NHE1 Inhibitor | BI-9627

Table of contents

Summary

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

Chemical Structure

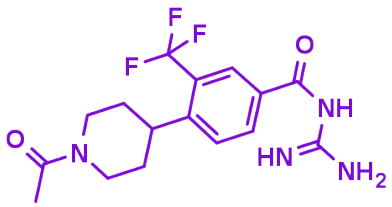

Figure 1: 2-D structure of BI-9627, a NHE1 antagonist

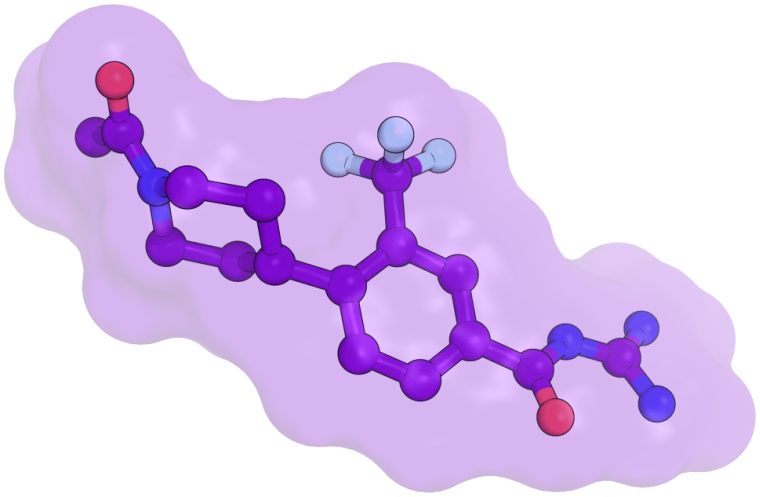

Figure 2: 3-D conformation of BI-9627

Highlights

BI-9627 shows high sodium–hydrogen exchanger isoform 1 (NHE1) potency, 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, excellent

pharmacokinetics in rat and dog, and remarkably potent activity in the isolated heart model of ischemia-reperfusion injury (Compound **60** in reference 1).[1] The compound also shows good selectivity against NHE2 and NHE3 and did not show strong hits in a Eurofins Safety Panel 44™ screen.

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]

