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Original Article

ANTIEPILEPTIC ACTIVITY OF SOME NOVEL SUBSTITUTED FLUORO BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

Objective: The aim of the study is to investigate and to reveal the antiepileptic activity of fluoro substituted benzothiazole derivatives (FBTDs) in experimental induced epilepsy in mice.

Methods: The acute oral toxicity was determined as per OECD guideline 423 and minimum effective dose was also determined for pharmacological screening. The antiepileptic activity of FBTDs was studied against maximal electroshock (MES) and strychnine (1 mg/kg, s. c.) induced seizures in mice.

Results: In MES test, the duration of tonic hind limb extension was significantly reduced by all FBTDs at a dose of 100 mg/kg except, P-3, and OX-9 whereas in strychnine induced model, the seizure latency was sustained by all FBTDs at a dose of 100 mg/kg except P-4. P-7 and OX-9.

Conclusion: The novels synthesized FBTDs shown very good activity and lead a route for further studies in this particular molecule.

Keywords: Antiepileptic activity, MES, Fluoro substituted benzothiazole derivatives.

INTRODUCTION

Epilepsy is a syndrome, not a disease characterized by paroxysmal, excessive and hyper synchronous discharges of the large number of neurons. Epilepsy is a common neurological disorder affecting a large section (0.5-1%) of the population throughout the world. Currently available antiepileptic drugs (AEDs) are symptomatically effective in only 65-75% patients [1]. Epilepsy is a tendency to have recurrent seizures. It can affect anyone, at any age, from any walk of life. It is one of the most common serious neurological conditions. Epilepsy is not a single condition. There are over 40 different types of epilepsy consisting of at least 29 syndromes, and further 12 or so clinically distinct groups defined by the specific cause or underlying cause. Approximately 60% of people have tonic clonic seizures, 20% complex partial. 12% mixed tonic, clonic and partial, 3% simple partial and less than 5% absence seizures, myoclonic seizures and other types. Around 3% of people with epilepsy are photosensitive and have seizures induced by photic stimuli [2].

Seizure is coined from the Latin word Sacire "To take possession of." Seizure (Convulsion) is therefore, a paroxysmal event due to abnormal, excessive hyper-synchronous discharges from aggregates of central (Cerebral) neurons [3].

Epilepsy affects QOL in a distinct way with its unique characteristics of early onset, chronicity and its effects on the social and cognitive development. The episodic and unpredictable nature of the disease imposes restrictions on the home and workplace environments of affected individuals. Epilepsy is also shown to be associated with higher rates of psychiatric comorbid conditions [4].

The chemistry and biologic study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. Benzothiazole derivatives are an significant class of compounds, which is becoming increasingly significant due to their broad spectrum of biologic activities. Literature survey shows that many Benzothiazole derivatives are known to exhibit pharmacological activities such as antitumor and antiviral, antiproliferative, anticancer, antimicrobial, antibacterial, and anthelmintic, as Cholinesterase inhibitors, antidiabetic, anti-Inflammatory, antimalarial, antifungal, etc. Hence, syntheses of such compounds are of considerable interest. It is well known that the introduction of a fluorine atom into an organic molecule causes dramatic changes in its biological profile, mainly due to high electronegativity of fluorine causes increases lipid solubility [5].

MATERIALS AND METHODS

Procurement of synthetic derivatives for the pharmacological screening

The Compounds were prepared and charecterised by the reported procedure [6].

Animals

Wister albino mice (weighing 20-25 g) of either sex were used during this study. They were procured from Sri Venkateshwara Enterprises, Bengaluru. The animals were acclimatized for one week under laboratory conditions. They were housed in polypropylene cages and maintained at 27 °C±2 °C under 12 hrs dark/light cycles. They were fed with standard rat feed (Gold Mohur Lipton India Ltd.) and water *ad libitum* was provided. The husk in the cages was renewed thrice a week to ensure hygiene and maximum comfort for animals.

