Bioorganic & Medicinal Chemistry Letters 28 (2018) 2055–2060

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of evocalcet, a next-generation calcium-sensing receptor agonist for the treatment of hyperparathyroidism

Hiroshi Miyazaki [a,*], Yousuke Ikeda [a], Osamu Sakurai [a], Tsutomu Miyake [a], Rie Tsubota [a], Jyunko Okabe [a], Masataka Kuroda [a], Yutaka Hisada [a], Tetsuya Yanagida [a], Hikaru Yoneda [a], Yukihito Tsukumo [b], Shin Tokunaga [b], Takehisa Kawata [b], Rikiya Ohashi [a], Hajime Fukuda [a], Koki Kojima [a], Ayako Kannami [a], Takayuki Kifuji [a], Naoya Sato [a], Akiko Idei [a], Taku Iguchi [a], Tetsuya Sakairi [a], Yasunori Moritani [a]

[a] Mitsubishi Tanabe Pharma Corporation, 1000, Kamoshida-cho, Aoba-ku, Yokohama 227-0033, Japan
[b] Kyowa Hakko Kirin Co., Ltd., 1188, Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8731, Japan

ARTICLE INFO

Article history:
Received 26 March 2018
Revised 19 April 2018
Accepted 23 April 2018
Available online 24 April 2018

Keywords:
Evocalcet
Calcium-sensing receptor (CaSR)
Allosteric calcium-sensing receptor agonist
Hyperparathyroidism
Cinacalcet

ABSTRACT

The calcium-sensing receptor (CaSR) plays an important role in sensing extracellular calcium ions and regulating parathyroid hormone secretion by parathyroid gland cells, and the receptor is a suitable target for the treatment of hyperparathyroidism. Cinacalcet hydrochloride is a representative CaSR agonist which widely used for the hyperparathyroidism. However, it has several issues to clinical use, such as nausea/vomiting and strong inhibition of CYP2D6. We tried to improve these issues of cinacalcet for a new pharmaceutical agent as a preferable CaSR agonist. Optimization from cinacalcet resulted in the identification of pyrrolidine compounds and successfully led to the discovery of evocalcet as an oral allosteric CaSR agonist. Evocalcet, which exhibited highly favorable profiles such as CaSR agonistic activity and good DMPK profiles, will provide a novel therapeutic option for secondary hyperparathyroidism.

Secondary hyperparathyroidism (SHPT), which causes the excessive production of parathyroid hormone (PTH) by the parathyroid glands, is a common mineral and bone disorder in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1] In this disorder, high serum PTH levels induce high-turnover bone disease and increase serum calcium and phosphate levels via efflux from the bone. This abnormity of calcium and phosphate metabolism is associated with risks of fracture, vascular calcification, and cardiovascular mortality.[2–5]

The calcium-sensing receptor (CaSR) is a class C G-protein coupled receptor (GPCR) that senses extracellular calcium ions and regulates PTH secretion by parathyroid gland cells.[6] Cinacalcet hydrochloride (**1**, Fig. 1), a calcimimetic agent which allosterically activates CaSR, is widely used for the oral treatment of SHPT in dialysis patients by decreasing the serum PTH, calcium and phosphate levels.[7–14] In addition, cinacalcet can slow the progress of cardiovascular calcification and reduce the risk of mortality.[15–17] However, cinacalcet has several drawbacks such as adverse effects on the gastrointestinal (GI) tract (e.g., nausea and vomiting)[18] and potential drug-drug interactions due to its strong inhibition of cytochrome P450 2D6 (CYP2D6).[19] In particular, these GI adverse effects limit the dose of cinacalcet and result in poor compliance or treatment discontinuation.[20,21]

As our initial drug discovery efforts targeting novel calcimimetic agents without the drawbacks of cinacalcet, we started an exploration of cinacalcet analogs. Efforts to improve its CaSR agonistic activity, oral exposure, and CYP2D6 inhibition successfully led to the discovery of evocalcet (**16**). In this study, we disclose the structure–activity relationships (SARs) and findings of evocalcet and its pyrrolidine derivatives.

