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LETTER

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Discovery of a Potent and Short−Acting Oral Calcilytic with a Pulsatile Secretion of Parathyroid Hormone

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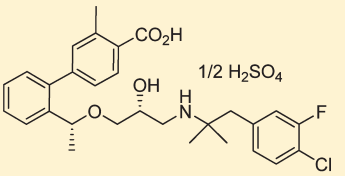
Supporting Information

ABSTRACT: Short-acting oral calcilytics, calcium-sensing receptor (CaSR) antagonists, have been considered as alternatives for parathyroid hormone (PTH), an injectable bone anabolic drug used in the treatment of osteoporosis. Previously, we identified aminopropandiol **1**, which transiently stimulated endogenous PTH secretion in rats. However, the inhibition of cytochrome P450 (CYP) 2D6 and the low bioavailability of **1** remain to be solved. Attempts to change the physicochemical properties of the highly lipophilic amine **1** by introduction of a carboxylic acid group as well as further structural modifications led to the discovery of the highly potent biphenylcarboxylic acid **15**, with a markedly reduced CYP2D6 inhibition and a significantly improved bioavailability. Compound **15** evoked a rapid and transient elevation of endogenous PTH levels in rats after oral administration in a dose-dependent manner at a dose as low as 1 mg/kg. The PTH secretion pattern correlated with the pharmacokinetic profile and agreed well with that of the exogenous PTH injection which exerts a bone anabolic effect.



JTT-305 (**15** hemisulfate)

KEYWORDS: Calcium-sensing receptor (CaSR) antagonist, calcilytics, PTH, short-acting, osteoporosis, cytochrome P450 inhibition

Osteoporosis is a bone disease marked by decreased bone strength and accompanied by an increased risk of bone fracture, affecting more than 75 million people in EU, U.S., and Japan.[1] The current mainstream drugs for osteoporosis are antiresorptive agents such as bisphosphonates, estrogen, and selective estrogen receptor modulators (SERMs).[2] These compounds suppress osteoclast cell function and prevent bone loss. However, an anabolic agent which stimulates osteoblast cells and leads to new bone formation is an attractive alternative.

The bone strength defined by bone density and quality is maintained through the balance of old bone resorption and new bone formation, known as bone remodeling. Parathyroid hormone (PTH) is a key intrinsic agent regulating bone remodeling in either the catabolic or the anabolic pathways, depending on the pattern of exposure to the hormone. Intermittent exposure to PTH is important to stimulate new bone formation and leads to anabolic effects, while prolonged exposure to elevated PTH levels increases bone turnover and results in bone loss.[3] Since daily subcutaneous injection of teriparatide, the recombinant 1−34 amino acid fragment of human parathyroid hormone (PTH), improved bone mineral density (BMD) in the lumbar spine and reduced bone fracture rates in patients with postmenopausal osteoporosis,[4] anabolic agents have received much attention. Currently, two injectable human PTH peptides, teriparatide and Preotact (hPTH 1−84), are on the market, but no orally administered anabolic drug is available.

Endogenous PTH is secreted from the parathyroid gland when lowered blood levels of ionized calcium are detected by the calcium-sensing receptor (CaSR), a G-protein coupled receptor expressed on the surface of parathyroid cells.[5] Thereby, the antagonists, known as calcilytics, reduce the sensitivity of this receptor to extracellular calcium and stimulate PTH secretion. This outcome was first shown by an orally available calcilytic, NPS-2143 (Figure 1).[6,7] At the same time, it was also reported that the long acting profile of this compound resulted in sustained high PTH levels and no net increase of bone mass. Therefore, research has been focused on the development of a CaSR antagonist with rapidly absorption and a short acting pharmacokinetic profile to achieve a PTH secretion pattern similar to that of the exogenously injected form.

