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ARTICLE

# SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF SUBSTITUTED 1,3,4-THIADIAZOLE DERIVATIVES AS ANTICONVULSANT AGENTS

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**Abstract:**

Epilepsy is considered as a brain disorder which involves repeated and spontaneous seizures. Seizures (convulsions) are defined as episodes of disturbed brain functions causing changes in attention or behavior. They are caused by abnormally excited electrical signals in the brain. Comprehensive literature assessment revealed that amongst the compounds studied for anticonvulsant activity; 1,3,4-thiadiazole nucleus showed potent anticonvulsant activity. Acetazolamide and methazolamide are the examples of 2,5-disubstituted-1,3,4- thiadiazole analogues. Hydrazine hydrate and isothiocyanate are used for formation of intermediate and reacted further with substituted aromatic aldehydes in the presence of thiourea to give final derivatives, substituted 1,3,4-thiadiazole. This title compound in step-1 was prepared by stirring of hydrazine hydrate with isothiocyanate whereas in step-2, substituted benzaldehyde was used in presence of thiourea. All synthesized compounds were characterized by physical and spectral characteristics. Structure elucidation of the synthesized compounds was carried out by spectral analysis, FTIR and Mass analysis. PTZ model was used to determine anticonvulsant activity of the final synthesized compounds using Carbamazepine as a standard drug. All synthesized compounds of showed no sedation side effect as compared to reference standard (carbamazepine). The present study indicated that 4-fluoro substituted compound **(6b)** showed significant protection against pentylenetetrazole induced convulsions as well as mortality within 24 h in mice. It also decreased number of

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convulsions (P<0.01) and increased onset time for clonic convulsion (P<0.05) which was statistically significant in comparison to control. Study could further be investigated to design & identify lead compound.

**Keyword:** Anticonvulsant agents, Carbamazepine, Convulsion, Epilepsy, Thiadiazole.

## Introduction

Epileptic seizures are responsible to cause brief injury of consciousness which leaves any individual at risk of injuring his/her own body and often interfering with day to day works, like family life, education, employment, etc. Available therapy for epileptic seizures and its consequences is symptomatic only as available drugs only inhibit seizures, but not effective as prophylaxis and not able to cure it completely. Major problem with epilepsy is compliance with medication and the reason behind this is need for long-term therapy without side effect [1].

One of the most common neurological disorder found in humans is epilepsy which affects around 2% of the global population. As per World Health Organization (WHO) data, 50 per 100 000 of the general population i.e. around 50 million people worldwide suffer from epileptic disorder. In United States of America, around 0.18 million new cases of epilepsy are observed every year. Around 2.5 million patients experienced active epileptic episodes in recent 5 years. Overall, around 1% of child populations and around 0.5% of adults have an experience of recurrent seizures. Approximately 3% of the population experienced at least one seizure in lifetime. Lifelong medication is must for most patients. Apart from this, vagal nerve stimulation and surgery at defined respectable seizure foci are alternate options for treatment of epilepsy.

Due to numerous economic and social issues with individuals having epileptic episode, patient gave little attention to disease as well as to treatment and makes quality of life poor. If these epileptic episodes become uncontrolled, then it results in substantial injury, mortality and economic burden to the patient. Healthcare industries costs at approximately $12.5 billion annually in USA [2]. Major causes of epilepsy includes; a brain injury (e.g. accident) infection or illness which affected development of brain of fetus during pregnancy; lack of oxygen during childbirth; encephalitis, meningitis or other infections affecting brain; brain tumours and lead or alcohol poisoning, etc. [3]