Structural information of CYP2D6 from homology models reveals that the characteristic features of CYP2D6 substrates are a basic nitrogen and a planar hydrophobic area[22], which might explain the strong CYP2D6-inhibitor effects of cinacalcet (IC_{50} < 0.1 μM). However, the basic nitrogen of cinacalcet in the center position interacts with Glu837 of CaSR, and this nitrogen moiety is essential for its agonistic activity, as will be described later.[23] In the design of new drugs, a strategy of hindering the basic amine surroundings was selected to weaken the affinity for CYP2D6 and decrease CYP2D6 inhibition. As a result, a diisopropylamine-type compound (i.e., pyrrolidine analog **2**) exhibited moderate agonistic efficacy toward human CaSR and reduced CYP2D6 inhibition (Fig. 2, Table 1).

* Corresponding author.
E-mail address: miyazaki.hiroshi@me.mt-pharma.co.jp (H. Miyazaki).

https://doi.org/10.1016/j.bmcl.2018.04.055
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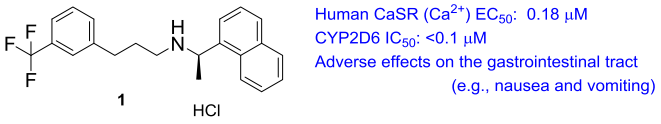

Fig. 1. Cinacalcet hydrochloride (**1**).

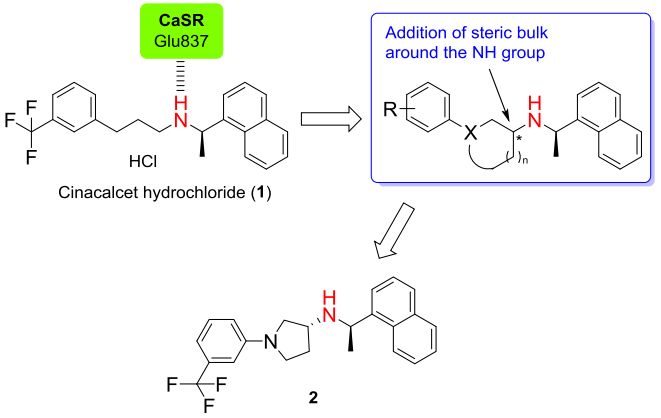

Fig. 2. Drug design and the structure of **2**.

The search for more attractive compounds focused on derivatives of **2**. Our design of CaSR agonists is summarized in Fig. 3, and their synthesis, including that of **2**, is depicted in Schemes 1 and 2. *tert*-Butyl 3-hydroxypyrrolidine-1-carboxylate was converted to the di-*tert*-butoxycarbonyl (Boc)-protected compounds **S2** and **S3** in a three-step reaction. Separation of diastereoisomers **S2** and **S3** via silica gel chromatography followed by deprotection of Boc gave **S4** and **S5**. In the case of piperidine compounds, 1-benzyloxycarbonyl-3-piperidone was converted to a diastereomeric mixture of carbamoyl chloride compounds in two steps that were separated via filtration and silica gel chromatography to give diastereomers **S7** and **S8**. Deprotection of the carbamoyl chloride and the benzyloxycarbonyl (Z) group by water and hydrogenation, respectively, afforded piperidines **S9** and **S10**. Key intermediates **S4**, **S5**, **S9**, and **S10** were transformed into designed CaSR agonists **2**–**11**, **13**–**15**, and evocalcet (**16**) using palladium coupling reactions with the corresponding aryl halide or some conventional

