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SYNTHESIS AND BIOLOGICAL SCREENING OF DIHYDROPYRIMIDINE SUBSTITUTED THIAZOLIDINONE DERIVATIVES

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Abstract: Substituted pyrimidine ring is an important pharmacophore in modern drug discovery. Pyrimidine nucleus exhibited remarkable pharmacological activities. Literature indicates that compounds having pyrimidine nucleus have wide range of therapeutic uses that include anti inflammatory, antibacterial, anticancer, antiviral, anti HIV, antimalarial, antihypertensive, sedatives and hypnotics, anticonvulsant and antihistaminic. A series of new substituted thiazolidinone were synthesized by appropriate route & evaluated for anticonvulsant activity. The structure of the synthesized compounds were confirmed by IR ,MASS, NMR spectroscopy. After i.p. injection of the compounds to mice at doses of 100 mg/kg body weights were examined in the subcutaneous pentylenetetrazole (sc-PTZ) induced seizure models.

Keywords: Pyrimidine, Thiazolidinone, Anticonvulsant

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INTRODUCTION

Epilepsy is the chronic disorder of the central nervous system manifested by recurrent unprovoked seizures. Epilepsy is the second most common neurological disorder after stroke. This disorder, if untreated, can lead to impaired intellectual function or death and is typically accompanied by psychopathological consequences such as lose of self-esteem.[1]

The worldwide prevalence of active epilepsy is between 4 to10 per 1000 population. The prevalence rate in India is 5.59 per 1000 with no statistically different rates between men and women or urban and rural residence.[2]

Incidence is the number of new cases of epilepsy occurring during a given time interval, usually one year, in a specified population. In the case of epilepsy, the annual incidence is usually calculated per 100,000 populations. The incidence of epilepsy ranges from 40 to 70 per 100,000 in most developed countries and from 100 to 190 per 100,000 in developing countries. In studies from India 74-78% of patients with epilepsy in rural areas were not receiving antiepileptic drugs (AEDs) on the prevalence assessment day and 17% in urban population.[3,4]

Epilepsy can also be caused by previous active pathology, such as birth trauma to the brain, during or following meningitis, trauma to the skull and brain later in life, cerebral abscesses, cerebral infarction, cerebral hemorrhage or subarachnoid hemorrhage. Other causes included head injury with/without intracranial hemorrhage, central nervous system and systemic infections.[5]

Partial seizures happen when the disturbance occurs in just one part of the brain.[6] Generalized seizures are produced by electrical impulses from throughout the entire e brain, once initiated; it spreads quickly into the entire or at least the greater part of the brain.[7]Absence seizures (also called petit mal (little illness) seizures because they occurred so frequently) are lapses of awareness, sometimes with staring, that begin and end abruptly, lasting only a few seconds. [8]Myoclonic seizures are rapid, brief contractions of body muscles, which usually occur at the same time on both sides of the body.[9]

The blockade of voltage-gated channel is the most common mechanism of action amongst currently available AEDs. Voltage- dependent Na^+ channels are responsible for the upstroke of the neuronal action potential, and ultimately control the intrinsic excitability of the nervous system.. Voltage sensitive calcium channels can be broadly classified into low or high threshold, according to the membrane potential at which they are activated. The low-threshold T-type Calcium channel is expressed predominantly in thalamocortical relay neurons. T-type channels are critically important in controlling the excitability of the postsynaptic compartment of neurons, both in normal and epileptic neurons. High threshold calcium channels are sub

classified by their pharmacological properties into L, N, P, Q, and R type. The L- type high voltage- activated, generating a long-lasting current; N, P, Q, and R-types expressed in nerve terminals and responsible for the calcium entry that triggers neurotransmitter release.[10,11]

An increase in membrane conductance to K^+ ions causes neuronal hyperpolarization and, in most cases, reduces firing frequency, exerting a strong inhibitory function on neuronal excitability. The current mediated by these channels is also referred to as the *'M-current'* considering its inhibition by the cholinergic agonist muscarine. This *M*-current contributes to after hyperpolarization following action potentials and to stabilization of the membrane potential thereby preventing repetitive action potentials discharges and burst responses. Therefore, enhancing *M- currents* can be considered a powerful approach to reduce neuronal excitability in the epileptic brain. [12]

