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Synthesis, Characterization And Anticonvulsant Activity Of Some Novel 1,2,4-Triazoles

(ANTICONVULSANT ACTIVITY OF SOME NOVEL 1,2,4-TRIAZOLES)

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Abstract: The object of the current paper is to synthesize and characterize of some novel 1,2,4-triazole derivatives for anticonvulsant activity. Various 1,2,4-triazole derivatives have been reported to possess diverse types of biological properties such as antibacterial, antifungal, anti-inflammatory, antihypertensive, antiviral, antileishmanial, and antimigraine activities. The final compounds of amino derivative of 5-aryl-4-(chloroacetylamino)-3-mercapto-1,2,4-triazole was synthesized and characterized by FT-IR, and NMR. The reaction monitored by TLC method. Total 10 compounds were synthesized and evaluated for anticonvulsant activity. Anticonvulsant screening of synthesized compounds AU1, AU5 and AU9 showed seizure protection at both 100 and 150 mg/kg dose after 30 min and 4 h showing quick onset of action. The synthesized compound AU2, AU6 and AU10 were somewhat less active than AU1, AU5 and AU9 reveals that their high concentration is required to cross blood brain barrier. Remaining compound (AU3, AU7, AU11, AU4, AU8, AU12) was inactive. Electron donating group of benzene ring exhibited better anticonvulsant activity as compared to unsubstitution. Study revealed that electron donating group exhibiting better activity.

Index Terms **– 1,2,4-triazole, anticonvulsant, TLC, FT-IR, NMR**

INTRODUCTION

Epilepsy is one of the most notorious disorders of brain affecting about 50 million people world-wide. It is a group of chronic and progressive CNS disorders characterized by the periodic and unpredictable occurrence of epileptic seizures that are cause by abnormal discharge of cerebral neurons **(Kucukguzel I et al., 2014).** It is not a disease but symptoms of different cerebral disorders. This symptom is characterized by paroxysmal excessive and hypersynchronus discharge of large number of neurons (in short paroxysmal cerebral dysrhythmia). Its manifestations are brief episode of seizure or disturbance in consciousness with or without characteristic body movement (convulsion). Recently committee of (classification and terminology of international league against epilepsy) gave following proposal based on EEG and Clinical Studies **(Almasirad A et al., 2004)**. Current drugs used for epilepsy :Barbiturates, hydantoins, iminostilbenes having common structural features. Due to this common structure have a common mechanism and side effects like: sedation, depression, drowsiness and dizziness. To elevate these certain recent developments are: AWD, harkoserides, pregabatrins, and various things to come are (Aryloxy) Aryl semicarbazones, AMP 397-A, V-594494-A and PD-151307. Traizoles compound have shown wide range of biological activity i.e., antibacterial, anthelmintic, antifungal, antifungal. Triazoles act by inhibiting the fungal cytochrome P-450 enzyme lanosterol 14-demethylase and thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14-a-methylsterols. These methylsterols may disrupt the close packing of acyl chains of phospholipids, impairing the functions of certain membrane-bound enzyme systems such as ATPase and enzymes of the electron transport system and thus inhibiting growth of the fungi. The lower toxicity of triazoles compared to imidazole has been correlated with their lower affinity for mammalian Cytochrome P-450 and lesser propensity to inhibit mammalian sterol synthesis **(Holla BS et al., 1994).** However, because they are active against certain bacteria as well (which do not have ergosterol) other mechanism also appear to be involved. In current paper differet amine substituted derivatives of 1,2,4-triazole have been synthesized, Characterized and evaluated for anticonvulsant activity.

NEED OF THE STUDY

Epilepsy is one of the common diseases seriously threatening life and health of human. More than 50 million people are suffering from this condition and anticonvulsant agents are the main treatment. However, side effects and intolerance, and a lack of efficacy limit the application of the current anticonvulsant agents. Epilepsy is a chronic disorder of brain whose treatment consists of controlling seizures with antiepileptic drugs that very often related with side-effects which in rare circumstances can be potentially life-threatening. The search for new anticonvulsant agents with higher efficacy and lower toxicity continues to be the focus and task in medicinal chemistry. Numbers of triazole derivatives as clinical drugs or candidates have been frequently employed for the treatment of various types of diseases, which have proved the importance of this heterocyclic nucleus in drug design and discovery.

