

Evaluation of Anticonvulsant and Sedative-Hypnotic Activities of Novel 2-Fluorobenzyloxy 4,6- Diphenylpyrimidin-2-Ol Derivatives in Mice

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Abstract : Introduction: Benzodiazepines (BZDs) have pharmacological effects, including anxiolytic, sedative-hypnotic, anticonvulsant, and muscle relaxant properties. However, they have adverse effects such as interaction with alcohol, ataxia, impaired learning, and psychological and physical dependence. According to the structure of zolpidem and on the basis of the structure-activity relationship of BZD receptor ligands, six novel derivatives of 2-fluorobenzyloxy 4,6- diphenylpyrimidin-2-ol have been synthesized. We studied the hypnotic, sedative, and anticonvulsant effects of the novel compounds. Method: In this study, we used male mice (18 to 25 g). All the substances were injected intraperitoneally. The hypnotic effect of the compounds was examined by pentobarbital induced sleeping test. The locomotor activities and sedative effects of the novel compounds were evaluated by open field and loss of righting reflex test, respectively. The anticonvulsant effects of the novel compounds were assessed by PTZ and MES tests. Results: In the pentobarbital induced sleeping and open field tests, compound 4-(2-((2-fluorobenzyl)oxy)phenyl)-6-(p-tolyl) pyrimidine-2-ol with ED₅₀=14.20 mg/kg and ED₅₀=47.88 mg/kg, respectively, was the most effective compound. None of the novel compounds showed a significant anticonvulsant effect in the PTZ test. In MES test, compound 4-(2-((2-fluorobenzyl)oxy)phenyl)-6-(p-tolyl)pyrimidine-2-ol with ED₅₀=12.92 mg/kg was the most effective compound. Flumazenil blocked the sedation and hypnosis of all the compounds. Conclusion: All of the novel derivatives showed significant sedative-hypnotic activities and caused the reduction of locomotor activities. The results show that the methyl lipophilic substitutes on the phenyl ring of 4,6-diphenylpyrimidin-2-ol derivatives can increase the sedative and hypnotic effects of the derivatives. Flumazenil antagonized the sedative, and the hypnotic effects of the compounds indicate that BZD receptors are involved in the effects.

Keywords : BZD, sedative, hyptonic, anticonvulsant, zolpidem, MES, PTZ, benzodiazepine, locomotor activities, pentobarbital induced sleeping tests

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