Approach to Discovery of Orally Active Cathepsin K Inhibitors from Substrate Library

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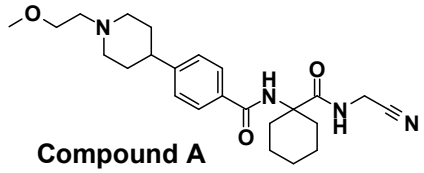
Cathepsin K has been shown to be extensively expressed in osteoclasts and to play an essential role in bone matrix degradation, and the enzyme inhibitors could represent a novel therapeutic approach for metabolic bone diseases like osteoporosis. The mechanism for the anti-osteoporosis by cathepsin inhibitors is quite different with the biphosphonate drugs which were widely used in worldwide. We thus started to study the discovery of selective cathespin K inhibitors since 1994 in Japan.

We devised ways of constructing substrate library to see the substrate specificity for cathepsin K. Initially, hydrolysis position of substrate sequence was replaced by a nitrile group as a warhead, which can make an reversible covalent bond with thiol group in cathepsin K enzyme, and then the optimization of P2 and P3 sites has been carried out. Their sites interact with S2 and S3 subsites in the enzyme and play a significant role for the potency and selectivity to cathepsin K, respectively.

Eventually, compound A derived from the lead compound inhibits cathepsin K with IC50 values of 2.5nM for human cathepsin K versus 4400nM for cathepsin B, 3700nM for cathepsin L and >10000nM for cathepsin S. An orally administrated cathepsin K inhibitor is able to effectively reduce bone resorption markers and to partially protect bone loss in ovariectomized rats. Taken these *in vivo* animal data together, it is expected that cathepsin K inhibitors will provide improved efficacy in metabolic bone diseases like osteoporosis.



Compound A