The search for new anticonvulsant agent with more selectivity and lower toxicity continues to be an area of rigorous investigation in medicinal chemistry. The literature survey revealed that 1,2,4-triazole nucleus is present in various chemotherapeutic agents such as fluconazole, terconazole, itraconazole, trazodone etc. Various 1,2,4-triazole derivatives have been reported to possess diverse types of biological properties such as antibacterial, antifungal, anti-inflammatory, antihypertensive, antiviral, antileishmanial, and antimigraine activities. The therapeutic importance of this nucleus prompted us to synthesize new compounds in which substituents could be arranged in a pharmacophoric pattern to display high order of pharmacological activities. Triazolam and Alprazolam are established drugs used in epilepsy which have triazole moiety. The potency and broad spectrum of the pharmacological response of triazole moiety as anticonvulsant agent have attracted the attention of medicinal chemists to explore this framework for its potential. Differet amine substituted derivatives of 1,2,4-triazole have been synthesized, Characterized and evaluated for anticonvulsant activity.

MATERIAL AND METHOD

Reagents and Solvents

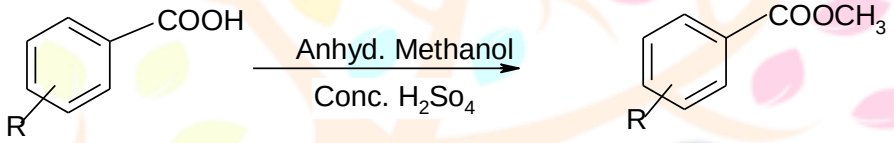
The chemicals used for the experimental work were of synthetic grade (E.Merck India Ltd., CDH etc). These compounds were purified and dried before their use.

Synthesis :

Synthesis of compounds were carried out as per following scheme:

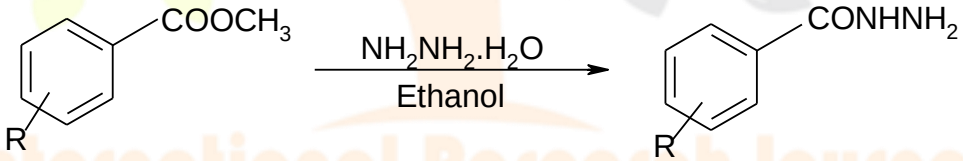
(Step-I) : Synthesis of esters of aromatic acid

A mixture of substituted benzoic acid (0.3 mol), 130 mL of absolute alcohol and 3.3 mL of conc. H_2SO_4 was refluxed for 2 h on water bath. After completion of reaction, excess of ethanol was distilled off and content was transferred into separating funnel containing 310 mL distilled water. Carbon-tetrachloride (20 mL) was added, aqueous layer and ester layer were separated. Ester layer (lower layer) was taken in another separating funnel and shaked it with a strong solution of sodium bicarbonate until all free acid was removed and no further evolution of carbon dioxide occur. Washed once with water and dried by pouring into a small conical flask containing 7.5g magnesium sulphate. Cork the flask, shaked for 2 minutes then carbon tetrachloride was distilled off under reduced pressure. The resulting colourless liquid was collected and the completion of reaction was checked by TLC using hexane and ethyl acetate (6:4) and iodine vapour as a detecting reagent **(Ampati S et al., 2010)**.



