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Development of a non-radioactive mass spectrometry-based binding assay at the μ-opioid receptor and its application for the determination of the binding affinities of 17 opiates/opioids as well as of the designer opioid isotonitazene and five further 2-benzylbenzimidazoles

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Radioactive ligand binding assays are the most commonly applied method for the determination of binding affinities of compounds at a particular receptor. While they are highly sensitive and high-throughput capable they come with major disadvantages due to the radioactive ligands utilized. Here we present the development of a mass-spectrometry-based binding assay for the determination of binding affinities at the human μ-opioid receptor using non-labelled DAMGO ([D-Ala, N-MePhe, Gly-ol]-enkephalin). The runtime of the LC-MS/MS method was 5.5 min per data point and allowed for the highly sensitive detection of 38.5 fg DAMGO on column. The assay shows low non-specific binding and the equilibrium dissociation constant of DAMGO was 0.57 nM. The assay was applied to determine the K values of 17 opiates/opioids and the results were in good agreement with the data from radioactive receptor binding assays published in the literature. Additionally, the K value of six 2-benzylbenzimidazoles, including the widely abused designer opioid isotonitazene, were determined ranging from 0.654 to 72.9 nM. Consequently, the developed assay provides a suitable alternative to radioactive binding assays as it allows for a reliable and rapid determination of receptor binding affinities of e.g. newly emerging designer opioids.

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