The design and synthesis of angiotensin-converting enzyme secretase inhibitors.

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Numerous membrane-associated proteins undergo proteolytic cleavage and release of a soluble ectodomain from the cell surface. This post-translational processing is known as "ectodomain shedding" and contributes to a diverse range of physiologically significant events (1). Angiotensin-converting enzyme (ACE) plays a critical role in the maintenance of blood pressure and fluid homeostasis and exists as both a type I integral membrane protein as well as a smaller soluble form present in various extracellular fluids.

The mechanism of ACE shedding has not yet been fully elucidated however a class of membrane proteases, collectively termed "secretases", has been implicated (2). Previous research has identified numerous similarities between the ACE secretase and A Disintegrin And Metalloprotease (ADAM) subfamily of the metzincin superfamily of metalloproteases. Both the ACE secretase and a number of the ADAM proteases are zinc-dependent and susceptible to inhibition by hydroxamate-based matrix metalloprotease (MMP) inhibitors (3).

We have used the inhibition profile of the ACE secretase with various hydroxamate-based benzothiophene inhibitors (4), initially designed to inhibit various MMP's, to synthesize a novel inhibitor with improved selectivity and potency. We have exploited the relative size and orientation of the secretase's proposed S_1' binding pocket to improve inhibition. The inhibitor is designed for use as an affinity ligand in the isolation of potential ACE secretase proteins from suitable tissue or cell lines.

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