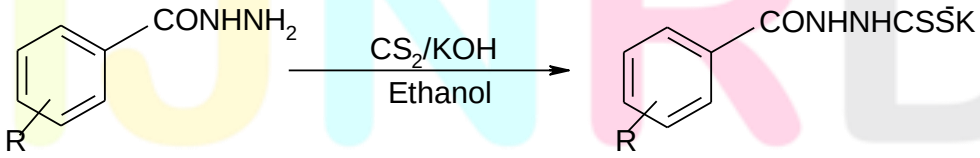
Step-II): Synthesis of hydrazide of synthesized ester

Produced aromatic esters (0.1 mol) and 80 % hydrazine hydrate (0.1 mol) was refluxed on a water bath for 15 min. Enough absolute ethanol was added to obtain a clear solution. Again contents were refluxed for 2 h. Excess alcohol was evaporated and solution was cool down**.** The solid obtained was separated and recrystallised from ethanol to get the needle shaped crystals **(Chen et al., 2007)**.



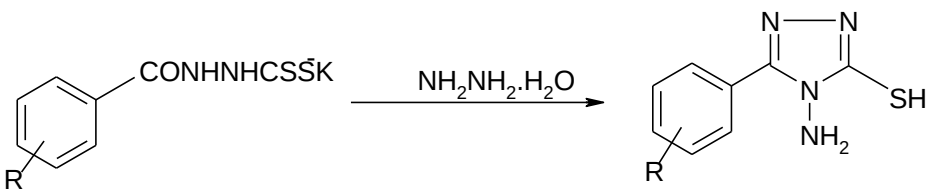
(Step-III) : Synthesis of potassium dithiocarbazinate

Substituted aromatic hydrazides (0.02 mol), KOH (0.012 mol) and CS_2 (0.015 mol) in absolute ethanol (350 mL) were stirred for 10 h. After the completion of reaction ether (200 mL) was added. The obtained precipitate was filtered, washed and dried. The synthesized dithiocarbazinate was used for the next step without further purification **(Gibson A et al., 2009)**..



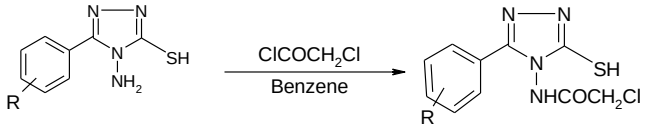
(Step-IV) : Synthesis of 5-aryl-4-amino-3-mercapto-1,2,4-triazole

Substituted produced dithocarbazinate (0.1 mol), hydrazine hydrate (0.3 mol) and water (30 mL) was refluxed for 3 h, H_2S was evolved during the reaction and clear solution resulted, enough cold water was added and cooled to 5^0c. Acidified the cooled solution with dil. HCl. Obtained precipitate was filtered, washed and recrystallized from 95% ethanol **(Guzeldemirci NU et al., 2010)**.

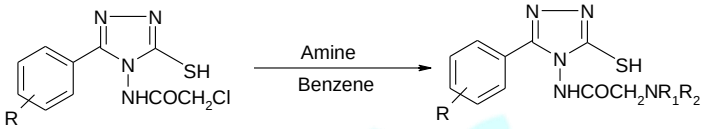


(Step-V): Synthesis of 5-aryl-4-(chloroacetylamino)-3-mercapto-1,2,4- triazole:

In a two necked flask fitted with reflux condenser containing 100 mL benzene and obtained compound and separating funnel contained chloro acetyl chloride in 30 mL benzene. The mixture was refluxed and chloro acetyl chloride was added in small portions. After addition of chloro acetyl chloride, solution was again refluxed for 5-6 h, cooled and contents were poured on crushed ice. The obtained precipitate was filtered, washed and recrystallized from absolute ethanol **(Husain A et al., 2011).**



(Step-VI) : Synthesis of amino derivative of 5-aryl-4-(chloroacetylamino)-3-mercapto-1,2,4-triazole:
Synthesized substituted 5-aryl-4-(chloroacetylamino)-3-mercapto-1,2,4- triazole (0.03 mol), respective amines (0.03 mol) and 75 mL benzene was taken in round bottom flask. The contents were refluxed for 5-6 h and cooled. Filtered the precipitate and washed with distilled water several times to remove traces of hydrochloride. Product obtained was recrystallized from appropriate solvent **(Kaushik D et al., 2010)**.



