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RESEARCH ARTICLE

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF 4-THIAZOLIDINONE ANALOGUES OF 2-AMINO-5-CHLOROPYRIDINE

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Abstract

The synthesis of 4-thiazolidinones of 2-amino-5-chloropyridine was performed by novel method of stirring involving the cyclocondensation of the appropriate Schiff's bases (2a–c) with thioglycolic acid, followed by the addition of zinc chloride in the presence of molecular sieves. Characterization of the synthesized compounds, determination of purity and identity of the compounds using following spectroscopic and chromatographic techniques- Solubility,Thin Layer Chromatographic studies, Ultra-Violet studies,Rotational and vibrational studies (FT-IR), ^{1}H-NMR studies. The compounds were investigated for their Anticonvulsant activity by isoniazid induced convulsions in mice model.Compound3-(5-chloropyridin-2-yl)-2-(4-fluorophenyl) thiazolidin-4-one(3c)was found to be the most activeand compound 3-(5-chloropyridin-2-yl)-2-(2-hydroxyphenyl) thiazolidin-4-one (3a) was found to be less active among the tested compound according to pharmacological evaluation exhibited anticonvulsant activity.

Introduction:-

Epilepsy is one of the most common and most disabling chronic neurologic disorders. People with epilepsy have recurrent unprovoked (spontaneous) seizures, which can be focal or generalized in nature. Seizures cannot be fully controlled in about a third of people with epilepsy, even though multiple antiseizure drugs (ASDs) may have been employed singly or in various combinations(1). Epilepsy is a serious neurological disorder with point prevalence of 6.38 per 1000 persons. Both conventional and newer antiepileptic drugs (AEDs) treat various types of seizures.The aim of treatment is to reduce seizure frequency within acceptable level of side effects. However, the currently used AEDs not only fail to control seizure in some patients, but it frequently causes side effects. The side effects are important reason of treatment failure with antiepileptic drugs. Cognitive impairment has been reported with the treatment of conventional as well as newer antiepileptic drugs. (2)

Nitrogen-containing heterocyclic rings are important structural elements in many known anticonvulsant drugs. In our previous studies 4-thiazolidinones containing 2-aminothiazole moiety are reported as promising anticonvulsant agents; they are structural analogs of a potential dual cyclooxygenase-2 and 5-lipoxygenase (COX-2/5-LOX) inhibitor darbufelon. Data on the anticonvulsant activity of classical non-steroidal anti-inflammatory drugs, the polypharmacological futures of 4-thiazolidinones and our experimental findings are sound arguments for further design of novel hetarylsubstituted 2-imino/amino4-thiazolidinones as potential anticonvulsant(3).Thiazolidinones

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are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds. 4-thiazolidinone scaffold is not only synthetically important but also possesses a wide range of promising biological activities. Broad and potent activities of 4-thiazolidinones established it as one of the biologically important scaffolds. Novel substituted thiazolidinonylcarbazoles were synthesized. The Staudinger's ketene-imine cycloaddition reaction is the most common method for the synthesis of thiazolidinones and has been reviewed till date by several researchers (Staudinger, 1907). Pyridine derivatives can be an important pharmacophore having wide range of biological activity. The synthesis of 4-thiazolidinones, using 2-amino-5-chloropyridine as the starting material has not been reported so far.

On the basis of the above findings and considering the need for the development of potent anticonvulsant agents, we were stimulated to explore new simplified 4-thiazolidinone analogues for their anticonvulsant activity.Over the past few years, there is a significant advancement of nitrogen-containing heterocycles for their varied pharmacological activities. (4)

Thiazolidinone frameis considered as cyclic mimetic of thiosemicarbazides and thioureas as well as (bio)isoster of hidantoin (imidazolidine-2,4-dione) [11]—approved scaffolds of known anticonvulsants and privileged (sub)structures for new anticonvulsants design (5)

Here, in this paper, we are reporting synthesis of 3-(5-chloropyridin-2-yl)thiazolidin-4-one analogues(3a–c) for the synthesis of new 4-thiazolidinone derivatives by green route method of stirring and their screening for anticonvulsant activity.

Experimental

General considerations

All research chemicals were purchased from Across organics (NY, USA), Sigma-Aldrich (St. Loius, Missiouri, USA) and used as such for the reactions. Melting points (mp) were determined on a Veego melting point apparatus (VMP PM, 32/1104) and are uncorrected. Reactions were monitored by thin layer chromatography carried out using pre-coated silica gel plates (E. Merck and Co., Darmstadt, Germany). UV studies were carried out on a UV Visible spectrophotometer (Shimadzu 1700) and the λmax of the respective synthesized compounds was determined using ethanol as the solvent. The IR spectra (KBr) were recorded on a FTIR spectrophotometer with Diffuse Reflectance attachment (Shimadzu 8400S).

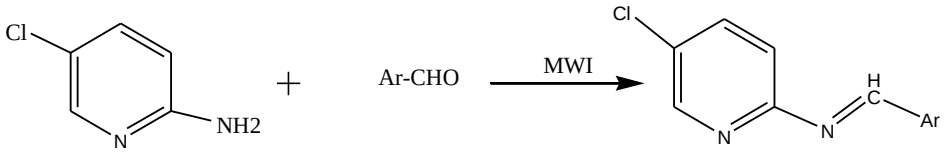
The ^{1}H NMR spectra were obtained on an NMR Spectrophotometer (Bruker Avance II 400 NMR) using DMSO as a solvent. Chemical shifts were expressed in parts per million relative to SiMe4 as an internal standard.

Synthesis

General procedure for the synthesis of aryl substituted N-benzylidene-5-chloropyridin-2-amine (Schiff's base).

STEP 1: Synthesis of Schiff's Bases of 2-amino-5-chloro-pyridine

By microwave irradiation



(1a-1c) (2a-2c)

Synthesis of compounds (2a–c) was performed according to our previously reported procedure (Thomas et al., 2009) (Scheme: 1). 2-Amino-5-chloropyridine (0.01 M) and appropriate aromatic aldehydes (0.01 M; 1a -c) in ethanol: water (5:5) solvent system were irradiated under microwave using a microwave synthesizer (Make-Raga's Scientific, India) at power level 3 (240 W, 35% irradiation) in an open vessel until the completion of the reaction. The reaction was monitored by TLC (Toulene: methanol:glacial acetic acid =8:2:0.3). The reaction mixture was then filtered, the residue obtained was washed with water, followed by sodium thiosulphate ($Na_2S_2O_3$) solution and dried. The crude product upon recrystallization from alcohol gave the pure Imines (2a–c). The synthesized compounds were characterized on the basis of their spectral and analytical data. (UV, IR, ^{1}HNMR).

