Journal of Applied Pharmaceutical Sciences and Research

E-ISSN: Awaiting Assignment

*JAPSR, 1(1):16-22*

Original Article

http://www.japsr.in



# ANTICONVULSANT ACTIVITY OF ISONICOTINIC ACID HYDRAZONE DERIVATIVES USING MES, scPTZ AND ROTOROD NEUROTOXICITY MODELS

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**ABSTRACT**

**Introduction:** Epilepsy is a chronic neurological disorder, involving group of nerve cells, or neurons, in the brain. Many classes of antiepileptic drugs are being prescribed and used by the stake holders but most of them are associated with serious side effects and toxicity. There is a strong need of new antiepileptic molecules with less side effects and toxicity. **Objective:** A series of aryl acid hydrazones of Isonicotinic acid hydrazide ($RINH_1$ -$RINH_{14}$) were synthesized and evaluated for Anticonvulsant activity. **Material and Method**: Compounds ($RINH_1$ -$RINH_{14}$) were synthesized by refluxing Isonicotinic acid hydrazide with different substituted benzaldehydes/ substituted acetophenones in absolute ethanol. Melting points of all synthesized compounds were monitored by open glass-capillary tube method on Digital Melting point apparatus and are uncorrected. The synthesized compounds were tested for anticonvulsant potential using MES and scPTZ whereas neurotoxicity was determined using Rotarod model. **Result and Discussion:** At 100mg/kg compound $RINH_{10}$ have shown 29% protection at both 0.5hr and 4.0 time interval .At 300mg/kg and 0.5 hr, compounds $RINH_4$ and $RINH_{10}$ showed 100% and 50 % protection respectively. Compounds $RINH_4$ and $RINH_{10}$ have better anti MES activity proving that halogens have prominent contribution in Anticonvulsant activity. In scPTZ screen, all synthesized Acid hydrazone **(**$RINH_1$- $RINH_{14}$ ) did not show any protection at 30, 100,300 mg/kg , at 0.5 hr and 4.0 hr duration .In rotorod test i.e neurotoxicity screen, compound $RINH_5$, $RINH_6$ , $RINH_{10}$ have shown toxicity. **Conclusion:** The synthesized new molecules were proved to be having anticonvulsant activity with less signs of neurotoxicity.

**Keywords:** Aryl acid Hydrazone,Anticonvulsant Activity,Isonicotinic acid hydrazone

***Article info:***
Received: Jan 21, 2018
Revised: Mar 16, 2018
Published Online: April 15, 2018
DOI: https://

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## INTRODUCTION

Epilepsy is a chronic neurological disorder, involving group of nerve cells, or neurons, in the brain. In epilepsy, the neurons, sometimes produces abnormal signals and cause seizures. [1] In general, nerve produces electrical and chemical signals but during a seizure, many neurons fire at the same time (500 times/second) much faster than normal which causes abnormal sensations, emotions, and behavior or epileptic seizures, muscle spasms, and loss of consciousness. It results in varying seizure types, its ability to have variations in severity and different effect from person to person, and its range of concurrent conditions. Few people may feels convulsions and lose consciousness.

People experience seizures in different modes. Epilepsy is a condition with recurrent seizures, can start at any age and may be caused by many different conditions that affect a person's brain but no definite cause can be found and effecting 0.5-1% of the population. There is continuing demand for new Anticonvulsant drugs as it has not been possible to control different kind of seizure with available drugs. [2]Acid hydrazones are an integral part of heterocycle containing medicinal compounds like antimicrobials, [3] anti-tubercular, [4] anti-cancer, [5] anti-fungal, [6] anti-viral, [7] anti-tumor, [8] anti-epileptics, [9] anti-bacterial and anti-malarial, [10] anti-inflammatory and anti-platelet. [11] The synthesis of compounds involves heating of appropriate aromatic acid hydrazides with aldehydes/ketones in various organic solvents like ethanol, methanol, tetrahydrofuran, n-butyl alcohol and glacial acetic acid.[12] The ease of preparatory procedures, better stability than imines towards hydrolysis, and easy crystallizability are all important features of hydrazones.