A seizure is considered as a paroxysmal event happened to human due to abnormal, hyper or excessive synchronous discharge from central nervous system (CNS) neurons. Based upon distribution of discharges, this abnormal CNS activity can lead from dramatic convulsive activity to empirical phenomena not readily noticeable by spectator. Occasionally fit is considered as epileptic seizure and is

defined as “a transient symptom of abnormal excessive or synchronous neuronal activity in the brain”. The superficial effect can be a rough movement (tonic-clonic seizure) or a brief loss of awareness. It marked the alteration of mental state, tonic or clonic actions, seizures, and various other cognitive signs. Sometimes, it is not accompanied by convulsions, but the person simply lost control of his/her body and collapse to ground. Medically, a condition of recurring, unprovoked seizures is termed as epilepsy, but seizures can arise in people who do not have epilepsy. Epileptic seizures are classified as, (i) partial seizures; (ii) primarily generalized seizures and (iii) unclassified seizures. [4-9]

Contemporary treatment of seizures was started in 1850 with the introduction of bromides. In 1910, phenobarbital was found to have anti-seizure activity and became the drug of choice. In 1940, phenytoin (PHT) showed effect in epilepsy and since then, it was being used as major first-line antiepileptic drug (AED) in the treatment of partial and secondarily generalized seizures. Carbamazepine (CBZ) was initially approved for treatment of trigeminal neuralgia in1968 and then in 1974, it was approved for partial seizures. Ethosuximide was used as drug of choice in treatment of absence seizures (without generalized tonic-clonic seizures) since 1958. Valproate was used as important drug which was licensed in Europe in 1960 and then in USA in 1978. Now, it is widely used throughout the world. It became the drug of choice in primary generalized epilepsies and in the mid-1990s was approved for treatment of partial seizures. Even though, availability of many drugs for epilepsy and for seizures, mortality rates remains high and thus there is need to develop novel compounds which are useful, not only in reducing seizures, but also reduce mortality rate. Thus, efforts were given to synthesize and evaluate novel thiadiazole derivatives as anticonvulsant agents.

## Results and Discussion

### Chemistry

Anticonvulsant agents, currently in use for treatment of epilepsy, have notable adverse effects and are inefficient in some types of seizures. Thus, there is clear need for safer and more effective antiepileptic drugs. Therefore, the development of new antiepileptic drug is major challenge for scientists working in the field of drug discovery. Acetazolamide and methazolamide are the examples of 2,5-disubstituted-1,3,4- thiadiazole analogs. Various structures were studied for anticonvulsant activity and it was decided to synthesize novel substituted 1,3,4-thiadiazole derivatives and proved them as effective with anticonvulsant activity.

In this study, sixteen new 1,3,4-thiadiazole derivatives was synthesized and evaluated for anticonvulsant activity against MES test. This title compounds were prepared from hydrazine hydrate and phenyl isothiocyanate or furan-2-carbonyl

isothiocyanate in presence of different thiourea and different aldehydes. In first step, isothiocyanate and hydrazine hydrate were reacted in presence of acetonitrile as a solvent to synthesize carbothiamide. In the second step, carbothiamide reacted with various substituted benzaldehyde and urea/thiourea to synthesize final derivatives, substituted 1,3,4-thiadiazole derivatives.

Title compounds showed N–H and C-H stretching bands in the region of 3300-3350 and 3100-3150 $cm^{-1}$, respectively, which indicated presence of secondary amine. However IR spectra do not give complete idea about ring formation. In both series, title compound showed other bands like C-S stretching in the region of 691 $cm^{-1}$, C=N stretching of thiadiazole in the 1500-1600 $cm^{-1}$ region, C-N stretching at 1350-1300 $cm^{-1}$ and aromatic C=C stretching band near 1600 $cm^{-1}$ and 1450 $cm^{-1}$ with overtone in the region of 1700-2000 $cm^{-1}$. Due to fermi resonance, overtone of N-H bending and C-N stretching, weak band was observed in the region of 3100 $cm^{-1}$. Aliphatic C=C band observed only in case of second series, in the region of 1600-1500 $cm^{-1}$ which indicates the presence of styryl moiety. The structures of final synthesized derivatives were verified by mass spectral analysis, where molecular ion peaks (m/z value) were in complete arrangement with the calculated molecular weight for all compounds. The compounds with presence of halogen showed prominent peaks.

