Bioorganic & Medicinal Chemistry Letters 20 (2010) 5161–5164

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Penta-substituted benzimidazoles as potent antagonists of the calcium-sensing receptor (CaSR-antagonists)

Marc Gerspacher *, Eva Altmann, René Beerli, Thomas Buhl, Ralf Endres, Rainer Gamse, Jacques Kameni-Tcheudji, Michaela Kneissel, Karl Heinz Krawinkler, Martin Missbach, Alfred Schmidt, Klaus Seuwen, Sven Weiler, Leo Widler

Novartis Institutes for BioMedical Research, Novartis Pharma AG, WKL-136.4.84, CH-4002 Basel, Switzerland

ARTICLE INFO

Article history:
Received 9 June 2010
Revised 2 July 2010
Accepted 3 July 2010
Available online 3 August 2010

Keywords:
Calcium-sensing receptor (CaSR)
Parathyroid hormone (PTH)
Bone formation
Osteoporosis
CaSR-antagonist
Benzimidazoles

ABSTRACT

A series of novel benzimidazole derivatives has been designed via a scaffold morphing approach based on known calcilytics chemotypes. Subsequent lead optimisation led to the discovery of penta-substituted benzimidazoles that exhibit attractive in vitro and in vivo calcium-sensing receptor (CaSR) inhibitory profiles. In addition, synthesis and structure–activity relationship data are provided.

Osteoporosis is a disease characterised by low bone mass and microarchitectural deterioration of bone tissue that leads to bone fragility and increased risk of fractures.[1] Most therapies for the treatment of osteoporosis inhibit bone resorption and prevent further bone loss. However, as many osteoporosis patients have already lost a substantial amount of bone at the time of diagnosis there is a need for agents that stimulate new bone formation.[2] The only currently commercially available anabolic treatment for osteoporosis are PTH (parathyroid hormone) or PTH fragments such as Forteo® (teriparatide, the 1–34 fragment of PTH), which causes a significant increase in bone mass and reduces vertebral fracture risk substantially.[3] However, this peptide must be administered by sc injections. An orally active low molecular weight compound with the same efficacy would be a highly attractive alternative for the patient. Instead of applying *exogenous* PTH, mobilisation of *endogenous* stores of the hormone can be envisaged. PTH is stored in relatively large amounts in parathyroid cells and its secretion is controlled by a calcium-sensing receptor (CaSR) located on the cell surface. As the release of PTH is *negatively* coupled to CaSR activation, CaSR-antagonists (calcilytics) mimic a state of hypocalcemia and thus stimulate PTH release into the blood stream.[4]

It is well documented that elevated levels of PTH only result in higher bone mass if they are transient, that is, they do not persist for more than about 2–4 h. Elevated PTH levels sustained for several hours activate not only osteoblasts but also osteoclasts leading to an increase in bone turnover instead of higher bone mass.[5] Therefore, the drug discovery goal of this approach is the identification of a CaSR-antagonist, that is, rapidly absorbed (short T_{max}) and fairly rapidly eliminated. At Novartis the starting point for lead optimisation towards a compound exhibiting such properties was the HTS hit **1** (Fig. 1), a close analogue of Proquazone (an analgesic). Lead optimisation led to compounds such as **2** and **3** that showed

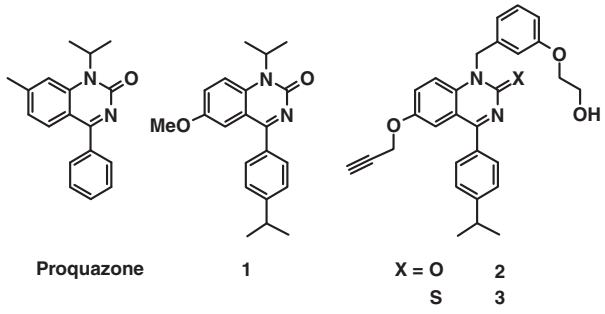


Figure 1. Proquazone and proquazone type calcilytics.

