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Simultaneous MOR/DOR targeting as useful strategy for pain management

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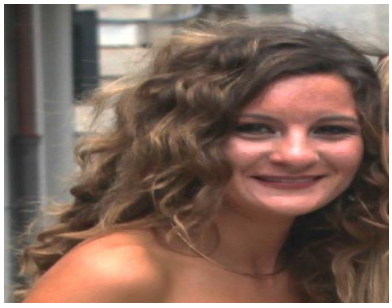

Abstract

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.

In this context, we identified the multitarget MOR/DOR ligand LP2 characterized by high MOR (K_i= 1.08 nM) and DOR (K_i= 6.6 nM) affinity coupled to an agonist profile versus these receptors (IC_{50}^{MOR}= 21.5 nM and IC_{50}^{DOR}= 4.4 nM). In tail flick test, LP2 produced a long-lasting antinociception naloxone-reversed (ED_{50} 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) (3) and a model of inflammatory pain (Formalin test) (4). Moreover, both 2R- and 2S- diastereoisomers of LP2 (Figure 1) 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 (5). Their pharmacological profile were compared each other and with LP2. Specifically, 2S-LP2 showed an increased antinociceptive effect than LP-2 consistent with the *in vitro* functional profile. Moreover, 2S-LP2 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 (6).

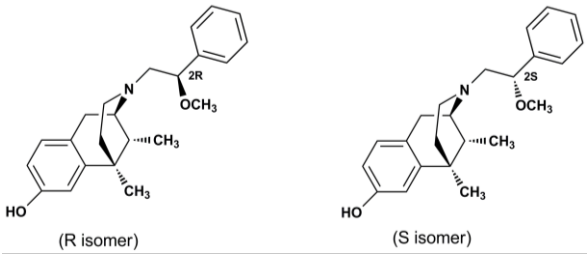

Figure 1: LP2 isomers

Recent Publications (minimum 5)

1. Turnaturi, R.; Aricò, G.; Ronsisvalle, G.; Parenti, C.; Pasquinucci, L. Eur. J. Med. Chem. 2016, 108, 211−228.
2. Pasquinucci, L.; Turnaturi, R.; Prezzavento, O.; Arena, E.; Aricò, G.; Georgoussi, Z.; Parenti, R.; Cantarella, G.; Parenti, C. Bioorg. Med. Chem. 2017, 25, 4745−4752.
3. Vicario N, Pasquinucci L, Spitale FM, Chiechio S, Turnaturi R, Caraci F, Tibullo D, Avola R, Gulino R, Parenti R, Parenti C. Simultaneous Activation of Mu and Delta Opioid Receptors Reduces Allodynia and Astrocytic Connexin 43 in an Animal Model of Neuropathic Pain. Mol Neurobiol. 2019, 56, 7338-7354.
4. Pasquinucci L, Turnaturi R, Montenegro L, Caraci F, Chiechio S, Parenti C.Simultaneous targeting of MOR/DOR: A useful strategy for inflammatory pain modulation. Eur J Pharmacol. 2019, 847:97-102.
5. Pasquinucci, L.; Turnaturi, R.; Calò, G.; Pappalardo, F.; Ferrari, F.; Russo, G.; Arena, E.; Montenegro L.; Chiechio, S.; Prezzavento, O.; Parenti, C. (2S)-N-2-methoxy-2-phenylethyl-6,7-benzomorphan compound (2S-LP2): Discovery of a biased mu/delta opioid receptor agonist. Eur J Med Chem. 2019, 168, 189-198.
6. Turnaturi R, Chiechio S, Salerno L, Rescifina A, Pittalà V, Cantarella G,Tomarchio E, Parenti C, Pasquinucci L. Progress in the development of more effective and safer analgesics for pain management. Eur J Med Chem. 2019, 183, 111701.

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Biography

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