**Anticonvulsant Activity**

The anticonvulsant activity of the title compounds was evaluated by using Pentylenetetrazole (PTZ) induced convulsions model (60mg/kg) in mice and carbamazepine was used as a reference standard (100 mg/kg). From the first series of compounds, **6b, 6f, 6g, 6k** and **6m** showed 100% protection against 1hr and 24 hours mortality, which were statistically significant ($P<0.05$) in comparison to control. It also decreased number of clonic convulsions ($P<0.05$) and increased onset time for clonic convulsions ($P<0.01$), which was statistically significant in comparison to control. Similarly, in second series of compounds, **10a** showed 66.66% protection against 1 hour mortality and 50% protection against 24 hours mortality as well as decreased number of clonic convulsions and increased onset for clonic convulsion which, however was not-significant in comparison to control. Data are shown in Table 1.

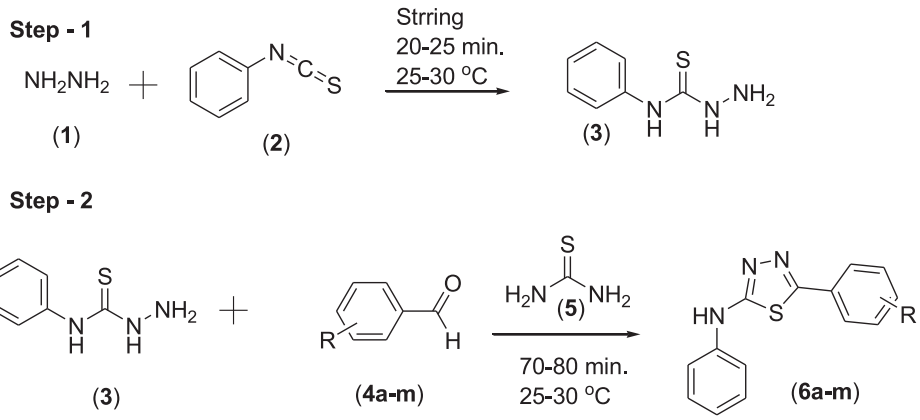
**Table 1. Effect of synthesized compounds on PTZ – Induced Seizure in Mice**

| Compounds (Dose - 100mg/kg) (Volume - 10ml/kg) | Clonic convulsions (Mean ± S.E.M) | | % of protection in 1 hr (mortality of animals N/F) | % of protection in 24 hrs (mortality of animals N/F) |
|---|---|---|---|---|
| | Onset of Clonic Convulsion* | No. of Clonic Convulsions* (in 30 min) | | |
| Vehicle | 10.00 ± 0.89 | 3.00 ± 0.25 | 2/6 = 0.33% | 1/6 = 16.66% |
| Carbamazepine | 25.50 ± 1.05 | 1.16 ± 0.16 | 6/6 = 100% | 6/6 = 100% |
| **6a** | 20.35 ± 1.57 | 1.66 ± 0.33 | 4/6 = 66.66% | 6/6 = 100% |
| **6b** | 20.32 ± 1.51 | 1.16 ± 0.33 | 6/6 = 100% | 6/6 = 100% |
| **6c** | 17.46 ± 0.99 | 2.00 ± 0.36 | 4/6 = 66.66% | 3/6 = 50% |
| **6d** | 20.71 ± 1.46 | 2.83 ± 0.30 | 4/6 = 66.66% | 3/6 = 50% |
| **6e** | 21.25 ± 1.15 | 2.00 ± 0.25 | 6/6 = 100% | 5/6 = 83.33% |
| **6f** | 17.61 ± 0.69 | 1.33 ± 0.21 | 6/6 = 100% | 6/6 = 100% |
| **6g** | 20.15 ± 0.92 | 1.16 ± 0.16 | 6/6 = 100% | 6/6 = 100% |
| **6h** | 16.97 ± 1.39 | 2.83 ± 0.47 | 3/6 = 50% | 3/6 = 50% |
| **6i** | 19.07 ± 1.07 | 1.66 ± 0.33 | 5/6 = 83.33% | 4/6 = 66.66% |
| **6j** | 16.35 ± 0.96 | 2.16 ± 0.47 | 5/6 = 83.33% | 3/6 = 50% |
| **6k** | 13.84 ± 1.22 | 1.66 ± 0.33 | 6/6 = 100% | 6/6 = 100% |
| **6l** | 17.18 ± 1.23 | 1.33 ± 0.21 | 4/6 = 66.66% | 6/6 = 100% |
| **6m** | 18.35 ± 1.13 | 1.50 ± 0.22 | 6/6 = 100% | 6/6 = 100% |
| **10a** | 8.69 ± 1.12 | 1.50 ± 0.22 | 4/6 = 66.66% | 3/6 = 50% |
| **10b** | 10.40 ± 0.99 | 1.66 ± 0.33 | 6/6 = 100% | 4/6 = 66.66% |
| **10c** | 13.91 ± 0.72 | 1.16 ± 0.16 | 5/6 = 83.33% | 4/6 = 66.66% |