Anticonvulsant Activity
Anticonvulsant activity was determined by Maximal Electro Shock (MES) induced method. All experiments were performed according to permission granted by institutional animal ethical committee (Reg. No. 379/01/ab/CPCSEA/13). Albino rats of either sex weighing 150-200 g were divided into different group for different synthesized compound, control and standard **(Korczyn AD et al., 2015)** The animals of all group were treated with 100 mg/kg, 150mg/kg in suitable solvent by i.p. route. except control group which received only solvent Standard group received (Phenytoin) 25 mg/kg body weight by i.p. route. The effect of drug was observed after 30 min and 4h of the drug treatment **(Prasit 2009)**. Seizure was produced in rats by 'Techno' convulsometer by delivering a current of 150 mA through the corneal electrodes for a period of 0.2 seconds. The animal was placed on the table and its head was fixed. The electrodes were dipped in normal saline and placed gently on the cornea. The shock was delivered by putting on the switch of the instrument **(Mavrova AT et al., 2009)**. The animals were observed for the following parameters includes tonic phases, Clonic phase, Stupor and Recovery/Death. Time for each phase was noted by stop watch. Drug treated animals, were observed for presence or absence of extensor and flexor component of tonic phase during seizures.

Results and Discussion

Synthesis
Total 10 compounds have been synthesized and Characterized by the IR and NMR.
Compound 1: AU-A
IR (cm^{-1}): 3080.8 (Aromatic C-H str.); 1685.0 (C=O Str.); 1580.0 (C=C Str.); 1516.9 (C=N Str.); 1226.7 (C-O Str.); 920.9 (O-H bending); 770.8 (C-H out of plane); **^{1}H NMR** (ppm): 12.1 (s, 1H, -COOH); 7.4-8.0 (m, 5H, -C_6H_5)
Compound 2: AU-B
IR (cm^{-1}): 3070.0 (Aromatic C-H str.); 2962.7 (C-H str.); 1720.0 (C=O Str.); 1594.0 (C=C Str.); 1481.1 (C-H bending); 1216.7 (C-O stretching); 862.0, 770.0 (C-H out of plane bending)**;** 1H NMR (ppm): 7.3-8.0 (m, 5H, -C6H5); 3.9 (s, 3H, -CH3)
Compound 3: AU-C
IR (cm^{-1})**:** 3319.1, 3263.2 (N-H str.); 3046.2 (Aromatic C-H Str.); 1654.5 (C=O Str.); 1579.9 (N-H bending); 1496.2 (C-N Str.); 786.7 (C-H out of plane bending); 1H NMR (ppm): 8.0 (t, 2H, -NH); 7.2-7.8 (m, 5H, -C6H5); 2.8 (d, 1H, -NH)

Compound 4: AU-D
IR (cm^{-1})**:** 3263.2 (N-H Str.); 3046.2 (Aromatic C-H Str.)etching; 1674.5 (C=O Str.); 1579.9 (N-H Str.); 1164.9 (C-N Str.); 1244.9 (C=S Str.); 856.7 (C-H out of plane bending); 661.5 (C-S stretch); 1H NMR (ppm): 8.0 (d, 1H, -NH); 7.4-7.9 (m, 5H, -C_6H_5); 2.0 (d, 1H, -NH)

Compound 5: AU-E
IR (cm^{-1})**:** 3456.5, 3406.0 (N-H Stretching); 3116.0 (Aromatic C-H stretching); 2584.5 (S-H stretching); 1614.8 (C=N stretching); 1580.0 (C=C stretching); 1244.2 (C=S Stretching); 740.8 (C-H out of plane bending); 1H NMR (ppm): 7.2-7.6 (m, 5H, -C_6H_5); 3.0 (s, 1H, -SH); 2.0 (s, 2H, -NH_2)
Compound 6: AU-F
IR (cm^{-1}): 3309.5 (N-H stretching); 3094.5, 3006.9 (Aromatic C-H stretching); 2946.8 (C-H stretching of methylene group); 2564.5 (S-H stretching); 1663.1 (C=O stretching); 1573.1 (C=C stretching); 758.5 (C-Cl stretching); 698.0 (C-S stretching); 1H NMR (ppm): 8.0 (s, 1H, -NH); 7.2-7.5 (m, 5H, -C6H5) ; 4.3 (s, 2H, -CH2) ; 3.0; (s, 1H, -SH).

