

## Synthesis and pharmacological evaluation of hybrids targeting opioid and neurokinin receptors.

### Autorzy

Karol Wtorek  
Anna Adamska-  
Bartłomiejczyk  
Justyna Piekielna-Ciesielska  
Federica Ferrari  
Chiara Ruzza  
Alicja Kluczyk  
Joanna Piasecka-Zelga  
Girolamo Calò  
Anna Janecka

### Rok wydania

2019

### Czasopismo

Molecules

### Numer woluminu

24

### Strony

4460/1-4460/14

### DOI

10.3390/molecules24244460

### Kolekcja

Naukowa

### Język

Angielski

### Streszczenie

Morphine, which acts through opioid receptors, is one of the most efficient analgesics for the alleviation of severe pain. However, its usefulness is limited by serious side effects, including analgesic tolerance, constipation, and dependence liability. The growing awareness that multifunctional ligands which simultaneously activate two or more targets may produce a more desirable drug profile than selectively targeted compounds has created an opportunity for a new approach to developing more effective medications. Here, in order to better understand the role of the neurokinin system in opioid-induced antinociception, we report the synthesis, structure–activity relationship, and pharmacological characterization of a series of hybrids combining opioid pharmacophores with either substance P (SP) fragments or neurokinin receptor (NK1) antagonist fragments. On the bases of the in vitro biological activities of the hybrids, two analogs, opioid agonist/NK1 antagonist Tyr-[d-Lys-Phe-Phe-Asp]-Asn-d-Trp-Phe-d-Trp-Leu-Nle-NH<sub>2</sub> (**2**) and opioid agonist/NK1 agonist Tyr-[d-Lys-Phe-Phe-Asp]-Gln-Phe-Phe-Gly-Leu-Met-NH<sub>2</sub> (**4**), were selected for in vivo tests. In the writhing test, both hybrids showed significant an antinociceptive effect in mice, while neither of them triggered the development of tolerance, nor did they produce constipation. No statistically significant differences in in vivo activity profiles were observed between opioid/NK1 agonist and opioid/NK1 antagonist hybrids.

### Słowa kluczowe

opioid receptors, neurokinin-1 receptor, peptide synthesis, receptor binding studies, functional assay, writhing test, tolerance

Typ publikacji

Artykuł

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Adres publiczny

<http://dx.doi.org/10.3390/molecules24244460>

Strona internetowa wydawcy

<http://www.mdpi.com/journal/metals>

Plik został wygenerowany dnia 2026-05-06 09:26:05

Adres w repozytorium <https://old.chem.uni.wroc.pl/pl/repozytorium/UI9AdVC>.