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**Design, Synthesis and X-ray Structure of Protein-Ligand Complexes: Important Insight into Selectivity of Beta-secretase Inhibitors.** Lin Hong, Arun K. Ghosh, Azhar K. Hussain, Lui Lei, Chun-Feng Liu, Thippeswamy Devasamudram, Vajira Weerasena, Robert Turner, Gerald Koelsch, Vajira Weerasena, Robert Turner, Geoffrey Bilcer, Jordan Tang, Zapaq Inc, Oklahoma City, OK 73104; Depts. of Chemistry and Medicinal Chemistry, Purdue Univ., West Lafayette, IN 47907; Protein Studies Program, Oklahoma Medical Research Foundation and Dept. of Biochemistry and Molecular Biology, Univ. of Oklahoma Health Science Center, Oklahoma City, OK 73104.

The proteolytic enzyme beta-secretase (memapsin 2, BACE-1) has emerged as a leading target for therapeutic intervention of Alzheimer's disease (AD). It is one of the two proteases that cleave the beta-amyloid precursor protein to generate the 40/42 residue amyloid-beta peptide. The excess level of A-beta leads to formation of amyloid plaques and neurofibrillary tangles in the brain, which are believed to be the pathological causes of AD. Our structure-based design led to the discovery of very potent and highly selective beta-secretase inhibitors and our X-ray structural analysis of protein-inhibitor complexes has uncovered potentially important molecular interactions useful in the design of selectivity for beta-secretase inhibitors.