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The discovery of odanacatib (MK-0822), a selective inhibitor of cathepsin K

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Dedicated to the memory of Dr. Gideon Rodan, deceased, January 1, 2006

Abstract—Odanacatib is a potent, selective, and neutral cathepsin K inhibitor which was developed to address the metabolic liabilities of the Cat K inhibitor L-873724. Substituting P1 and modifying the P2 side chain led to a metabolically robust inhibitor with a long half-life in preclinical species. Odanacatib was more selective in whole cell assays than the published Cat K inhibitors balicatib and relacatib. Evaluation in dermal fibroblast culture showed minimal intracellular collagen accumulation relative to less selective Cat K inhibitors.

Cathepsin K (Cat K) is a lysosomal cysteine protease that is highly expressed in osteoclasts, the cells responsible for bone degradation during bone remodeling. Type I collagen is a major component of bone and Cat K has high collagenase activity, particularly at the acidic pH that is required to dissolve the calcium hydroxyapatite component of bone. Emerging evidence that Cat K is the primary enzyme involved in osteoclastic bone resorption has made it an important target for the treatment of osteoporosis.[1] Several studies have shown that Cat K deficiency leads to an increase in bone mineral density (BMD).[2] Pharmacological studies of Cat K inhibitors in rats[3] and monkeys[4] have shown reductions in biochemical markers of bone resorption and

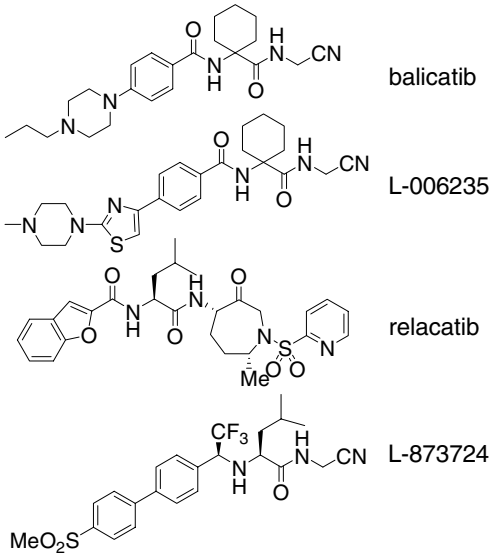

Figure 1. Published Cat K inhibitors.

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increased BMD. Recently, clinical data have been disclosed for the Cat K inhibitor balicatib (Fig. 1), demonstrating a reduction of biochemical markers of bone resorption and increases in BMD over 1 year of treatment.[5]

We have previously reported on our effort to identify potent and selective inhibitors of Cat K.[6] Our initial proof-of-concept compound, L-006235, was highly selective over cathepsins B, L, and S in enzyme assays and had good pharmacokinetics.[7] However more detailed studies revealed that the selectivity profile ns was severely eroded in more physiologically relevant cell-based enzyme occupancy assays.[8] The relevance of these data was demonstrated in a Cat S-dependent B cell line assay in which L-006235 blocked antigen presentation. This loss of selectivity in cell-based assays can be explained by the lysosomotropic properties of these basic, lipophilic compounds. Since off-target cathepsins are found in lysosomes (pH 4–5), the lysosomal accumulation of a basic Cat K inhibitor results in an apparent increase in potency on these anti-targets. High selectivity will be important to the success of a development candidate, precluding the use of a basic moiety in inhibitor design.

Balicatib is structurally related to L-006235 and is also lysosomotropic.[8] Whole cell assays showed poor selectivity as was observed for L-006235. Recently it was announced that the Phase II development of balicatib has been discontinued due to skin rash and rarer incidences of morphea-like skin changes.[9] Another Cat K inhibitor in clinical development, relacatib, is non-basic and therefore not lysosomotropic, but has poor selectivity over cathepsins B, L, S, and V in enzyme assays.[10]

