Reviews Journal of Medicinal Chemistry

Extended Abstract
Vol. 4, Iss. 1
2017

Synthesis and Anti Convulsant Activity of Novel Oxadiazole Substituted Phenothiazine Derivatives

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The research is directed towards a synthesis and evaluation of novel agents for the treatment of various neurological disorder. The phenothiazine nucleus has been well explored for the various biological activities in past. The oxadiazole substituted phenothiazine had a keen interest as a drug candidate for the treatment of the various neurological disorders. In view of these an attempt has been made to synthesize substituted phenothiazine and explore them to promising anti convulsant activity. The anti-convulsant activity of synthesized compounds had been done by using Strychnine induced and 4-amino pyridine induced models. A convulsion is a medical condition where body muscles contract by relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body. Because of convulsion is often a symptom of an epileptic seizure, the term convulsion is sometimes used as a synonym for seizures [1-3]. However, not all epileptic seizures lead to convulsion, and not all convulsions are caused by epileptic seizures. Convulsion is also consistent with an electric shock and improper Enriched Air scuba diving [4]. A seizure occurs when nerve cells by the brain send out sudden, excessive, uncontrolled electrical signals. Everyone's brain has continuous electrical activity. When something goes wrong with this activity of your child may have a seizure. Seizure can produce a variety of symptoms depending on what part of the brain is involved. Generalized and partial seizure are the main types of seizures. Convulsion is caused by a chemicals in the blood as well as infection like meningitis or encephalitis. A very common cause of convulsion is a fevers. Other possibilities include head trauma, stroke, or lack of oxygen to the brain. Sometimes convulsion can be caused by a genetic defect or brain tumors. Synthesis of 7, 8 or 9 substituted aniline Benzoic acid derivatives Equimolar amount of substituted aniline was added to a chloro benzoic acid in 20 mL of DMF and 0.1% of potassium hydroxide solution, the reaction mixture was heated under refluxed at about 80°C temperature, for 2 h. TLC indicated the end of reaction. The mixture was cooled by addition of a water/ice mixture. The solid was filtered in excellent yield [I]. Synthesis of 7, 8 or 9 substituted 10 H-phenothiazine 1 carboxylic acid derivatives Equimolar amount of 7, 8 or 9 substituted Anilino Benzoic acid was added by a solution of sulfur powder and iodine in 5 mL of ethanol. Reaction mixture was heated under reflux with stirring for about 2 h and poured into ice/water mixture. The precipitate is filtered and washed with cold water [II]. Synthesis of derivatives of ethyl 10H-phenothiazine-1-carboxylate: 0.01 mole of 10 H-phenothiazine-1-carboxylic acid was reflux with conc. H_2SO_4 using ethanol as solvent for 1 hour in 250 ml RBF. After which has a resulting reaction mixture was kept in ice cold water [III]. Synthesis of derivatives of 10H-phenothiazine-1-carbohydrazide: 0.01 mole of compound A was reflux with 3 ml to 4 ml of hydrazine hydrate for 1 hour. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried (IV). Synthesis of derivatives of N'-benzylidene-10H-phenothiazine-1- carbohydrazide 0.01 mole of compound B was reflux with 0.01 mole of substituted aromatic aldehyde for 1 hour. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried and recrystallized from ethanol (V). Synthesis of derivative of 2-chloro-1-(1-(2,3-dihydro-1,3,4-oxidiazole carbonyl)-10H-phenothiazine-10yl)ehanone 0.01 mole of a compound VI (1,3,4-oxadiazol-3(2H)-yl) (10H-phenothiazin-1-yl) methanone was reflux with 0.01 mole of substituted 2-chloroacetyl chloride for 1 hour. After which the resulting reaction mixture was allow to cool in ice bath SCHEME 1. The resulting precipitate was collected and dried and recrystallized from ethanol (VII) [7-9]. Anti-Convulsant Activity Strychnine induced model The experimental animals are treated by test compound and standard drug respectively. The occurrence of clonic seizure, tonic seizures and death and recovery was recorded after 0.5 h, 1 h, 2h, and 4 h respectively. Thiosemicarbazide induced model The experimental animals are treated with test compound and standard drug respectively. the animals were injected with a subcutaneous dose of 20 mg/kg Thiosemicarbazide. The occurrence of clonic seizure, tonic seizures and death and recovery was recorded after 0.5 h, 1 h, 2h, and 4 h respectively. 4-Amino pyridine induced model neurotoxicity testing The experimental animals are treated with test compounds and standard. Test drug were administered at a dose of 30 mg/kg body weight intraperitonially, 30 min prior to subcutaneous injection of 4-aminopyridine at a dose of 13.3 mg/kg. Control injection of 4-aminopyridine at a dose of 13.3 mg/kg. Controls treated with 4-aminopyridine only exhibit characteristic behavioral signs, such as hyper reactivity, trembling, intermitted forelimb/hind limb clones and followed by hind limb extension, tonic seizures, opisthosomas and death. The standard drug phenytoin at a dose of 30 mg/kg body weight was taken for comparison. Neurotoxicity screening Activity of the drugs interfering with motor coordination was checked by the rotarod test. The mice were trained to say on an accelerating rotarod that rotate at 6 revolutions per minute. The dose, at which the animals were unable to grasp the rotarod, was determined. The compounds were found to be non-neurotoxic at a dose of 30 mg/kg body weight [10,11]. The synthesized compounds show anti-convulsant activity using strychnine induced convulsions, 4-Amino pyridine induced convulsions. The controls protected only up to 15 min which was followed by death in all cases. All of synthesized compounds were evaluated for their anticonvulsant activity using various chemical induced convulsion models on albino mice (20 g to 25 g). The vehicle and Standard drug called Diazepam was used. All the synthesized compounds show significant anti-convulsant activity at a dose of 30 mg/kg body weight. The compounds A3, A5, A7 and A9 were found to be most active amongst all the screened compounds using strychnine induced model and against Thiosemicarbazide induced model respectively and none of the compound showed anticonvulsant activity using 4-amino pyridine. The synthesized compounds show significant anti-convulsant activity due to presence of electron withdrawing groups like Chlorine has a substituent. The synthesized compounds can be proved as an potential candidate for the treatment of epilepsy and other disorders in future.

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