Although many CaSR antagonists have been reported in the literature to date,[8−16] the proof of concept in humans was recently shown by ronacarelet[17] and JTT-305[18] (MK-5442, **15** hemisulfate) (Figure 1). We have reported a new aminopropandiol class of calcilytics **1** (Figure 1) which demonstrated a rapid and transient stimulation of PTH secretion after oral administration in rats.[12,19] However, compound **1** possessed a strong CYP2D6 inhibition (IC_{50} of 0.5 μM) and low bioavailability (BA, 13%). Here, we report our research efforts to improve the CYP

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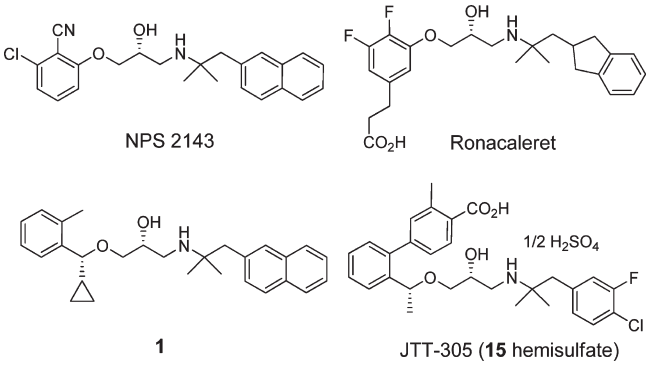


Figure 1. Structures of selected calcilytics.

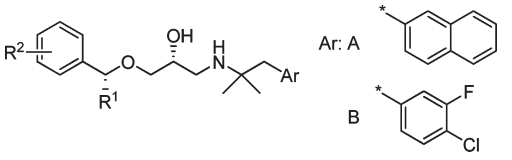
inhibition and the low BA, which led to the discovery of short-acting oral calcilytic **15** with pulsatile secretion of PTH.

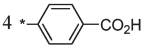
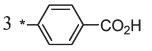
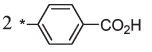
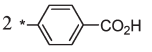
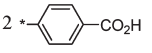
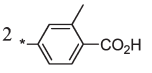
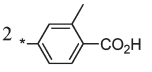
Molecules that are basic in character and highly lipophilic are conducive to CYP2D6 inhibition and also block the human ether-a-go-go related gene (hERG) ion channel.[20] NPS-2143 and compound **1** exhibit both of these physicochemical characteristics. NPS-2143 has been reported to inhibit CYP2D6 and hERG strongly.[10] In an examination of the metabolites of **1** in rats, two products in which the methyl group on the benzene ring was oxidized to either the alcohol or to the carboxylic acid were identified. Both these oxidative metabolites have reduced lipophilicity compared to that of parent compound **1**. While the alcohol **2** still inhibited CYP2D6 (IC_{50} of 1.2 μM), the inhibitory potency of carboxylic acid **3** (diastereomixture) toward CYP2D6 activity was significantly weakened (IC_{50} > 10 μM). Although **3** exhibited significantly decreased CaSR antagonist activity, changing the position of the COOH group to the *meta* site (**4**) restored the antagonist activity (IC_{50} of 1.0 μM) and reduced CYP2D6 inhibition (IC_{50} > 10 μM). In light of this result, we attempted to introduce a carboxylic acid group into the molecule in an effort to develop an orally active aminopropandiol calcilytic without the unfavorable off-target activities. The compounds described in this paper were tested in the human CaSR antagonist assay (PC12h cells reporter gene assay) (Table 1) and by measurement of PTH secretion in rats (Table 2), as previously reported.[19]

The initial phase of the investigation focused on defining the site in the molecule where a COOH group could be introduced without affecting CaSR antagonist activity, as compared to **1**. Benzoic acid analogue **5**, having a COOH group at the *para* position of the left benzene ring, and **6**, a methyl analogue of **3** with a benzylic substituent, exhibited significantly decreased antagonist activity, while the phenylacetic acid derivative **7** maintained the antagonist activity (IC_{50} of 2.2 μM). Further extension of the methylene chain to the phenylpropionic acid structure (**8**) increased inhibitory potency 100-fold (IC_{50} of 0.024 μM), which is comparable to that of compound **1**, indicating that the COOH group in the area *ortho* to the site of attachment of the aminopropandiol chain could be accommodated. Compound **8** showed significantly reduced CYP2D6 inhibition (IC_{50} of 9.6 μM).