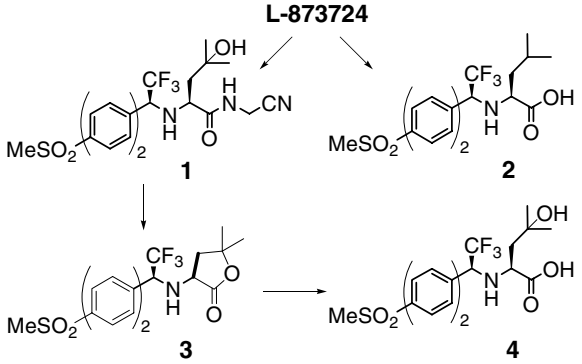
Our initial attempts to remove the basic substituent in P3 led to Cat K inhibitors with poor activity, selectivity, and pharmacokinetic properties. The loss in activity was attributed to the loss of a beneficial ionic interaction between the charged amine and Asp^{61} in the S3 pocket.[7] Since this residue is absent in the off-target cathepsins, the potencies against the anti-targets were not dramatically affected and selectivity was consequently reduced. Replacing the P2 amide bond with a trifluoroethylamine provided a 10- to 20-fold increase in potency on Cat K.[11] Using this motif, neutral inhibitors with high potency and selectivity were prepared. L-873724 was identified as a 0.2 nM Cat K inhibitor with >800-fold selectivity over other cathepsins. In vivo studies showed that this neutral Cat K inhibitor suppressed biochemical markers of bone resorption in a rhesus monkey model.[12]

L-873724 has metabolic liabilities that prevented its further development. An analysis of its metabolic profile provided guidance for addressing these liabilities. Subsequent blocking of the key metabolic sites resulted in the identification of odanacatib (MK-0822) which is currently in clinical development.

The pharmacokinetics of L-873724 in rat, dog, and monkey have been reported.[12] The short half-life (2 h) and clearance (Cl = 7.5 mL/min/kg) in monkey raised concerns that this compound may not be suitable for once-daily dosing in humans. Incubations in human hepatocytes showed that the major route of metabolism was hydroxylation on the methine of the leucine side chain (**1**)[13] as shown in Scheme 1. A minor pathway leading to the hydrolysis of the P1 amide bond (**2**) was also observed. Analysis of plasma from several species showed several circulating metabolites. In particular, the lactone **3** was found to be circulating at high levels in rhesus monkey (10× L-873724 concentration at 8 h) even though it was only a minor component in rat plasma. To understand the potential relevance of this metabolite to humans, a synthetic standard of **3** was incubated in fresh plasma from rat, rhesus monkey, and human. In all three species, the lactone hydrolyzed to hydroxyacid **4** over the course of the incubation (37 °C, 1 h). However this hydrolysis was much more efficient in rat plasma (50% conversion) than in rhesus monkey plasma (5% conversion). The extent of hydrolysis in human plasma was intermediate (28–40% conversion) leading us to conclude that this metabolite would likely circulate in humans.

Further investigations revealed that the leucine hydroxylation occurred exclusively due to CYP3A activity. Adding the CYP3A inhibitor ketoconazole to the hepatocyte incubations resulted in a near-complete blockade of metabolism. When L-873724 was incubated for 1 h in pooled human microsomes, only a 10% recovery of the parent drug was observed. Microsomal incubation in the presence of a CYP3A inhibitory antibody gave >90% recovery of parent drug. Finally, incubation with several recombinant CYPs (1A1, 2D6*1, 3A4, 2C9*1, 2C9*2, 2C9*3, and 2C19) showed that only CYP3A led to detectable metabolite formation. Metabolism by only CYP3A can lead to variable exposure when co-dosed with other drugs that are CYP3A inhibitors and inducers.

To address the metabolic liabilities listed above, both the P1 and P2 residues were modified to minimize leucine hydroxylation, amide hydrolysis, and lactonization (Table 1). Most P1 substituents resulted in a loss of activity. One of the more active compounds (**14**) was provided by incorporation of an (*S*)-benzyl group, but the corresponding increase in potency on cathepsins B, L, and S resulted in a poor selectivity profile. The (*R*)-



Scheme 1. Metabolic pathways for L-873724 based on in vitro and in vivo studies.