Electroshock Seizure test, screens the designed compounds are required to possess large hydrophobic groups in close proximity to

two electron donor nitrogen atoms.[13] This condition is fulfilled by acid hydrazones as it contains carbonyl group, hydrazono group (having two nitrogen atoms) and aryl group necessary for binding to the hydrogen binding site & aryl binding site respectively. [14] They believed to exhibit similar binding properties as that of semicarbazones. [15] Lone pair of electron on Nitrogen renders hydrazone carbon atom electron rich and because of it, this carbon atom makes acid hydrazones significantly bioactive.[16, 17]

## MATERIALS AND METHODS

### *Materials*

All chemicals & reagents used were procured from agencies such as Sigma Aldrich, Rankem, CDH, SD Fine Chem and Qualigens. Silica gel G and Silica gel $GF_{254}$ of E.Merck grade were used for thin layer Chromatography studies. Melting points of all synthesized compounds were monitored by open glass-capillary tube method on Digital Melting point apparatus (Veego India) and are uncorrected. Infra Red (IR) spectra of all compounds were recorded using KBr disc on Brucker Alpha-II FTIR Spectrophotometer. [18] 1H NMR spectrum was recorded on BRUKER DPX-300 (300 MHz) and BRUKER Avance-400 (400MHz) spectrometer in DMSO-d6/CDCl3 using tetramethylsilane as internal reference.

### *Synthetic Procedure*

Equimolar quantities of substituted benzaldehydes/ substituted acetophenone (0.01mol) and the Isonicotinic acid hydrazides (0.01mol) in 50ml of absolute ethyl alcohol were refluxed for the time duration 6-10 hrs. The conformation of product formation was done by TLC using appropriate solvents on silica gel G plates. Then the reaction mixture was poured in ice cold water, filtered the precipitate and dried in oven at low temperature. Compounds $RINH_1$ – $RINH_{14}$ were synthesized according to the synthetic scheme as given in Figure 1. The products were recrystallized from absolute ethylalcohol. [19] Physicochemical properties of synthesized compounds are given in Table 1.

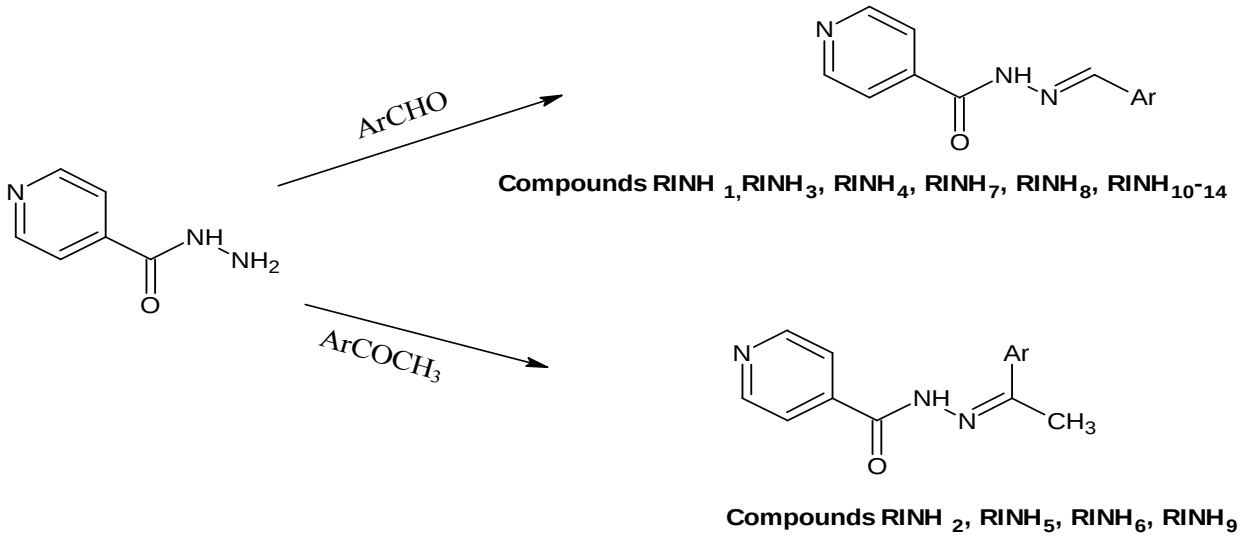


**Figure 1: Synthesis Scheme.**

### *Anticonvulsant Screening*

The evaluation for anticonvulsant activity of all the synthesized compounds was performed under Anticonvulsant Screening Program (ASP) at National Institute for Neurological Disorders and Stroke (NINDS), Rockville, USA using their reported procedures. [20]

