

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

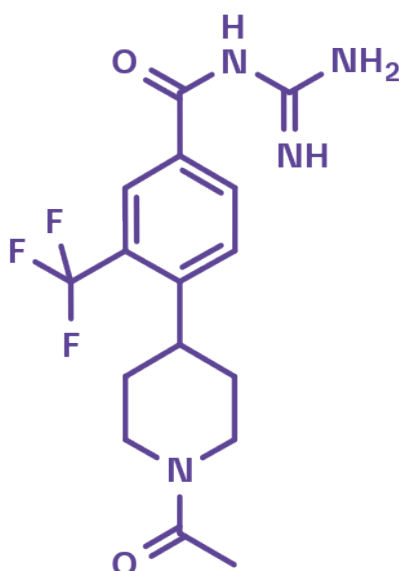


Figure 1: 2D structure of BI-9627, a NHE1 antagonist

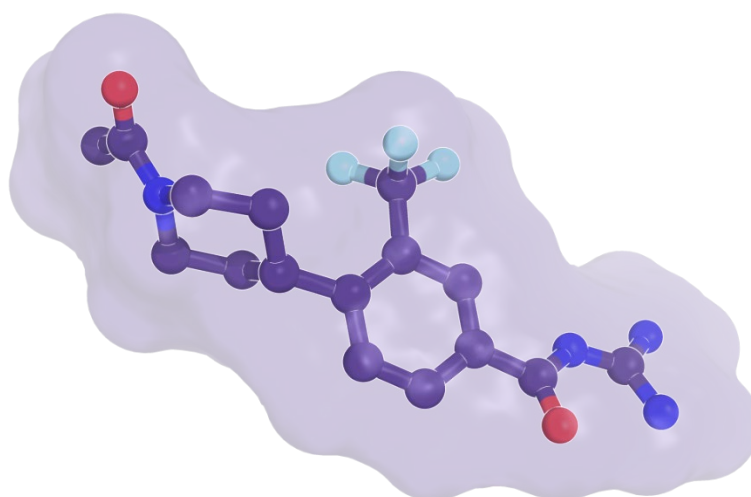


Figure 2: 3D conformation of BI-9627

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 protons².

NHE1 is a member of a family of such proteins which encompasses nine variously expressed isoforms. While NHE1 is ubiquitously expressed³, it is the predominant NHE present in myocardial tissue where it plays a central role in the regulation of intracellular pH in cardiomyocytes⁴.

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 IC₅₀ of 6 nM in the pH_i change assay and an IC₅₀ of 31 nM in the human platelet swelling inhibition (hPSA) assay¹.

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 5 μg /plate -S9	negative	n.a.
AMES Q 5 μg /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>i.v.</i> 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.

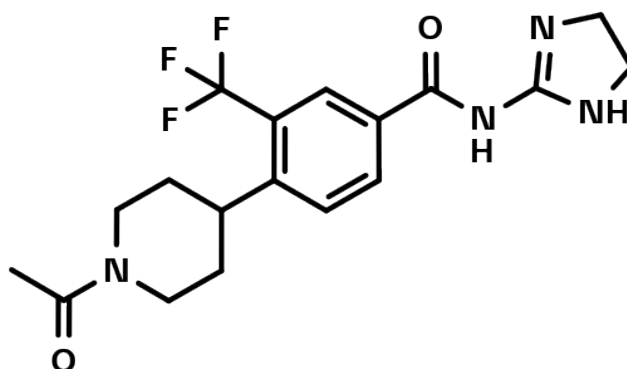


Figure 4: Chemical structure of the negative control BI-0054

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.

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)⁵. Significant inhibition (modulation) observed for 3 of the 315 GPCRs tested @ 10 µM (DAT 78%Inh, 5HT2A -23%Inh, Alpha1D 50%Inh).

SELECTIVITY DATA AVAILABLE	BI-9627	BI-0054
SafetyScreen44™ with kind support of  eurofins	Yes	Yes
PRESTO-TANGO (PDSP)	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

See reference 1

Supplementary data

2-D structure files can be downloaded free of charge from [openMe](#).

References

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