

Design, synthesis, and pharmacological evaluation of novel 1,2,4-triazol-3-amine derivatives with anticonvulsant and hypnotic effects

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In the current study, a series of novel 1,2,4-triazol-3-amine derivatives were designed, synthesized, and biologically evaluated *in vivo* for their anticonvulsant and hypnotic effects in the pentylenetetrazole (PTZ)-induced seizures, maximal electroshock (MES)-induced seizures, and pentobarbital-induced sleeping tests. Furthermore, the possible side effects of the most potent compounds on the memory, motor coordination, and muscle strength were evaluated in passive avoidance, rotarod, and grip strength tests, respectively. The designed compounds with the main benzodiazepine pharmacophores including aromatic ring and proton accepting group completely mimicked the structure of zolpidem as an α 1-selective agonist of GABAA receptor. Compounds 5c (ED50 \approx 52.5 mg/kg) and 5g (ED50 \approx 16.5 mg/kg) in the PTZ test were the most potent compounds among the designed compounds. In the MES test, the observed ED50s for compounds 5c and 5g were reduced to around 11.8 mg/kg and 10.5 mg/kg, respectively. The considerable hypnotic effect in a dose-dependent manner was observed following the administration of newly synthesized compounds. In all experiments administration of flumazenil as an antagonist of benzodiazepines receptor fully antagonized observed effects which indicated the involvement of GABAA receptors. Since there was no negative effect on memory, motor coordination, and muscle strength following the administration of compounds 5c and 5g as the most potent compounds, it could be concluded that the novel compounds most likely act through α 1-containing GABAA receptors and possess no affinity for α 5-containing receptors. The newly designed compounds could be considered as leading compounds in synthesizing novel GABAA receptor agonists with minimum side effects.

Keywords: 1,2,4-triazol-3-amine, Anticonvulsant, Benzodiazepine, Sedative-hypnotic, Synthesis, Toxicity