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

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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_2 (**2**) and opioid agonist/NK1 agonist Tyr-[d-Lys-Phe-Phe-Asp]-Gln-Phe-Phe-Gly-Leu-Met-NH_2 (**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