To define the optimum position for the COOH group, we prepared three carboxylic acids **9**−**11** in which the position of the COOH groups were fasten by the rigid biphenyl structure. Two of those, **10** and **11**, with *meta* and *ortho* substituents, respectively, showed antagonist activities that were comparable to or more potent than those of **1**. On the other hand, para substituent (**9**) displayed poor activity. Since these compounds are diastereomixtures at the benzylic Me substituent, we prepared an

Table 1. *In Vitro* hCaSR Antagonist Activity of the Aminopropandiol Derivatives



Compd	R^1	R^2	Ar	hCaSR IC_{50} μM[a]
1	c-Pr	2 -Me	A	0.023[b]
2	c-Pr	2 -CH_2OH	A	0.018
3	c-Pr (*RS*)[c]	2 -CO_2H	A	>3
4	c-Pr (*RS*)	3 -CO_2H	A	0.96
5	c-Pr (*RS*)	4 -CO_2H	A	>3
6	Me (*RS*)	2 -CO_2H	A	>3
7	Me	2 -CH_2CO_2H	A	2.2
8	Me	2 -$CH_2CH_2CO_2H$	A	0.024
9	Me (*RS*)	4 	A	1.5
10	Me (*RS*)	3 	A	0.018
11	Me (*RS*)	2 	A	0.011
12	Me	2 	A	0.004
13	Me	2 	B	0.023
14	Me	2 	A	0.005
15	Me	2 	B	0.012

[a] *In vitro* hCaSR antagonist activity was determined in PC12h cells, as described in ref 24. Values are means of three experiments. [b] Reference 12. [c] Diastereomixture.

R,R-isomer of **11** (compound **12**) with the same configuration as that of compound **1** . The *R,R*-enantiomer **12** showed the most potent antagonist activity of all tested analogues (IC_{50} of 0.004 μM) and a reduced CYP2D6 inhibition (IC_{50} > 10 μM).

We also examined the PTH secretion activity of **8** and **12** (Table 2). An oral dose of **12** at 10 mg/kg in rats elicited PTH 1−34 levels that were comparable to those obtained with a 30 mg/kg dose of **1**. At the lower dose of 3 mg/kg, compounds **8** and **12** exhibited similar PTH secretion activities. These results confirmed that these carboxylic acid derivatives are orally active. However, their potencies in PTH secretion activity were not largely improved compared to that of **1**, indicating that BA was not much improved in these compounds. In fact, a pharmacokinetic

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Table 2. *In Vivo* PTH Secretion Activity of the Selected Compounds in Rats

	PTH secretion[a]		
compd	1 mg/kg	3 mg/kg	10 mg/kg
8	NT	+	NT
12	−	+	++
13	+	++	NT
14	−	++	NT
15	++	++	++

[a] Increases of serum PTH 1−34 levels (Δ) were compared with levels observed in control rats treated with vehicle. The peak levels, measured at 15 or 30 min after oral administration of the compounds in rats (n = 5), were compared with the levels observed in animals treated with compound **1** (30 mg/kg, po, ∼2−4-fold increases). ++, >80% of compound **1**; +, 50−80% of compound **1**; −, <50% of compound **1**; NT, not tested.

