BACE1 is a key enzyme responsible for APP processing into Ab formation. Thus, BACE1 selective inhibitors are attractive disease modifying drugs for AD. The hit compounds were discovered by chemical synthesis of the designed molecules, based on the molecular modeling study of the known three dimensional co-crystal structure of BACE1-inhibitor complexes. The hit compounds with various structures were synthesized and evaluated their in vitro activity and selectivity over BACE2 and cathepsin D. Lead compounds were further optimized to maximize their in vitro and in vivo efficacies and to have excellent PK and toxicological profiles.