NHE1 inhibitor | BI-9627

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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

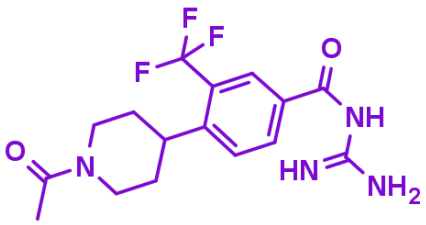

Figure 1: 2-D structure of BI-9627, a NHE1 antagonist

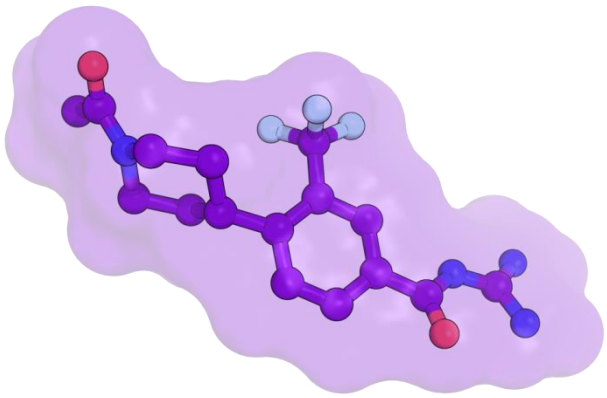

Figure 2: 3-D conformation of BI-9627

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-Panlabs 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]

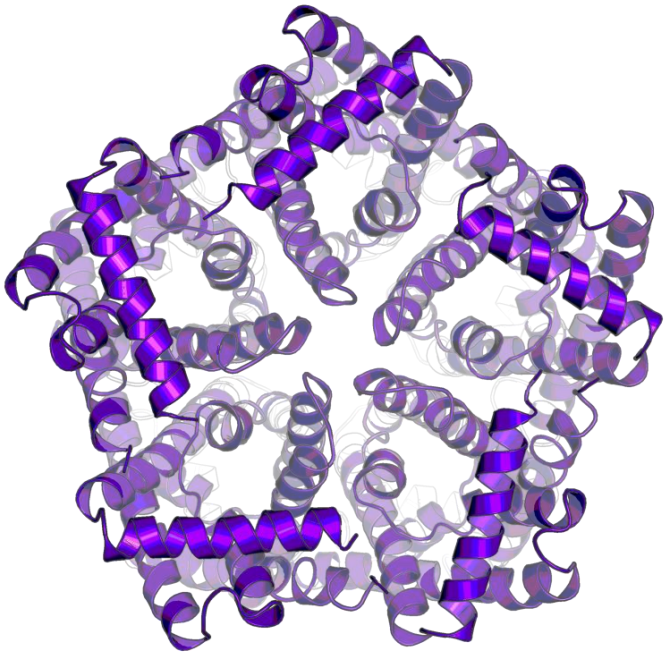

Figure 3: X Structure of an ion channel (nitrate channel from Salmonella typhimurium, PDB code: 4FC4)

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_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}) [nM]	31	>10,000
rPSA (IC_{50}) [nM]	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.	

Pharmacokinetic parameters of BI-9627 upon *iv* application of 1 mg/kg

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 *iv* application of 1 mg/kg

Selectivity

NHE isoform selectivity: BI-9627 shows >30 fold selectivity against NHE2 and NHE3. Eurofins-Panlabs screen on 68 targets @ 10 µM did not give strong hits. Selectivity data is available.

BI-9627	SELECTIVITY DATA AVAILABLE
Cerep®	No
Eurofins-Panlabs®	Yes
Invitrogen®	No
DiscoverX®	No
Dundee	No

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.

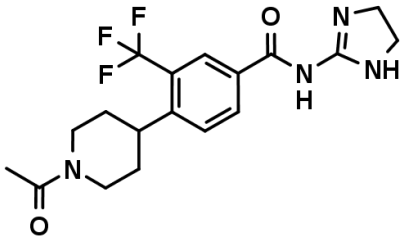

Figure 4: Chemical structure of the negative control BI-0054

Reference molecule(s)

See reference 1

Summary

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.[1] The compound also shows good selectivity against NHE2 and NHE3 and did not show strong hits in a Eurofins-Panlabs screen. BI-0054 is close analog of BI-9627 which shows no NHE1 potency and can be ordered as negative control compound. BI-9627 can be used an *in vitro* and *in vivo* probe compound to test NHE1 biology.

Supplementary data

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

References

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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. Full text link, PubMed.

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.