2.2.1.1. 2-(5-chloropyridin-2-ylimino) methyl) phenol
Yellow crystal, Yield 95.60%, mp 111-116 ^{0}C, IR (KBr) υ/cm^{-1}: 3375(-OH), 3051 (-CH), 1606 (-C=N), 719 (-C-Cl), 1HNMR (400 MHz, $CDCl_3$): δ ppm 9.4 (S, Pyridine 1H), 8.5 (S, =CH- 1H), 7.85,7.98 (D, Pyridine 1H), 7.2-7.67 (M, Aromatic 3H), 6.94,6.99 (D, Aromatic 2H), 5.8 (S, -OH 1H) .

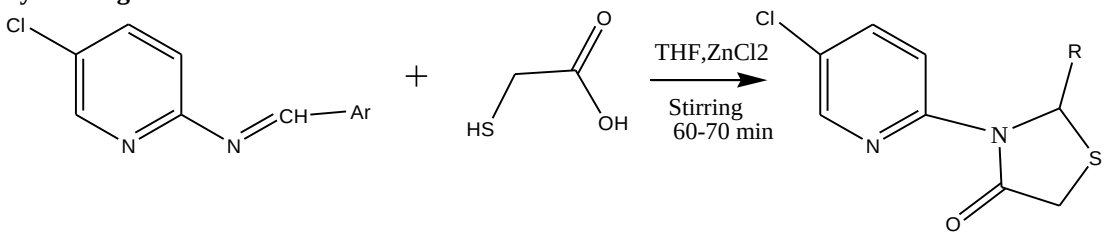
2.2.1.2. 4-(5-chloropyridin-2-ylimino) methyl) phenol
White amorphous Powder, Yield 90.70%, mp 175-179 ^{0}C, IR (KBr) υ/cm^{-1}: 3456 (-OH), 3055 (-CH), 1629 (-C=N), 748 (-C-Cl). 1HNMR (400 MHz, $CDCl_3$): δ ppm 9.1 (S, Pyridine 1H), 8.28, 8.3 (D, Pyridine 1H), 8.03 (S, =CH-, 1H), 7.85, 7.87 (D, Pyridine, 1H), 4.62 (S, -OH, 1H).

2.2.1.3. N-(4-flurobenzylidene)-5-chloropyridin-2-amine
White amorphous powder, Yield 93.81%, mp 95-102 ^{0}C, IR (KBr) υ/cm^{-1}: 3039 (-CH), 1604 (-C=N), 1373 (-C-F), 717 (-C-Cl). 1HNMR (400 MHz, $CDCl_3$): δ ppm 9.1 (S, Pyridine 1H), 7.99, 8.02 (D, Pyridine 1H), 7.74 (S, =CH-1H), 7.37, 7.40 (D, Pyridine 1H), 7.1, 7.3 (D, Aromatic 2H), 6.4 (D, Aromatic 2H).

2.2.2. General procedure for synthesis of 3-(5-chloropyridin-2-yl) thiazolidin-4-one (3a–c) using synthesized Schiff's bases.

STEP 2: Synthesis of 4-thiazolidinone analogues from Schiff's bases of 2-amino-5-chloro-Pyridine

By Stirring-



2a-c 3a-c

The 4-thiazolidinones (3a–c) were synthesized as per our reported methods of stirring (Thomas et al., 2010).To the appropriate Schiff's base (2a–c,2.0mmol) dissolved in 10 ml of tetrahydrofuran (THF), pinch of zinc chloride was added to the reaction mixture and thioglycolic acid (6.0mmol)was added drop wise with constant stirring at low temperature (0–5 ^{0}C). The reaction was carried out in the presence of molecular sieves [MS (1–2 g, 3A · 1.5 mm)]. The reaction mixture was further stirred at room temperature until the completion of reaction. [TLC (Toulene: methanol:glacial acetic acid = 8:2:0.3)]. The product obtained was washed with water and sodium bicarbonate solution and then dried. The crude product on recrystallization from alcohol yielded the pure 4-thiazolidinones (3a–c) of 2-amino-5-chloropyridine.The synthesized compounds was characterized on the basis of their spectral and analytical data (UV, IR, ^{1}H NMR).

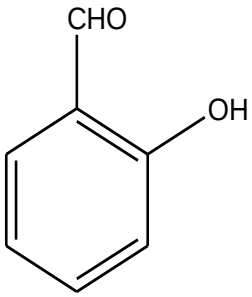
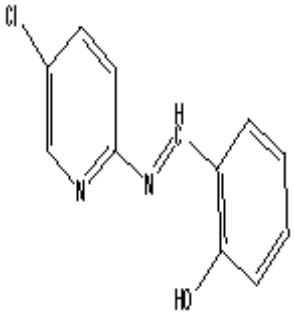
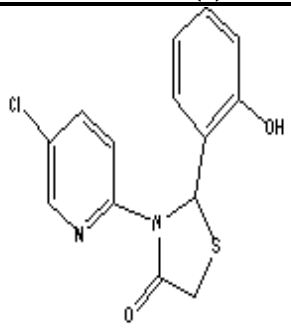
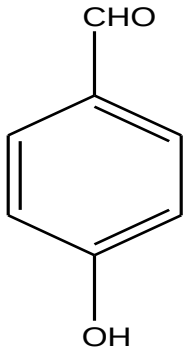
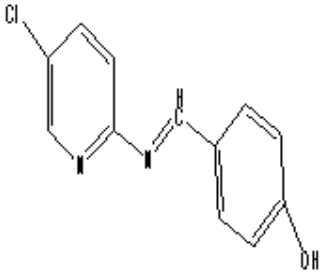
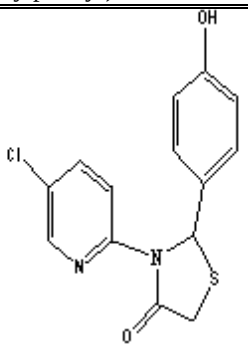
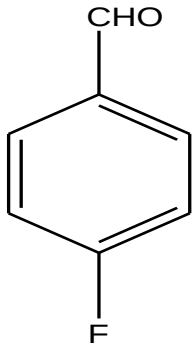
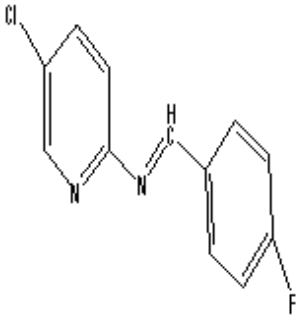
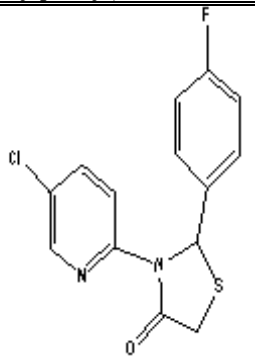
2.2.2.1. 3-(5-chloropyridin-2-yl)-2-(2-hydroxyphenyl) thiazolidin-4-one
CreamWhite crystals; mp 260-264^{0}C.Reaction time: 180 min. 88.5% yield. IR (KBr) υ/cm^{-1}: 3165 (OH), 3037 (CH), 1724 (ring C=O), 1571 (-C=N), 700 (C-Cl); ^{1}H NMR (DMSO-d_6),δ in ppm: 8.3,8.4 (D,Pyridine 1H), 8.1,8.2 (D,pyridine 1H), 8.9 (S,Pyridine 1H), 7.5,7.6 (D, Aromatic 1H), 7-7.2 (M,Aromatic 2H), 6.8-6.9(D, Aromatic 1H),),6.3 (S, -OH), 5.87 (S, C2Thia ring 1H),3.4,3.5 (D,C5 Thia ring 1H),3.2,3.3 (D,C5 Thia ring 1H)

