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Meeting abstract

Synthesis, opioid receptor binding profile and SAR studies of 14-alkoxy-substituted indolo- and benzofuromorphinans

Alexander Staaf, Mariana Spetea, Harald Mittendorfer 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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On the basis of pharmacological, behavioral and biochemical studies, opioid receptors have been classified into three major types, μ, δ and κ, belonging to the family of the G protein-coupled receptors. All three receptor types are expressed in the central and peripheral nervous systems of both animals and human. Receptor type selective opioid agonists and antagonists are of interest both as pharmacological tools and as potential therapeutic agents for the treatment of pain, addiction, constipation or immunological diseases. During the past 3 decades, one of the major aims of medicinal chemistry and opioid pharmacology has been to develop opioids with high affinity and/or selectivity for each of the three receptor types. In this study, 14-alkoxy analogues of naltrindole, naloxindole and naltriben with different benzyloxy substitution in position 14 have been investigated to elaborate on structure-activity relationships (SAR) of the morphinan class of compounds. To this aim, several 14-benzyloxy substituted indolo- and benzofuromorphinans were prepared by multi-step synthesis using naloxone and naltrexone as starting materials. Binding affinities and selectivities to opioid receptors (μ, δ and κ) were determined using *in vitro* binding assays with rodent brain membranes employing selective opioid radioligands. Examination of the chemical structure and opioid binding profile i.e. affinities and selectivities reveals certain SAR for the investigated compounds. Opioid binding affinity was sensitive to the character and length of the substituent in position 14. Introduction of 14-benzyloxy groups resulted in reduced affinity and selectivity for the δ receptor. The replacement of the N-allyl by an N-cyclopropylmethyl group in position 17 resulted in increased δ affinity without affecting δ receptor selectivity. The results of the present study indicate that position 14 of indolo- and benzofuromorphinans represents a critical site that could be a trigger to develop opioid compounds with increased δ affinity and/or selectivity. These findings provide further evidence that the nature of the substituent at position 14 has a major impact on the abilities of morphinans to interact with opioid receptors.