In the anticonvulsant evaluations, male albino CF No. 1 mice (12-25g) and male albino Sprague-Dawley rats (100-150g) were used as experimental animals. All animals were allowed free access to both food and water. Test compounds were prepared in 0.5% w/v methylcellulose in water and administered either orally (p.o.) or intraperitonially (i.p.) at the dose of 0.01ml/g and 0.04ml/g body weight in mice and rats respectively. The chemical convulsants were administered subcutaneously and results were compared with Phenytoin, a standard anticonvulsant drug.

### *Maximal electroshock method (MES)*

The MES model is used for generalized tonic-clonic (GTC) or grand mal seizures. This prevents spread of seizure with an indication of a compound's ability when all neuronal brain circuits are maximally active. These seizures are highly reproducible and

are electro physiologically consistent with human seizures. In rodents 60 Hz alternating current (50mA for mice and 150mA for rats) was delivered for 2sec by corneal electrodes which have been primed with an anesthetic agent (0.5% Tetracaine HCl) in electrolyte solution. Test compounds (0.01ml/g) were given i.p. at the doses of 30, 100 and 300mg/kg and mice were tested. An animal was considered "protected" from MES induced seizures upon abolition of the hind limb tonic extensor component of the seizure. Standard dose was given of 30mg/kg orally and rats were tested at time intervals between 0.25 and 4.0 hrs. [21, 22]

***Subcutaneous Pentylene Tetrazole/ Metrazole (scPTZ/scMet) test***

Metrazol, given via subcutaneously produces clonic seizures in laboratory animals. The test detects the raised seizure threshold of a test compound in an animal and protect from clonic seizure. Pretreatment of animals were done by various doses of the test compound given by intraperitoneal route while chemical convulsant i.e. Metrazol ($CD_{97,}$ 85mg/kg mice) was injected into a loose fold of skin in the midline of the neck. To minimize stress, the animals were placed in isolation cage and observed for 30min for the presence or absence of a seizure. An episode of clonic spasm (3-5sec) of the fore and/or hind limbs and jaws was taken as the end point. Animals which do not meet these criterions were considered protected. [23]

***Acute toxicity***

Rotorod procedure was used in the determination of the toxicity study. In the procedure, rod was rotated at a speed of 6rpm. When the animal was placed on that rod, normally it could maintain its equilibrium for long time. In mice, the rotorod procedure was used to disclose minimal muscular or neurological impairment. When a mouse was placed on a rod that rotates at a speed of 6 rpm, the animal could maintain its equilibrium for long periods of time. The animal was considered toxic if it falls off this rotating rod three times during one min period. In addition to MMI, animals may exhibit a circular or zigzag gait, abnormal body posture, and spread of legs, tremors, loss of placing response and change in muscle tone. [24]

**RESULTS AND DISCUSSION**

The basic nucleus of the derivatives is presented in Figure 2.