HCN_1 channels are prominently expressed in the cortex and the hippocampus, particularly in dendrites. In contrast, HCN_2 channels, which are highly responsive to cAMP, are expressed mainly in the thalamus, where they are believed to limit burst firing. In recordings from hippocampal or cortical neurons, the current produced by opening of the HCN channels is referred to as *Ih.*.[13]

The major inhibitory neurotransmitter, GABA, interacts with 2 major subtypes of receptor: $GABA_A$ and $GABA_B$ receptors $GABA_A$ receptors are found post synaptically, while $GABA_B$ receptors are found pre synaptically, and can thereby modulate synaptic release. [14]

Glutamate is the major excitatory neurotransmitter in the CNS. There are two major categories of glutamate receptors:

Ionotropic - fast synaptic transmission

Metabotropic - slow synaptic transmission [15]

2. MATERIAL & METHOD

Melting points were determined in open capillary tubes . The IR spectra were recorded in FT-IR and bruker alpha ATR and ^1H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker spectrometer at 400 MHz respectively. Mass spectra were obtained using LCMS Shimadzu instrument. .All physical and spectral characteristics are shown in **Table 3.1 to 3.4.**

2.1 Synthesis Of 3-(4-chlorophenyl)-1-phenylprop-2en-1one (1)

The main method for the synthesis of chalcones is classical claisen- Schmidt condensation in the presence of aqueous alkaline bases.

A mixture of acetophenone (0.01 mole) & p-chloroaldehyde (0.01 mole) was dissolved in ethanol (30 ml) & NaOH solution (40%), was added to make it alkaline.

The reaction mixture was stirred for 2 hours, allowed to stand reaction mixture for 24 hours. pH of the reaction mixture was made neutral by addition of dil.HCL .

The product was filtered under vaccum & washed with excess distilled water & recrystalized from rectified spirit.

2.2 Synthesis Of 6-(4-chlorophenyl)-4-phenyl-pyrimidin-2-amine (2)

A mixture of 3-(4-chlorophenyl)-1-phenylprop-2en-1one (0.01 mol) and guanidine hydrochloride (0.01 mol) in ethanol (75 ml) was refluxed, while a solution of sodium hydroxide (0.02 mol) in water (10 ml) was added portion wise for 2 h. Refluxing was continued for further 10 h and the mixture was poured into ice cold water. The formed solid was separated by filtration and recrystallized from rectified spirit.

2.3 Synthesis Of [4-(4-chlorophenyl)-6-phenylpyrimidin-2-yl]- 1-(substitutedphenyl) methanimine (3a-f)

General procedure:

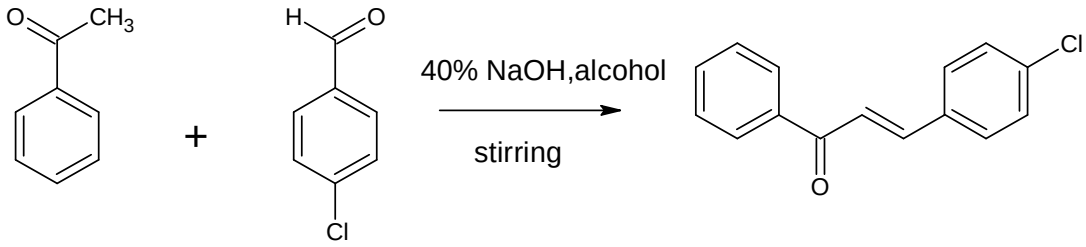
To a mixture of 6-(4-chlorophenyl)-4-phenyl-pyrimidin-2-amine (0.01 mol) & substituted aldehyde (0.01mol) in ethanol(30 ml),catalytic amount of glacial acetic acid added then the resultant mixture was refluxed for (7-8 hours), progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into crushed ice stirred well; solid obtained was recrystalized from rectified spirit.

