

Positive allosteric modulators (PAMs) of calcium sensing receptor (CaSR) for hyperparathyroidism

Tech ID: 34718 / UC Case 2024-043-0

TECHNOLOGY DESCRIPTION

The **Unmet Need**: Current treatments for secondary hyperparathyroidism including CaSR agonists Cinacalcet and Etelcalcetide have significant drawbacks including the risk of hypocalcemia, gastrointestinal problems, hypotension, and adynamic bone disease. There is a need for CaSR modulators that modulate PTH secretion without causing the dose-limiting hypocalcemia of the approved drugs.

The **Target**: Calcium Sensing Receptor (CaSR) is highly expressed in the parathyroid glands and kidneys, where it maintains calcium homeostasis by regulating PTH secretion and renal calcium reabsorption and excretion. Loss or gain of function in CaSR results in conditions such as familial hypocalciuric hypercalcemia, primary hyperparathyroidism, and autosomal dominant hypocalcemia. CaSR is also involved in nutrient sensing, vascular tone, and insulin secretion, with implications in osteoporosis and several cancers.

The **Compounds**: The team docked libraries of 2.7 million and 1.2 billion molecules against the CaSR structure with the goal of identifying compounds that bind CaSR but are topologically novel with novel pharmacology. Structure-based optimization led to nanomolar leads. In ex vivo organ assays, one of these PAMs was 100-fold more potent than the standard of care, cinacalcet, and reduced serum parathyroid hormone (PTH) levels in mice without the hypocalcemia typical of CaSR drugs.

Potential **Indications**: Secondary hyperparathyroidism, Chronic Kidney Disease (CKD), Primary

Hyperparathyroidism, Parathyroid Carcinoma

RELATED MATERIALS

- ▶ [Liu, Fangyu et al. "Large library docking identifies positive allosteric modulators of the calcium-sensing receptor." Science \(New York, N.Y.\) vol. 385,6715 \(2024\): eado1868. doi:10.1126/science.ado1868](#)

PATENT STATUS

Patent Pending

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