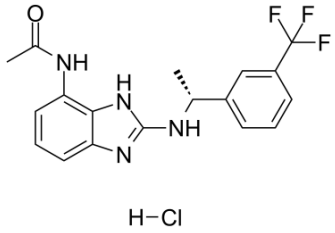
AP14145 hydrochloride

Cat. No.:	HY-120355A
CAS No.:	2387505-59-9
Molecular Formula:	$C_{18}H_{18}ClF_3N_4O$
Molecular Weight:	398.81
Target:	Potassium Channel
Pathway:	Membrane Transporter/Ion Channel
Storage:	Please store the product under the recommended conditions in the COA.



BIOLOGICAL ACTIVITY

Description	AP14145 hydrochloride is a potent **$K_{Ca}2$ (SK)** channel negative allosteric modulator with an **IC_{50}** of 1.1 μM for $K_{Ca}2.2$ (SK2) and $K_{Ca}2.3$ (SK3) channels. AP14145 hydrochloride inhibition strongly depends on two amino acids, S508 and A533 in the channel. AP14145 hydrochloride prolonged atrial effective refractory period (AERP) in rats and demonstrates antiarrhythmic effects in a Vernakalant-resistant porcine model of atrial fibrillation (AF)[1][2].
IC_{50} & Target	IC50: 1.1 μM ($K_{Ca}2.2$) and 1.1 μM ($K_{Ca}2.3$)[1]
In Vitro	AP14145 (10 nM-30 μM) inhibits both $hK_{Ca}2.2$ and $hK_{Ca}2.3$ channel currents in a concentration-dependent fashion. AP14145 (10 μM) inhibits 50% of the $hK_{Ca}1.1$ current, 90% of the $hK_{Ca}2.1$ current and has no effect on $hK_{Ca}3.1$ channel. AP14145 (10 μM) increases the EC_{50} of Ca^{2+} on $K_{Ca}2.3$ channels from 0.36 to 1.2 μM[1]. AP14145 hydrochloride demonstrates an IC_{50} in whole-cell patch clamp on the human SK3 channel of 1.3 μM. AP14145 inhibits hERG ($K_V11.1$) with an IC_{50} of 71.8 μM and $K_{ir}3.1/K_{ir}3.4$ (I_{KACh}) with an IC_{50} of 9.3 μM and does not produce any significant effects on $K_V1.5$ (I_{Kur}), $K_V7.1$/KCNE1 (I_{Ks}), $K_V4.3$/KChiP2 (I_{to}), and $K_{ir}2.1$ (I_{K1}) in 30 μM or on $Na_V1.5$ (15 μM; I_{Na}) on a panel of cardiac ion channels. AP14145 (1-10 μM) produces no significant block of $Ca_V1.2$[2].
In Vivo	AP14145 (10 μM) increases the duration of the atrial effective refractory period (AERP) in isolated perfused rat hearts [1]. AP14145 (2.5 and 5 mg/kg; bolus injections (iv)) increases the duration of the atrial effective refractory period in male sprague-dawley rats (250-350 g, 1-3 months old)[1]. AP14145 (5 mg/kg; bolus injections) has a C_{max} of 8355 nmol/L, a $t_{½}$ of 24.3 minutes in landrace pigs (12-13 weeks old, 30-35 kg gilts)[2].

REFERENCES

[1]. Rafel Simó-Vicens, et al. A New Negative Allosteric Modulator, AP14145, for the Study of Small Conductance Calcium-Activated Potassium ($K_{Ca}2$) Channels. Br J Pharmacol. 2017 Dec;174(23):4396-4408.

[2]. Jonas Goldin Diness, et al. Termination of Vernakalant-Resistant Atrial Fibrillation by Inhibition of Small-Conductance Ca^{2+}-Activated K^+ Channels in Pigs. Circ Arrhythm Electrophysiol. 2017 Oct;10(10):e005125.

Caution: Product has not been fully validated for medical applications. For research use only.

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