Compound 7: AU-G
IR (cm^{-1}): 3310 (N-H stretching); 3116.0 (Aromatic C-H stretching); 2962.6 (C-H stretching); 2858.7 (C-H Stretching); 2584.5 (S-H Stretching); 1660.6 (C=O stretching); 1614.8 (C=N stretching); 1580.0 (C=C stretching); 760.8 (C-H out of plane bending); 670.0 (C-S stretching). 1H NMR (ppm): 8.0 (s, 1H, -NH); 7.2-7.6 (m, 5H, -C6H5); 3.25 (s, 2H, -CH2); 3.1 (s, 1H, -SH); 2.3 (s, 6H, -CH3)
Compound 8: AU-H
IR (cm^{-1}): 3349.1 (N-H stretching); 3116.2 (Aromatic C-H stretching); 2968.0 (C-H stretching); 2848.9 (C-H stretching); 2556.4 (S-H stretching); 1664.0 (C=O stretching); 1579.9 (C=C stretching); 786.7 (C-H out of plane bending); 661.5 (C-S stretching); 1H NMR (ppm): 8.0 (s, 1H, -NH); 7.2-7.5 (m, 5H, -C_6H_5); 3.25 (s, 2H, -CH2); 3.1 (s, 1H, -SH); 2.5 (q, 3H, -CH_3); 1.2 (t, 2H, -CH2).

Compound 9: AU-I

IR (cm^{-1}): 3355.1 (N-H stretching); 3116.2 (Aromatic C-H stretching); 2968.0 (C-H stretching); 2848.9 (C-H stretching); 2556.4 (S-H stretching); 1662 (C=O stretching); 1579.9 (C=C stretching); 1416.1 (C=N stretching); 823.0 (C-H out of plane bending); 661.5, 623.1 C-S stretching. 1H NMR Spectral Analysis of AU-3 (ppm): 8.0 (s, 1H, -NH); 7.2-7.5 (m, 5H, -C_6H_5); 3.25 (s, 2H, -CH_2); 3.1 (s, 1H, -SH); 2.9 (t, 2H, -CH_2); 1.7 (m, 5H, -CH_2CH_3); 1.1 (t, 2H, -CH_2)

Compund 10: AU-J

IR (cm^{-1}): 3325.5 (N-H stretching; 3102.5 (Aromatic C-H stretching); 2580.1 (S-H stretching); 1662.7 (C=O stretching); 1575.6 (C=C stretching); 1429.3 (C=N stretching; 1365.5 (C-H bending); 921.6 (C-H bending(rocking); 819.1 (C-H out of plane bending); 630.1 (C-S stretching).

RESULT AND DISCUSSION

Table 5.1: Effect of Synthesized Compounds on Maximal Electro Shock Convulsion in albino rats (at 100mg/kg dose after 30 min)

