opnMe by Boehringer Ingelheim

NHE1 Inhibitor

BI-9627

Boehringer Ingelheim

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Summary

BI-9627 is a highly potent NHE1 inhibitor with low DDI potential, excellent pharmacokinetics, and good selectivity against NHE2 and NHE3.

Chemical Structure

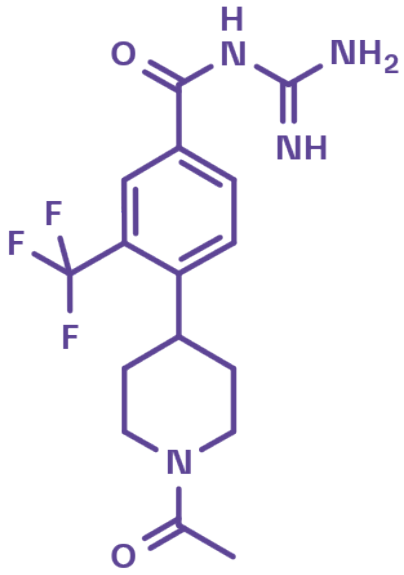

Figure 1: 2D structure of BI-9627, a NHE1 antagonist

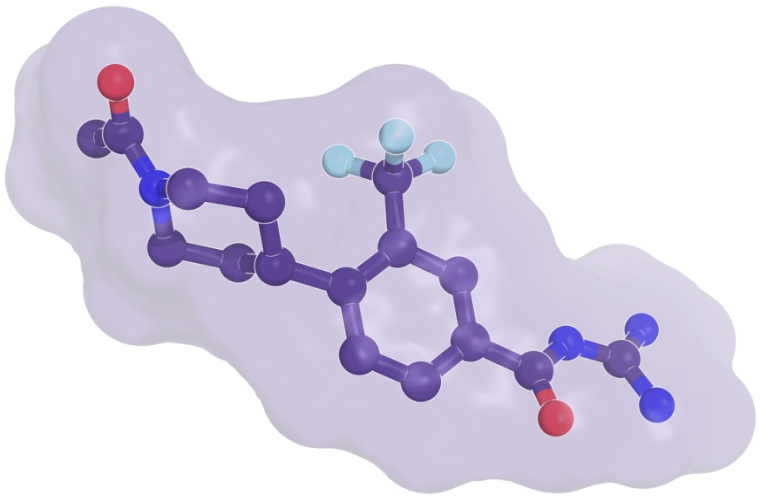

Figure 2: 3D conformation of BI-9627

Highlights

BI-9627 is a highly potent sodium–hydrogen exchanger isoform 1 (NHE1) inhibitor (IC_{50} = 6 nM). It shows good selectivity against NHE2 and NHE3, low potential of drug-drug interactions, low potency for potassium channels such as hERG, and excellent pharmacokinetics following intravenous administration in rat models. This compound is suitable for both *in vitro* and *in vivo* experiments.

Target information

Sodium–hydrogen exchanger isoform 1 (NHE1) is a ubiquitously expressed transmembrane ion channel responsible for the regulation of intracellular pH via the electroneutral exchange of sodium ions and protons[2].

NHE1 is a member of a family of such proteins which encompasses nine variously expressed isoforms. While NHE1 is ubiquitously expressed[3], it is the predominant NHE present in myocardial tissue where it plays a central role in the regulation of intracellular pH in cardiomyocytes[4].

BI-9627 shows remarkably potent activity in the isolated heart model of ischemia-reperfusion injury (Compound **60** in reference 1)[1].

Figure 3: X-ray Structure of an ion channel (nitrate channel from Salmonella typhimurium, PDB code: 4FC4)

In vitro activity

BI-9627 shows an IC_{50} of 6 nM in the pH_i change assay and an IC_{50} of 31 nM in the human platelet swelling inhibition (hPSA) assay[1].

PROBE NAME / NEGATIVE CONTROL	BI-9627	BI-0054
MW [Da, free base][a]	356.3	382.4
pH_i change NHE1 (IC_{50}) [nM]	6	>10,000
pH_i change NHE2 (IC_{50}) [nM]	231	>10,000
pH_i change NHE3 (IC_{50}) [nM]	>16,000	>10,000
hPSA (IC_{50}) [µM]	31	>10,000
rPSA (IC_{50}) [µM]	138	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

The molecule shows low DDI potential as measured by CYP inhibition, CYP 3A4 inactivation, and PXR mediated CYP 3A4 induction, low hERG potency with concomitant absence of effects in lengthening action potential duration.

