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Identification of a Lead Compound for Selective Inhibition of Nav1.7 to Treat Chronic Pain

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Abstract : Chronic pain (CP) therapeutic approaches have limited efficacy. As a result, doctors are prescribing opioids for chronic pain, leading to opioid overuse, abuse, and addiction epidemic. Therefore, the development of effective and safe CP drugs remains an unmet medical need. Voltage-gated sodium (Nav) channels act as cardiovascular and neurological disorder's molecular targets. Nav channels selective inhibitors are hard to design because there are nine closely-related isoforms (Nav1.1-1.9) that share the protein sequence segments. We are targeting the Nav1.7 found in the peripheral nervous system and engaged in the perception of pain. The objective of this project was to screen a 1.5 million compound library for identification of inhibitors for Nav1.7 with analgesic effect. In this study, we designed a protocol for identification of isoform-selective inhibitors of Nav1.7, by utilizing the prior information on isoform-selective antagonists. First, a similarity search was performed; then the identified hits were docked into a binding site on the fourth voltage-sensor domain (VSD4) of Nav1.7. We used the FTrees tool for similarity searching and library generation; the generated library was docked in the VSD4 domain binding site using FlexX and compounds were shortlisted using a FlexX score and SeeSAR hyde scoring. Finally, the top 25 compounds were tested with molecular dynamics simulation (MDS). We reduced our list to 9 compounds based on the MDS root mean square deviation plot and obtained them from a vendor for in vitro and in vivo validation. Whole-cell patch-clamp recordings in HEK-293 cells and dorsal root ganglion neurons were conducted. We used patch pipettes to record transient Na^+ currents. One of the compounds reduced the peak sodium currents in Nav1.7-HEK-293 stable cell line in a dose-dependent manner, with IC50 values at 0.74 µM. In summary, our computer-aided analgesic discovery approach allowed us to develop pre-clinical analgesic candidate with significant reduction of time and cost.

Keywords : chronic pain, voltage-gated sodium channel, isoform-selective antagonist, similarity search, virtual screening, analgesics development
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