2.2.2.2. 3-(5-chloropyridin-2-yl)-2-(4-hydroxyphenyl)thiazolidin-4-one
White crystals; MP 283-289℃ Reaction time: 120 min. 86.4% yield. IR (KBr) υ/cm^{-1}: **3575** (OH), **3132** (CH), 1712 (ring C=O), 1569 (-C=N), 648 (C-Cl); ^{1}H NMR (DMSO-d_6),δ in ppm: 8,8.1 (D,Pyridine 1H), 7.8,7.9 (D,pyridine 1H), 8.8 (S,Pyridine 1H), 6.9-7.1 (D, Aromatic 2H), 6.5-6.7(D, Aromatic 2H)),5.8 (S, -OH), 6.0 (S, C2Thia ring 1H),3.6,3.7 (D,C5 Thia ring 1H),3.5,3.62 (D,C5 Thia ring 1H)

2.2.2.3. 3-(5-chloropyridin-2-yl)-2-(4-fluorophenyl)thiazolidin-4-one
Pale yellow; mp 268-273℃ Reaction time: 120 min. 89.7% yield. IR (KBr) υ/cm^{-1}:**3005** (CH), **1726** (ring C=O), **1552** (-C=N), 702 (C-Cl); ^{1}H NMR (DMSO-d_6),δ in ppm: 8.4,8.5 (D,Pyridine 1H),7.9,8.0 (D,pyridine 1H), 8.9

(S,Pyridine 1H), 7.4-7.5 (D, Aromatic 2H), 7-7.1 (D, Aromatic 2H)), 5.7 (S, C2Thia ring 1H),3.3,3.4 (D,C5 Thia ring 1H),3.1,3.2 (D,C5 Thia ring 1H)

Table No. One:- Imines and their 4-Thiazolidinone analogues.

Sr.No	Aldehydes (1)	Imines (2)	4-Thiazolidinones (3)
a		 2-[(E)-(5-Chloro-pyridine-2yl imino) methyl] phenol	 3-(5- Chloro-pyridine-2yl) -2- (2-Hydroxy phenyl) Thiazolidin-4-one
B		 4-[(-E)-(5-Chloro-pyridine-2yl imino) methyl] phenol	 3-(5- Chloro-pyridine-2yl)-2- (4-Hydroxy phenyl) Thiazolidin-4-one
C		 (E)-N-(4-Fluorobenzylidene)-5-Chloro-pyridin-2-amine	 3-(5- Chloro-pyridine-2yl)-2- (4-Fluoro phenyl) Thiazolidin-4-one

Results & Discussion:-

The Imines and 4-thiazolidinone analogues of 2-amino-5-chloro-Pyridine were synthesized by microwave irradiation and stirring respectively. The purity and identity of the synthesized compounds were determined by using various spectroscopic (UV, IR, ^{1}H-NMR) and chromatographic techniques.

The results of the synthesized imines are given as follows:

Table. No. Two:- Comparative data of the synthesized intermediate Imines.

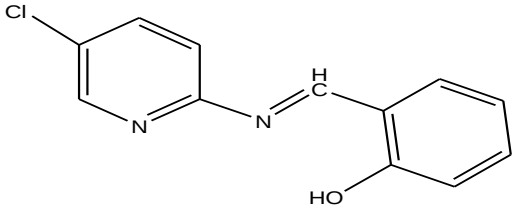
Sr. No.	Compound	Yield (%)	Reaction Time (Min)	Melting Point $^{o}C^{a}$	Rf Value[b]	λ_{max} [c]	νC=N vibration for imines[d]
1.	2a	95.60	7	111-116	0.65	313	1606
2.	2b	90.70	9	175-179	0.64	285.5	1629
3.	2c	93.06	9	95-102	0.72	247.5	1604

[a] All melting points were uncorrected.
[b]Mobile Phase [Toulene : methanol : glacial acetic acid=8 :2 :0.3]
[c] λ_{max} were measured in ethanol AR grade.
[d] Expressed in cm^{-1}; KBr.
(2a) 2-[(5-chloropyridin-2-ylimino) methyl] phenol
(2b) 4-[(5-chloropyridin-2-ylimino) methyl]phenol
(2c) N-(4-fluorobenzylidene)-5-chloropyridin-2-amine

Ethanol was employed for recrystallisation.

(2a) 2-[(5-chloropyridin-2-ylimino) methyl] phenol

Structure-



Solubility- Completely soluble in dimethyl formamide and dimethyl sulphoxide, slightly soluble in chloroform, insoluble in water.

Spectral data of 2a:

1) **Ultraviolet-Visible spectroscopic studies-**

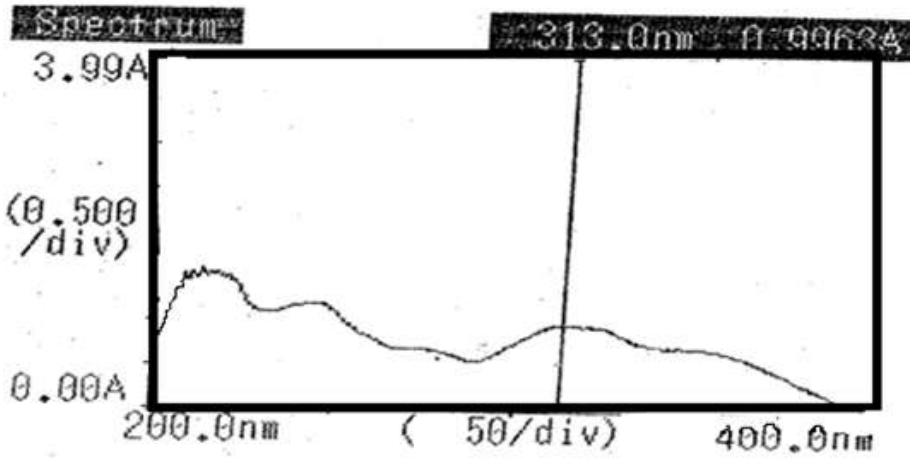


Fig. No. One:- UV absorption spectra of 2a.

