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Abstract

Melanin-concentrating hormone (MCH) has been known to be an appetite-stimulating peptide for a number of years. However, it is only recently that MCH has been discovered to be the natural ligand for a previously “orphan” G-protein-coupled receptor, now designated MCH-1R. This receptor has been shown to mediate the effects of MCH on appetite and body weight, and consequently, drug discovery programs have begun to exploit this information in the search for MCH-1R antagonists for the treatment of obesity. In this paper, we report the rapid discovery of multiple, structurally distinct series of MCH-1R antagonists using a variety of virtual screening techniques. The most potent of these compounds (12) demonstrated an IC50 value of 55 nM in the primary screen and exhibited antagonist properties in a functional cellular assay measuring Ca2+ release. More potent compounds were identified by follow-up searches around the initial hit. A proposed binding mode for compound 12 in a homology model of the MCH-1R is also presented.