Developing Molecular Tools for the Study and Detection of Calcium-Sensing Receptor

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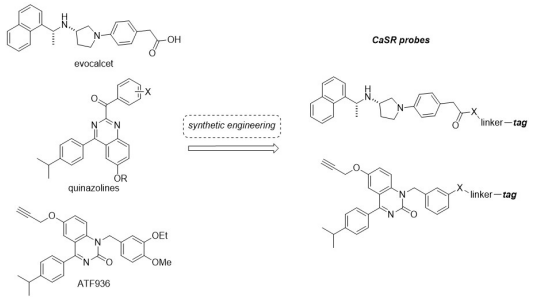
Background: The calcium-sensing receptor (CaSR) is a G protein-coupled receptor that plays a central role in the regulation of calcium homeostasis in humans.[1] It is highly expressed in parathyroid glands, pancreatic endocrine cells and kidneys. Impaired expression or function of CaSR causes several diseases and enlarged parathyroid glands, in particular, can lead to a pathological shift of calcium homeostasis and necessitate surgical removal in some cases.[2] Thus, the accurate pre- and intraoperative localisation of parathyroid glands is essential to avoid persistent complications that can significantly impair the patient's quality of life.[3] Molecular tools currently used in the clinic are not specific to the parathyroid glands and false-positive and false-negative readouts are common. Several small compounds and peptides have been developed to target and modulate CaSR as allosteric ligands, some of which are used in the clinic as so-called calcimimetic drugs to increase CaSR activity (e.g. cinacalcet, evocalcet and etelcalcetide).

Aim: To develop synthetic molecular probes for the study, modulation and localisation of the CaSR in cells and tissue.

Methods and Results: To this end, we have synthesised derivatives and conjugates of calcilytics (i.e. negative allosteric CaSR modulators), such as quinazolines and quinazolinones, and derivatives of evocalcet (positive allosteric modulator). In this context, we present our work on the synthesis of these probes and their preliminary biological assessment.



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