NATURAL PRODUCTS AS LEAD STRUCTURES FOR THE DISCOVERY OF NEW ACTIVATORS/INHIBITORS OF TRPV1 AND RELATED CHANNELS

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Transient receptor potential (TRP) channels are a family of cation channels characterised by a bewildering range of properties and mechanisms of activation (thermal, osmotic, mechanical, chemical), that in some cases represent previously unrecognised modes of ion channel gating. The exact physiological function and regulation of most TRP channels is still elusive, but, despite a limited degree of orthology, a sensory function for obnoxious stimuli seems well established for TRPV1, TRPM8 and TRPA1 within evolutionary different phyla. It is therefore hardly surprising that a host of ligands for these channels have been employed by plants (as well as by animals) to deter predation, and that these compounds (capsaicin, menthol, isothiocyanates) have played a critical role for the characterisation of TRPV1, TRPM8 and TRA1. These ion channels, along with TRPV4, are the best characterised TRP channel in terms of chemical agonists and antagonists, and a bewildering range of structurally unrelated chemotypes of ligands has originated from the natural products pool.

Patents for TRPV1 modulators span a wide range of diseases that includes chronic pain, neuropathies, bladder disorders, headache, irritable bowel syndrome, gastro-oesophageal reflux disease, and cough. Furthermore, since TRPM8 and TRPA1 were first described as cancer markers, their ligands hold promise also in oncology, both as drugs and as diagnostic agents. Our understanding of the pathophysiological role of TRP channels is still fragmentary, and this gap warns against waiting too much and too soon from TRP ligands. Nevertheless, there is a great shortage of drugs for several conditions where modulation of TRP signalling can in principle be beneficial, and this explains the current medicinal chemistry efforts in what is still substantially a clinically poorly validated area.

Our efforts in the field of TRP ligands have focused on the discovery of new natural product chemotypes, on the elucidation of their structure-activity relationships, and on their use as prototypes to design totally synthetic analogues with improved potency. Given the partial overlapping in terms of endogenous ligands between vanilloid and cannabinoid receptors, the relevance of natural products to explore this fertile interface has also been explored with designer probes. Several lessons of general meaning for the use of natural products in drug discovery programs have been learned and will be discussed.