λ max= 313 .0 nm (In Ethanol AR)

Rotational and vibrational studies

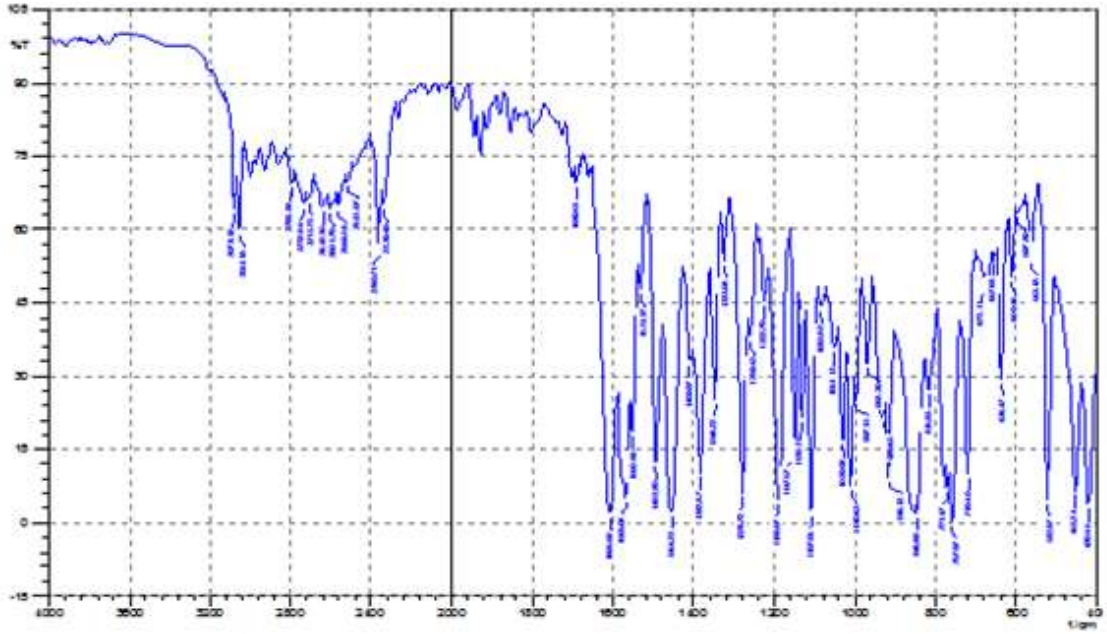


Fig.No. Two:- IR spectra of 2a

Table.No. Three:- IR data of 2a.

Frequency cm^{-1}	**Characteristic functional group**
3375	-OH stretching
3051	Aromatic - CH stretching
1606	(-C=N) stretching
1492	-OH bending
757	Aromatic o-disubstituted –CH bending
719	-C-Cl stretching

^{1}H-NMR studies

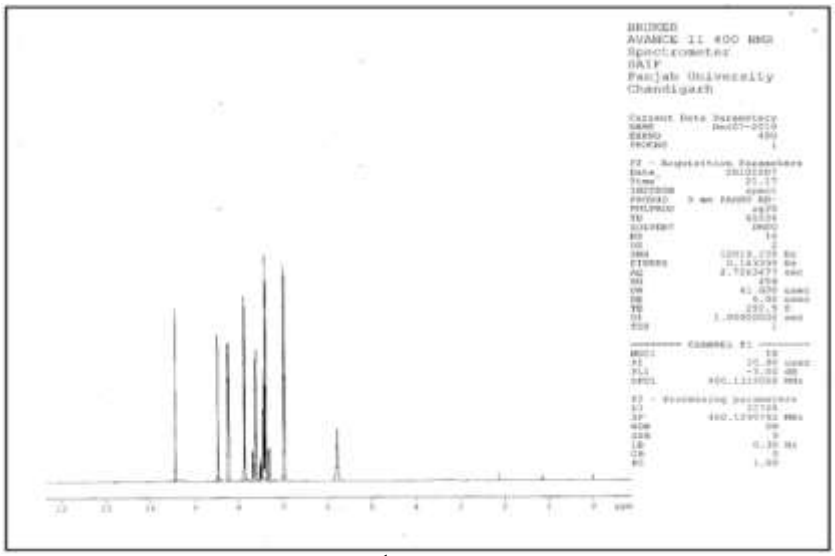
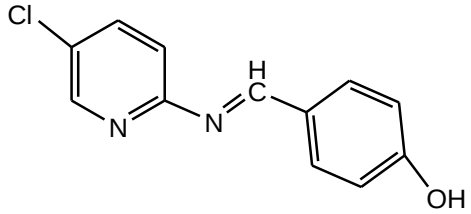


Fig.No Three:- ^{1}H-NMR spectra of 2a.

Table.No. Four:- ^{1}H-NMR data of 2a.

Chemical shift (δ)	**Proton or signal characteristic**
9.4	Singlet, Pyridine 1H
8.5	Singlet, =CH- 1H
7.85,7.98	Doublet, Pyridine 1H
7.2-7.67	Multiplet, Aromatic 3H
6.94,6.99	Doublet, Aromatic 2H
5.8	Singlet, -OH

(2b) 4-((E)-(5-chloropyridin-2-ylimino) methyl)phenol
Structure



Solubility- Completely soluble in dimethyl formamide and dimethyl sulphoxide, slightly soluble in chloroform, insoluble in water.

Spectral data of 2b:

1) Ultraviolet-Visible spectroscopic studies

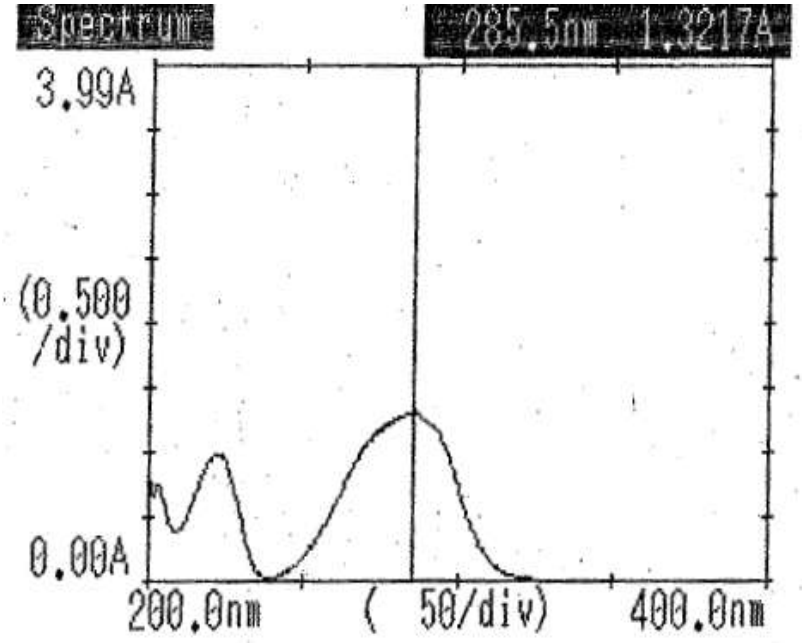


Fig.No. Four:- UV absorption spectra of 2b.

