EURO BIOPHARMA 2021: Multitarget MOR/DOR antinociceptive ligands as useful profile in pain management: synthesis and pharmacological studies of 6,7- benzomorphan-based LP2 and its isomers - Rita Turnaturi- University of Catania

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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 drugopioid receptor interaction (3). Their pharmacological profile were compared each other and with LP2 (1). Specifically, 2SLP2 (3) showed an increased antinociceptive effect than LP-2 consistent with the in vitro functional profile. Moreover, 2SLP2 (3) resulted a biased MOR/DOR agonist with functional selectivity for G-p te n s gn ng nd educed Narrestin 2 recruitment, an effectiveness profile in chronic pain conditions management.

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