The receptor for advanced glycation endoproducts (RAGE), which plays an important role in transferring β-amyloid from plasma to brain, is a novel and validated target in the BBB for the development of AD drugs. The small molecule antagonists to block the role have been discovered based on in vitro and in vivo assays developed by our technology. Lead compounds having >120% in vitro and in vivo potencies compared to reference (TPP-488) were discovered. For the design of RAGE antagonists, the pharmacophores of compounds reported in patents were analyzed and its pharmacophoric model was established. On the basis of the model, 500 target compounds were designed and synthesized and their efficacies of in vitro and in vivo were evaluated. Several in vitro assays, such as NFkB-luciferase reporter, β-amyloid uptake, artificial BBB assays and protein-small molecule interaction, for synthesized RAGE antagonists were performed. Among them, 50 compounds including CKH-66 were selected as 1st lead compounds to have >120% activity compared to reference. For the evaluation of in vivo efficacy, the double transgenic mouse (APPswe/PS1Ed9) was used. With nine selected antagonists including CKH-66, the extent of β-amyloid clearance in brain and memory recovery were found. The level of β-amyloid in the brain was decreased and memory test such as Y-maze and fear conditioning showed nice recovery after compound treatment to Tg animal.