λ max= 285.5 nm (In ethanol AR)

2) Rotational and vibrational studies

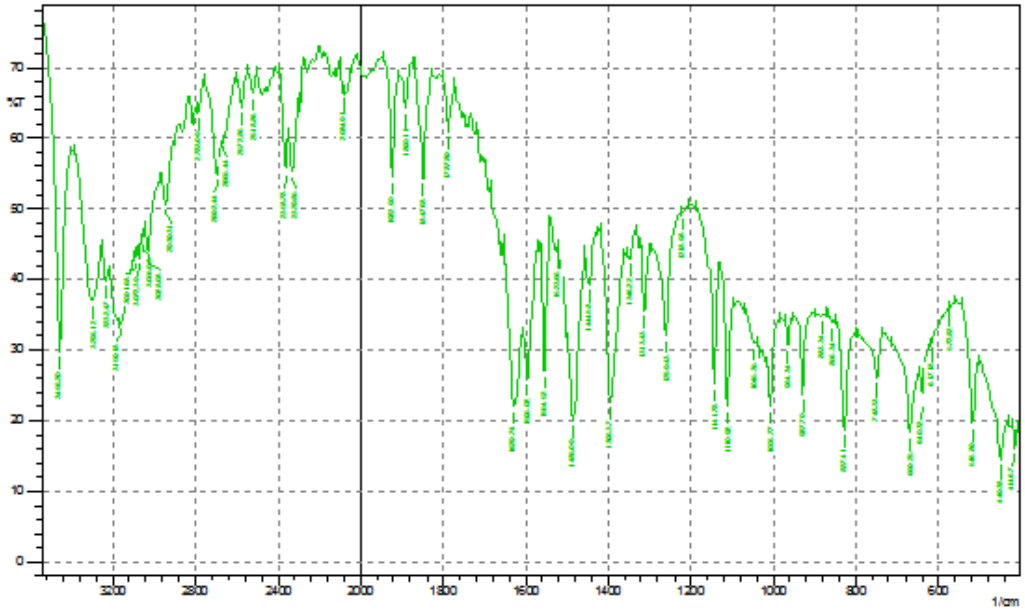


Fig.No.Five:- IR spectra of 2b.

Table.No.Five:- IR data of 2b.

Frequency cm^{-1}	**Characteristic functional group**
3456	-OH stretching
3055	Aromatic - CH stretching
1629	(-C=N) stretching Vibration
1485	-OH bending
748	-C-Cl stretching
827	Aromatic p- disubstituted –CH bending

3)^{1} H-NMR studies

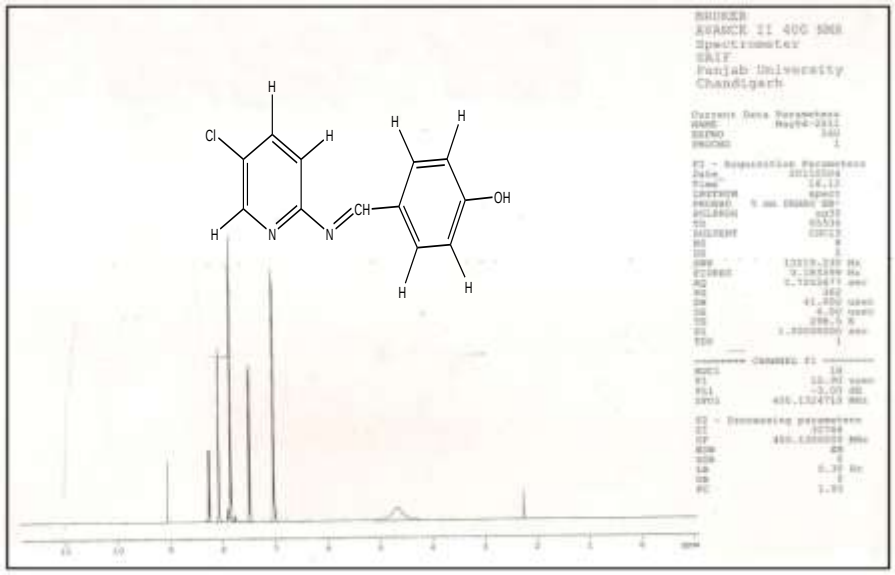
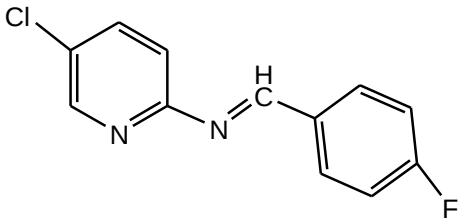


Fig.No.Six:- ^{1}H NMR spectra of 2b.

Table.No.Six:- ^{1}H NMR data of 2b.

Chemical shift (δ)	**Proton or signal characteristic**
9.1	Singlet, Pyridine 1H
8.28 , 8.3	Doublet, Pyridine 1H
8.03	Singlet, =CH- 1H
7.85,7.87	Doublet, Pyridine 1H
7.45,7.46	Doublet, Aromatic 2H
6.99, 7	Doublet, Aromatic 2H
4.62	Singlet, -OH

(2c) N-(4-fluorobenzylidene)-5-chloropyridin-2-amine
Structure



Solubility- Completely soluble in dimethyl formamide and dimethyl sulphoxide, Slightly soluble in chloroform, insoluble in water.

Spectral data of2c

1) Ultraviolet-Visible spectroscopic studies-

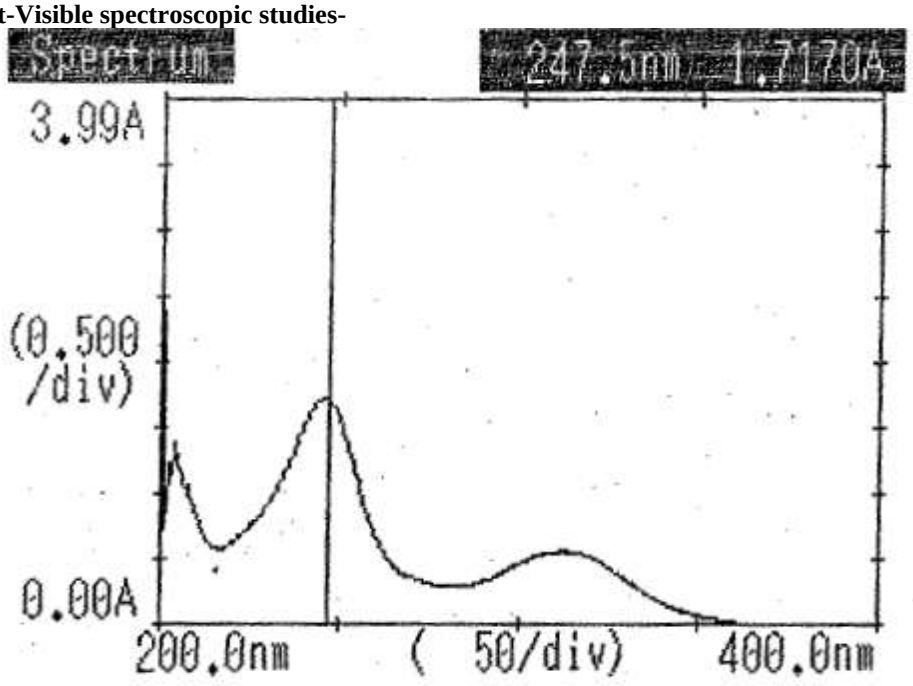


Fig.No.Seven:- UV absorption spectra of 2c.

