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Abstract

Serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase, AANAT) is a member of the GCN5 N-acetyltransferase (GNAT) superfamily and catalyzes the penultimate step in the biosynthesis of melatonin; a large daily rhythm in AANAT activity drives the daily rhythm in circulating melatonin. We have used a structure-based computational approach to identify the first druglike and selective inhibitors of AANAT. Approximately 1.2 million compounds were virtually screened by 3D high-throughput docking into the active site of X-ray structures for AANAT, and in total 241 compounds were tested as inhibitors. One compound class, containing a rhodanine scaffold, exhibited low micromolar competitive inhibition against acetyl-CoA (AcCoA) and proved to be effective in blocking melatonin production in pineal cells. Compounds from this class are predicted to bind as bisubstrate inhibitors through interactions with the AcCoA and serotonin binding sites. Overall, this study demonstrates the feasibility of using virtual screening to identify small molecules that are selective inhibitors of AANAT.