*** No of animals - 6**

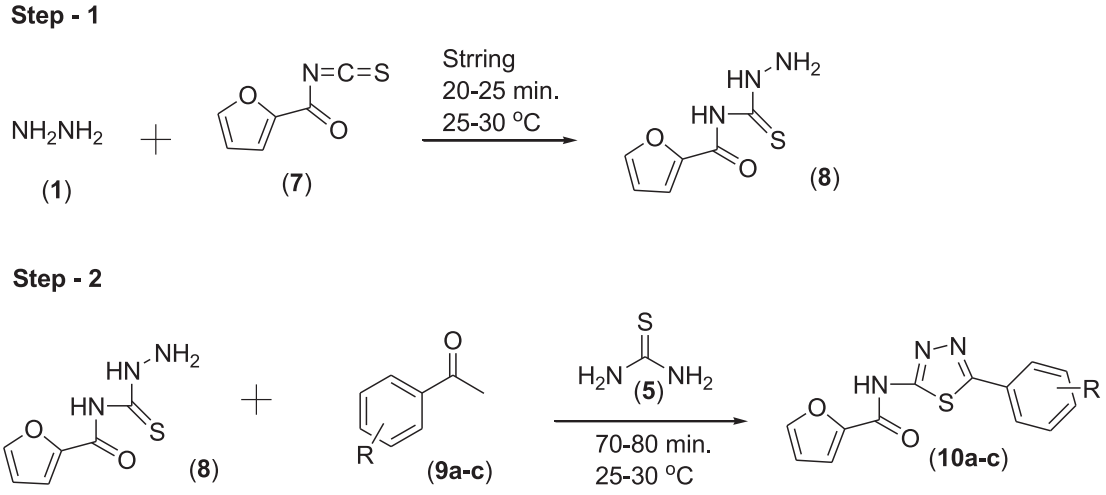
## Experimental Section

### General procedure for synthesis of 1,3,4-thiadiazol derivatives:




**Scheme 1.** Synthesis of 5-substituted-N-phenyl-1,3,4-thiadiazol-2-amine derivatives

To a round bottom flask, hydrazine hydrate **(1)**, phenyl isothiocyanate **(2)** and acetonitrile as a solvent were mixed properly and was stirred for 20-25 min at 25-30 °C to form 4-phenylthiosemicarbazide **(3)**. In this mixture, substituted benzaldehyde **(4a-m)** and thiourea **(5)** were added. The reaction mixture is then stirred at 25-30°C for 70-80 min. After completion of reaction, the resulted precipitates of 5-substituted-N-phenyl-1,3,4-thiadiazol-2-amine derivatives **(6a-m)** were vacuum filtered. The precipitate was further purified with methanol and results were reported. [10-13]