λ max= 247.5 nm (In ethanol AR)

2) Rotational and vibrational studies

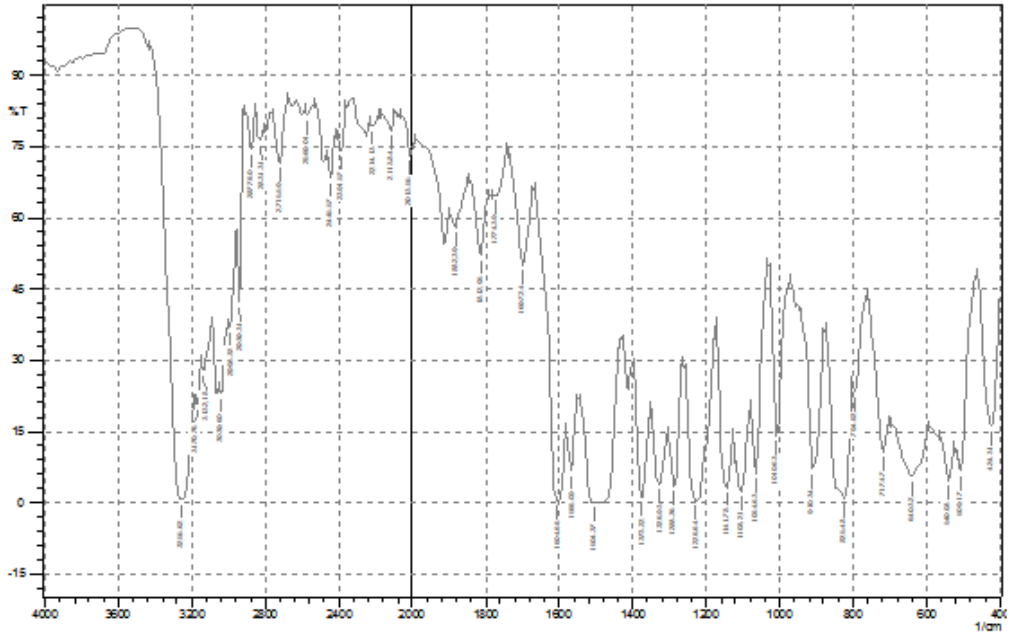


Fig.No.Eight:- IR spectra of 2c.

Table.No.Seven:- IR data 2c.

Frequency cm^{-1}	**Characteristic functional group**
3039	Aromatic - CH stretching
1604	(-C=N) Stretching Vibration
1373	-C-F Stretching
717	-C-Cl Stretching
825	Aromatic p- disubstituted –CH bending

3) ^{1}H-NMR studies

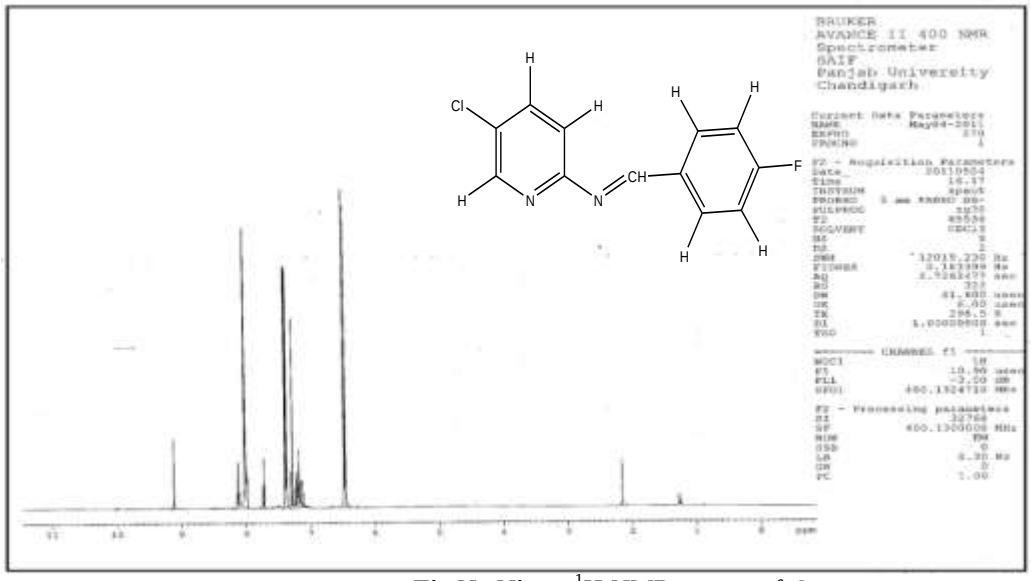


Fig.No.Nine:- ^{1}H-NMR spectra of 2c.

Table.No.Eight:- H-NMR of 2c.

Chemical shift(δ)	**Proton or signal characteristic**
9.1	Singlet, Pyridine - 1H
7.99 , 8.02	Doublet, Pyridine 1H
7.74	Singlet, =CH- 1H
7.37,7.30	Doublet, Pyridine 1H
7.1 , 7.3	Doublet, Aromatic 2H
6.4	Doublet, Aromatic 2H

The results of the synthesized 4-thiazolidinone analogues are as follows:

Table No. Nine:- Comparative data of the synthesized 4-thiazolidinone analogues.

Compounds	**Yield (%)**	**Reaction Time (Min)**	**Melting Point $^{o}C^{a}$**	**Rf value[b]**	**λ_{max}[c]**	**vC=O stretch of thiazolidinone nucleus[d]**
3a	88.5	180	260-264	0.58	236	1724
3b	86.4	120	283-289	0.56	222.5	1712
3c	89.7	120	268-273	0.57	242	1726

[a] All melting points were uncorrected
[b]Mobile Phase [Toulene : methanol : glacial acetic acid=8 :2 :0.3]
[c] λ_{max} were measured in ethanol AR grade.
[d] Expressed in cm^{-1}; KBr.
3a: 3-(5-chloropyridin-2-yl)-2-(2-hydroxyphenyl)thiazolidin-4-one
3b: 3-(5-chloropyridin-2-yl)-2-(4-hydroxyphenyl) thiazolidin-4-one
3c : 3-(5-chloropyridin-2-yl)-2-(4-fluorophenyl) thiazolidin-4-one
Ethanol was employed for recrystallisation

3. Biological activity

3.1. Experimental Animals

Swiss albino mice (20-25 g) of either sex were obtained from National Toxicological Centre, Pune, India. They were housed under standard conditions like temperature (24 $\pm 1^{0}$ C), relative humidity (65±10%) and light and dark cycles (14:10 h). The animals were fed with standard pellet food (Amrut Laboratory, Pune) and water *ad libitum.* .The screening protocol was approved by the Institution of Ethics Committee protocol (Protocol No.DYPIPSR/IAEC/10-11/P-19).