* Corresponding author. Tel.: +41 61 696 76 36; fax: +41 61 696 62 46.
E-mail address: marc.gerspacher@novartis.com (M. Gerspacher).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.07.016

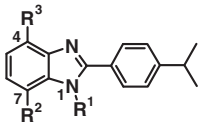
IC_{50} values in the nanomolar range in the in vitro receptor assay and also displayed the appropriate PK- and PTH-release properties as demonstrated in in vivo experiments in rats and dogs (short T_{max}, sharp PTH plasma peak).[6]

In an attempt to identify another template, three structures **4**, **5** and **6** of the proquazone (or structurally related) series were superimposed as shown in Figure 2. Based on this superimposition a new template **7**, a benzimidazole derivative, displaying the structural features thought to be necessary for adequate receptor affinity, was designed (morphed) and subsequently prepared. Testing of **7** revealed an IC_{50} of 2.5 μM in the in vitro assay.

A fluorimetric assay was used as the primary screen to determine inhibitory potency of the compounds against the CaSR. The assay (FLIPR assay) measures calcium mobilisation in hamster fibroblasts transfected with the human receptor.[6]

At the initial stages of lead optimisation (Table 1), derivatives **7–9** showed that methoxy-ethyl as the R^1 residue (leading to slightly more soluble compounds, compared to the *n*-butyl derivatives) can easily replace *n*-butyl and that the isopropyloxy residue (R^3) can be replaced by the smaller methoxy without any significant loss in potency. The unsubstituted derivative **10** (R^1, R^2 = H) was less active. It could also be demonstrated that moving the methoxy residue from the 4 to the 7 position (**11**) is tolerated. Replacement of the 7-OMe residue with a methyl-group was also tolerated (**12**). Introduction of an additional methyl residue at position 7 of **9** leading to **13** did not have much impact on potency of the resulting compound. Surprisingly, however, was the 10-fold increase in potency of **14** where the positions of the 4- and the 7-residues have been switched. Further increases in activity could be achieved with the introduction of halogens or trifluoromethyl residues at position 4, with bromo- and iodo-residues being most preferred (**15**, **16**, **17** and **18**). The 4,7-dimethoxy- and the 4-methoxy-7-chloro-derivatives **19** and **20** proved to be significantly less potent than the 4-chloro-7-methoxy derivative **15**. It was observed, that fairly lipophilic R^1 residues were needed for good potency. The *N*-dimethylamino-ethyl derivative **22** showed a ca. 10-fold lower activity in comparison with the methoxy-ethyl compound **16** and the propyl derivative **23** showed a fourfold decrease in potency. An amide moiety as present in **24** led to a substantial loss of activity.

Table 1
In vitro activity of compounds **7–24**



Compd	R^1	R^2	R^3	CaSR FLIPR IC_{50} (μM)
7	*n*-Bu	H	*i*-PrO	2.55
8	Methoxy-ethyl	H	*i*-PrO	1.95
9	*n*-Bu	H	MeO	4.69
10	Methoxy-ethyl	H	H	17
11	Methoxy-ethyl	MeO	H	1.90
12	Methoxy-ethyl	Me	H	2.10
13	Methoxy-ethyl	Me	MeO	1.90
14	Methoxy-ethyl	MeO	Me	0.21
15	Methoxy-ethyl	MeO	Cl	0.05
16	Methoxy-ethyl	MeO	Br	0.022
17	Methoxy-ethyl	MeO	I	0.013
18	Methoxy-ethyl	MeO	CF_3	0.051
19	Methoxy-ethyl	MeO	MeO	1.82
20	Methoxy-ethyl	Cl	MeO	0.77
21	Methoxy-ethyl	Br	Br	1.00
22	*N*,*N*-Dimethyl-amino-ethyl	MeO	Br	0.19
23	*n*-Pr	MeO	Me	0.79
24	*N*,*N*-Dimethyl-acetamido	MeO	Br	>10

