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Role of dynamic nonprime binding of sampatrilat for the development of domain selective inhibitors

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Sampatrilat is a vasopeptidase inhibitor that inhibits both angiotensin I-converting enzyme (ACE) and neutral endopeptidase. ACE is a zinc dipeptidyl carboxypeptidase that contains two extracellular domains (nACE and cACE). In this study the molecular basis for the selectivity of sampatrilat for nACE and cACE was investigated. Enzyme inhibition assays were performed to evaluate the *in vitro* ACE domain selectivity of sampatrilat. The inhibition of the Cdomain (Ki=13.8 nM) by sampatrilat was 12.4-fold more potent than that for the N-domain (171.9 nM), indicating differences in affinities for the respective ACE domain binding sites. Interestingly, replacement of the P2 group of sampatrilat with an aspartate abrogated its C-selectivity and lowered the potency of the inhibitor to activities in the micromolar range. The molecular basis for this selective profile was evaluated using molecular modeling methods. We found that the C-domain selectivity of sampatrilat is due to occupation of the lysine side chain in the S1 and S2 subsites and interactions with Glu748 and Glu1008, respectively. This study provides new insights into ligand interactions with the nonprime binding site that can be exploited for the design of domain selective ACE inhibitors.

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