Lead compounds for the treatment of pain

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Technology description

MARKETS ADDRESSED:
Although peptides have shown some promise in clinical trials as therapeutic agents, their success has largely been limited by several factors, including rapid degradation by peptidases, poor cell permeability, and a lack of binding specificity resulting from conformational inflexibility. Science has overcome these limitations with the advance of peptidomimetics--a system for the production of modified chemical compounds capable of mimicking the structural and or functional properties of peptides. A fertile ground for such efforts lies in the discovery of ligands for nervous system receptors that mediate the sensation of pain. Researchers at Harvard University have developed a novel approach to generate nonpeptidic ligands to a key receptor involved in pain relief, the mu opioid receptor (MOR). This approach has far-reaching implications for the discovery of next-generation therapeutics for the treatment of pain.

The peptidomimetic mu receptor ligands generated as a result of this synthetic platform are lead compounds for the treatment of pain. The market for pain therapeutics is very large. In one example, there are 45 million Americans that suffer from chronic headaches, while nearly 6 million reported case of chest pain.

The invention is a novel synthetic pathway to the generation of nonpeptidic ligands for the mu opioid class of G-protein coupled receptors. The system uses stereochemical variation and acyclic geometric stereocontrol to generate diversity among its members. The template structure (shown in 2 below) utilized to generate the stereodiversity is based upon the ligand for the mu opioid receptor (MOR), the tetrapeptide endomorphin-2. The dense array of stereocenters in 2 combined with the rigidifying olefin generates the geometric diversity.

Sixteen stereoisomers of 2 were screened for competitive binding to MOR. The stereoisomer with the highest affinity exhibited a Ki of 8.8 nM, a value within an order of magnitude of the Ki measured for endomorphin-2. Moreover, several compounds demonstrated a 107-600-fold selectivity for MOR over other opioid receptors, such as the delta opioid receptor (DOR) and kappa opioid receptor (KOR).

Current peptidomimetic combinatorial strategies use a single fixed scaffold that attaches varied side

chains to a rigid, cyclic scaffold. Although these libraries incorporate a large amount of structural diversity, the single fixed scaffold limits the amount of functional diversity. This novel platform technology offers diversification through extensive stereochemical diversification. The small molecule libraries have exhaustive variation at every sp3-hybridized center. The system is not limited to the synthesis of libraries of peptide mimics-encompasses the broader concept of providing any collection (peptidomimetics and non-peptidomimetics) of chemical compounds having stereodiversity. The monomers can also be obtained in high yield.

Institution

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