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TECHNOLOGY INFO SHEET

Synthesis of deuterated morphine derivatives with high and selective μ-opioid receptor activity

Development status

- Drug discovery
- **Pre-clinical**
- Phase I.
- Phase II.
- Phase III.

IP status

- In priority year
- PCT I.
- PCT II.
- **National/regional phase**
- Validation

Challenge

Morphine is the most widely used narcotic analgesic agent for treatment of severe chronic and acute pain. In the last two decades there was a dramatic increase in the use of strong opioids for chronic non-cancer pain but only one novel opioid derivative, tapentadol, was introduced to therapeutic use. The principle aim of the present invention is the provision of compounds with higher receptor binding affinity resulting in improved pharmacological properties e.g. in higher analgesic activity, with longer duration of action and reduced adverse effects through the administration of lower doses, and additionally with a reduced risk of the possibility of drug abuse.

Technology

This method applies new deuterated morphine derivatives, which show broad utility by exhibiting high and selective μ-opioid receptor activity, so they are useful for pain treatment or can be used as antitussive agents with a reduced risk of possible drug abuse. Toxicity of deuterium is very low and human body tolerates very high heavy water content. Due to the unique way of introducing deuterium, the deuterium atoms cannot be exchanged to hydrogen atoms; consequently the deuterium loading of the body does not increase. The compounds of the invention can be synthesized easily using commercially available starting materials, e.g. 7,8-didehydro compounds, or their derivatives. Deuterium is introduced in one single chemical step, therefore the synthesis is cheap and can be easily performed.

Keywords

Deuterated morphine, metabolism changes, drug development

Benefits

- Novel morphine derivatives show high and selective μ-opioid receptor binding activity.
- Higher analgesic activity at lower doses induces reduced adverse effects.
- Duration of the effect is extended, meaning less frequent doses.
- Incorporated deuterium atoms in the morphine ring are not affected by the first steps of the metabolic pathway, so the presence of the compounds or their metabolites can be followed up easily in a patient.
- Derivates have reduced risk of the possibility of drug abuse.

Development status

The μ and δ-opioid receptor binding assays and behavioral pharmacological antinociceptive tests were performed in order to prove that deuterated morphine derivatives show higher affinity to μ-opioid receptors than morphine. These results suggest that the compounds can be used as effective μ-receptor ligands. The side effects have not been investigated. The compounds are ready to enter into pre-clinical development and there is no further chemistry required to find a clinical lead.

IP status

The Hungarian patent application (P1300221) was submitted in 2013.

PCT examination (PCT//HU14/00030) was submitted in 2014. The PCT examination was extended to Europe (EP 14727037.5) and US (14/781,116): The US patent was granted in 2016 (Patent No.: 9,447,108), the European patent is in progress.

What we are looking for

The University of Szeged is looking for partners to carry out comparative safety studies between deuterated morphine derivatives and morphine, in order to investigate the side effects like, addictive potential, constipation or respiratory suppression. After that we are ready to enter into pre-clinical development.

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