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Discovery of a class of calcium sensing receptor positive allosteric modulators; 1-(benzothiazol-2-yl)-1-phenylethanols

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1-(benzothiazol-2-yl)-1-phenylethanols

ABSTRACT

1-(Benzothiazol-2-yl)-1-(4-chlorophenyl)ethanol (**1**) was identified as a positive allosteric modulator (PAM) of the CaSR in a functional cell-based assay. This compound belongs to a class of compounds that is structurally distinct from other known positive allosteric modulators, for example, the phenylalkylamines cinacalcet, a modified analog (**13**) potentially suppressed parathyroid hormone (PTH) release in rats, consistent with its profile as a PAM of CaSRs.

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The ability of a drug to produce its effect on an organism is dependent on its molecular properties. Hence, structurally different ligands exerting their effect at the same target could potentially give rise to a ligand-specific pharmacology based on differences in pharmacokinetic properties, pharmacodynamic properties, or both.^{1,2} Herein we report on the discovery and structure–activity relationship (SAR) of a novel class of calcium sensing receptor (CaSR) positive allosteric modulators (PAMs) (e.g., **1**, Fig. 1). This class of compounds is structurally distinct from the reported CaSR PAMs, for example, cinacalcet hydrochloride (**2**) and calindol.

Cinacalcet hydrochloride is the first GPCR PAM to reach the market and is used for the treatment of secondary hyperparathyroidism (SHPT) in patients with end-stage renal disease receiving hemo-dialysis and of primary hyperparathyroidism (PHPT) caused by parathyroid cancer. The essential role of the CaSR in calcium homeostasis makes it an important drug target and offers an

attractive means to control hormonal disorders related to calcium homeostasis.^{3,4} In addition to PHPT and SHPT, PAMs targeting the CaSR may also be effective drugs for treating mineral and bone

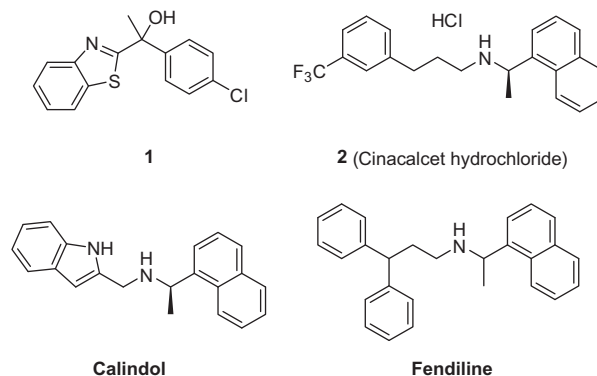


Figure 1. Selected CaSR ligands.

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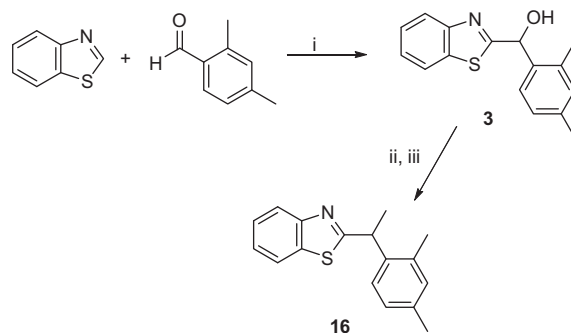
disorders in chronic kidney disease, dominant hyperparathyroidism, familial hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, and hypercalcemia caused by autoantibodies that inhibit CaSR.

The calcium sensing receptor is a member of the GPCR superfamily and belongs to the group C family of GPCRs and is most closely related to the GABA_B receptor and metabotropic glutamate receptors.^{5–8} The receptor is expressed in calcitropic hormone-secreting organs (parathyroid glands and C-cells of the thyroid glands), kidney, bone, and intestinal cells.⁴ The CaSRs primarily functions are to maintain systemic Ca²⁺ homeostasis mainly by causing suppression of parathyroid hormone secretion by the parathyroid glands, and by influencing rates of renal tubular calcium reabsorption and secretion of calcitonin by C-cells of the thyroid.^{9,10}

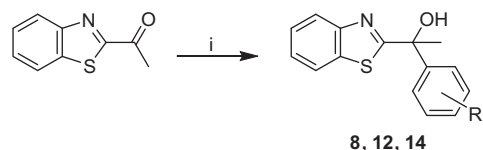
A chemical library containing 250,000 small drug-like compounds was screened for agonist activity using a cell-based functional assay called Receptor Selection and Amplification Technology (R-SAT).¹¹ In the screen cells were maintained in standard tissue culture medium containing Dulbecco's modified Eagle's medium (DMEM) and 0.8 mM MgCl₂ and 1.6 mM CaCl₂ to increase the sensitivity for detecting hits. A number of active compounds representing distinct structural classes were identified. Based on the structurally interesting features compared with reported PAMs, the benzothiazole class (e.g., **1**) was chosen for further studies. In contrast to **1**, most of the reported CaSR PAMs today including, NPS R-467, NPS R-568, calindol, and cinacalcet hydrochloride (**2**) are phenylalkylamines, which are structurally derived from fendiline. In addition, compound **1** is not cationic at physiological pH which further differentiates it from previously reported calcimimetics, including the PAMs, the L-amino acids, and obviously cations such as Ca²⁺ and Mg²⁺.

