Virtual screening to identifying in vitro modulators of cyclic adenosine diphosphate ribose (cADPR) calcium signalling in sea urchin egg homogenate.

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Intracellular calcium signalling has been shown to be involved in numerous cellular processes and pathologies mediated by second messengers. Cyclic adenine diphosphate ribose (cADPR) is a Ca^{2+} mobilising second messenger molecule implicated in regulation of excitation-contraction coupling in cardiac cells. Evidence suggests that injections of cADPR antagonists inhibit arrhythmogenic oscillations of Ca^{2+} in ventricular myocytes. This indicates the cADPR-signalling pathway may be a new target for arrhythmia treatments. However, current drug therapies for cardiac arrhythmias have low therapeutic indexes and numerous side-affects, including proarrhythmia.

Traditional medicinal chemistry modifications of cADPR such as the competitive antagonist 8-NH_2-cADPR, whilst showing anti-arrhythmogenic activity, are not stable or cell permeant. Therefore, new tools to investigate cADPR’s mode of action are needed to probe model calcium signalling systems. Ligand-based virtual screening was used to identify and rank “drug-like” compounds possessing a similar 3D shape and pharmacophores to known cADPR analogues. High-ranking compounds were purchased and a fluorimetric biological screen was performed in vitro using a sea urchin egg homogenate model system to monitor calcium signalling.

Several ‘hits’ have shown an ability to non-competitively inhibit calcium release from intracellular stores in this system at the μM concentration.