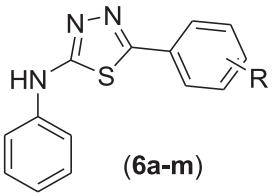



**Scheme 2.** Synthesis of N-(5-substituted-1,3,4-thiadiazol-2-yl)furan-2-carboxamide derivatives

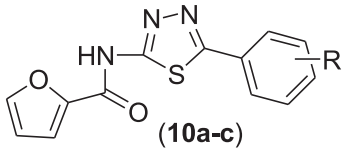
To a round bottom flask, hydrazine hydrate **(1)**, furan-2-carbonyl isothiocyanate **(7)** and acetonitrile as a solvent were mixed properly and was stirred for 20-25 min at 25-30 °C to form N-(hydrazinecarbonothioyl) furan-2-carboxamide **(8)**. In this mixture, substituted benzaldehyde **(9a-c)** and thiourea **(5)** were added. The reaction mixture is then stirred at 25-30 °C for 70-80 min. After completion of reaction, the resulted precipitates of N-(5-substituted-1,3,4-thiadiazol-2-yl)furan-2-carboxamide derivatives **(10a-c)** were vacuum filtered. The precipitate was further purified with methanol and results were reported. [10-13]

All synthesized compounds were characterized by physical characteristics like melting point and Rf. All synthesized compounds were characterized by FT-IR. Few compounds were also characterized by Mass spectral analysis.

**Table 2. Physical characteristics of synthesized compounds.**




(6a-m)




(10a-c)

| Comp. No. | Molecular Formula | Substitution | % Yield | $R_f$ * | M.P. (in °C) |
|---|---|---|---|---|---|
| **6a** | $C_{14}H_{10}N_3SCl$ | 4-chlorophenyl | 61.02 | 0.78 | 176-178 |
| **6b** | $C_{14}H_{10}N_3SF$ | 4-fluorophenyl | 57.04 | 0.64 | 158-160 |
| **6c** | $C_{14}H_{11}ON_3S$ | 3-hydroxyphenyl | 70.53 | 0.77 | 169-172 |
| **6d** | $C_{16}H_{15}O_2N_3S$ | 3,4-dimethoxy phenyl | 64.66 | 0.69 | 186-188 |
| **6e** | $C_{14}H_{10}N_3SBr$ | 3-bromophenyl | 40.22 | 0.79 | 178-180 |
| **6f** | $C_{14}H_{10}O_2N_4S$ | 2-nitrophenyl | 55.33 | 0.81 | 158-160 |
| **6g** | $C_{14}H_{10}N_3SCl$ | 2-chlorophenyl | 58.71 | 0.71 | 113-115 |
| **6h** | $C_{15}H_{13}ON_3S$ | 4-methoxyphenyl | 42.81 | 0.75 | 170-171 |
| **6i** | $C_{14}H_{10}O_2N_4S$ | 3-nitrophenyl | 30.31 | 0.70 | 166-168 |

| | | | | | |
|---|---|---|---|---|---|
| **6j** | $C_{16}H_{16}N_4S$ | 4-dimethylamino phenyl | 52.62 | 0.65 | 164-166 |
| **6k** | $C_{14}H_{11}ON_3S$ | 4-hydroxyphenyl | 47.86 | 0.80 | 170-172 |
| **6l** | $C_{19}H_{14}N_4S$ | Nicotinaldehyde | 74.50 | 0.83 | 170-172 |
| **6m** | $C_{18}H_{13}ON_3S$ | 4-furan | 66.04 | 0.69 | 170-172 |
| **10a** | $C_{13}H_8O_2N_3SF$ | 4-fluorophenyl | 58.91 | 0.79 | 158-160 |
| **10b** | $C_{15}H_{13}O_4N_3S$ | 3,4-dimethoxy phenyl | 51.43 | 0.84 | 181-183 |
| **10c** | $C_{13}H_8O_2N_3SCl$ | 4-chlorophenyl | 48.94 | 0.77 | 169-170 |