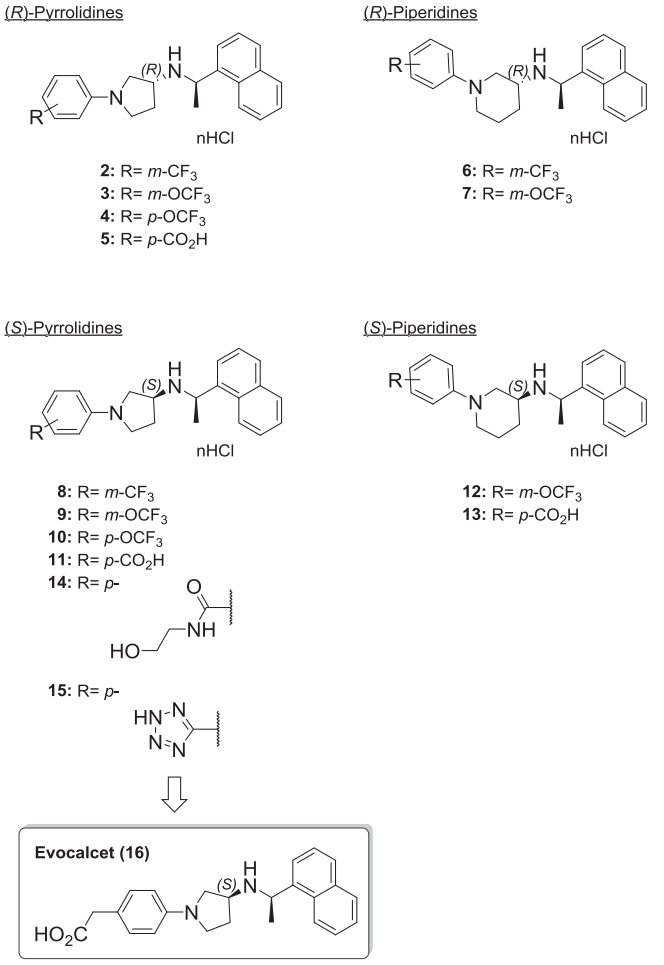

Fig. 3. Compound **2**, its derivatives and evocalcet (**16**).

chemical conversions. Regarding the reactions of **S4**, **S5**, **S9**, and **S10** in Scheme 2, these compounds were specifically reacted at the less hindered ring nitrogen atom. Compound **12** was synthesized from 3-hydroxypiperidine and obtained via separation from its diastereoisomer.

Table 1
Calcium-sensing receptor (CaSR) agonistic efficacies, inhibitory effects on parathyroid hormone (PTH) production in rat parathyroid cells, and DMPK profiles.

Compound	Human CaSR (Ca^{2+})	Inhibition of rat PTH production	CYP2D6 inhibition (%)			CLint (μL/min/mg protein)	
	EC_{50} (μM)	IC_{50} (nM)	10 μM	1 μM	0.1 μM	Human	Rat
2	0.43	9.7	nt	60.0	3.0	421	302
3	0.32	4.3	nt	61.2	15.8	206	270
4	0.23	116	nt	nt	nt	nt	nt
5	8.8	nt	nt	nt	nt	nt	nt
6	0.38	2.1	87.6	78.7	54.8	662	610
7	0.19	1.4	85.2	82.6	54.0	370	231
8	0.45	13.1	nt	87.5	85.1	171	370
9	0.60	11.7	nt	88.4	85.9	84	176
10	0.12	7.8	79.8	62.5	15.8	nt	nt
11	0.29	8.0	14.1	14.1	0.0	97	92
12	0.60	31.8	92.5	86.4	79.0	225	442
13	1.1	>100	nt	nt	nt	nt	nt
14	0.050	0.91	30.7	3.4	4.4	197	667
15	0.017	0.47	75.3	nt	nt	312	42
Evocalcet (**16**)	0.093	30.8	-[a]			68[b]	34[b]

nt: not tested.
[a] IC_{50} of evocalcet for CYP2D6 was higher than 50 μM.
[b] nHCl salt data.