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Comparison of physicochemical properties and biological activities of opioid morphinans interacting with mu opioid receptors

Muhammad F Asim, Catalina-Roxana Bohotin, Mariana Spetea and Helmut Schmidhammer*

Address: Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences, University of Innsbruck, 6020 Innsbruck, Austria

Email: Helmut Schmidhammer* - helmut.schmidhammer@uibk.ac.at

* Corresponding author

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Morphinans play an important role among therapeutically valuable opioids. They include powerful pain relieving agents such as naturally occurring alkaloids (e.g. morphine, codeine), semisynthetic derivatives (e.g. oxycodone, oxymorphone, buprenorphine), and synthetic analogues (e.g. levorphanol, butorphanol). These opioid drugs produce their biological actions through three receptor types, μ, δ and κ, belonging to the family of seven transmembrane G protein-coupled receptors. All three opioid receptors are located in the central and peripheral nervous systems of many species including human. Morphine and related opioids currently prescribed as potent analgesics for the treatment of severe pain produce their analgesic activity primarily through their agonist action at μ opioid receptors, which is the main receptor type targeted for pharmacotherapy of pain. Despite their widespread use, opioid drugs have a number of severe side effects including respiratory depression, emesis, sedation, constipation, tolerance, and physical dependence. Consequently, a great deal of effort was spent trying to develop safer, more efficacious and non-addicting compounds, with the goal of an improved therapeutic index. Optimal physicochemical properties are often an important consideration for the development of bioactive molecules as therapeutic agents. Therefore, a significant aim in medicinal chemistry research and drug development is to predict the behavior of targeted molecules based on their physicochemical features. This task, however, cannot be accomplished without correlating and understanding the differences in the physicochemical and pharmacological properties of existing opioid morphinans. Toward this goal, we performed a comparative study on physicochemical properties and biological activities of well-known opioid morphinans such as the naturally occurring alkaloid morphine, and semisynthetic analogues e.g. oxymorphone. Besides the classical and clinically relevant opioid analgesics, synthetic morphinans developed by our group were included in the study, the 14-O-methyl derivative of oxymorphone and its 5-methyl substituted analogue, 14-methoxymetopon. The major physicochemical parameters (pK_a, log*P* and log*D*) have been experimentally determined using a Sirius PCA200/Cheqsol Instrument. *In vitro* binding affinities and selectivities to opioid receptors were determined in rodent brain membranes using binding assays. Analgesic potencies were evaluated after subcutaneous administration to mice using tail-flick and hot-plate tests. The structure-activity relationship observations, combining physicochemical and biological data, will be discussed. Altogether, the present study indicate that specific structural elements are required to confer high affinity/selectivity for μ opioid receptors and potent agonist and analgesic activity in the morphinan class of opioids, and are important in drug development.