3.2. Acute toxicity study

The synthesized compounds were administered to mice at different doses up to 2000 mg/kg p.o. and observed for any toxicity and behavioural changes continuously for 30 min, 2 hr and up to 24 hr to detect changes in the autonomic or behavioural responses and also for tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma. They were then monitored for anymortality for the following 14 days. The acute toxicity studies were carried out according to OECD/OCDE Guidelines 423 (2004). As there was no toxic reaction or mortality observed, the synthesized compounds were found to be devoid of any toxicity upto the dose level of 2000 mg/kg and were found to be safe. From the acute toxicity studies, the dose of 100 mg/kg was selected for further evaluation of anticonvulsant activity.

3.3. Evaluation of Anticonvulsant activity

Isoniazid-induced convulsions model in mice

The anticonvulsant activity of the synthesized 4-thiazolidinones was evaluated using the Isoniazid-induced convulsions model in mice(Nandhakumar et al.,2008;). Albino mice of either sex weighing 20– 25 g were selected and divided into seven groups of six animals each separately for the experimental model. Different groups of animals were treated. The Normal Control group (NC) (Group1) vehicle D.W. (10 ml/kg, p.o.) and CMC 1%,(Group2) treated by Isoniazid 500mg/kg i.p. Positive control (Group3) treated by Isoniazid 500mg/kg i.p in distilled water with standard drug Diazepam (1 mg/kg, i.p) in vehicle. The treatment of synthesized test drugs (2a-c; 3a-c) 100mg/kg p.o given to Group 4-7 with inducer Isoniazid 500mg/ kg in distilled water i.p.

Results & Discussion:-

Synthesis

The aryl substituted N-benzylidene-5-chloropyridin-2-amine (2a-c) were prepared in excellent yields in a one-step reaction of 2-amino-5-chloropyridine with various substituted aryl aldehydes (1a–c) in ethanol:water solvent using our previously reported microwave irradiation method. The conventional reaction for the synthesis of Schiff's bases require longer reaction times (360–420 min reflux) for the completion of the reaction. In contrast, the microwave method required shorter reaction times (7–9 min for completion of reaction) with improved yields (90.7-95.6%).The synthesised Schiff's base intermediates (2a–c) were characterised by the presence of strong band at 1604–1629 cm^{-1} for the N,C imino group. The ^{1}H NMR spectra also showed a singlet signal equivalent to 1 proton for =CH- group between 7.74 and 8.5 ppm, confirming the formation of Schiff's bases.

The synthesised intermediates were further utilised for the synthesis of C-2 substituted 3-(5-chloropyridin-2-yl) thiazolidin-4-one analogues(3a–c) containing 4 –thiazolidinone nucleus by our reported method of stirring. The reaction was carried out in the presence of molecular sieves [MS (1– 2 g, 3A· 1.5 mm)] to remove the water generated during the cycloaddition reaction. The stirring method gave the 4 –thiazolidinone derivatives in high yields (86.4-89.7%) in shorter reaction times(120-180 min). The IR spectra of the synthesised derivatives were characterised by the presence of a strong band at 1712–1726 cm^{-1} for the ring carbonyl group, which is considered a strong confirmation for the thiazolidinone nucleus formation. Another piece of evidence for cyclization is the appearance of a singlet signal equivalent to 1 proton in 1H NMR spectrum between 5.7and 6.0 ppm (C2, CH) a doublet signal equivalent to 1 proton between 3.3 and 3.6 ppm (C5, CH) and a doublet signal equivalent to 1 proton between 3.1 and 3.5 ppm (C5, CH) which represent the formation of thiazolidinone nucleus.

Biological study

All the newly synthesised N-benzylidene-5-chloropyridin-2-amine (2a-c) and 3-(5-chloropyridin-2-yl)thiazolidin-4-one analogues(3a–c) were tested in animal models for their anticonvulsant activity.

The anticonvulsant activity was evaluated by the Isoniazid-induced convulsions model in mice. The results of the anticonvulsant screening of synthesized imines and 4-thiazolidinones were evaluated using Dunnett's test for multiple comparison. The values were expressed as mean ±S.E.M. values and *$p<0.05$, **$p< 0.01$ when compared with vehicle treated control group Pretreatment with test drugs significantly ($p< 0.01$**$p<0.05$*) delayed the appearance latency of the first complete convulsion, as well increased the survival time. The synthesized imines at the dose levels of 100 mg/kg, i.p significantly inhibited ($p<0.01$**) isoniazid induced convulsions in mice. However, the 4-thiazolidinones were found to exhibit more significant ($p< 0.01$**) anti-convulsant activity as compared to their imines. All the tested compounds were less active as compared to the standard Diazepam. Among all the synthesized 4-thiazolidinones, compound 3c, 3-(5-chloropyridin-2-yl)-2-(4-fluorophenyl) thiazolidin-4-one with a p-fluoro substituted aryl ring at C2 position of the 4-thiazolidinone nucleus showed highest activity and 3a compound 3-(5-chloropyridin-2-yl)-2-(2-hydroxyphenyl) thiazolidin-4-one with 2–OH substituted aryl ring at C2 position shows lowest activity. The results of the Anticonvulsant study are given in Figure No. 1, 2 respectively.

