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3-ALKYL FENTANYL ANALOGUES: STRUCTURE-ACTIVITY-RELATIONSHIP STUDY

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Fentanyl, the prototype of the 4-anilidopiperidine class of a synthetic opioid analgesics, is widely used to supplement general anesthesia or to treat postoperative and cancer pain. In order to discover an analgesic with the improved pharmacodynamic and pharmacokinetic profile, extensive efforts during last five decades have been devoted to synthesis of a large number of fentanyl analogues and establishing the structure-activity-relationship (SAR) of the 4-anilido-piperidine class of analgesics. This study is aimed to examine the analgesic activity of some newly synthesized 3-alkyl fentanyl analogues and compared with fentanyl. Antinociception is measured by using tail-immersion test in male Wistar rats.The relative potency was: (±)cis-3-methyl fentanyl (8)>(±)trans-3-methyl fentanyl (2)≥(±)cis-3-ethyl fentanyl (1.5)>fentanyl (1)≥(±)trans-3-ethyl fentanyl (0.9)>(±)cis-3-butyl fentanyl (0.064)≥(±)trans-3-butyl fentanyl (0.035)>(±)cis-3-benzyl fentanyl (0.008)≥(±)trans-3-benzyl fentanyl (0.0055). The duration of action (ED_{99}) was: (±)cis-3-methyl fentanyl (90min)>(±)trans-3-methyl fentanyl (40min)≤(±)cis-3-ethyl fentanyl (60min)≥(±)trans-3-ethyl fentanyl (40min)≤fentanyl (50min)=(±)cis-3-butyl fentanyl (50min)=(±)trans-3-butyl fentanyl (50min)=(±)cis-3-benzyl fentanyl (50min)=(±)trans-3-benzyl fentanyl (50min). Pharmacological results show that groups in position 3 of the piperidine ring, which are larger than methyl, severely reduce the analgesic potency compared to fentanyl. It is likely that the steric factor (i.e. voluminosity of the group and cis/trans isomerism) plays a crucial role in the analgesic potency of this series. Although the duration of action, in general, does not depend on the stereochemistry, longer action of the most potent 3-alkyl fentanyl analogues such as cis-3-methyl- and cis-3-ethyl fentanyl, is more likely influenced by pharmacodynamic, rather than pharmacokinetic variables.

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