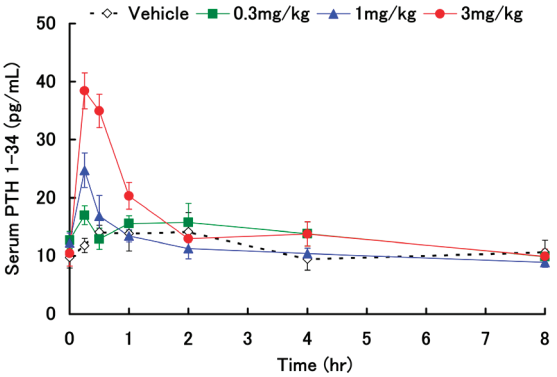


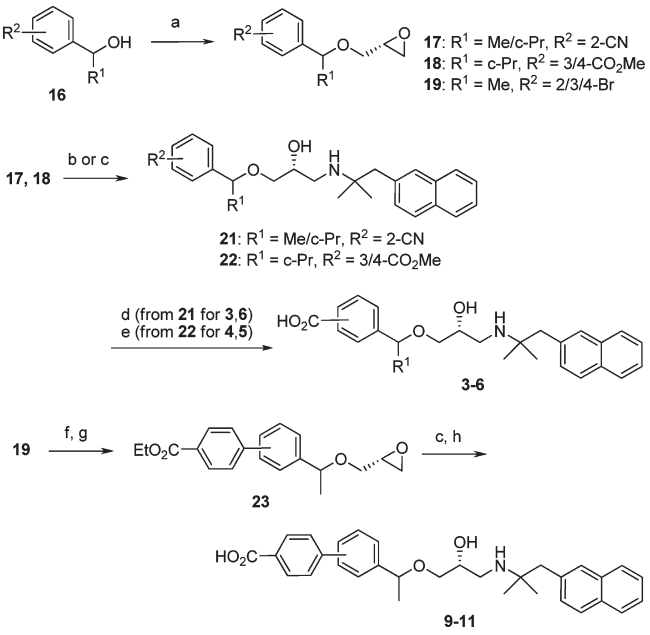
Figure 2. Time courses of PTH 1−34 levels after oral administration of **15** hemisulfate in rats. Data are expressed as mean values ± standard deviation, n = 5.

study of **12** in rats showed low BA (6.4%). We considered that the naphthyl structure on the right-hand side of the molecules might contribute to the low BA of this series. Among the compounds examined to improve BA, 4-chloro-3-fluorophenyl derivative **13** showed a better potency *in vivo* compared to **12** (PTH secretion levels at 3 mg/kg dose of **13** were similar to those at 10 mg/kg dose of compound **12**), although the antagonist potency was lower (IC_{50} of 0.023 μM).

Another concern for the metabolism of these derivatives was the formation of conjugated metabolites (e.g., glucuronic acid conjugation). We hypothesized that the introduction of a Me group *ortho* to the COOH on the phenyl ring (compound **14**) might cause steric hindrance and interfere with the glucuronate conjugate reaction. As a result, compound **14** exhibited a sustained antagonist activity but an improved potency *in vivo* compared to **12**. Finally, all these modifications were successfully combined, as exemplified by compound **15**, which showed a high antagonist activity (IC_{50} of 0.012 μM) and a potentiated PTH secretion activity *in vivo* (10-fold more potent than **12**).

A PTH secretion time course study after oral administration of **15** in rats was conducted (Figure 2). Compound **15** afforded elevated endogenous PTH 1−34 levels rapidly, transiently, and in a dose-dependent manner at a dose as low as 1 mg/kg. A maximal level was observed at 15 min and was restored to baseline within 2 h. The PTH secretion pattern is in good agreement with that

Scheme 1[a]



[a] Reagents and conditions: (a) (*R*)-(−)-glycidyl 3-nitrobenzenesulfonate, NaH, DMF or THF−DMSO, rt; (b) [1,1-dimethyl-2-(2-naphthalenyl)ethyl]amine (**20**), EtOH, 60 °C, 12 h; (c) **20**, $LiClO_4$, CH_3CN or toluene, reflux, 12 h; (d) KOH, ethylene glycol, 160 °C, 8 h; (e) 2N NaOH aq, MeOH; (f) 4-formylphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, EtOH−toluene reflux; (g) MnO_2, KCN, EtOH, rt; (h) 2N NaOH aq, THF−MeOH.

observed with exogenous PTH injection,[21,22] indicating that compound **15** could be a bone anabolic agent for osteoporosis. A bone anabolic effect of compound **15** on ovariectomized (OVX) rats has been observed (manuscript submitted).[23] A pharmacokinetic study of **15** showed that the short-acting character of this compound was well correlated with the pharmacokinetic profile. It was rapidly absorbed after oral administration in rats (1 mg/kg, T_{max} of 0.5 h, C_{max} of 475 ng/mL) and disappeared shortly thereafter ($T_{1/2}$ of 1.8 h). The BA was dramatically improved (64%). The strong CYP2D6 inhibition activity observed with compound **1** (IC_{50} of 0.5 μM) was significantly reduced in compound **15** (IC_{50} of 11 μM). Compound **15** showed a weak inhibition for β_2-adrenergic receptor binding (IC_{50} of 1.7 μM) and did not show binding inhibition for α_2-adrenergic receptor, dopamine transporter (D_1), and serotonin receptors up to 10 μM.

