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Unraveling the Molecular Basis of Kv7 Modulation by Maxipost (bms-204352)

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Ion channels are involved in many cellular mechanisms, and cellular excitability is one of the most critical. Most of the potassium channels allow the efflux of the potassium ions, leading to the cell repolarization. The voltage-gated potassium channels (Kv) Kv7 family (also known as KCNQ) has five members, Kv7.1-Kv7.5, expressed in cardiac and smooth muscle and in the nervous system. Thus, loss-of-function mutations of these channels are often the cause of several cardiac and neurological disorders, but we still lack efficient treatments for Kv7-related disorders. Here, we investigate the modulation mechanism of a compound called MaxiPost (BMS-204352), which has been shown to be a positive modulator of Kv7.4 and Kv7.5. Although experimental evidence shows that MaxiPost and Retigabine share a common interaction (Trp242), it is not clear why MaxiPost is not a postive modulator of other Kv7 channels. We performed a computational search for MaxiPost binding poses that were refined and evaluated through molecular dynamics simulations. This procedure allowed us to find a unique binding mode that has been validated through mutagenesis and electrophysiology experiments. Understanding the molecular mechanism of MaxiPost, and other Kv7 modulators, will pave the way to design better drugs targeting specific Kv7 channels.