

5-[Aryloxypyridyl (or Nitrophenyl)]-4H-1,2,4-Triazoles as Flexible Benzodiazepine Analogs: Synthesis, Receptor Binding Affinity and the Lipophilicity-Dependent Anti-Seizure Onset of Action

Authors : Latifeh Navidpour, Shabnam Shabani, Alireza Heidari, Manouchehr Bashiri, Azadeh Ebrahim-Habibi, Soraya Shahhosseini, Hamed Shafaroodi, Sayyed Abbas Tabatabai, Mahsa Toolabi

Abstract : A new series of 5-(2-aryloxy-4-nitrophenyl)-4H-1,2,4-triazoles and 5-(2-aryloxy-3-pyridyl)-4H-1,2,4-triazoles, possessing C-3 thio or alkylthio substituents, was synthesized and evaluated for their benzodiazepine receptor affinity and anti-seizure activity. These analogues revealed similar to significantly superior affinity to GABAA/ benzodiazepine receptor complex (IC₅₀ values of 0.04–4.1 nM), relative to diazepam as the reference drug (IC₅₀ value of 2.4 nM). To determine the onset of anti-seizure activity, the time-dependent effectiveness of i.p. administration of compounds on pentylenetetrazole induced seizure threshold was studied and a very good relationship was observed between the lipophilicity (cLogP) and onset of action of studied analogues ($r^2 = 0.964$). The minimum effective dose of the compounds, determined at the time the analogues showed their highest activity, was demonstrated to be 0.025–0.1 mg/kg, relative to diazepam (0.025 mg/kg).

Keywords : 1,2,4-triazole, flexible benzodiazepines, GABAA/benzodiazepine receptor complex, onset of action, PTZ induced seizure threshold

Conference Title : ICRAOBMC 2022 : International Conference on Recent Advances in Organic, Bioorganic and Medicinal Chemistry

Conference Location : Paris, France

Conference Dates : February 17-18, 2022