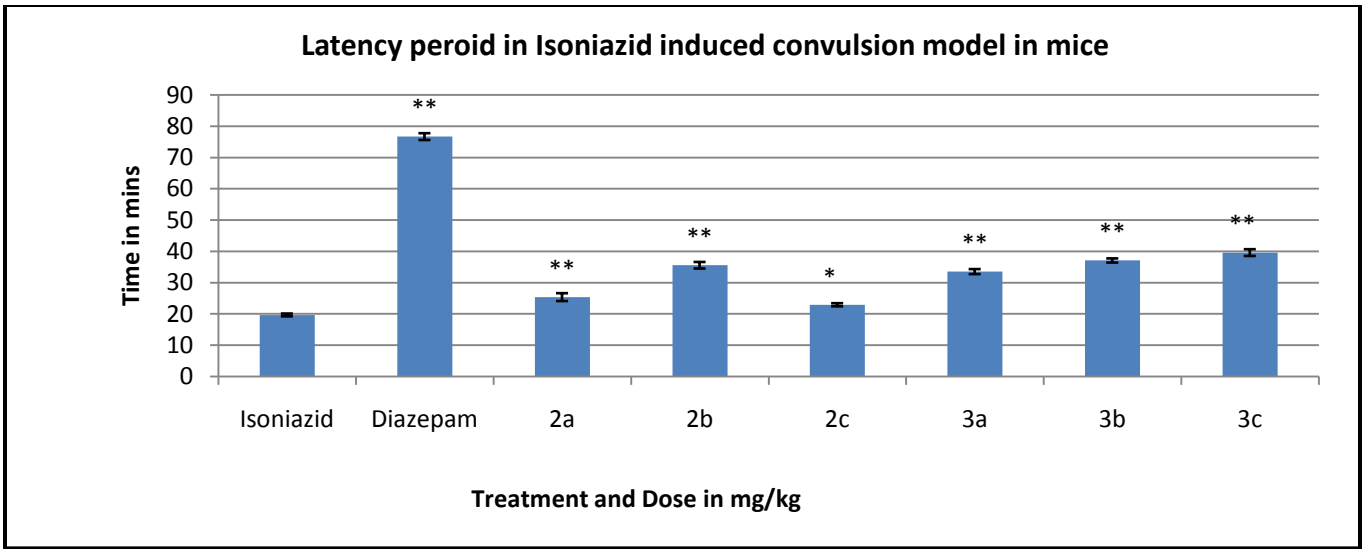


Figure.No.Ten:- Effect of synthesized imines and 4-thiazolidinone derivatives on isoniazid induced convulsions in mice.

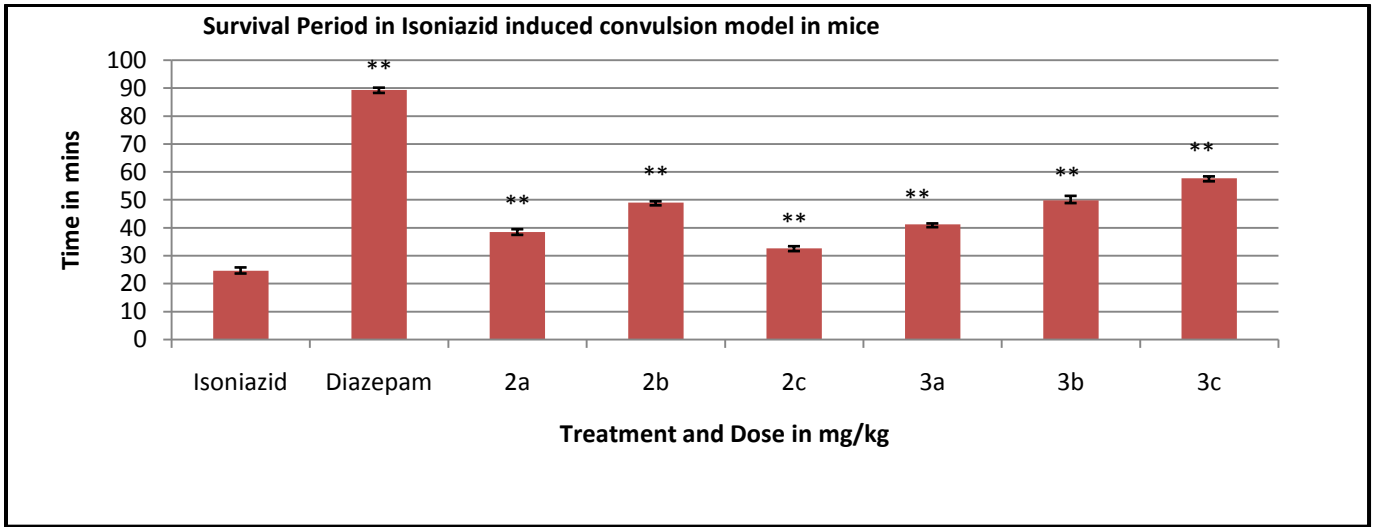


Figure.No.Eleven:- Effect of synthesized imines and 4-thiazolidinone derivatives on Isoniazid induced convulsions in mice.

Conclusion:-

In the present study, the docking, synthesis and anticonvulsant activity of 4-thiazolidinone derivatives have been described. The synthesis of the aryl substituted N-benzylidene-5-chloropyridin-2-amine (Schiff's base) and C-2 substituted 3-(5-chloropyridin-2-yl)thiazolidin-4-one (3a–c) were carried out by us using a new green route method of microwave irradiation and stirring resulting with improved yields in shorter reaction times. It was observed that 4-F, 4-OH moiety on phenyl ring of 4-thiazolidinones was found to have anticonvulsant activity in the animal models. These results confirm the fact that the 4-thiazolidinone skeleton has potential as anticonvulsant agents. In conclusion, it can be stated that the 4-thiazolidinones deserve further investigation to gain insight into development of more potent and safe anticonvulsant active agents for therapeutic use.

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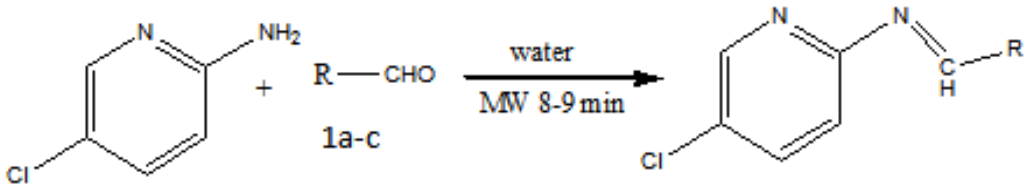
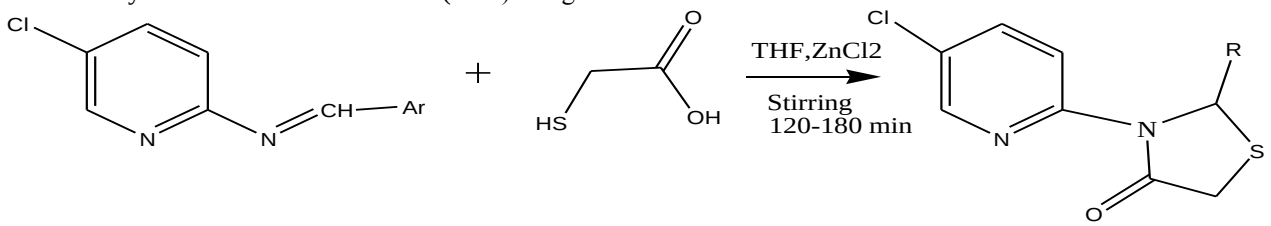
Scheme 1 Microwave assisted Synthesis of intermediate Imines (Schiff's base) using 2-Amino-5-chloro pyridine



Scheme 2 Synthesis of 4-thiazolidinones (3a–c) using Schiff's bases



Entry	Ar
2a/3a	2-OHC_6H_5
2b/3b	4-OHC_6H_5
2c/3c	4-FC_6H_5

Conflict of Interests:
Declared None.

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