Benztropinamine Analogs as Dopamine Transport Inhibitors

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Technology description

Summary

Dopamine is a neurotransmitter that is directly involved in motor activity, motivation and reward, and cognition. The dopamine transporter is expressed on the plasma membrane of dopamine neurons and is responsible for clearing dopamine released into the extracellular space, thereby regulating neurotransmission. The dopamine transporter plays a significant role in neuropsychiatric diseases, such as Parkinson's disease, drug abuse (especially cocaine addiction), Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder (ADD/ADHD), narcolepsy and a number of other CNS disorders. Therefore, the dopamine transporter is a target for research and potential therapeutics for the treatment of these indications.

Benztropine and its analogs are an important class of dopamine transport inhibitors that are indicated for the treatment of cocaine abuse and ADHD. They bind with high affinity to the dopamine transporter and block dopamine uptake, but generally do not produce behavioral effects comparable to those produced by cocaine. In animal models of drug abuse, many benztropine analogs have been shown to 1) reduce cocaine-induced locomotor stimulation, 2) have long-lasting effects, and 3) lack a significant abuse liability. This suggests they may be useful medications for the treatment of human diseases where dopamine-related behavior is compromised, especially in situations in which an (partial) agonist treatment is indicated.

However, some of the reported analogs have limited or poor solubility in aqueous systems or poor stability characteristics. To remedy this, the 3-position benzhydrylether moiety of the benztropine analogs was replaced with the isosteric benzhydrylamine system in order to reduce hydrolysis of the less stable ether function, observed in the benztropine series, and further reduce lipophilicity to ultimately increase water solubility and bioavailability for improved therapeutic formulation and utility.

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