2.4 Synthesis Of 3-(4-(4-chlorophenyl)6-phenylpyrimidine-2-yl)-2-(substitutedphenyl)-1,3-thiazolidin-4-one

General procedure:

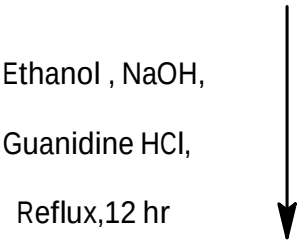
Cyclocondesation of Schiff base 4-(4-chlorophenyl)-6-phenyl-pyrimidin-2-yl]-1-(4-substituted phenyl) methanimine (0.01 mol) with thioglycolic acid (0.01mol) in dioxane, then the resultant mixture was refluxed for (9-10 hr), progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into crushed ice stirred well; solid obtained was recrystalized from rectified spirit.

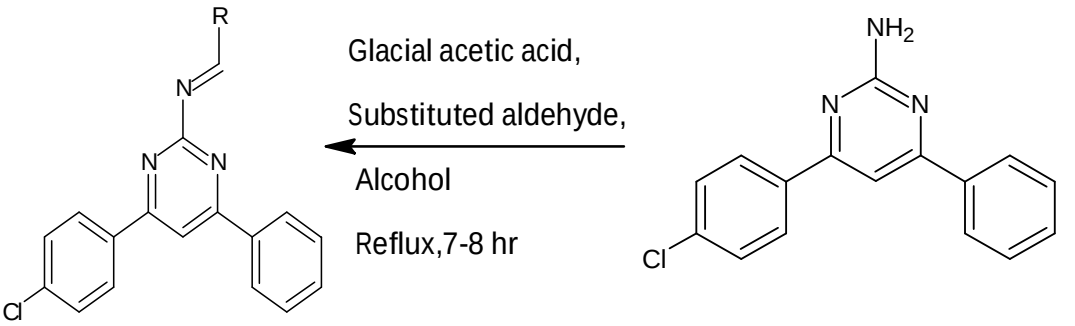
2.5 SCHEME OF SYNTHESIS :



Acetophenone p-chloro benzaldehyde 3-(4-chlorophenyl)-1-phenylprop-2en-1one

(1)





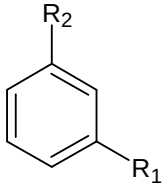
4-(4-chlorophenyl)-6-phenylpyrimidin-2-amine

(2)

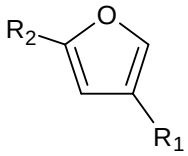
[4-(4-chlorophenyl)-6-phenylpyrimidin-2-yl]Substituted methanimine

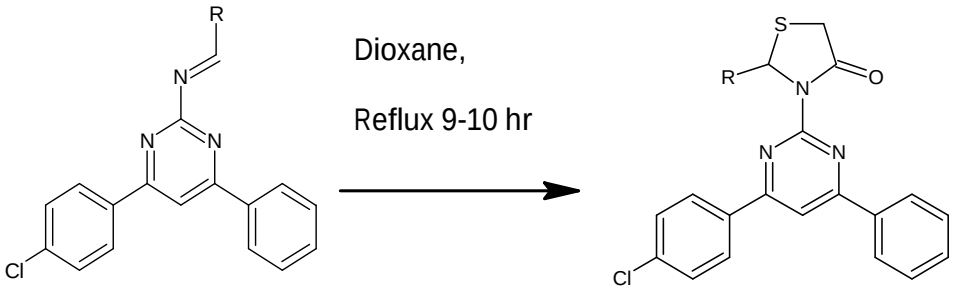
(3, a-e)

(3 a-e) R =



(3 f) R=



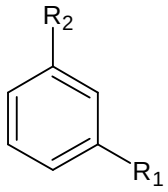


[4-(4-chlorophenyl)-6-phenylpyrimidin-2-yl] Substituted methanimine

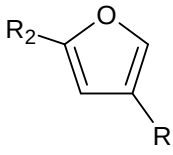
3-(4-(4-chlorophenyl)-6-phenylpyrimidine-2yl) Substituted-1,3-thiazolidin-4-one

	R_1	R_2
4a	H	OCH_3
4b	OH	H
4c	H	Cl
4d	Cl	H
4e	H	CH_3
4f	H	H

(4 a-e) R=



(4-f) R=



2.6 Biological evalution:

Anti-convulsant activity:

The anti-convulsant activity of newly synthesized thiazolidinone derivatives was carried out using chemically induced seizure in animal model.