Code No.	Time (sec) in various phase of convulsion				
	Flexion (mean±SE)	Extensor (mean±SE)	Clonic (mean±SE)	Stupor (mean±SE)	Recovery /Death
AU1	0.3±0.04	5.7±0.4	1.6±0.2	97±0.7	Recovery
AU2	1.2±0.25	6.7±0.47	2.8±0.2	102±0.47	Recovery
AU3	2.5±0.34	10.7±0.47	6.4±0.3	120±0.64	Recovery
AU4	3.7±0.47	11.9±0.4	6.1±0.3	125±0.6	Recovery
AU5	-	5.2±0.2	1.0±0.2	93±0.47	Recovery
AU6	1.2±0.3	6.4±0.7	2.7±0.2	98±0.6	Recovery
AU7	2.6.± 0.3	11.1±0.4	6.4±0.3	131±0.6	Recovery
AU8	3.6±0.3	13.2±0.3	6.8±0.4	128±0.6	Recovery
AU9	0.7±0.2	6.1±0.4	1.9±0.2	101±0.7	Recovery
AU10	1.4±0.2	6.8±0.2	3.0±0.2	108±0.7	Recovery
AU11	2.9± 0.2	12.6±0.4	5.9±0.4	123±0.5	Recovery
AU12	3.8±0.2	12.8±0.4	7.2±0.3	126±0.2	Recovery
C	4.0±0.3	13.8±0.5	7.8±0.3	133±0.4	Recovery
Sd	-	4±0.7	0.8±0.3	86±1.8	Recovery

* C: control * Sd: standard (phenytoin) * - : no activity

Table 5.2: Effect of Synthesized Compounds on Maximal Electro Shock Convulsion in albino rats (at 100mg/kg dose after 4 h)

Code No.	Time(sec) in various phase of convulsion				
	Flexion (mean±SE)	Extensor (mean±SE)	Clonic (mean±SE)	Stupor (mean±SE)	Recovery /Death
AU1	1.1±0.2	6.2±0.6	2.0±0.3	102±0.6	Recovery
AU2	1.8±0.2	7.0±0.7	3.8±0.3	112±0.6	Recovery
AU3	2.8±0.3	11.3±0.7	7.0±0.3	129±0.6	Recovery
AU4	3.9±0.4	11.9±0.7	6.1±0.6	125±0.6	Recovery
AU5	0.8±0.2	5.8±0.6	1.6±0.3	98±0.4	Recovery
AU6	1.5±0.2	6.5±0.7	3.1±0.3	106±0.7	Recovery
AU7	2.7±0.3	11.3±0.7	6.8±0.6	132±0.6	Recovery
AU8	3.6±0.4	13.2±0.7	6.8±0.6	133±0.5	Recovery
AU9	1.7±0.2	7.1±0.6	3.4±0.3	111±0.6	Recovery
AU10	2.1±0.3	7.3±0.6	3.6±0.4	117±0.6	Recovery
AU11	2.9±0.3	12.8±0.7	6.2±0.6	125±0.7	Recovery
AU12	3.8±0.4	12.9±0.7	7.2±0.6	126±0.7	Recovery
C	4.0±0.3	13.8±0.5	7.8±0.3	133±0.4	Recovery
Sd	-	4±0.7	0.8±0.3	86±1.8	Recovery

* C: control * Sd : standard (phenytoin)* - : no activity

Table 5.3: Effect of Synthesized Compounds on Maximal Electro Shock Convulsion in albino rats. (at 150 mg/kg dose after 30 min)

Code No.	*Time (sec) in various phase of convulsion*				
	Flexion (mean±SE)	Extensor (mean±SE)	Clonic (mean±SE)	Stupor (mean±SE)	Recovery /Death
AU1	-	5.6±0.5	1.5±0.3	92±0.4	Recovery
AU2	1.2±0.2	6.4±0.5	2.7±0.3	100±0.2	Recovery
AU3	2.1.± 0.2	9.8±0.7	5.9±0.3	113±0.2	Recovery
AU4	3.9±0.2	11.9±0.5	6.1±0.2	125±0.2	Recovery
AU5	-	5.0±0.5	1.0±0.3	91±0.3	Recovery
AU6	1.2±0.2	6.3±0.7	2.2±0.2	98±0.2	Recovery
AU7	1.9.± 0.2	9.1±0.6	5.4±0.3	105±0.4	Recovery
AU8	3.6±0.4	13.2±0.5	6.8±0.3	128±0.2	Recovery
AU9	0.6±0.2	5.8±0.5	1.6±0.4	98±0.2	Recovery
AU10	1.4±0.3	6.6±0.6	2.9±0.4	103±0.3	Recovery
AU11	2.7.± 0.2	12.6±0.5	5.8±0.3	119±0.2	Recovery