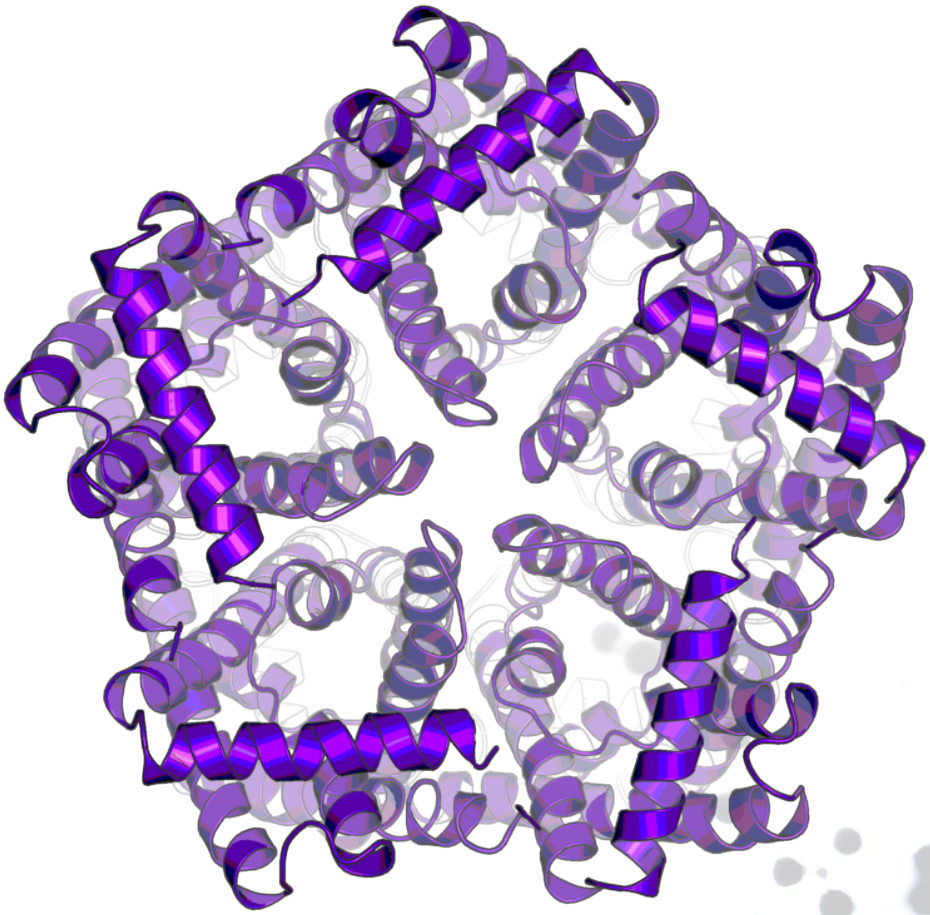

Figure 3: X Structure of an ion channel (nitrate channel from Salmonella typhimurium, PDB code: 4FC4)

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]	356.3	382.4
ph_1 change NHE1 (IC_{50}) [nM]	6	>10,000
ph_1 change NHE2 (IC_{50}) [nM]	231	>10,000
ph_1 change NHE3 (IC_{50}) [nM]	>16,000	>10,000
hPSA (IC_{50}) [µM]	31	>10,000
rPSA (IC_{50}) [µM]	138	n.d.

In vitro DMPK and CMC parameters

PROBE NAME	BI-9627		BI-0054	
Solubility @ pH 7 [µg/ml]	90.5		<38	
LogD (pH 7.4)	2.0		n.d.	
PAMPA rating	high		n.d.	
Microsomes [% Q_H] human/rat	<11	11	<30	n.d.
Hepatocyte clearance [% Q_H] human/rat	17	6	n.d.	

Plasma protein binding [%] human/rat	77.4	92	n.d.
Cytotoxicity [µM]	>100		n.d.
hERG PatchExpress [µM]	>30		n.d.
Phospholipidosis [µM]	>50		n.d.
Cyp inhibition 2C19 [µM]	>30		n.d.
Cyp inhibition 2C9 [µM]	>30		n.d.
Cyp inhibition 2D6 [µM]	>30		n.d.
Cyp inhibition 3A4 [µM]	>30		n.d.
AMES Q 5µg/plate directly	negative		n.d.
AMES Q 5µg/plate S9	negative		n.d.

In vivo DMPK parameters

PROBE NAME	BI-9627	
Species	rat	dog
F [%]	73	33
CL [% Q_H]	5.7	13
V_{ss} [l/kg]	0.76	1.4
MRT [h]	3.2	6.2

Pharmacokinetic parameters of BI-9627 upon *i.v.* application of 1 mg/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.

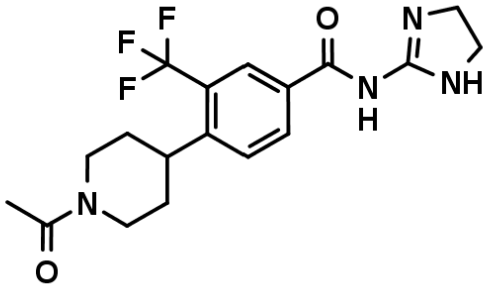

Figure 4: Chemical structure of the negative control BI-0054

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 of support of eurofins	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

See reference 1

Summary

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

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

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3. Orlowski, J; Kandasamy, R. A.; Shull, G. E. Molecular cloning of putative members of theNa/H exchanger gene family: cDNA cloning, deduced amino acid sequence, and mRNAtissue expression of the rat Na/H exchanger NHE-1 and two structurally related proteins. *J.Biol. Chem.* **1992**, *267*, 9331−9339. Full text link, PubMed.

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