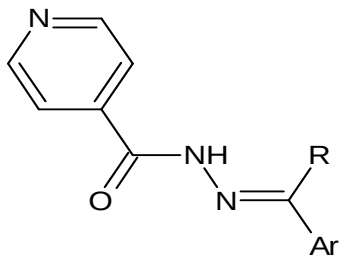


**Figure 2: Basic nucleus**

**Table 1: Physicochemical properties of compounds $RINH_1$-$RINH_{14}$**

| Comp. No. | R | Ar | Reflux time (Hrs) |
|---|---|---|---|
| **$RINH_1$** | H | 4-Pyridyl | 8 |
| **$RINH_2$** | $CH_3$ | 4-Chlorophenyl | 10 |
| **$RINH_3$** | H | 4-Bromophenyl | 6 |
| **$RINH_4$** | H | Phenyl | 7 |
| **$RINH_5$** | $CH_3$ | Phenyl | 14 |
| **$RINH_6$** | $CH_3$ | 4-Fluorophenyl | 10 |
| **$RINH_7$** | H | 2- Nitrophenyl | 12 |
| **$RINH_8$** | H | 2-Hydroxy phenyl | 6 |
| **$RINH_9$** | $CH_3$ | 4- Bromo phenyl | 8 |
| **$RINH_{10}$** | H | 4-chlorophenyl | 7 |
| **$RINH_{11}$** | H | 2-Hydroxy-3-methoxy phenyl | 8 |
| **$RINH_{12}$** | H | pyrol-2-yl | 9 |
| **$RINH_{13}$** | H | 3-Bromophenyl | 8 |
| **$RINH_{14}$** | H | 3-Hydroxy-5-chlorophenyl | 10 |

**COMPOUND $RINH_1$**

Mol. Formula $C_{12}H_{10}N_4O$; Mol. wt: 226.11; %yield: 46; $R_f$: 0.64 [(**$CHCl_3$**: EtOAc: $CH_3OH$) (1:3:0.2)]; m.p: 191-3°C; IR (KBr, $cm^{-1}$): 3370, 2998, 1688, 1568, 1470, 687;$^1$HNMR (DMSO-$d_6$, δppm): 12.319 (s, 1H, CH): 8.79 (br s, 3H, Ar-H): 8.65 (br s, 2H, Ar-H): 8.44 (s, 1H, Ar-H): 7.82 (br s, 2H, Ar-H): 7.67-7.66 (d, 2H, Ar-H).

**COMPOUND $RINH_2$**

Mol. Formula $C_{14}H_{12}N_3OCl$; Mol. wt: 273.58; %yield: 46; $R_f$: 0.35 [(**$CHCl_3$** EtOAc: $CH_3OH$) (1:3:0.1)]; m.p: 174-6°C; IR (KBr, $cm^{1}$): 3187, 2990, 1544, 1387, 749;$^1$HNMR (DMSO-$d_6$, δppm):). 10.09 (s, 1H, =NNH): 8.74 ( s, 1H, pyridyl-H): 8.69-8.67 (d, 2H, pyridyl-H): 7.95-7.92 (d, 1H, pyridyl-H): 7.88-7.85 (d, 1H, Ar-H): 7.71-7.70 (m, 2H, Ar-H): 7.57-7.54 (d, 1H, Ar-H): 2.55-2.35(m, 3H, CH).

**COMPOUND $RINH_3$**

Mol. Formula $C_{13}H_{10}N_3OBr$; Mol. wt: 303.62; %yield: 62.3; $R_f$: 0.26 [(**$CHCl_3$** EtOAc: $CH_3OH$) (1:3:0.1)]; m.p: 171-2°C; IR (KBr, $cm^{-1}$): 3254, 2980, 1667, 1552, 1401, 998,676.$^1$HNMR (DMSO-$d_6$, δppm): 12.08 (s, 1H, CH): 8.78-8.76 ( br s, 2H, Ar-H): 8.42 (s, 1H, CH): 7.81-7.64 (m, 6H, Ar-H).

**COMPOUND $RINH_4$**

Mol. Formula $C_{13}H_{11}N_3O$; Mol. wt: 225.12; %yield: 32.7; $R_f$: 0.23 [(**$CHCl_3$** EtOAc: $CH_3OH$) (1:3:0.2)];m.p: 154-6°C; IR (KBr, $cm^{-1}$):3193,3019,2990,1689,1563, 1409,763.54.$^1$HNMR (DMSO-$d_6$, δppm): 12.08 (s, 1H, CH): 8.79 (br s, 2H, pyridyl-H): 8.48 (br s, 1H=NNH): 7.84-7.83 (d, 2H, pyridyl-H): 7.76-7.75 (d, 2H, phenyl-H): 7.46-7.39 (m, 3H, phenyl-H).

