

D-Amino acid oxidase inhibitors as pharmaco-enhancers of D-serine

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Abstract: D-serine, a full agonist at the glycine modulatory site of the N-methyl-D-aspartate (NMDA) receptor, has been actively explored as a potential therapeutic agent for the treatment of schizophrenia. DAAO (EC 1.4.3.3) is a flavoenzyme that catalyzes the oxidation of D-amino acids including D-serine to the corresponding α -keto acids. In mammals, DAAO is present in kidneys, liver, and brain. Therefore, a substantial amount of orally administered D-serine is expected to be metabolized prior to reaching the site of action. To this end, our group has pursued discovery of potent and drug-like DAAO inhibitors that can be co-administered with D-serine to enhance its plasma and brain exposure. This presentation will summarize some highlights from our efforts to develop small molecule DAAO inhibitors as pharmaco-enhancers of D-serine therapy.