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Optimisation of small molecule inhibitors of TRPCa ion channels as cardiovascular protective agents

This project seeks to identify and develop small molecule inhibitors of TRPCa ion channel function as therapeutics for treatment of a range of cardiovascular disorders.

The family of TRPC channels are newly-discovered calcium channel that crucially maintains calcium in the cell. Recent prominent studies suggest their importance in causation or aggravation of atherosclerosis and rheumatoid arthritis, as well as a range of other cardiovascular diseases. No potent and selective inhibitors of TRPCa have previously been reported.[1]

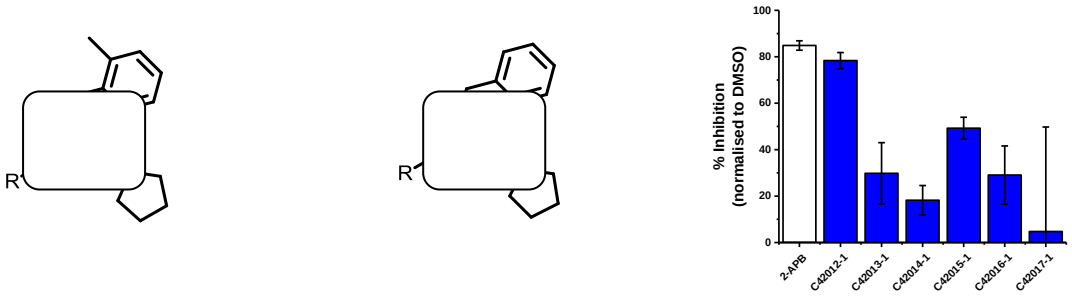
Plan of investigation:

(a) Optimisation of TRPCa inhibitors: We have recently identified a novel series of inhibitors of TRPCa following a high-throughput screen (HTS). The compounds are moderately potent and selective for a panel of homologous TRPC ion channels and the cardiotox channel, hERG. A key focus of this project will be to optimise the inhibitors for TRPCa potency (generate low nM potency hits), selectivity and physiochemical properties consistent with the properties of an orally bioavailable therapeutic. This will be achieved by strategic modification of the compounds by consideration of SAR and rationalisation of a pharmacophore model for TRPCa modulation, as well as optimisation of physicochemical properties directed by computational prediction and *in vitro* assay. All synthesised compounds will be tested for TRPCa activity using appropriate cellular *in vitro* assays and for selectivity using a panel of TRPCa assays, as well as other ion channels of relevance to the project. The aim of the project will be to generate a compound with appropriate potency, selectivity and pharmacokinetic properties to be progressed to *in vivo* determination of TRPCa function.

(b) Optimisation of TRPCb inhbitors: In parallel we will optimise hits for TRPCb activity using an analogous strategy as for the TRPCa project above. The overall aim will be to generate a selective set of compounds for both TRPCa and TRPCb modulation in order to appropriately and comparatively probe the biology of these critically important ion channels.

(c) Binding site identification: In collaboration with others in the School of Chemistry we will aim to validate the binding site of the inhibitors at the TRPCa/b channel by using a chemoproteomic strategy incorporating affinity and activity based probes. It may also be possible to validate the binding site of the inhibitors through use of structural biology (high resolution cryo-EM).

The project would suit a student with general interests at the interface between chemistry and biology and with more specific interests in medicinal chemistry and chemical biology.



Structure of hits and demonstration of potent effects of inhibitors in vitro

References

[1] Beech, D. J. Characteristics of transient receptor potential canonical calcium-permeable channels and their relevance to vascular physiology and disease. *Circulation journal* **77**, 570-579 (2013). Bon, R. S. & Beech, D. J. In pursuit of small molecule chemistry for calcium-permeable non-selective TRPC channels - mirage or pot of gold? *British journal of pharmacology* **170**,459-474 (2013).