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Multitarget MOR/DOR antinociceptive ligands as useful profile in pain management: synthesis and pharmacological studies of 6,7- benzomorphan-based LP2 and its isomers

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Abstract

Opioid analgesics, such as morphine, elicit analgesic effects primarily through mu opioid receptor (MOR), whose activation determines not only analgesia but also a sequel of unwanted side effects. Although indispensable for the management of acute severe pain, the classical analgesics are unsuccessful for inflammatory and neuropathic pain treatment. Multitarget MOR/delta opioid receptor (DOR) agonists, showing synergic antinociceptive activity with low side-effects induction in preclinical models, represent a strategy to overcome the default in chronic pain treatment (1).

In this context, we identified the multitarget MOR/DOR ligand LP2 (1) characterized by high MOR (Ki= 1.08 nM) and DOR (Ki= 6.6 nM) affinity coupled to an agonist profile versus these receptors (IC50MOR= 21.5 nM and IC50DOR= 4.4 nM). In tail flick test, LP2 produced a long-lasting antinociception naloxone-reversed (ED50 of 0.9 mg/kg i.p.) (2). Building upon these evidences, our efforts were focused on demonstrating whether the LP2 multitarget profile could be useful for persistent pain states. Thus, LP2 is evaluated in a model of neuropathic pain induced by chronic constriction injury (CCI) and a model of inflammatory pain (Formalin test). Moreover, both 2R- (2) and 2S- (3) diastereoisomers of LP2 were synthesized in order to investigate the role of the stereocenter at the N-substituent of the 6,7-benzomorphan scaffold in drug-opioid receptor interaction (3). Their pharmacological profile were compared each other and with LP2 (1). Specifically, 2S-LP2 (3) showed an increased antinociceptive effect than LP-2 consistent with the in vitro functional profile. Moreover, 2S-LP2 (3) resulted a biased MOR/DOR agonist with functional selectivity for G-protein signaling and reduced β-arrestin 2 recruitment, an effectiveness profile in chronic pain conditions management.

Biography:

Rita Turnaturi completed her PhD in Medicinal Chemistry from University of Catania. Currently she is performing fellowship at the Department of Drug Sciences of University of Catania. She has published more than 30 papers in reputed peer-reviewed journals.

Speaker Publications:

1. "Intercellular communication and ion channels in neuropathic pain chronicization"; Inflammation Research volume 69, pages841–850(2020)
2. "Sigma Receptor Ligands Carrying a Nitric Oxide Donor Nitrate Moiety: Synthesis, In Silico, and Biological Evaluation"; ACS Med. Chem. Lett. 2020, 11, 5, 889–894
3. "Exploiting the Power of Stereochemistry in Drug Action: 3-[(2S,6S,11S)-8-Hydroxy-6,11-dimethyl-1,4,5,6-tetrahydro-2,6-methano-3-benzazocin-3(2H)-yl]-N-phenylpropanamide as Potent Sigma-1 Receptor Antagonist"; ACS Chem. Neurosci. 2020, 11, 7, 999–1005.
4. "Novel N-Substituted Benzomorphan-Based Compounds: From MOR-Agonist/DOR-Antagonist to Biased/Unbiased MOR Agonists"; ACS Med. Chem. Lett. 2020, 11, 5, 678–685

5. "Tuning Properties for Blood–Brain Barrier Permeation: A Statistics-Based Analysis"; ACS Chem. Neurosci. 2020, 11, 1, 34–44.

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