In order to further increase the potency of these benzimidazole derivatives certain additional residues in position 5 can be beneficial as shown in Table 2. At position 5, halogens and especially a benzyl residue in combination with a halogen or trifluoro moiety at position 4 led to a slight increase in potency, while a cyano residue was just tolerated (compounds **25–29** and **33**). However, an ethyl or phenyl residue led to loss in potency (compounds **30** and **32**). The reduced activity of **31** showed that substitution of the 5 position alone is not sufficient for producing potent compounds and that a residue (e.g., halogen or trifluoromethyl) at position 4 was needed for good activity. Introduction of additional substituents in the meta- and para-positions of the 5-benzyl residues led to a decrease in activity (compounds **34–36**), while introduction of an ortho SO-Me moiety (**37**) resulted in a highly potent compound. Replacement of 5-benzyl with a 3-pyridine-methyl- (**38**) group was tolerated as well. Introduction of an additional substitutent such as 2-methoxy, 2-methyl-sufanyl and 2-methyl-sulfinyl into the pyridine moiety was not only well tolerated but can lead to a further slight increase in potency as shown specifically for compounds **39–42**. The thiazolyl-methyl-moiety (**43**) led to another highly potent compound.

The synthesis scheme (Scheme 1) illustrates the synthetic preparation of the compounds **40**, **41** and **42**. The commercially available aniline **44** was converted into **45** via O-methylation and Sandmeyer reaction. Introduction of the methoxyethyl-amino residue via nucleophilic substitution of the chlorine by treatment with methoxy-ethylamine, followed by selective bromination at position 5 led to **47** in a reasonable overall yield. Reduction of the nitro group with Raney-Ni, acylation of the aniline nitrogen with 4-isopropyl benzoic acid followed by cyclisation to the benzimidazole derivative **48** proceeded in almost quantitative overall yield. Palladium assisted replacement of the bromo moiety by a cyano residue followed by Raney-Ni reduction afforded the aldehyde **49** in moderate yield. Reaction of **49** with the lithium derivative obtained from **50**

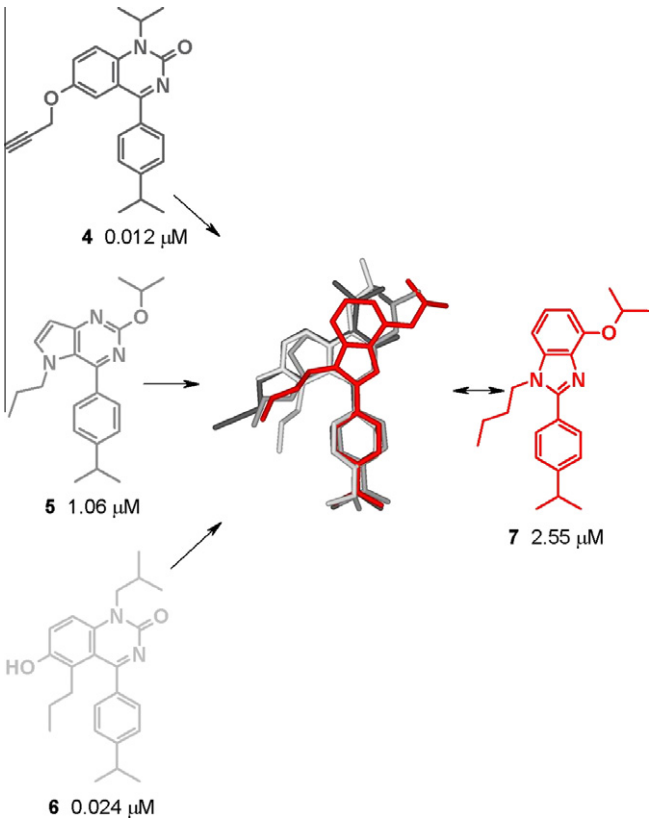


Figure 2. Overlay of structures and scaffold morphing.