**COMPOUND RINH$_5$**

Mol. Formula $C_{14}H_{13}N_3O$; Mol. wt: 239.13; %yield: 4.85; $R_f$: 0.37 [(CHCl$_3$ EtOAc: CH$_3$OH) (1:3:0.2)]; m.p: 128-30$^o$C; IR (KBr, cm$^{-1}$): 3170, 3002, 2900, 1639, 1538, 1440,755,671;$^1$HNMR (DMSO-d$_6$, δppm): 8.76 (br s, 2H, pyridyl-H): 7.87-7.80 (m, 3H, phenyl-H): 7.61 (br s, 1H, =NNH): 7.45 (br s, 2H, pyridyl-H): 7.35 (br s, 1H, phenyl-H): 2.39-2.33 (br s, 3H, CH$_3$).

**COMPOUND RINH$_6$**

Mol. Formula $C_{14}H_{12}N_3OF$; Mol. wt: 257.12; %yield: 15.56; $R_f$: 0.55 [(CHCl$_3$:CH$_3$O )(4:0.5)]; m.p: 151-3$^o$C; IR (KBr, cm$^{-1}$): 3270, 2990, 1684, 1580, 1520, 666;$^1$HNMR (DMSO-d$_6$, 300MHz, δppm): 8.76 (s, 2H, NH & pyridyl-H: 7.92-7.80 (d, 3H, pyridyl-H): 7.61 (br s, 1H,phenyl-H): 7.28 (m, 3H, phenyl-H): 2.378 (s, 3H, CH$_3$).

**COMPOUND RINH$_7$**

Mol. Formula $C_{13}H_{10}N_4O_3$; Mol. wt: 270.1; %yield: 80.0; Rf: 0.55 [(CHCl$_3$ EtOAc: CH$_3$OH) (1:3:0.2)]; m.p: 177-8$^o$C; IR (KBr, cm$^{-1}$): 3187, 3008, 1678, 1563, 1520, 1149;$^1$HNMR (DMSO-d$_6$, 300MHz, δppm): 12.420 (s, 1H, CH): 8.84-8.78 (d, 2H, pyridyl-H): 8.78-8.73 (br s, 1H, =NNH): 7.90-7.88 (d, 2H, pyridyl-H): 7.90-7.88 (d, 2H, pyridyl-H): 7.46-7.36 (m, 1H,phenyl-H): 7.00-6.84 (m, 2H,phenyl-H)

**COMPOUND RINH$_8$**

Mol. Formula $C_{13}H_{11}N_3O_2$; Mol. wt: 241.11; %yield: 70.7; Rf: 0.45 [(CHCl$_3$:CH$_3$OH) (4:1)]; m.p: 201-3$^0$C; IR (KBr, cm$^{-1}$): 3121, 3002, 1678, 1563, 1488, 1404;$^1$HNMR (DMSO-d$_6$, 300MHz, δppm): 12.33 (s, 1H, CH): 11.17 (s, 1H, phenolic-OH): 8.84-8.78 (d, 2H, pyridyl-H): 8.78-8.73 (br s, 1H, =NNH): 7.90-7.88 (d, 2H, pyridyl-H): 7.68-7.60 (d, 1H, phenyl-H): 7.46-7.36 (m, 1H, phenyl-H): 7.00-6.84 (m, 2H, phenyl-H).

**COMPOUND RINH$_9$**

Mol. Formula $C_{14}H_{12}N_3OBr$; Mol. wt: 317.63; %yield: 11.9; Rf: 0.78 [(CHCl$_3$: EtOAc: CH$_3$OH) (1:3:0.1)]; m.p: 193-5$^0$C; IR (KBr, cm$^{-1}$): 3187, 2900, 1669, 1549, 1500, 990;$^1$HNMR (DMSO-d$_6$, 300MHz, δppm): 11.07 (s, 1H, =NNH): 8.78-8.77 (br s, 2H, pyridyl-H): 7.83-7.81 (br s, 4H, phenyl-H): 7.67-7.61 (d, 2H, pyridyl-H): 2.37 (s, 3H, CH$_3$).

**COMPOUND RINH$_{10}$**

Mol. Formula; $C_{13}H_{10}N_3OCl$ Mol. wt: 288.0 %yield: 67.18; Rf: 0.52 [(CHCl$_3$: EtOAc: CH$_3$OH) (1:3:0.1)]; m.p: 162-4$^0$C ; IR (KBr, cm$^{-1}$): 3267, 2840, 1667, 1591, 1485, 822.