Ethical clearance for usage of the animals was obtained from the Institutional animal ethical committee (Certificate reference no: *SCSCP/*626/A 2012-13 dated: 09-01-2013) prior to the beginning with the project work.

Acute toxicity studies

The toxicities of FBTDs were determined by using female albino mice (20-25 g), maintained under standard husbandry conditions. The animals were fasted for 3-4 hours prior to the experiment. Animals were administered with a single dose of Fluoro substituted Benzothiazole derivatives observed up to 48 hours study period for its mortality (short term toxicity). Based on the short-term toxicity profile, the next doses were determined as per OECD guidelines No 423 [7].

Determination of minimum effective dose

The minimum effective dose of FBTDs was determinate at the dose of 30, 100, 150 and 250 mg/kg body weight of an animal to carry out screening of anticonvulsant activity.

Maximal electro shock (MES) induced convulsion in mice

Albino mice of either sex with a body weight 20-25g were divided into 12 groups of 6 animals in each. Group 1 given with 2 % w/v gum acacia served as normal and received MES (60 mA for 0.2 Sec). Group 2 was administered phenytoin (25 mg/kg p. o) and serves as

standard. Group 3-12 were administered orally with compound 1–10 at a dose of 100 mg/kg respectively. One hour after oral administration of the compound/vehicle/standard drug, MES seizures were induced by electro convulsometer. A 60mA current was delivered transauricularly for 0.2 sec in mice.

This current intensity should elicit complete tonic extension of the hind limbs in control mice. The onset time of seizures, duration of tonic hind limb extension and mortality for each animal was observed. Decrease in duration of hind limb extension was considered as a protective action [8, 9].

Strychnine induced convulsions in mice

Mice of either sex were randomly allotted to 12 groups of 6 animals each. Group 1 was served as control and receives 2%w/v gum acacia, Group 2 as standard and treated with diazepam (5 mg/kg p. o). Group 3–12 were administered with compound 1–10 at a dose of 100 mg/kg respectively. One hour after oral administration of the compound/vehicle/standard drug, strychnine nitrate 1 mg/kg was administered subcutaneously.

Each animal was then placed into individual plastic cages during the test session. Mice that did not convulse 30 min after strychnine administration were considered to be protected. The parameters such as an onset of seizures, durations of tonic-clonic seizures and percentage of mortality for each animal were observed during the test session [10, 11].

Statistical analysis

Results were expressed as mean±SEM, (n=6). Statistical analyses were performed with one way analysis of variance (ANOVA) followed by Dunnet's multiple comparison test by using graph pad instant software. p value less than 0.05 was considered to be statistically significant. *p<0.05, *p<0.01 and **p<0.01, when compared with control and toxicant group as applicable.

RESULTS

In the present investigation, it is evident that phenytoin as a standard drug (25 mg/kg) exhibit extremely significant (***P<0.01) P-1, P-9 exhibit a very significant effects (**P<0.01 P-2, P-6 and P-7 exhibit significant (*p<0.05) antiepileptic effect as compared to control by increasing onset time of seizures and reducing the duration of tonic extensor phase and tonic-clonic seizures. Hence, the anticonvulsant activity of FBTDs against MES induced convulsions to involve blockade of seizure spread, which perhaps occurred by inhibiting voltage dependent Na^+channels.

Strychnine is an alkaloid which is an inhibitor of glycine (inhibitory neurotransmitter) synthesis. It is an antagonist to excitatory neuro transmitters like AMPA and NMDA and it also opposes Ca^{2+}induced excitotoxicity in the neurons. These factors are proepileptogenic and precipitate seizures. Hence, inhibition of glycine leads to clonic and tonic seizures in laboratory animals. Thus, it is used as a research tool to induce seizures in the animals. It was revealed that diazepam as a standard drug (5 mg/kg) exhibit extremely significant (***P<0.001). P-2, P-5, and P-9 exhibit the very significant effects (**P<0.01). P-3, P-6, and P-13 exhibit significant (*P<0.05) antiepileptic effect as compared to control by prolonging onset time of seizures (Latency) and reducing the duration of tonic-clonic seizures.

