Structure/activity analysis of task-3 channel antagonists based on a 5,6,7,8 tetrahydropyrido[4,3-d]pyrimidine

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TASK-3 potassium (K+) channels are highly expressed in the central nervous system, regulating the membrane potential of excitable cells. TASK-3 is involved in neurotransmitter action and has been identified as an oncogenic K+ channel. For this reason, the understanding of the action mechanism of pharmacological modulators of these channels is essential to obtain new therapeutic strategies. In this study we describe the binding mode of the potent antagonist PK-THPP into the TASK-3 channel. PK-THPP blocks TASK-1, the closest relative channel of TASK-3, with almost nine-times less potency. Our results confirm that the binding is influenced by the fenestrations state of TASK-3 channels and occurs when they are open. The binding is mainly governed by hydrophobic contacts between the blocker and the residues of the binding site. These interactions occur not only for PK-THPP, but also for the antagonist series based on 5,6,7,8 tetrahydropyrido[4,3-d]pyrimidine scaffold (THPP series). However, the marked difference in the potency of THPP series compounds such as 20b, 21, 22 and 23 (PK-THPP) respect to compounds such as 17b, inhibiting TASK-3 channels in the micromolar range is due to the presence of a hydrogen bond acceptor group that can establish interactions with the threonines of the selectivity filter.

5,6,7,8 tetrahydropyrido[4,3-d]pyrimidine derivatives

Drug-protein interaction

Molecular docking

Molecular dynamics

Mutagenesis screen

Pk-thpp

Task channels blockers

TASK-3 channel

5,6,7,8 tetrahydropyrido [4,3 d] pyrimidine

neurotransmitter

potassium channel blocking agent

pyrimidine derivative

task 3 channel

threonine

unclassified drug

KCNK9 protein, human

potassium channel blocking agent

protein binding

pyridine derivative

pyrimidine derivative

tandem pore domain potassium channel

tetrahydropyrido(4,3-d)pyrimidine

Article

binding affinity

binding site

chemical interaction

conformational transition

drug binding site

electrophysiology

entropy

fenestration

hydrogen bond

IC50

lipophilicity

membrane potential

molecular docking

molecular dynamics

molecular mechanics

mutagenesis

nonhuman

pharmacophore

protein interaction

receptor binding

relative binding affinity

sequence alignment

steady state

structure activity relation

structure analysis

two dimensional quantitative structure activity relationship

Xenopus laevis

animal

antagonists and inhibitors

chemistry

human

molecular docking

Xenopus

Animals

Binding Sites

Humans

Molecular Docking Simulation

Potassium Channel Blockers

Potassium Channels, Tandem Pore Domain

Protein Binding

Pyridines

Pyrimidines

Xenopus