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MOLECULES

Biaryl piperidine melanin-concentrating hormone-1 receptor antagonists for obesity

Melanin-concentrating hormone (MCH) is a cyclic 19-membered amino-acid neuropeptide expressed in mammalian brains. This hormone plays an important role in the regulation of food intake and energy homeostasis. It has been demonstrated that central administration of MCH in mice stimulates food intake, whereas fasting results in an increase in MCH expression [1].

MCH knockout mice are hypophagic and leaner than wild-type mice, but otherwise healthy. Transgenic mice overexpressing MCH are susceptible to obesity and insulin resistance [2]. MCH interacts with two G-protein-coupled receptors (GPCRs) in the brain – MCH1R and MCH2R. MCH1R is present in all mammals and is implicated in the regulation of food intake and energy homeostasis based on knockout experiments with *mch1r*$^{-/-}$ mice [3]. These findings have provided impetus to the discovery of MCH1R antagonists as potential treatments for obesity.

Recent work has disclosed the discovery of a new series of biaryl piperidine MCH1R antagonists, through the use of solid-phase combinatorial chemistry [4]. Among the various combinatorial techniques in use today, the encoded combinatorial libraries on polymeric support (ECLiPS^{TM}) technology has proved to be a powerful tool for the discovery of new leads against a wide variety of biological targets [5]. As part of a program to synthesize libraries targeting GPCRs, an aryl and biaryl piperidine-based library (general structure **i**) was constructed. This library took several starting scaffolds **(ii)** and coupled them to the solid-phase via reductive amination (starting resin had R = CHO on the photocleavable linker L). The resin-bound secondary amines **(iii)** were then capped at nitrogen (R2) with a variety of acid chlorides, sulphonyl chlorides, isocyanates and chloroformates to give **(iv)**. The boc group was removed with acid (TFA) and the subsequently exposed nitrogen reacted with aldehydes, ketones, acid chlorides, sulphonyl chlorides, isocyanates and chloroformates (R3) to give resin-bound **(v)**. Thus, this 'split and pool' approach yielded a library of 19,470 members.

Screening of this 19,470-member library in a scintillation proximity assay (SPA), based on [^{125}I]-MCH binding to membranes prepared from CHO cells that express human MCH1R, was carried out in two stages. First, a survey screen was performed in which one copy of each sub-library was arrayed in a 96-well plate as a mixture of approximately ten compounds per well (approximately 10 μM per compound, through photolytic cleavage of the compound from the resin bead) and screened to identify active sub-libraries. These active sub-libraries were then selected for a follow-up screen, in which three copies of each sub-library were arrayed in 96-well plates, in a single-compound per well format, to identify active individual compounds. Once a well was determined to contain an active compound (at least 50% inhibition at the 10 μM screening concentration), the structures of the active compounds were determined by analyzing the haloaromatic tags via oxidative cleavage from the source-resin bead.

In total, 84 active structures were identified from several sub-libraries, with many of these structures found multiple times, indicating a specific interaction of the monomer fragment with the biological target. Active members were resynthesized as singletons and screened for a MCH1R K_i determination. One of the most potent compounds isolated was **(vi),** which displayed a K_i of 98 nM against MCH1R. A further follow-up library around compound **(vi)** provided even more-potent analogues, with K_is <1 nM. Synthesis of potent MCH1R antagonists has been achieved via use of an ECLiPS^{TM} combinatorial library. More work in this area is warranted to further optimize the drug properties of aryl and biaryl piperidine-based compounds that are active as potent antagonists of MCH1R.

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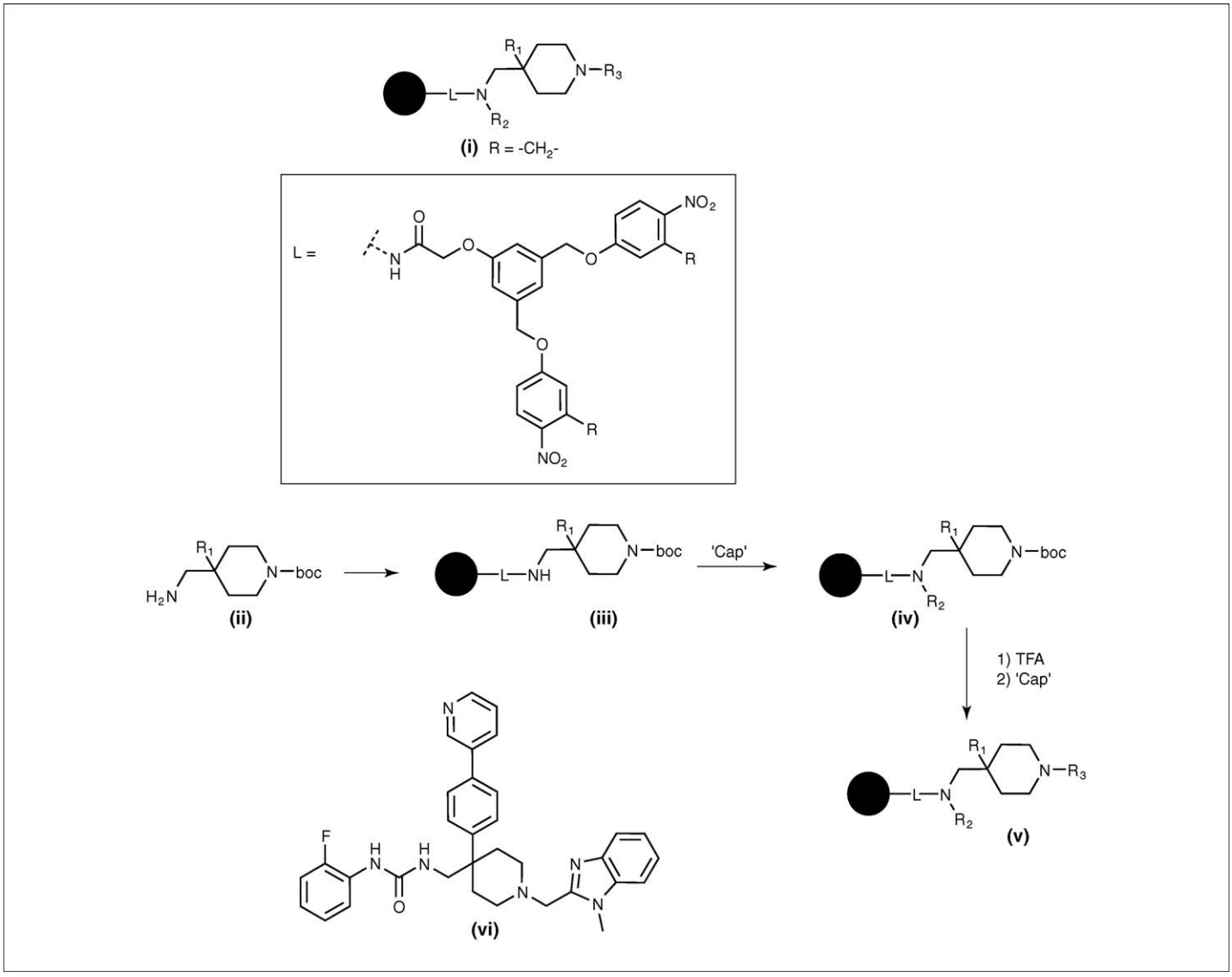

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