Animals used:	Swiss Albino Mice
Age /weight:	18-25gm
Sex:	male/female
No. of animals used	3(in each group)
Dose of Standard	85 mg/kg phenytoin
Dose of test	100 mg/kg synthesized compound
Route of administration	Intra Peritoneal

Group I Normal control group.

Group-II Phenytoin control group (85 mg/kg)

Group-III-VIII Were treated with synthesized compounds. The synthesized compounds were dissolved in suspension of 0.5% CMC.

- **Requirements:**

- **Chemicals:** 0.5 % CMC
- **Standard drug :** Phenytoin (85mg/kg) aqueous solution was prepared using 0.5%CMC.
- **Test compounds:** Solution of compounds was prepared and administered orally similar to that of standard drug
- **Apparatus:** syringes (1ml, 2ml)

Experimental design and procedure:

- The animals will be kept fasting for 24 h with water and normal saline was administered animal were divided into eight groups (n=3) starved overnight with water.
- The control group received vehicle orally. While other group received test drug and standard drug respectively.
- The test compounds and standard drug were suspended in Tween 80 (1%) or in a 0.5% methyl cellulose water mixture.
- The test will be carried out by subcutaneous (s.c.) PTZ injection half an hour after intraperitoneal (i.p.) injection of the test compounds.
- Each animal will be placed into individual observation cage for 2 h. The time of seizure onset, percentage of seizure, the occurrences of tonic-clonic seizure, seizure duration and seizure behavioural score were recorded. Seizures were classified according to modified Racine scale (Becker et al., 1995) as follows:

- Stage 0 : no response,
- Stage 1: ear and facial twitching,
- Stage 2: myoclonic jerks without rearing,
- Stage 3: myoclonic jerks,
- Stage 4: turning over into side position, bilateral clonic–tonic seizures,

- Stage 5: turning over into back position, generalized clonic and tonic seizures.

The exhibited values of anticonvulsant activity and graphical plots of the compounds are shown in **Table 3.5 and Figure 3.1** respectively.

3. RESULT AND DISCUSSION

3.1 Physical characteristics

All the compounds synthesized were pale yellow coloured crystalline solids. All compounds were soluble in ethanol, chloroform and other solvents like methanol, benzene, DMF. The melting points of compounds were in the range of 115-210°C. None of compounds were freely soluble in water.

3.2 Spectral characteristics

UV spectra

UV spectra of all the compounds were studied in UV-1700 Shimadzu spectrophotometer. UV spectra of all the compounds were studied in methanol. All the compounds were found to have absorption λmax in range of 200 nm to 400 nm.

IR spectra

IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr. All the synthesized compounds have shown characteristic of –NH stretching in the range of 3100-3350 $cm^{-1}$and C-Cl around 800-1000 $cm^{-1}$and C=O around1647-1720 cm^{-1}

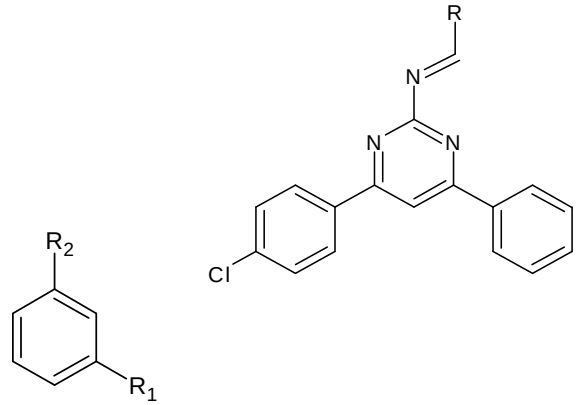
Mass spectra

Mass spectra were obtained using 2010EV LCMS Shimadzu instrument. All compounds possess characteristics molecular ion peak M+1, M-1, M+2,M+4 peak.

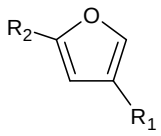
^{1}H NMR spectra

The ^{1}H NMR spectra of some of the compounds were studied in $CDCl_3$. All the compounds shows characteristic chemical shift from TMS in terms of δ, ppm. All the compounds showed multiplet in the range from 6.5-7.9 ppm due to presence of aromatic rings.