**COMPOUND RINH$_{11}$**

Mol. Formula $C_{14}H_{13}N_3O_3$; Mol. wt: 271.11; %yield: 75.1; Rf: 0.22 [(CHCl$_3$ EtOAc: CH$_3$OH) (1:3:0.1)]; m.p: 229-31$^0$C; IR(KBr, cm$^{-1}$): 3121, 3002, 1678, 1563, 1488, 1459.$^1$HNMR (DMSO-d$_6$, 300MHz, δppm): 12.08 (s, 1H, CH): 11.96 (s, 1H, CH): 8.78-8.77 (br s, 2H, pyridyl-H): 7.83-7.81 (br s, 3H,phenyl-H): 7.67-7.61 (d, 2H, pyridyl-H): 2.37 (s, 3H, CH$_3$)

**COMPOUND RINH$_{12}$**

Mol. Formula $C_{11}H_{10}N_4O$; Mol. wt: 214.1; %yield: 14.6; Rf: 0.51 [(CHCl$_3$: EtOAc: CH$_3$OH) (1:3:0.1)]; m.p: 240-2$^0$C; IR (KBr, cm$^{-1}$): 3280, 3008, 1678, 1560, 1520;$^1$HNMR (DMSO-d$_6$, 300MHz, δppm): 12.16-12.10 (br s, 1H, CH): 8.79 (br s, 2H, pyridyl-H): 8.48 (br s, 1H, =NNH): 7.84-7.83 (d, 2H, pyridyl-H): 7.76-7.75 (d, 2H pyrrol -H): 7.46-7.39 (m, 1H, pyrrol-H).

**COMPOUND RINH$_{13}$**

Mol. Formula $C_{13}H_{10}N_3OBr$; Mol. wt: 303.62; %yield: 13.0; Rf: 0.72 [(CHCl$_3$: EtOAc: CH$_3$OH) (1:3:02)]; m.p: 236-8$^0$C; IR (KBr, cm$^{-1}$): 3250, 2930, 1670, 1552, 1440, 990; $^1$HNMR (DMSO-d$_6$, 300MHz, δppm): 12.22-12.15 (br s, 1H, CH: 8.80-8.74 (s, 2H, NH & pyridyl-H): 8.43 (s, 1H, pyridyl-H): 8.07-8.03 (d, 1H, pyridyl-H): 7.95-7.92 (m, 2H, phenyl-H): 7.83-7.82 (m, 2H, phenyl-H).

**COMPOUND RINH$_{14}$**

Mol. Formula $C_{13}H_{10}N_3O_2Cl$; Mol. wt: 275.56; %yield: 76.0; Rf: 0.82 [(CHCl$_3$: EtOAc: CH$_3$OH) (1:3:0.1)]; m.p: 246-8$^0$C; IR (KBr, cm$^{-1}$): 3280, 2990, 1680, 1570, 1526, 1450, 666;$^1$HNMR (DMSO-d$_6$, 300MHz, δppm): 12.37 (s, 1H, CH): 11.36 (s, 1H, phenolic-OH) :(8.79-8.70 (br s, 2H, pyridyl-H): 7.85-7.83 (br s, 2H, pyridyl-H): 7.68-7.64 (m, 1H, NH:6.96-6.86 (m, 3H, phenyl-H).

***Synthesis***

Compounds (RINH$_1$ to RINH$_{14}$) were synthesized by refluxing Isonicotinic acid hydrazide with different substituted benzaldehydes/ substituted acetophenones in absolute ethanol. All synthesized Acid hydrazones have shown sharp melting point followed by single spot in TLC. Chemical structures of synthesized compounds (RINH$_1$ to RINH$_{14}$) are further confirmed by IR, 1H NMR spectroscopy. All compounds of have shown characteristic peak of NH and CH functional groups in IR spectra. The absence of peak in the region 1740-1700 cm$^{-1}$ has indicated completion of reaction and formation of desired product.