* n-Hexane : Ethyl acetate :: 4:1

**Table 3. Spectral characteristics of synthesized compounds.**

| Comp. No. | Substitution | FT-IR ($cm^{-1}$) | Mass |
|---|---|---|---|
| **6a** | 4-chlorophenyl | 3309, 3137, 2550, 1670, 1500, 1083 | 288 ($M^+ + 1$) |
| **6b** | 4-fluorophenyl | 3330, 3145, 2510, 1690, 1480, 1089 | 273 ($M^+ + 1$) |
| **6c** | 3-hydroxyphenyl | 3100, 3145, 2530, 1680, 1520, 1090 | 272 ($M^+ + 2$) |
| **6d** | 3,4-dimethoxy phenyl | 3310, 3158, 2490, 1695, 1495, 1097 | 314 ($M^+$) |
| **6e** | 3-bromophenyl | 3280, 3133, 2525, 1650, 1470, 1098 | 333 ($M^+ + 1$) |
| **6f** | 2-nitrophenyl | 3230, 3110, 2470, 1650, 1474, 1091 | 301 ($M^+ + 2$) |
| **6g** | 2-chlorophenyl | 3309, 3137, 2550, 1670, 1500, 1083 | 289 ($M^+ + 2$) |
| **6h** | 4-methoxyphenyl | 3290, 3100, 2515, 1678, 1514, 1075 | 284 ($M^+ + 1$) |
| **6i** | 3-nitrophenyl | 3230, 3110, 2470, 1650, 1474, 1091 | 299 ($M^+$) |
| **6j** | 4-dimethylamino phenyl | 3330, 3210, 2570, 1490, 1091 | 298 ($M^+ + 1$) |
| **6k** | 4-hydroxyphenyl | 3100, 3145, 2530, 1680, 1520, 1090 | 271 ($M^+ + 1$) |

| | | | |
|---|---|---|---|
| **6l** | Nicotinaldehyde | 3225, 3090, 2512 1650, 1515, 1070 | 333 ($M^+$ + 2) |
| **6m** | 4-furan | 3269, 3110, 2550, 1690, 1550, 1089 | 318 ($M^+$ + 1) |
| **10a** | 4-Fluorophenyl | 3310, 3108, 2495, 1705, 1510, 1090 | 257 ($M^+$ + 1) |
| **10b** | 3,4-dimethoxy phenyl | 3290, 3150, 2480, 1653, 1515, 1100 | 300 ($M^+$ + 1) |
| **10c** | 4-chlorophenyl | 3230, 3105, 2525, 1690, 1510, 1110 | 274 ($M^+$ + 2) |

**Pharmacological Evaluation**

The pharmacological screening protocol was approved by the Institutional Animal Ethics Committee.

**Pentylenetetrazole (Metrazol) induced convulsions**

The assay is used primarily to evaluate antiepileptic drugs.

***Procedure***

Mice of either sex with a body weight between 18 and 22 g were used. The test compounds or the reference drug were injected s.c. or i.p. or given orally to groups of 6 mice. Another group of 6 mice served as control. Fifteen min after sc.-injection or 30 min after i.p.-injection or 60 min after oral administration, 60 mg/kg MTZ (Metrazol) was injected, subcutaneously. Each animal was placed into an individual plastic cage for observation lasting for 1 h. Seizures and tonic-clonic convulsions were recorded. It is noted that at least 80% of the animals in the control group showed convulsions [14].

**Evaluation**

The number of protected animals in the treated groups is calculated as percentage of affected animals in the control group. Furthermore, the time interval between MTZ-injection and occurrence of seizures was measured. The delay of onset was calculated in comparison with the control group.