Table No.3.1 Physical characteristics of [4-(4-chlorophenyl)-6-phenylpyrimidine-2-yl] Substituted methanimine



(3 a-e) R =

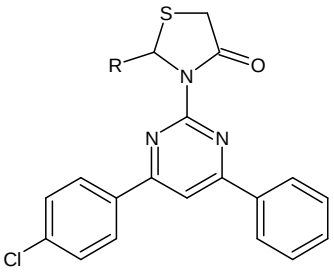


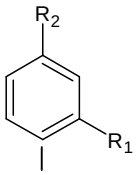
(3 f) R =

Comp. code	R_1	R_2	Molecular Formula	Molecular Weight (g/mol)	MP (°C)	Yield (%w/w)	Rf
1	-	-	$C_{15}H_{11}OCl$	242.70	115-117 (113-117)	78.67	0.57
2	-	-	$C_{16}H_{12}N_3Cl$	281.73	146-148 (150-151)	70.20	0.61
(3a)	H	*p*-OCH3	$C_{24}H_{18}N_3OCl$	399.87	160-165	67.11	0.59
(3b)	OH	2-OH	$C_{23}H_{16}N_3OCl$	385.86	154-158	67.21	0.65
(3c)	H	*p*-Cl	$C_{23}H_{15}N_3Cl_2$	404.29	174-176	65.33	0.62
(3d)	Cl	2-Cl	$C_{23}H_{15}N_3Cl_2$	404.29	172-175	62.25	0.64
(3e)	H	CH_3	$C_{24}H_{18}N_3Cl$	383.87	163-167	63.48	0.67
(3f)	H	H	$C_{21}H_{14}N_3OCl$	359.80	157-161	67.65	0.56

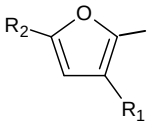
Mobile Phase: chloroform:Methanol = 7:3

Table No. 3.2 Physical characteristics of 3-(4-(4-chlorophenyl)-6-phenyl pyrimidine-2yl substituted-1,3-thiazolidin-4-one





(4 a-e) R =



(4 f) R =

Comp. code	R_1	R_2	Molecular Formula	Molecular Weight (g/mol)	MP (oC)	Yield (%w/w)	Rf
(4a)	H	*p*-OCH3	$C_{26}H_{20}N_3O_2ClS$	473.97	180-185	57.23	0.61
(4b)	OH	*2*-OH	$C_{25}H_{18}N_3O_2ClS$	459.94	170-175	59.14	0.52
(4c)	H	*p*-Cl	$C_{25}H_{17}N_3OCl_2S$	478.39	196-200	53.24	0.67
(4d)	Cl	2-Cl	$C_{25}H_{17}N_3OCl_2S$	478.39	194-198	52.36	0.65
(4e)	H	CH_3	$C_{26}H_{20}N_3OClS$	457.97	188-192	56.48	0.60
(4f)	H	H	$C_{23}H_{16}N_3O_2ClS$	433.91	182-186	58.20	0.59

Mobile Phase: Chloroform:Methanol = 8:2

Table No. 3.3 Spectral characteristics of [4-(4-chlorophenyl)-6-phenylpyrimidin-2-yl] Substituted methanimine

Comp. code	UV λmax (nm)	IR (υ, cm^{-1})	Mass (m/z)	1H NMR(δ, ppm)
1	235	3031(=C-H), 2918(Ar-CH), 1654.8(C=O Ketone)	-	-
2	275	3492,3313(-NH_2), 3024(Ar-CH),1542 (C=N), 1095((-C-Cl))	282.8 (M+1), 283.8 (M+2)	-
(3a)	335	2916 (Ar-CH), 1741 (C=N), 1495 (C=C (aromatic), 1030 (C-Cl)	401.3 (M+2)	3.81(s, 3H,OC**H**$_3$), 7.07 (d, 2H,Ar-**H**), 7.49-7.60 (m, 5H, Ar-**H**), 7.89-7.97 (m, 6H, Ar-**H**), 8.58(s,1H,-C**H**-pyrimidine).9.50(s,1H,N=C**H**)
(3b)	320	3620 (O-H), 2916 (Ar-CH), 1696 (C=N), 1495(C=C (aromatic)	384.7(M-1), 387.2(M+2)	-
(3c)	358	2917 (Ar-CH), 1632 (C=N), 1492(C=C (aromatic), 1017 (C-Cl)	406.2(M+2), 408.7 (M+4)	-
(3d)	330	2922 (Ar-CH), 1699 (C=N), 1507(C=C(aromatic), 1017 (C-Cl)	406.6(M+2), 408.8 (M+4)	-
(3e)	325	2913 (Ar-CH), 1616 (C=N), 1593(C=C(aromatic), 969(C-Cl)	382.5(M-1), 385.5(M+2)	-
(3f)	310	3125, 2922 (Ar-CH), 1699 (C=N), 1575(C=C(aromatic), 1017 (C-Cl)	361.2 (M+2)	-

