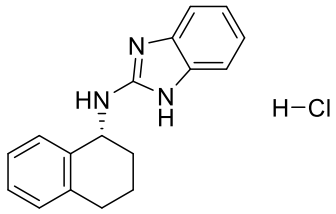
Product data sheet

MedKoo Cat#: 532372 Name: NS8593 HCl CAS#: 875755-24-1 (HCl) Chemical Formula: C17H18ClN3 Molecular Weight: 299.8	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

NS8593 HCl is a selective KCa2 (SK) channel negative modulator. NS8593 inhibits SK channel currents (Kd values are 0.42, 0.6 and 0.73 μM for SK1, SK2 and SK3 respectively at 0.5 μM Ca2+). It exhibits selectivity for SK channels over KCa1.1 (BK), KCa3.1 (IK), Kv, Nav and Cav channels.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	56.66	188.98

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	3.34 mL	16.68 mL	33.36 mL
5 mM	0.67 mL	3.34 mL	6.67 mL
10 mM	0.33 mL	1.67 mL	3.34 mL
50 mM	0.07 mL	0.33 mL	0.37 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Sørensen US, Strøbaek D, Christophersen P, Hougaard C, Jensen ML, Nielsen EØ, Peters D, Teuber L. Synthesis and structure-activity relationship studies of 2-(N-substituted)-aminobenzimidazoles as potent negative gating modulators ofsmall conductance Ca2+-activated K+ channels. J Med Chem. 2008 Dec 11;51(23):7625-34. doi: 10.1021/jm800809f. PMID: 18998663.
2. Voringer S, Schreyer L, Nadolni W, Meier MA, Woerther K, Mittermeier C, Ferioli S, Singer S, Holzer K, Zierler S, Chubanov V, Liebl B, Gudermann T, Muehlich S. Inhibition of TRPM7 blocks MRTF/SRF-dependent transcriptional and tumorigenic activity. Oncogene. 2020 Mar;39(11):2328-2344. doi: 10.1038/s41388-019-1140-8. Epub 2019 Dec 16. PMID: 31844251.

In vivo study

1. Diness JG, Sørensen US, Nissen JD, Al-Shahib B, Jespersen T, Grunnet M, Hansen RS. Inhibition of small-conductance Ca2+-activated K+ channels terminates and protects against atrial fibrillation. Circ Arrhythm Electrophysiol. 2010 Aug;3(4):380-90. doi: 10.1161/CIRCEP.110.957407. Epub 2010 Jun 19. PMID: 20562443.
2. Haugaard MM, Hesselkilde EZ, Pehrson S, Carstensen H, Flethøj M, Præstegaard KF, Sørensen US, Diness JG, Grunnet M, Buhl R, Jespersen T. Pharmacologic inhibition of small-conductance calcium-activated potassium (SK) channels by NS8593 reveals atrial antiarrhythmic potential in horses. Heart Rhythm. 2015 Apr;12(4):825-35. doi: 10.1016/j.hrthm.2014.12.028. Epub 2014 Dec 24. PMID: 25542425.

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7. Bioactivity

Biological target:

NS8593 hydrochloride reversibly inhibits SK3-mediated currents with a Kd value of 77 nM, inhibits all the SK1-3 subtypes Ca2+-dependently (Kds of 0.42, 0.60, and 0.73 μM, respectively, at 0.5 μM Ca2+), and does not affect the Ca2+-activated K+ channels of intermediate and large conductance (hIK and hBK channels, respectively).

In vitro activity

To unravel the mechanism by which the channel TRPM7 blockade inhibits MRTF-A and resultant target gene expression, the RhoA activation status in HuH7 cells treated with NS8593 was first assessed. By immunoprecipitation with an antibody specifically recognizing GTP-loaded RhoA, it was found that the amount of GTP-loaded RhoA was reduced by more than 50% in HuH7 cells treated with NS8593, whereas total RhoA levels were unaltered. Likewise, the downstream effector of RhoA, ROCK2, was downregulated upon TRPM7 blockade. Treatment with the TRPM7 channel blocker NS8593 also resulted in a pronounced decrease in the mean cellular F-actin content. Immunofluorescence analysis using a fluorescent phalloidin conjugate showed that stress fibers, particularly in the nuclear and perinuclear region, were strongly reduced and reorganized in cortical actin networks upon treatment with NS8593.

Reference: Oncogene. 2020 Mar;39(11):2328-2344. https://pubmed.ncbi.nlm.nih.gov/31844251/

In vivo activity

In rat, guinea pig, and rabbit ex vivo and in vivo models of atrial fibrillation (AF), 3 different SK channel inhibitors, UCL1684, N-(pyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (ICA), and NS8593, were used to assess the hypothesis that pharmacological inhibition of SK channels is antiarrhythmic. In an in vivo rat model of acute AF induced by burst pacing, injection of 5 mg/kg of either NS8593 or amiodarone shortened AF duration significantly to (23.2+/-20.0%, P<0.001, n=5, and 26.2+/-17.9%, P<0.001, n=5, respectively) as compared with injection of vehicle (96.3+/-33.2%, n=5). In conclusion, inhibition of SK channels prolongs atrial effective refractory period without affecting QT interval and prevents and terminates AF ex vivo and in vivo, thus offering a promising new therapeutic opportunity in the treatment of AF.

Reference: Circ Arrhythm Electrophysiol. 2010 Aug;3(4):380-90. https://pubmed.ncbi.nlm.nih.gov/20562443/

Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.