The compounds investigated in this study were synthesized as shown in Schemes 1 and 2. Alcohols **16**[12] were converted to the glycidyl ethers **17**−**19** by alkylation with (*R*)-(−)-glycidyl 3-nitrobenzensulfonate in the presence of NaH in DMF or in THF−DMSO. Epoxy-opening reaction of **17** or **18** with 1,1-dimethyl-2-(2-naphthalenyl)ethylamine **20**[19] gave the amino-alcohol **21** or **22**, respectively. Hydrolysis of the nitrile group in **21** by KOH in ethylene glycol or the ester group in **22** by aq NaOH in MeOH afforded the carboxylic acids **3**−**6**. Biphenyl carboxylic acids **9**−**11** were prepared from the glycidyl ether **19** in four steps as follows. Suzuki coupling of **19** with 4-formylphenylboronic acid and subsequent oxidation of the aldehyde by MnO_2 in the presence of KCN in EtOH gave the esters **23**, which were reacted with an amine **20** and hydrolyzed to the corresponding carboxylic acids **9**−**11**. Optically active compounds **7**,

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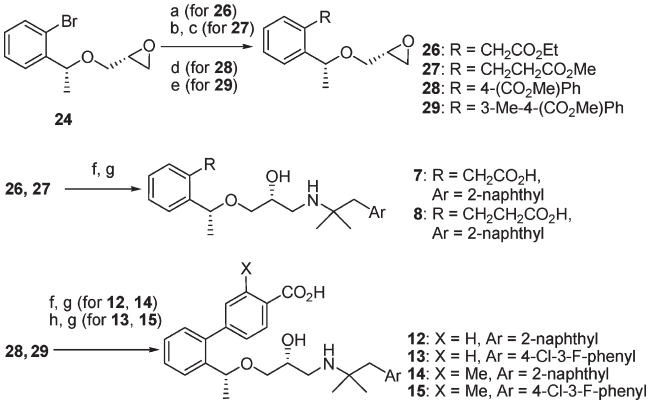
Scheme 2[a]



[a] Reagents and conditions: (a) ethyl tributylstannyl acetate, $Pd(PPh_3)_4$, toluene, reflux, 5 h; (b) methyl acrylate, $P(o\text{-tolyl})_3$, $Pd(OAc)_3$, Et_3N, CH_3CN, reflux, 12 h; (c) H_2, $Rh\text{-}Al_2O_3$ (cat), MeOH; (d) 4-methoxycarbonylphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, EtOH−toluene reflux; (e) 4-(methoxycarbonyl)-3-methylphenylboronic acid pinacol ester (**25**),[24] $PdCl_2$(dppf), Na_2CO_3, EtOH−toluene reflux; (f) [1,1-dimethyl-2-(2-naphthalenyl)ethyl]amine (**20**), $LiClO_4$, CH_3CN or toluene, reflux; (g) 2 N NaOH aq, THF−MeOH; (h) 2-(4-chloro-3-fluorophenyl)-1,1-dimethylethylamine (**30**), $LiClO_4$, toluene, reflux.

8, and **12**−**15** were synthesized from chiral glycidyl ether **24** (prepared from the corresponding chiral alcohol by the same method described in Scheme 1). Either a coupling reaction of **24** with ethyl tributylstannyl acetate in the presence of $Pd(PPh_3)_4$, a Heck reaction of **24** with methyl acrylate followed by hydrogenation of the double bond in the presence of Rh/Al_2O_3, or Suzuki couplings with the corresponding boronic acids[24,25] gave the epoxides **26**−**29**, which were converted to **12**−**15** by epoxy-opening reaction with the corresponding amine **20** or **30**[24] and subsequent hydrolysis of the ester, respectively.

In conclusion, we have discovered a potent and short-acting oral aminopropandiol calcilytic **15**, bearing a biphenylcarboxylic acid structure. The strong CYP2D6 inhibition seen in the prototype compound **1** was significantly reduced by the introduction of a COOH group. Modification of the naphthylethylamine part and the incorporation of a biphenylcarboxylic acid moiety bearing a substituent on the position *ortho* to the COOH provided a significant improvement of BA in rats. Oral administration of **15** in rats led to a pulsatile secretion of endogenous PTH, which is a required profile for a bone anabolic agent. Compound **15** is now in a phase 2 clinical study.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details for the synthesis and characterization of the tested compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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