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论文

3-甲基芬太尼衍生物QSAR研究

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摘要：

Hansch途径研究了一系列3-甲基芬太尼衍生物理化性质与镇痛活性间的关系。初步结果表明,镇痛活性与化合物的油/水分配系数之间无规律性变化;与R_2取代基的立体效应(如L,B_1～B_4及MR_{R2})和疏水常数(π_{R2})间有一定的匹配关系,与R_3取代基的Hammen常数(σ)呈抛物线型。引入1-β羟基亦颇为有利。从作用机理推测,该类衍生物的R_2和可能是与受体相结合的基团,R_1可能仅起药物转运的载体作用,1-β羟基也可能通过氢键参与与受体的互补部位缔合。

关键词： 芬太尼衍生物 3-甲基芬太尼 镇痛活性 分配系数(logP) 疏水常数(π) 克分子折射率(MR) Verloop常数(L,B_1,B_2,B_3,B_4) Ha

STUDIES ON QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) OF 3-METHYLFENTANYL DERIVATIVES

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Abstract:

The correlation between physicochemical properties and analgesic activities of a series of 3-methylfentanyl derivatives was studied. Physicochemical parameters used in the multiple regression analysis were partition coefficient (log P), molecular weight (log MW) of compounds, hydrophobic parameters (π) of substituents R_1, R_2 and R_3, Verloop constants (L, B_1, B_2, B_3, B_4), molar refractivity. (MR) of R_2 and Hammett constants (σ) of R_3. The indicator variable I_0 was assigned the value of 1 for compounds containing OH group at the asterisked carbon, otherwise, 0. Correlation analysis was performed in five sub-sets and the results are as follows:1. No regular relationship between the analgesic activity and partition coefficients was found. The log P values in tables 1 and 2 showed that these compounds have higher lipid solubility. Thus, they could readily penetrate through blood-brain barrier and reach receptor sites. Their analgesic potency was mainly dependent on their specific receptor binding affinity.2. The best correlation in each sub-set is equations 8, 20, 32, and 36. Their squared correlation matrices between different parameters used in the most significant equations showed that there is some degree of intercorrelation except equations 8 and 12.3. σ^2 (equations 27～32) was found to be an important parameter (σ_0=0.04, T>2).4. Introducing a β-hydroxy group is beneficial to analgesic activity.5. According to the result of equation 32 a new compound 44 (fig 3) was designed and prepared, the observed log 1/c of which is very close to the calculated value.In summary, the bioactivity is closely dependent on the physicochemical properties of substituents R_2 and R_3: strict parameter requirements of hydrophobic constant, steric parameters for R_2 and Hammett constants for R_3. They are important groups interacting with receptor. R_3 may interact with receptor through Van der Waals-type forces and R_2 may bind to a hydrophobic cavity of certain size on the receptor surface, whereas substituent R_1 only play a carrier role in the drug transport process.

Keywords: 3-Methylfentanyl Analgesic activity Partition coefficient (log P) Hydrophobic constant(π) Molar refractivity (MR) Verloop constants (L, B_1, B_2 B_3, B_4) Hammett constant(σ) QSAR Fentanyl derivatives

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