Journal of Applied Pharmaceutical Sciences and Research

E-ISSN: 2581-5520

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

Sinha R[1]*, Singh UVS[2], Khosa RL[3], Jain J[1]

[1]RamEesh Institute of Vocational & Technical Education, Greater Noida, Uttar Pradesh-201310
[2]M.C. Saxena College of Pharmacy, Lucknow
[3]School of Pharmacy, Bharat Institute of Technology, Meerut, Uttar Pradesh-250103

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://doi.org/10.31069/japsr.v1i01.13058

Correspondence:
Reema Sinha, Assistant Professor, Ram-Eesh Institute of Vocational & Technical Education, Greater Noida (UP), India.
Phone: 7838439189
Email: sinhareema2@gmail.com

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, [1] 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.

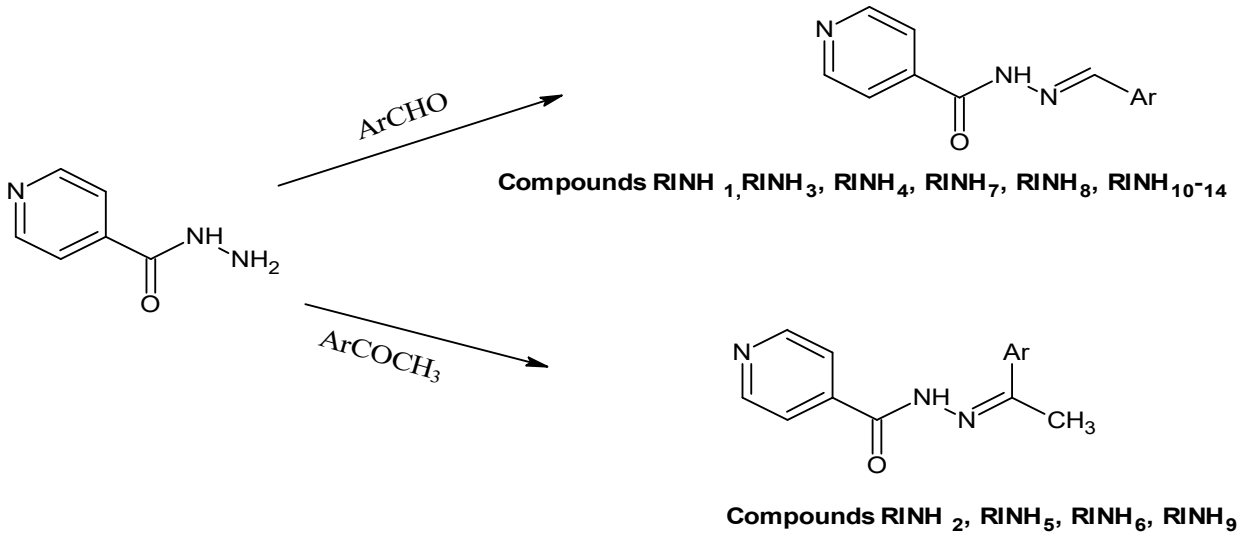

Figure 1: Synthesis Scheme.

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.

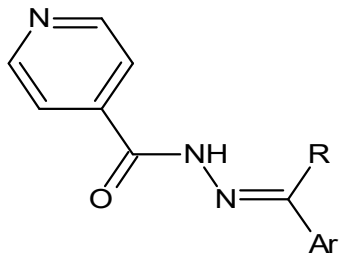

Figure 2: Basic nucleus

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: 128-30ºC; 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: 151-3ºC; 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: 177-8ºC; 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

REFERENCES

1. http://www.ninds.nih.gov/disorders/epilepsy/epilepsy.htm.

2. Kumar N, Singh L, Dashora N, Sharma C. Anticonvulsant potential of Hydrazone derivative: A Review. Scholars Academic Journal of Pharmacy. 2014; 3(5): 366-373.