Table No. 3.4 Spectral characteristics of 3-(4-(4-chlorophenyl)-6-phenyl pyrimidine-2yl substituted-1,3-thiazolidin-4-one

Comp. code	UV λmax (nm)	IR (υ, cm-1)	Mass (m/z)	1H NMR(δ, ppm)
(4a)	350	3010 (Ar-CH), 1702 (-C=O) , 1665 (-N-C=O), 1362(-C=N), 848 (C-Cl), 630 (C-S)	475.1(M+2)	3.81 (S, 3H, OC**H**$_3$), 3.85-3.95(S,2H,-C**H**$_2$ thiazolidinone), 6.44(s,1H,-C**H**-thiazolidinone), 6.89 (d ,2H, Ar-**H**) 7.49-7.6 (m ,5H, Ar-**H**) 7.83-7.97(m, 6H, Ar-H) 8.43(s,1H,C**H**-pyrimidine)
(4b)	340	3630 (O-H) , 2985(Ar-CH) 1703(-C=O) , 1665(-N-C=O), 1494(-C=N), 1050(C-Cl), 689(C-S)	458.3 (M-1) 461.7(M+2)	
(4c)	330	2913(Ar-CH), 1630 (-C=O), 1665(-N-C=O), 1537(-C=N), 997(C-Cl), 688(C-S)	479.5(M+2), 481.2(M+4)	3.87-3.97(S,2H,-C**H**$_2$ thiazolidinone), 6.44(s,1H,-C**H**-thiazolidinone), 7.22 (d ,2H, Ar-**H**), 7.38 (d ,2H, Ar-**H**), 7.50-7.60 (m ,4H,Ar-**H**), 7.95-7.98 (m ,5H,Ar-**H**), 8.43(s,1H,C**H**-pyrimidine)
(4d)	335	2942(Ar-CH), 1730(-C=O), 1590(-C=N), 1092(C-Cl), 692(C-S)	479.8(M+2), 481.7(M+4)	-

(4e)	329	2985(Ar-CH), 1731(-C=O), 1658 (-N-C=O), 1558(-C=N), 747(C-Cl), 692(C-S)	456.3(M-1), 459.7(M+2)	-
(4f)	320	3010(Ar-CH), 1703 (-C=O) , 1665 (-N-C=O), 1513(-C=N), 689(C-Cl), 630(C-S)	435.1(M+2)	-

3.3 *In-vivo* anticonvulsant activity by chemical induced seizures:

One-way ANOVA ($p<0.05$ consider for significance) Followed by post test, Dunnett's multiple comparison tests.

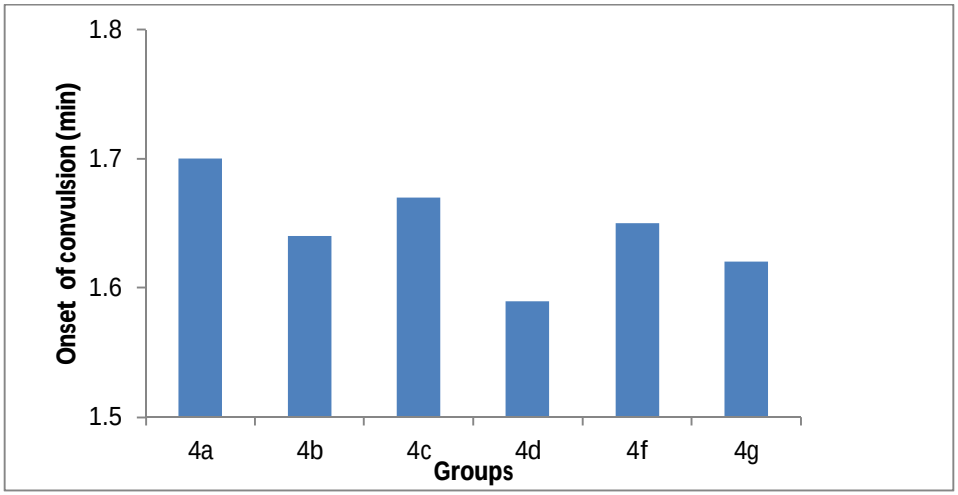
Effect of synthesized compound on PTZ induced convulsion

