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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Facile synthesis, molecular docking and toxicity studies of 4-Phenyl-3-phenylamino-4H-[1,2,4]thiadiazol-5-one analogs as $GABA_A$ receptor agonists

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Abstract A series of 4-Phenyl-3-phenylamino-4H-[1,2,4]thiadiazol-5-one derivatives was synthesized by a simple method and their structures were established by physical and spectroscopic methods like infrared, mass and nuclear magnetic resonance spectroscopy. Elemental formulae of all the compounds were determined by elemental analysis and compared with the calculated value. Log *P* value and in vitro hydrolysis, in simulated gastric fluid and simulated intestinal fluid, for all the compounds were determined by standard methods. Synthesized 1, 2, 4-thiadiazolines were screened for their anticonvulsant activity against maximal electroshock method and isoniazid induced seizures. All the compounds showed good anticonvulsant activity. The compound 4-(3,4-dichloro-phenyl)-3-(3,4-dichloro-phenylamino)-4H-[1,2,4]thiadiazol-5-one (**3a**) was found to be the most potent member of the series. Molecular docking studies of the synthesized compounds depicted their stable ligand–receptor complex conformation with the typical binding pocket of γ-aminobutyric acid A receptor protein. Compound **3a** confined its effect in the molecular docking studies also with non-covalent interactions with Tyr 157, Phe 200 and Tyr 205, the key interacting residues of γ-aminobutyric acid A receptor protein 4COF. In silico absorption, distribution, metabolism and elimination performance of all the compounds also appear to favour anticonvulsant effect. "LAZAR" and "OSIRIS" property explorer predicted nontoxic, nonmutagenic, non-carcinogenic, etc. nature for all the compounds. In conclusion, some γ-aminobutyric acid A receptor agonists have been synthesized in this study with promising drug-like properties, which merit further development.

Keywords Thiourea · Thiadiazole · ADME · $GABA_A$ · LAZAR · OSIRIS

Introduction

Epilepsy is a chronic and often progressive disorder characterized by the periodic and unpredictable occurrence of epileptic seizures, which are caused by abnormal discharge of cerebral neurons. Epilepsy is not a disease, but a syndrome of different cerebral disorders of the central nervous system (CNS). This syndrome is characterized by paroxysmal, excessive and hyper synchronous discharges of a large number of neurons that result from too much excitation or too little inhibition in the area in which the abnormal discharge starts (Barbara, 2008; Rang et al., 2003; Gidal and Garnett, 1993). Excitation and inhibition of neurons may be mediated by different neurotransmitters. γ-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the cerebral cortex (Schwartz, 1988). GABA is localized primarily in short-axon interneurons that synapse on cell bodies and proximal axons, and serves to maintain inhibitory tone that counterbalances neuronal excitation. When this balance is perturbed, seizures may ensue. It is released into the synapse and then acts at one of

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