***Anticonvulsant and Neuroprotective Screening***

Compounds RINH$_1$- RINH$_{14}$ were evaluated in MES test at 30, 100 & 300 mg/kg dose level at 0.5 hr & 4.0 hr time interval. At 30 mg/kg, all synthesized Acid hydrazone (RINH$_1$- RINH$_{14}$) did not show any protection at both time intervals. At 100mg/kg compound RINH$_{10}$ have shown 29% protection at both 0.5hr and 4.0 time interval .At 300mg/kg and 0.5 hr, compounds RINH$_4$ and RINH$_{10}$ showed 100% and 50 % protection respectively. Results are presented in Table 2.In scPTZ screen, all synthesized Acid hydrazone (RINH$_1$- RINH$_{14}$) did not show any protection at 30, 100,300 mg/kg , at 0.5 hr and 4.0 hr duration .In rotorod test i.e neurotoxicity screen, compound RINH$_5$, RINH$_6$ , RNH$_{10}$ have

shown toxicity whereas compound $RINH_1$, $RINH_2$, $RINH_3$, $RINH_4$, $RINH_7$, $RINH_8$, $RINH_9$, $RINH_{11}$, $RINH_{12}$, $RINH_{13}$ and $RINH_{14}$ were found to be nontoxic. At 100mg/kg compound $RINH_6$, have shown 30% toxicity at 0.5hr time interval and 100% toxicity 4.0 hr duration while $RINH_{10}$, have shown 60% toxicity at 0.5hr time interval and 25% toxicity 4.0 hr duration.Compound $RINH_5$ were also found toxic at 300mg/kg and have shown 50% at 0.5 hr and 100% at 4.0 hr duration respectively. Compound $RINH_6$ were also found toxic at 300mg/kg and have shown 100% toxicity at 0.5 hr and 4.0 hr duration. The observations were presented in Table 3, Table 4, Table 5 and Table 6.

## CONCLUSION

Above data have indicated that Isonicotinic acid aryl hydrazones, $RINH_4$ and $RINH_{10}$ have better anti MES activity proving that halogens have prominent contribution in Anticonvulsant activity. In scPTZ screen, all synthesized Acid hydrazone **(**$RINH_1$- $RINH_{14}$ ) did not show any protection at 30, 100,300 mg/kg , at 0.5 hr and 4.0 hr duration .In rotorod test i.e neurotoxicity screen, compound $RINH_5$, $RINH_6$ , $RINH_{10}$ have shown toxicity.The MES ED50 of Phenytoin is 6.71mg/kg (i.p, 1.0 hrs.) and scPTZ TD50 is 51.02 ( i.p, mouse).

## ACKNOWLEDGEMENTS

Authors are highly thankful to the Principal, Department of Pharmacy, Ram-Eesh Institute of Vocational and Technical Education, Greater Noida, Uttar Pradesh, India for providing necessary infrastructure for undertaking the project. Authors deeply acknowledge support of members of ASP, NINDS, NIH, MD, USA for undertaking the pharmacological screening of synthesized compounds. We are also thankful to IIT Delhi, India for generating spectral data.

## CONFLICT OF INTERESTS

Authors do not have any conflict of interests

**Table 2: Preliminary anticonvulsant activity of RINH1, $RINH_2$ and $RINH_3$**

| TIME (HRS) | | 0.5 | 4.0 | 0.5 | 4.0 | 0.5 | 4.0 |
|---|---|---|---|---|---|---|---|
| | | **$RINH_1$** | | **$RINH_2$** | | **$RINH_3$** | |
| TEST | **DOSE** | **N/F** | **N/F** | **N/F** | **N/F** | **N/F** | **N/F** |
| MES | **30** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | **100** | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 |
| | **300** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| SCMET | **30** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | **100** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | **300** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| TOX | **30** | 0/4 | 0/2 | 0/4 | 0/2 | 0/4 | 0/2 |
| | **100** | 0/8 | 0/4 | 0/8 | 0/4 | 0/8 | 0/4 |
| | **300** | 0/4 | 0/2 | 0/4 | 0/2 | 0/4 | 0/2 |