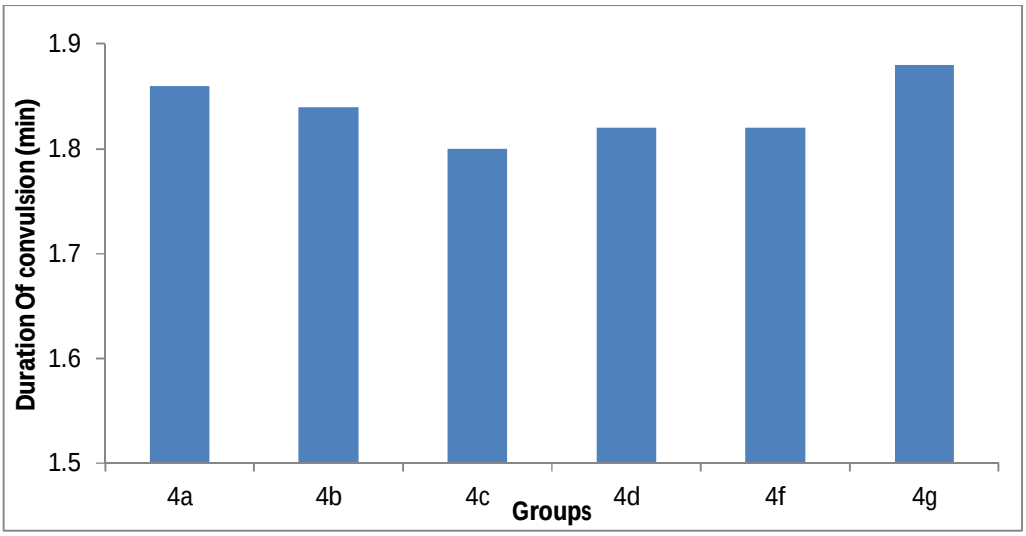
Table 3.5 Effect of synthesized compound on PTZ induced convulsion

Experimental Group	Dose	Onset of Convulsion (min)	Duration of convulsion (min)
Normal control (1% CMC in D.W)	5 ml/kg p.o	0	0
Standard control (phenytoin)	85 mg/kg i.p	00	00
4a	100 mg/kg i.p	1.71±0.17	1.86±014
4b	100 mg/kg i.p	1.64±0.20	1.84±015
4c	100 mg/kg i.p	1.67±0.18	1.80±0.19
4d	100 mg/kg i.p	1.59±0.15	1.82±0.17
4e	100 mg/kg i.p	1.65±0.16	1.82±0.23
4f	100 mg/kg i.p	1.62±0.20	1.88±0.21

All values are expressed as Mean ± S.E.M, n=3 in each group $p<0.05$.

Figure 3.1 : Histogram of Anticonvulsant activity





3.4 DISCUSSION:

➢ All the synthesized compounds were characterized by using IR, Mass and some by NMR spectroscopy.

➢ All the synthesized compounds activity were compared with the standard drug Phenytoin.

➢ From the above activity table it is evident that the entire synthesized compounds give a moderate anticonvulsant activity.

➢ Compounds 4a, 4c and 4f were found to be having moderate anticonvulsant effect as compared to control and standard.

➢ Other compounds like 4b, 4d and 4e were found to be lower active as compared to standard and other derivatives.

➢ Synthesized compounds were screened for anticonvulsant activity by chemical induced seizure method.

➢ Compound 4a, 4b and 4c significantly reduced the duration of convulsion in the mice against pentylenetetrazole induced convulsion. The standard anti- epileptic drug phenytoin (85mg/kg i.p) completely antagonized the seizures produced by pentylenetetrazole.