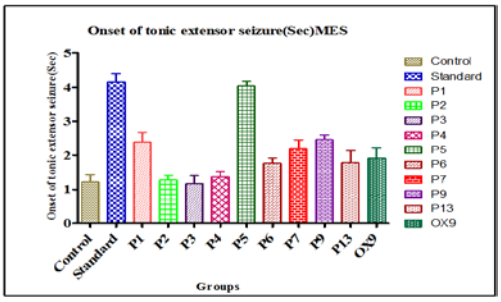

Fig. 1: Onset of tonic extensor seizure (sec.) in MES model

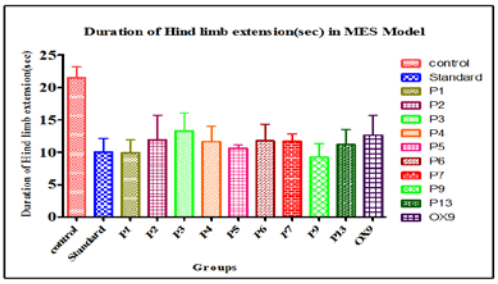

Fig. 2: Duration of tonic extensor seizure (sec.) in MES model

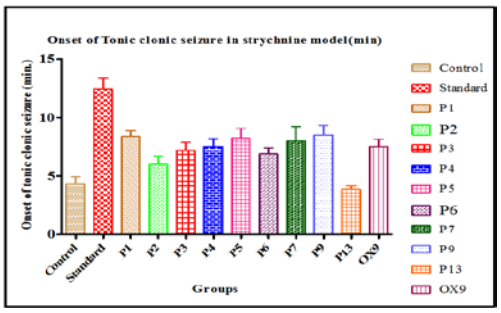

Fig. 3: Onset of tonic-clonic seizure (min.) in Strychnine model

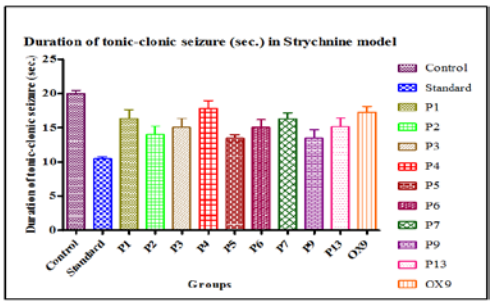

Fig. 4: Duration of tonic-clonic seizure (min.) in Strychnine model

DISCUSSION

For measuring the antiepileptic in mice has been mostly undertaken using a few classical animal models such as the strychnine induced convulsions and MES induced convulsions. Studies have proved that the agents which increase the brain GABA content and administration of centrally active GABA mimetic agents have been used as an effective therapeutic approach for treatment of epilepsy [12]. Currently available Antiepileptic drugs are able to efficiently control epileptic seizures in about 50 % of the patients. Another 25 % may show improvements were as the remaining dose may not benefit significantly instead it affects metabolism of other drugs. Furthermore, undesirable side effects from the drugs used to clinically often render treatment difficult so that a demand for new types of anticonvulsants exists. One of the approaches to search for new antiepileptic drugs is the investigation of synthetic compounds, which may belong to new structural classes and shows the desirable effects with more beneficial effects compared to the existing drugs [13].

These results provoke the interest in searching the novel derivatives from the synthetic origin because the results are the strong evidence, and probably there is a need to study whether the activity is due to particular mechanism of action perfectly, but as per the other moieties concerned like chalcones, pyrazoles and some other molecules FBTDs shown equal and even more potency which can be

identical to suximides and even some of the hydantoins, which has to be confirmed with more accurate *in vivo* models.

CONCLUSION

The Present Investigation revealed that the FBTDs exhibit antiepileptic activity. The antiepileptic action of FBTDs is better against strychnine induced seizures than MES seizures**.** P-2, P-6 and P-9 were shown significant antiepileptic activity against both MES and strychnine induced models.

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CONFLICT OF INTERESTS

Declared None

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