**Table 3: Preliminary anticonvulsant data of $RINH_4$, $RINH_5$ and $RINH_6$**

| TIME (HRS) | | 0.5 | 4.0 | 0.5 | 4.0 | 0.5 | 4.0 |
|---|---|---|---|---|---|---|---|
| | | **$RINH_4$** | | **$RINH_5$** | | **$RINH_6$** | |
| TEST | **DOSE** | **N/F** | **N/F** | **N/F** | **N/F** | **N/F** | **N/F** |
| MES | **30** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | **100** | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 |
| | **300** | 1/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| SCMET | **30** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | **100** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | **300** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/0 |
| TOX | **30** | 0/4 | 0/2 | 0/4 | 0/2 | 0/4 | 0/2 |
| | **100** | 0/8 | 0/4 | 0/8 | 0/4 | 3/8 | 4/4 |
| | **300** | 0/4 | 0/2 | 2/4 | 2/2 | 4/4 | 1/1 |

**Table 4: Preliminary anticonvulsant data of $RINH_7$, $RINH_8$ and $RINH_9$**

| TIME (HRS) | | 0.5 | 4.0 | 0.5 | 4.0 | 0.5 | 4.0 |
|---|---|---|---|---|---|---|---|
| | | $RINH_7$ | | $RINH_8$ | | $RINH_9$ | |
| TEST | DOSE | N/F | N/F | N/F | N/F | N/F | N/F |
| MES | 30 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 100 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 |
| | 300 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| SCMET | 30 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 100 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 300 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| TOX | 30 | 0/4 | 0/2 | 0/4 | 0/2 | 0/4 | 0/2 |
| | 100 | 0/8 | 0/4 | 0/8 | 0/4 | 0/8 | 0/4 |
| | 300 | 0/4 | 0/2 | 0/4 | 0/2 | 0/4 | 0/2 |

**Table 5: Preliminary anticonvulsant data of $RINH_{10}$, $RINH_{11}$, $RINH_{12}$**

| TIME (HRS) | | 0.5 | 4.0 | 0.5 | 4.0 | 0.5 | 4.0 |
|---|---|---|---|---|---|---|---|
| | | $RINH_{10}$ | | $RINH_{11}$ | | $RINH_{12}$ | |
| TEST | DOSE | N/F | N/F | N/F | N/F | N/F | N/F |
| MES | 30 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 100 | 2/7 | 2/7 | 0/3 | 0/3 | 0/3 | 0/3 |
| | 300 | 2/5 | 0/5 | 0/1 | 0/1 | 0/1 | 0/1 |
| SCMET | 30 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 100 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 300 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| TOX | 30 | 0/4 | 0/2 | 0/4 | 0/2 | 0/4 | 0/2 |
| | 100 | 5/8 | 1/4 | 0/8 | 0/4 | 0/8 | 0/4 |
| | 300 | 3/4 | 0/2 | 0/4 | 0/2 | 0/4 | 0/2 |

**Table 6: Preliminary anticonvulsant data of $RINH_{13}$ and $RINH_{14}$**

| TIME (HRS) | | 0.5 | 4.0 | 0.5 | 4.0 |
|---|---|---|---|---|---|
| | | $RINH_{13}$ | | $RINH_{14}$ | |
| TEST | DOSE | N/F | N/F | N/F | N/F |
| MES | 30 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 100 | 0/3 | 0/3 | 0/3 | 0/3 |
| | 300 | 0/1 | 0/1 | 0/1 | 0/1 |
| SCMET | 30 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 100 | 0/1 | 0/1 | 0/1 | 0/1 |
| | 300 | 0/1 | 0/1 | 0/1 | 0/1 |
| TOX | 30 | 0/4 | 0/2 | 0/4 | 0/2 |
| | 100 | 0/8 | 0/4 | 0/8 | 0/4 |
| | 300 | 0/4 | 0/2 | 0/4 | 0/2 |

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**How to cite this article:** Sinha R, Singh UVS, Khosa RL, Jain J. Anticonvulsant Activity of Isonicotinic Acid Hydrazone Derivatives using MES, scPTZ and Rotorod neurotoxicity models. Journal of Applied Pharmaceutical Sciences and Research 2018; 1(1):16-22.