Discovery of novel TASK-3 channel blockers using a pharmacophore-based virtual screening

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TASK-3 is a two-pore domain potassium (K2P) channel highly expressed in the hippocampus, cerebellum, and cortex. TASK-3 has been identified as an oncogenic potassium channel and it is overexpressed in different cancer types. For this reason, the development of new TASK-3 blockers could influence the pharmacological treatment of cancer and several neurological conditions. In the present work, we searched for novel TASK-3 blockers by using a virtual screening protocol that includes pharmacophore modeling, molecular docking, and free energy calculations. With this protocol, 19 potential TASK-3 blockers were identified. These molecules were tested in TASK-3 using patch clamp, and one blocker (DR16) was identified with an IC50 = 56.8 ± 3.9 μM. Using DR16 as a scaffold, we designed DR16.1, a novel TASK-3 inhibitor, with an IC50 = 14.2 ± 3.4 μM. Our finding takes on greater relevance considering that not many inhibitory TASK-3 modulators have been reported in the scientific literature until today. These two novel TASK-3 channel inhibitors (DR16 and DR16.1) are the first compounds found using a pharmacophore-based virtual screening and rational drug design protocol.

Drug design

Lead optimization

Pharmacophore-based virtual screening

TASK channels blockers

TASK-3 channel

potassium channel blocking agent

KCNK9 protein, human

potassium channel blocking agent

tandem pore domain potassium channel

Article

binding site

carbon nuclear magnetic resonance

controlled study

crystal structure

Fourier transform infrared spectroscopy

high throughput screening

human

human cell

hydrogen bond

mass spectrometry

molecular docking

molecular dynamics

patch clamp technique

pharmacophore

protein conformation

protein expression

proton nuclear magnetic resonance

stereochemistry

drug design

HEK293 cell line

molecular docking

Drug Design

HEK293 Cells

Humans

Molecular Docking Simulation

Potassium Channel Blockers

Potassium Channels, Tandem Pore Domain