AU12	3.8±0.2	12.8±0.5	7.2±0.3	126±0.2	Recovery
C	4.0±0.3	13.8±0.5	7.8±0.3	133±0.4	Recovery
Sd	-	4±0.7	0.8±0.3	86±1.8	Recovery

* C: control * Sd : standard (phenytoin) * - : no activity

Table 5.4: Effect of Synthesized Compounds on Maximal Electro Shock Convulsion in albino rats. (at 150 mg/kg dose after 4 h)

Code No.	Time(sec) in various phase of convulsion				
	Flexion (mean±SE)	Extensor (mean±SE)	Clonic (mean±SE)	Stupor (mean±SE)	Recovery /Death
AU1	0.9±0.1	5.9±0.3	2.0±0.2	99±0.2	Recovery
AU2	1.6±0.2	6.9±0.3	3.1±0.2	112±0.2	Recovery
AU3	2.8±0.2	11.5± 0.6	6.9±0.3	129±0.2	Recovery
AU4	3.9±0.3	11.8±0.6	6.9±0.3	128±0.2	Recovery
AU5	0.6±0.2	4.9±0.7	0.8±0.3	90±0.2	Recovery
AU6	1.5±0.2	6.5±0.7	3.1±0.2	106±0.3	Recovery
AU7	2.8±0.3	11.3±0.6	6.8±0.2	125±0.3	Recovery
AU8	3.8±0.3	13.8±0.6	6.8±0.3	133±0.2	Recovery
AU9	1.0±0.2	7.1±0.7	3.4±0.2	111±0.2	Recovery
AU10	2.1±0.2	7.5±0.7	3.9±0.3	121±0.3	Recovery
AU11	2.6.± 0.2	12.8±0.5	5.9±0.4	121±0.2	Recovery
AU12	3.9±0.4	13.4±0.4	7.3±0.2	132±0.2	Recovery
C	4.0±0.3	13.8±0.5	7.8±0.3	133±0.4	Recovery
Sd	-	4±0.7	0.8±0.3	86±1.8	Recovery

* C: control * Sd : standard (phenytoin) * - : no activity

Discussion:

1. Effect of substituents on benzene ring

AU5>AU1>AU9**;** From present study it was found that methyl substituted ring was most active and unsubstituted ring was least active. Methoxy substituted compound was intermittent in activity. Study revealed that electron releasing\donating group generally exhibiting activity.

2. Effect of chain length

AU1>AU2>AU3>AU4>AU5>AU6>AU7>AU8>AU9>AU10; Study revealed that as chain length of compounds is increased from methyl to propyl or isopropyl the activity of compounds decreases. It may be due to steric hindrance. Electron donating group of benzene ring exhibited better anticonvulsant activity as compared to unsubstitution.

Conclusion

Various 1,2,4-triazole derivatives were prepared by reacting aromatic acid esters (synthesized from aromatic acid) with hydrazine hydrate followed by reaction with alcoholic potassium hydroxide and carbon disulphide. The obtained potassium dithiocarbazinates were cyclized with hydrazine to yield 1,2,4-triazole. 1,2,4-triazole was further reacted with chloro acetyl chloride and then with amines to give title compound. All the synthesized compounds were recrystallized and their purity was checked by performing thin layer chromatography. The structure of the compounds was confirmed on the basis of IR & 1H NMR spectral data. The synthesized compounds were then evaluated for their anticonvulsant studies. The anticonvulsant studies were performed on albino rats by Maximal Electro Shock (MES) induced method using Phenytoin as the reference drug. It was found that the compound AU-1, AU -5, AU -9 showed better activity while compounds AU-2, AU-6, AU-10 showed good activity and the remaining other compounds were inactive. Electron donating group of benzene ring exhibited better anticonvulsant activity as compared to unsubstitution. Further work may be undertaken on this nucleus for the search of better anticonvulsant agents with less toxicity.

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