Conference abstract PO-27

# Ligand Determinants of Drug Trapping in hERG Potassium Channels

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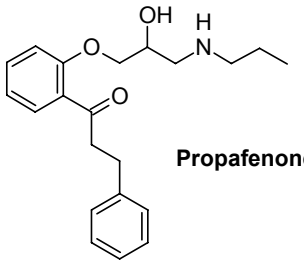
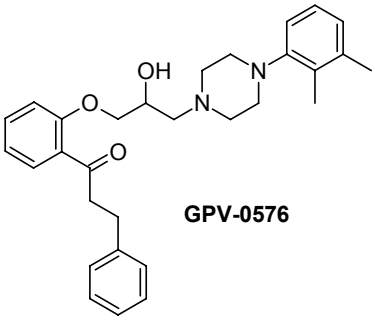
Inhibition of hERG channels prolongs the ventricular action potential and correspondingly the QT-interval with the risk of *torsade de pointes* arrhythmias which may result in sudden cardiac death. Drug induced hERG channel block arises as an unwanted side effect of a surprisingly large number of structurally diverse compounds. To investigate how differences in the chemical structure influence the characteristics of hERG inhibition we studied systematically the onset and recovery of hERG channel block by new propafenone derivatives with conserved pharmacophore structure but different side chains attached. hERG channels were expressed heterologously in *Xenopus* oocytes and currents were measured with the two microelectrodes voltage clamp technique. All compounds tested displayed a similar potency of hERG inhibition with $IC_{50}$ values in the range of 1–7 µM. No substantial recovery from block was observed for 5 (propafenone group) out of 9 compounds, whereas hERG channels recovered from block by the remaining 4 compounds (GPV-0576 group) within approximately 2 minutes. Our data suggest that all compounds bind to the open channel state but exhibit different dissociation properties. While GPV-0576 group compounds apparently dissociate from both, the open and the closed channel state, dissociation of the propafenone group seems to be restricted to the open channel state. This condition is commonly described as "Drug Trapping". It is hypothesized that drugs which lack dissociation from closed channel state are captured in the inner cavity of the channel by closure of the activation gate. Not-trapped compounds are known to block channels in a frequency-dependent manner, whereas trapped compounds act independent from frequency of stimulation.




**Propafenone**




**GPV-0576**

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