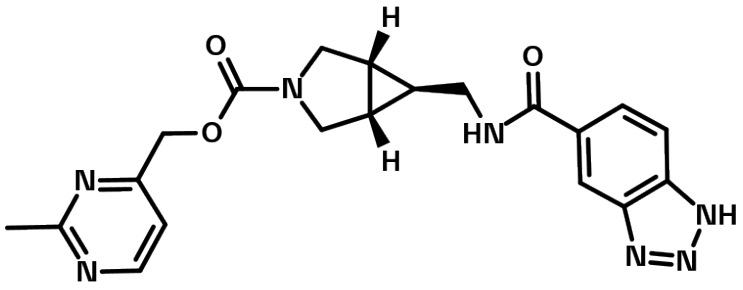

Figure 4: Chemical structure of the negative control BI-3017

Selectivity

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)[7]. Significant inhibition (modulation) observed for 3 of the 315 GPCRs tested @ 10 µM (GABA/PBR 64%Inh, 5HT2A 51%Inh, Sigma1 51%Inh).

SELECTIVITY DATA AVAILABLE	BI-2545	BI-3017
SafetyScreen44™ with kind support of eurofins	Yes	Yes
PRESTO-TANGO (PDSP)	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

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

The X-ray co-crystal structure of ATX with BI-2545 can be found in reference 6.

Reference molecule(s) – Inhibitors

See reference 1.

Supplementary data

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

References

1. Joncour A., Desroy N., Housseman C., Bock X., Bienvenu N., Cherel L., Labeguere V., Peixoto C., Annoot D., Lepissier L., Heiermann J., Hengeveld W. J., Pilzak G., Monjardet A., Wakselman E., Roncoroni V., Le Tallec S., Galien R., David C., Vandervoort N., Christophe T., Conrath K., Jans M., Wohlkonig A., Soror S., Steyaert J., Touitou R., Fleury D., Vercheval L., Mollat P., Triballeau N., van der Aar E., Brys R., Heckmann B. 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.

2. Castagna D., Budd D. C., Macdonald S. J., Jamieson C., Watson A. J. 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. Benesch M. G. K., Ko Y. M., McMullen T. P. W., Brindley D. N. 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. Jones S. B., Pfeifer L. A., Bleisch T. J., Beauchamp T. J., Durbin J. D., Klimkowski V. J., Hughes N. E., Rito C. J., Dao Y., Gruber J. M., Bui H., Chambers M. G., Chandrasekhar S., Lin C., McCann D. J., Mudra D. R., Oskins J. L., Swearingen C. A., Thirunavukkarasu K., Norman B. H. 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. Perrakis A., Moolenaar W. H. Autotaxin: structure-function and signalling *J.Lipid Res.* **2014**, *55*, 1010-1018. DOI: 10.1194/jlr.R046391, PubMed.
6. Kuttruff C. A., Ferrara M., Bretschneider T., Hoerer S., Handschuh S., Nosse B., Romig H., Nicklin P., Roth G. J. Discovery of BI-2545: A Novel Autotaxin Inhibitor That Significantly Reduces LPA Levels in Vivo *ACS Med. Chem. Lett.* **2017**, 8, 1252-1257. DOI: 10.1021/acsmedchemlett.7b00312, PubMed.
7. Kroeze W. K., Sassano M. F., Huang XP., Lansu K., McCorvy J. D., Giguère P. M., Sciaky N., Roth B. L. PRESTO-Tango as an open-source resource for interrogation of the druggable human GPCRome *Nat Struct Mol Biol*. **2015**, 22(5):362-9. DOI: 10.1038/nsmb.3014, PubMed.