5-hydroxyindole-2-carboxylic acid amides: novel histamine-3 receptor inverse agonists for the treatment of obesity

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Obesity is a major risk factor in the development of conditions such as hypertension, hyperglycemia, dyslipidemia, coronary artery disease, and cancer. Several pieces of evidence across different species, including primates, underscore the implication of the histamine 3 receptor (H(3)R) in the regulation of food intake and body weight and the potential therapeutic effect of H(3)R inverse agonists. A pharmacophore model, based on public information and validated by previous investigations, was used to design several potential scaffolds. Out of these scaffolds, the 5-hydroxyindole-2-carboxylic acid amide appeared to be of great potential as a novel series of H(3)R inverse agonist. Extensive structure-activity relationships revealed the interconnectivity of microsomal clearance and hERG (human ether-a-go-go-related gene) affinity with lipophilicity, artificial membrane permeation, and basicity. This effort led to the identification of compounds reversing the (R)-alpha-methylhistamine-induced water intake increase in Wistar rats and, further, reducing food intake in diet-induced obese Sprague-Dawley rats. Of these, the biochemical, pharmacokinetic, and pharmacodynamic characteristics of (4,4-difluoropiperidin-1-yl)[1-isopropyl-5-(1-isopropylpiperidin-4-yloxy)-1H-indol-2-yl]methanone 36 are detailed.
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