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INTRINSIC ACTIVITY

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*MEETING ABSTRACT*

## A2.13

### Novel oxymorphone analogues, as bifunctional μ/δ opioid receptor agonists, produce antinociception in mice without the risks of antinociceptive tolerance and physical dependence

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**Background:** Opioids are highly effective painkillers for the treatment of moderate-to-severe pain. Chronic use of opioids is associated with analgesic tolerance, physical dependence and addictive potential. Opioids mediate their pharmacological effects via activation of opioid receptors, μ (MOR), δ (DOR) and κ (KOR). The MOR is the primary target for the therapeutic analgesic effect, but also for severe side effects. Currently, alternative chemical and pharmacological strategies are explored to mitigate the deleterious effects of MOR agonists and to limit abuse and misuse, amongst which are multifunctional ligands. Bifunctional opioid ligands gained a particular interest over the recent years. In this study, we present the *in vitro* and *in vivo* pharmacology of two novel oxymorphone analogues that emerge as bifunctional MOR/DOR agonists.
**Methods:** Radioligand binding assays were performed with rat (MOR and DOR) and guinea-pig brain (KOR) membranes. [$^{35}$S]GTPγS binding assays were performed with membranes from Chinese hamster ovary (CHO) cells stably expressing the human MOR, DOR or KOR. Antinociception after s.c. administration was assessed in pain models of acute nociception (tail-flick test) and inflammatory pain (formalin test) in mice. Antinociceptive tolerance was measured in mice treated daily over a 5-day period, with tail-flick latencies measured on days 1 and 5. Physical dependence was determined using naloxone-precipitated withdrawal.
**Results:** Radioligand binding studies showed the new oxymorphone derivatives to display very high affinities (picomolar to subnanomolar range) to the rodent MOR, DOR and KOR. In the [$^{35}$S]GTPγS functional assays, they were very potent and full agonists to the human MOR and DOR, and partial agonists to the human KOR. *In vivo*, both oxymorphone analogues displayed dose-dependent antinociceptive efficacy in experimental models of acute nociception and inflammatory pain after s.c. administration to mice. Their antinociceptive effect was reversed by selective antagonists of MOR (β-funaltrexamine) and DOR (naltrindole), but not by a KOR antagonist (nor-binaltorphimine), demonstrating the involvement of MOR and DOR to the antinociceptive action. Chronic s.c. drug treatment of mice did not cause antinociceptive tolerance and withdrawal syndrome.
**Discussion:** We show that targeted structural modifications on the oxymorphone scaffold resulted in significant alterations in opioid activity by influencing the pharmacological properties of the ligands. Oxymorphone, a potent and selective MOR agonist, was converted into bifunctional MOR/DOR agonist ligands. The dual activation of the MOR and DOR by the novel oxymorphone analogues produces effective antinociception without the CNS-mediated risks of antinociceptive tolerance and physical dependence. These findings pave the way to new pain therapeutics with limited side effects on both acute and chronic use.
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**Keywords:** opioid receptors – bifunctional opioid ligands – pain – analgesia – oxymorphone

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