Compound **1** displayed partial agonism and nM activity at the CaSR (pEC₅₀ 6.4 and 68% efficacy), but also had a high intrinsic clearance in human liver microsomes of >200 µL/min mg.

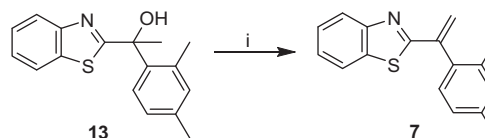
Based on the lead compound **1**, a focused set of analogues were synthesized to establish the SAR and to improve on the metabolic stability. To be able to easily introduce a variety of substituents (R) on the benzylic position, different synthetic strategies were developed (Schemes 1–4). Lithiation of benzothiazole at low temperature (–78 °C),¹² followed by addition of a variety of ketones gave products **1**, **4–6**, **9–11**, **13**, **15**, **17–18** in medium to good yields (Scheme 1).^{13,14} Of these only the synthesis of **9** was difficult, and a modest 32% yield was achieved. The low yield was attributed to the decreased reactivity of cyclic ketone compared to the acetophenones in combination with the low stability of the lithiated benzothiazole. The lithiated benzothiazole is reported to start decomposing when increasing the temperature for at –40 °C being totally cracked.¹² To investigate the significance of the hydroxyl and the methyl group on the benzylic carbon, analogues **3** and



Scheme 2. Reagents and conditions: (i) *n*-BuLi, THF, –78 °C, 46%; (ii) CH₃SO₂Cl/Et₃N, CH₂Cl₂, rt; (iii) CH₃MgBr, THF, rt, 77% two steps.



Scheme 3. Reagents and conditions: (i) ArMgX, X = Cl, Br, THF, rt, 62–77%.



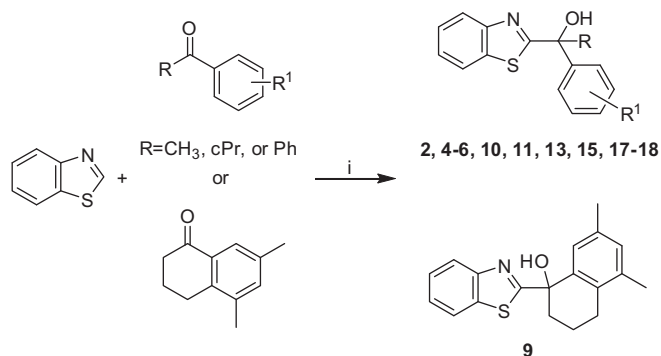
Scheme 4. Reagents and conditions: (i) PPA, THF/Ac₂O, rt, 41%.

16 were synthesized. Lithiation of benzothiazole followed by reaction with 2,4-dimethylbenzaldehyde gave alcohol **3** in 46% yield (Scheme 2). Analogue **16** was made in two steps, one-pot, from alcohol **3** as follows; compound **3** was reacted with CH₃SO₂Cl/Et₃N followed by nucleophilic substitution with CH₃MgBr to yield compound **16** in 77% yield.

Analogues **8**, **12**, and **14** were made by reacting acetylbenzothiazole with the corresponding Grignard reagent (Scheme 3). Treatment of compound **13** with poly phosphoric acid (PPA) gave exo-methylene **7** in 41% yield (Scheme 4).

The in vitro activity of these analogs was measured using R-SAT (Table 1). Experiments using media partially depleted of MgCl₂ and various concentrations of CaCl₂ confirmed that our compounds cooperate with divalent cations to activate the CaSR (Fig. 2).¹⁵

From the SAR it reads that the phenyl substituents have a large impact on the activity of this class of compounds (Table 1). Replacing the phenyl with the larger naphthyl gives a slightly less active analogue compared with the hit **1**. A more rigid structure was well tolerated, and analogue **9** retained the activity (pEC₅₀ 6.5 ± 0.2 and Eff. 81 ± 6). Whereas the *o*-methyl compound **11** had comparable activity with the *p*-chloro compound **1**, the electron donating *o*-methoxy group (**10**) had a negative effect and the activity dropped 10 times to pEC₅₀ 5.4. With these substantial changes in activity in mind we further elaborated with small substituents, for example, Me, Cl, and F to give an initial SAR. Compounds **11** (*o*-CH₃) and **12** (*m*-CH₃-*p*-F), pEC₅₀ at 6.6 and 6.8, respectively, had slightly higher activity than the hit **1** (pEC₅₀ 6.4). However, a more substantial increase in activity was seen when a disubstitution pattern with methyl and chloro groups was introduced (Table 1, compounds **5** and **13–15**). The two most active racemic compounds tested were **13** (pEC₅₀ 7.6 ± 0.1 Eff. 91 ± 4) and **14** (pEC₅₀ 7.5 ± 0.2 Eff. 82 ± 9). Another predominant feature of the structure–activity relationship is that a small non-hydrogen R substituent is manda-



Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, –78 °C, 32–80%.

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