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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

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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 (r2 = 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/bezodiazepine receptor complex, onset of action, PTZ induced seizure threshold

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