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Binding modes of diverse sodium channel inhibitors inside the pore

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Small molecule inhibitors of voltage gated sodium channels are common pharmacological agents used to treat a variety of cardiac and nervous system pathologies. They bind within the pore to directly block the conduction pathway and/or stabilise a non-conductive state. Despite their abundant clinical use, we lack specific knowledge of the drug binding sites and drug-protein interactions, and how this differs between different classes of inhibitors.

This study puts forth a molecular perspective of how 11 different compounds with disparate clinical uses, access and bind in the pore cavity of the sodium channel Nav1.5, while drawing on knowledge of these compound's mechanism of action from pre-existing experimental literature.

Using enhanced sampling molecular dynamics simulations, we find most compounds share a common location of pore binding - in the central cavity near the mouth of the DII-III fenestration, associating with the high number of aromatic residues at this region. In contrast, a smaller set of compounds prefer to bind within the lateral fenestrations. Lipids found in the fenestrations are displaced in the presence of drug binding. Overall, our simulation results suggest that the drug binding within the pore is highly promiscuous, with a number of minima identified to be possible low affinity binding sites. Access to the pore interior via two out of four of the hydrophobic fenestrations is favourable for majority of compounds.

As we do not have structures in the channel in all functional conformations, the complete picture of inhibition remains elusive. However, we show the distinct binding modes of known compounds within the sodium channel, in effort to supplement this field of drug discovery.