**Maximal electroshock seizure (MES) in mice**

***Purpose and Rationale***

The electroshock assay in mice is used primarily as an indication for compounds which are effective in grand mal epilepsy. Tonic hind limb extensions are evoked by electric stimuli which are suppressed by anti-epileptics but also by other centrally active drugs.

***Procedure***

Groups of 6 male NMRI mice (20–25 g) were used. The test was started 30 min after i.p. injection or 60 min after oral treatment with the test compound or the vehicle. An apparatus with corneal or ear electrodes was used to deliver the stimuli. The intensity of stimulus 12 mA, 50 Hz for 0.2 s was used for screening.

**Evaluation**

The animals were observed closely for 2 min. Disappearance of the hind leg extensor tonic convulsion were used as positive criterion. Percent of inhibition of seizures relative to controls were calculated.

**Measurement of the Activity**

Carbamazepine (100 mg/kg i.p.) and the dose of Pentylenetetrazole which induced convulsions in 97% of animals (CD97: 60 mg/kg s.c mice) were used. A suspension of 5% sodium carboxyl methyl cellulose (CMC) at a dose of 10 ml/kg was used as control. All synthesized derivatives were administered as a suspension of 5% sodium CMC. Swiss albino mice of either sex (5-6-weeks-old) weighing 30-35g were housed under standard laboratory conditions (relative humidity 55-56 %, room temperature 23.0 ± 2.0 °C and 12 h light:dark cycle).The animals were fed with standard diet and water ad libitum. They were fasted overnight prior to experiment. [15]

The mice were divided into groups of 6 animals each. One group was served as control which received 5% sodium CMC (10 ml/kg i.p.) 30 min before administration of PTZ (60 mg/kg s.c.). PTZ were administered by injecting into a loose fold of skin in the midline of the neck. Second group received carbamazepine (100 mg/kg i.p.) dissolved in a suspension of 5% sodium CMC as a standard reference drug. Remaining groups received test compounds, at a dose of 100 mg/kg i.p. dissolved in suspension of 5% sodium CMC respectively 30 min before the administration of PTZ (60 mg/kg s.c.). Each animal was placed into an individual plastic cage for observation lasting 0.5 h. The time taken before the onset of clonic convulsions, the duration of clonic convulsions and percentage of mortality protection were recorded

**Conclusion**

Epilepsy is a diseased condition characterized by recurrent seizures of cerebral origin. It is associated with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness. Currently used anticonvulsant agents for treatment of epilepsy have certain disadvantages and a clear need for safer and more effective antiepileptic drugs is of urgent need. Therefore, the development of new antiepileptic drugs with greater effects is an important challenge for scientists working in the field of drug discovery. In present work, for getting synergistic response of mentioned moiety, series of potential anticonvulsant agents belonging to substituted 1,3,4-thiadiazole were synthesized. Reaction monitoring was done by TLC, using precoated Sillica gel G plates. The synthesized compounds were characterized for physical constants like melting point. Structure elucidation of synthesized compounds was done by FTIR and Mass spectroscopy. The anticonvulsant activity of the final derivatives was evaluated by using PTZ model (60mg/kg) and carbamazepine taking as a reference standard (100 g/kg). All synthesized compounds showed no sedation side effect

as compared to carbamazepine. From all synthesized compounds, few compounds showed significant protection against pentylenetetrazole induced convulsions as well as mortality within 24 h in mice and also decreased number of clonic convulsions ($P<0.01$) and increased onset time for clonic convulsion ($P<0.05$) which was statistically significant in comparison to control. Among these, few compounds gave anticonvulsant activity comparable to the standard carbamazepine and emerged as a lead compounds in the series when they were subjected to preliminary anticonvulsant screenings. They also showed 100% protection against mortality. These can be regarded as strong candidates for future investigations.

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