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PATENT HIGHLIGHT

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Inhibition of Cathepsin K: A Novel and Promising Treatment for Osteoporosis

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Title:	Cathepsin Cysteine Protease Inhibitors		
Patent Application Number:	WO 2015/051479 A1	**Publication date:**	16 April 2015
Priority Application:	None listed	**Priority date:**	---
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Disease Area:	Abnormal bone resorption disorders such as osteoporosis	**Biological Target:**	Cathepsin K cysteine protease

Summary:

The invention in this patent application relates to heterocyclic compounds represented generally by formula (I). These compounds are inhibitors of cysteine proteases, including but not limited to, cathepsins K, L, S, and B, which may be useful for treating diseases in which inhibition of bone resorption is indicated, such as osteoporosis.

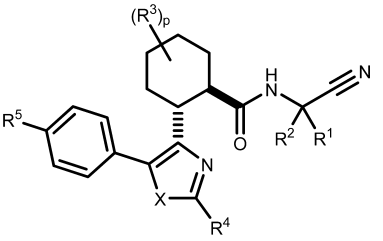
Abnormal bone resorption causes several disorders including osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, hypercalcemia of malignancy, or multiple myeloma. Osteoporosis is a systemic skeletal disease that causes low bone mass and microarchitectural deterioration of bone tissue. This may progress to increased bone fragility and susceptibility to fracture, which are major causes of morbidity and mortality in a large segment of the elderly population. It is estimated that about one-half of women and one-third of men will experience an osteoporotic fracture. There is a need to develop effective treatments to prevent and treat osteoporosis and other conditions associated with bone resorption. The inhibition of cathepsin cysteine proteases, particularly cathepsin K, is a promising biological target that may provide such a needed treatment.

Cathepsins are proteases that belong to the papain superfamily of cysteine proteases. They are found in a wide variety of human, animal, and other organism tissues. Some of the known cathepsins are cathepsins B, C, F, H, L, K, O, S, V, W, and Z. These proteases function in both normal physiological as well as pathological degradation of connective tissues. They play major roles in processes that include continuous bone resorption and formation such as intracellular protein degradation and turnover and remodeling. Aberrant activities of some cathepsins may be associated with several diseases and disorders. For example, cathepsin L is implicated in normal lysosomal proteolysis as well as metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease, atherosclerosis, chronic obstructive pulmonary disease, and certain autoimmune disorders, including juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis, and Hashimoto's thyroiditis; allergic disorders such as asthma; and allogenic immune responses such as rejection of organ transplants or tissue grafts. Aberrant activity of cathepsin B is implicated in several diseases such as rheumatoid arthritis, osteoarthritis, pneumocystisis carinii, acute pancreatitis, inflammatory airway disease, and bone and joint disorders. Additionally, increased levels and redistribution of cathepsin B are observed in tumors, which indicate a possible role for this enzyme in tumor invasion and metastasis.

Cathepsin K is abundant in osteoclasts. It can degrade the human type I collagen, the major collagen in bone, and it plays a key role in bone resorption and remodeling. *In vitro* studies with antisense oligonucleotides to cathepsin K have shown diminished bone resorption, possibly caused by reduction in translation of cathepsin K mRNA. The inhibition of cathepsin K offers an attractive therapeutic target that may potentially prevent and treat the harmful effect of osteoporosis by reducing bone resorption. In addition, inhibitors of cathepsin K may potentially provide needed treatments for other diseases associated with the activities of this protease such as glucocorticoid induced osteoporosis, Paget's disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease, and cancer including metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma.

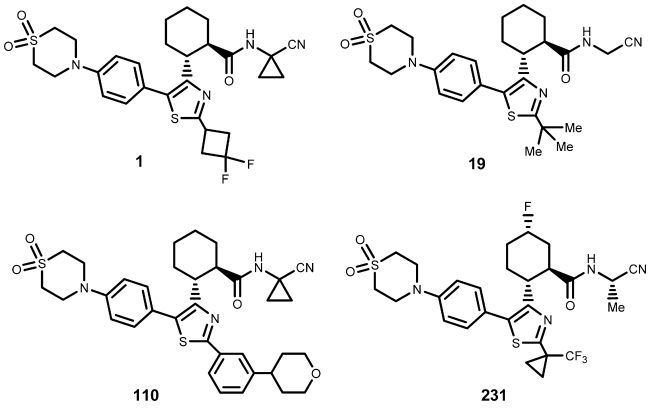
Received: May 6, 2015
Published: May 13, 2015

Important Compound Classes:



Formula (I)

Key Structures: The inventors described the structures of 248 examples of formula (I) including the following four representative examples:



Biological Assay:

- Cathepsin K Assay (hrbCat K)
- Cathepsin L Assay
- Cathepsin B Assay
- Cathepsin S Assay
- Cathepsin F Assay (hCat F)

Biological Data: The compounds of the invention showed activity in the above assays. Representative data are listed in the following table:

Compound	hrbCat K IP (nM)	hCat F IP (nM)
1	5.8	1000
19	0.7	851
110	1.7	3333
231	2.8	3142

Recent Review Articles:

1. Gora, J.; Latajka, R. *Curr. Med. Chem.* **2015**, *22* (8), 944−957.
2. Ng, K. W.; Martin, T. J. *Curr. Opin. Pharmacol.* **2014**, *16*, 58−63.
3. Novinec, M.; Lenarcic, B. *Biol. Chem.* **2013**, *394* (9), 1163−1179.
4. Helali, A. M.; Iti, F. M.; Mohamed, I. N. *Curr. Drug Targets* **2013**, *14* (13), 1591−1600.

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Notes

The authors declare no competing financial interest.