3. Rollas S, Gulerman N, Erdeniz H. Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5-disubstituted-1,3,4-oxadiazol ines. Farmaco. 2002; 57: 171-174.
4. Umut SG, Nesrin GK, Ozgur G, Yavuz K, Ekrem K, Samil I, Goknur A, Meral O. Synthesis, analgesic-anti-inflammatory and antimicrobial activities. Bioorganic & Medicinal Chemistry. 2007; 15: 5738–5751.
5. Bijev A. New heterocyclic hydrazones in the search for antitubercular agents: Synthesis and in vitro evaluations. Letters in Drug Design & Discovery. 2006; 3:506-512.
6. Loncle C, Brunel J, Vidal N, Dherbomez M, Letourneux Y. Synthesis and antifungal activity of cholesterol-hydrazone derivatives. European Journal of Medicincal Chemistry. 2004; *39:1067*-1071.
7. Abdel-Aal MT, El-Sayed WA, El-Ashry EH. Synthesis and antriviral evaluation of some sugar arylglycinoylhydrazones and their oxadiazoline derivatives. Archiv der Pharmazie. 2006; 339:656-663
8. El-Hawash SAM, Abdel-Wahab AE, El-Dewellawy MA. Cyanoacetic acid hydrazones of 3-(and 4-) acetylpyridine and some derived ring systems as potential antitumor and anti-HCVagents. Archiv der Pharmazie. 2006; *339:* 14-23.
9. Dimmock JR, Vashishtha SC, Stables JP. Anticonvulsant properties of various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds. European Journal of Medicincal Chemistry. 2000; 35:241-248.
10. Rollas S, Kucukguzel SG. Biological activities of hydrazone derivatives. Molecules. 2007; 12:1910-1939.
11. Todeschini AR, Miranda AL, Silva CM, Parrini SC, Barreiro EJ. Synthesis and evaluation of analgesic, antiinflammatory and antiplatelet properties of new 2-pyridylarylhydrazone derivatives. European Journal of Medicincal Chemistry. 1998; *33:189*-199.
12. Bala S, Uppal G, Kajal A, Kamboj S, Sharma V. Hydrazones as promising lead with diversity in bioactivity- therapeutic potential in present scenario. International Journal of Pharmaceutical Sciences Review and Research. 2013; 18: 65-74.
13. Rajput AP, Rajput SS. Synthesis of benzaldehyde substituted phenyl carbonyl hydrazones and their formylation using Vilsmeier-Haack reaction. International Journal of PharmTech Research. 2009; 1(4): 1605-1611.
14. Jain J, Kumar Y, Sinha R, Kumar R, Stables J. Menthone aryl acid hydrazones: a new class of anticonvulsants. Medicinal Chemistry. 2011; 7:56-61.
15. Jones GL, Woodbury DM. In, Antiepileptic Drugs. 2nd edition, Woodbury DM, Penry JK and Pippenger. 1982 CE, Eds., Raven Press, New York. pp. 167-175.
16. Singh M, Raghav N. Biological activities of hydrazones: A Review. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3(4):26-32.
17. Singh N, Ranjana R, Kumari M, Kumar B. A Review on Biological Activities of Hydrazone Derivatives. International Journal of Pharmaceutical and Clinical Research. 2016; 8(3):162-166.
18. Silverstein RM, Webster FX. In, Spectrometric Identification of Organic Compounds. 6th Edition, Wiley India edition, India, 2006 pp.165-201.
19. Jain J, Kumar Y, Sinha R, Kumar R, Stables J. Menthone aryl acid hydrazones: a new class of anticonvulsants. Medicinal Chemistry. 2011*;* 7:56-61.
20. Porter RJ, Cereghino JJ, Gladding GD, Hessie BJ, Kupferberg HJ, Scoville B, White BG. Antiepileptic Drug Development Program. Cleveland Clinics Q. 1984, 51, 293.
21. White HS, Woodhead JH, Franklin MR. General principles: experimental selection, quantification and evaluation of anticonvulsants, In: Antiepileptic Drugs, 3rd edition, RH Levy, RH Mattson, BS Meldrum, JK Penry, FE Dreiffus. 1995a, Eds. Raven Press, New York. pp. 97-105.
22. White HS, Woodhead JH, Franklin MR. General principles: experimental selection, quantification and evaluation of anticonvulsants, In: Antiepileptic Drugs. 4th edition, RH Levy, RH Mattson, BS Meldrum, JK Penry, FE Dreiffus. 1995b, Eds. Raven Press, New York. pp. 167-175.
23. Swinyard EA, Wolff HH, Franklin MR, Woodhead JH, Kupferberg HJ, Stables JP. 1992. The Profile of Anticonvulsant Activity and Minimal Toxicity of ADD 199002 and some Prototype Antiepileptic Drugs in Mice and Rats. *NIH report,* contract no. NOI-NS-9-2328.
24. Dunham MS, Miya TA. A note on simple apparatus for detecting neurological deficit in rats and mice. Journal of the American Pharmaceutical Association. 1957; 46: 208-209.

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.