3.5 Conclusion:

➢ All the synthesized compounds were characterized by using UV, IR, Mass and some of by ^{1}H-NMR spectroscopy & report of them support the structures of compounds.

➢ As per synthetic point of view all the synthesized final derivatives of compounds have good yield except compound **4b, 4d** and **4f** have less yield because of the steric hindrance by the ortho substituent of benzaldehyde.

➢ All the synthesized final compounds were screened for anticonvulsant activity by chemical induced seizures Method against standard reference drug phenytoin.

➢ Synthesized compounds having mainly electron donating group at para position of phenyl ring gives moderate anticonvulsant activity.

➢ When aromatic ring was replaced by heterocyclic rings like furan, the anticonvulsant activity was altered and has exhibited less significant effect.

➢ In sc-PTZ induced seizers among the tested compounds 4c, having chloro phenyl substituent was found to be highly effective as compared to other substituent having reduced the duration of convulsion.

➢ Evaluation of anticonvulsant activity revealed that compounds with pyrimidine ring having the thiazolidinedione moiety gives moderate biological activity having electron donating group at the 4th position of the phenyl ring i.e., **4a, 4c and 4e** having moderate activity with electron releasing functional groups .

➢ **Activity Scale:**

4c > 4a > 4e > 4b > 4d > 4f

REFERENCES

1. Pitkanen A and Lukasiuk K, "Molecular and cellular basis of epileptogenesis in symptomatic epilepsy." Epilepsy Behaviour, 2009, 14, p.16-25.

2. Banerjeea PN, Filippi DC and Hausera WA, "The descriptive epidemiology of epilepsy." Epilepsy Research, 2009, 85, p.31-45.

3. Bharucho NE. "Epidemiology of epilepsy in India." Epilepsia, 2003, 44, p.9-11.

4. Sridheran R and Murthy BN, "Prevalence and pattern of epilepsy in India." Epilepsia, 1999, 40, p. 631-637.

5. Rang HP, Dale MM, Ritter JM and Moore PK, Pharmacology. 5th Edition; Elsevier India Ltd, NewDelhi, 2005, p. 550-561.

6. Schachter SC, "Epilepsy.com", February 2011, URL:http://www.epilepsy.com/Epilepsy/seizure_simple partial

7. Dolren PJ, "Epilepsy foundation", February 2011, http://www.epilepsyfoundation.org/answerplace/Medical/seizures/types/genConvulsive/seizuremyoclonic.cfm

8. Snead OC," Antiabsence Seizure Activity of Specific GABA, and y-Hydroxybutyric Acid Receptor Antagonist." Pharmacol Biochem Behaviour, 1996, 53, p.73-79.

9. Rogers SJ, Cavazos JE. Epilepsy. In: Dipiro JT, Talbert RL, Yee GC, MatzkeGR, Wells BG, Posey LM, editors, Pharmacotherapy a pathophysiological approach, 7th edition; New York: McGraw-Hill, 2008, p.927-51.

10. Patrick Kwan, Graeme J. Sills, Martin J. Brodie, "The mechanisms of action of commonly used antiepileptic drugs." Pharmacology & Therapeutics , 2001 , 90, p.21– 34.

11. Brian S. Meldrum and Michael A. Rogawski, "Molecular Targets for Antiepileptic Drug Development." Neurotherapeutics, 2007, 4, p.18-61.

12. Rogawski MA, Bazil CW, "New Molecular Targets for Antiepileptic Drugs: α2δ, SV2A, and Kv7/KCNQ/M Potassium Channels." Current Neurology and Neuroscience Reports, 2008, 8(4), p.345–52.

13. Nicholas P. Poolo, "The h-channel: A potential channelopathy in epilepsy?." Epilepsy & Behavior , 2005, 7, p.51–56.

14. Zeyden MV, Oldenziel WH, Rea K, "Microdialysis of GABA and glutamate: analysis, interpretation and comparison with microsensors." Pharmacol Biochem Behaviour, 2008, 90 (2), p.135-47.

15. Czapinski P and Blaszczyk B. "Mechanisms of Action of Antiepileptic Drugs." Current Topic in Medicinal Chemistry, 2005, 5, p.3-14.