5-(Indol-2-yl)pyrazolo[3,4-b]pyridines as a new family of task-3 channel blockers: A pharmacophore-based regioselective synthesis

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Abstract
TASK channels belong to the two-pore-domain potassium (K_{2P}) channels subfamily. These channels modulate cellular excitability, input resistance, and response to synaptic stimulation. TASK-channel inhibition led to membrane depolarization. TASK-3 is expressed in different cancer cell types and neurons. Thus, the discovery of novel TASK-3 inhibitors makes these bioactive compounds very appealing to explore new cancer and neurological therapies. TASK-3 channel blockers are very limited to date, and only a few heterofused compounds have been reported in the literature. In this article, we combined a pharmacophore hypothesis with molecular docking to address for the first time the rational design, synthesis, and evaluation of 5-(indol-2-yl)pyrazolo[3,4-b]pyridines as a novel family of human TASK-3 channel blockers. Representative compounds of the synthesized library were assessed against TASK-3 using Fluorometric imaging plate reader—Membrane Potential assay (FMP). Inhibitory properties were validated using two-electrode voltage-clamp (TEVC) methods. We identified one active hit compound (MM-3b) with our systematic pipeline, exhibiting an $IC_{50} \approx 30$ µM. Molecular docking models suggest that compound MM-3b binds to TASK-3 at the bottom of the selectivity filter in the central cavity, similar to other described TASK-3 blockers such as A1899 and PK-THPP. Our in silico and experimental studies provide a new tool to predict and design novel TASK-3 channel blockers.

Author keywords
Drug design; Molecular docking; Pharmacophore; Pyrazolo[3,4-b]pyridines; TASK-3 channel blockers