PROBE NAME	BI-9627	BI-0054
Solubility @ pH 7 [µg/mL]	90.5	<38
logD @ pH 7.4	2.0	1.6
PAMPA rating	high	n.a.
Microsomes stability (human/rat) [% Q_H]	<11/ 11	<30 / n.a.
Hepatocyte stability (human/rat) [% Q_H]	16 / 1	n.a.
Plasma Protein Binding (human/rat) [%]	77.4 / 92	n.a.
Cytotoxicity [µM]	>100	n.a.
hERG (IC_{50}) [µM]	>77	n.a.
Phospholipidosis [µM]	>50	n.a.

Cyp inhibition 2C19 [µM]	>30	n.a.
Cyp inhibition 2C9 [µM]	>30	n.a.
Cyp inhibition 2D6 [µM]	>30	n.a.
Cyp inhibition 3A4 [µM]	>30	n.a.
AMES Q 5µg/plate -S9	negative	n.a.
AMES Q 5µg/plate +S9	negative	n.a.

In vivo DMPK parameters

PROBE NAME	BI-9627	
Species	rat[a]	dog[b]
F [%]	73	33
Clearance [% Q_H]	5.7	13
V_{ss} [L/kg]	0.7	1.4
Mean residence time after *i.v.* dose[h]	3.2	6.2

[a] *i.v.* dose: 1 mg/kg, *p.o.* dose: 10mg/kg
[b] *i.v.* dose: 1 mg/kg, *p.o.* dose: 5mg/kg

Negative control

BI-0054 is a close analog of BI-9627 but is inactive against NHE1, NHE2 and NHE3 in the pH_i change assay (all >10,000 nM). BI-0054 can be ordered as negative control compound.

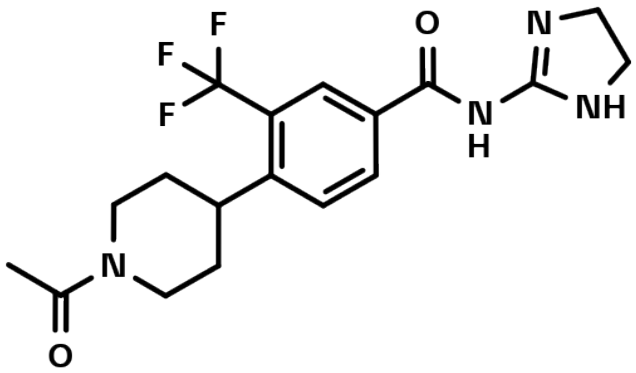

Figure 4: Chemical structure of the negative control BI-0054

Selectivity

NHE isoform selectivity: BI-9627 shows >30-fold selectivity against NHE2 and NHE3. Eurofins Safety Panel 44™ screen on 68 targets @ 10 µM did not give strong hits.

SELECTIVITY DATA AVAILABLE	BI-9627	BI-0054
SafetyScreen44™ with kind support of eurofins	Yes	Yes
PDSP[5]	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

See reference 1

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

1. Huber J. D., Bentzien J., Boyer S. J., Burke J., De Lombaert S., Eickmeier C., Guo X., Haist J. V., Hickey E. R., Kaplita P., Karmazyn M., Kemper R., Kennedy C. A., Kirrane T., Madwed J. B., Mainolfi E., Nagaraja N., Soleymanzadeh F., Swinamer A., Eldrup A. B. Identification of a Potent Sodium Hydrogen Exchanger Isoform 1 (NHE1) Inhibitor with a Suitable Profile for Chronic Dosing and Demonstrated Cardioprotective Effects in a Preclinical Model of Myocardial Infarction in the Rat *J. Med. Chem.* **2012**, *55*, 7114-7140.DOI: 10.1021/jm300601d, PubMed: 22803959.

2. Karmazyn M., Gan X. T., Humphreys R. A., Yoshida H., Kusumoto K. The myocardial Na+ −H+ exchanger: Structure, regulation, and its role in heart disease *Circ. Res.* **1999**, *85*,777−786. DOI: org/10.1161/01.RES.85.9.777, PubMed: 10532945.

3. Orlowski J, Kandasamy R. A., Shull G. E. Molecular cloning of putative members of the Na/H exchanger gene family: cDNA cloning, deduced amino acid sequence, and mRNA

tissue expression of the rat Na/H exchanger NHE-1 and two structurally related proteins *J.Biol. Chem.* **1992**, *267*, 9331–9339. PubMed: 1577762.

4. Fliegel L., Dyck J. R. B. Molecular biology of the cardiac sodium/hydrogen exchanger *Cardiovasc. Res.* **1995**, *29*, 155–159. DOI: org/10.1016/S0008-6363(96)88563-4, PubMed: 7736488.

5. 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.