Heteroaryl-substuted Semicarbazones: Synthesis and Anticonvulsant Activity of *N*-(3-Methylpyridin-2-yl)-substituted Semicarbazones

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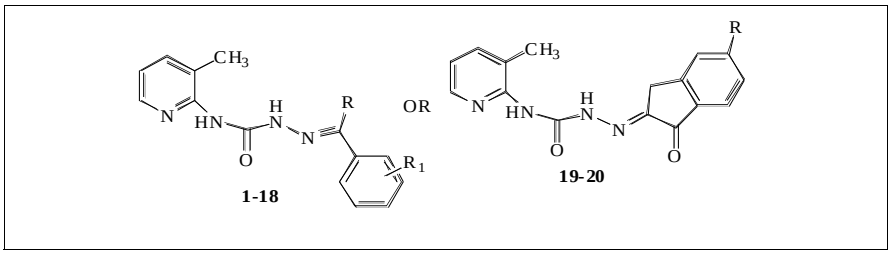

A series of substituted *N*-(3-methylpyridin-2-yl) semicarbazones was designed and synthesized to meet the structural requirements essential for anticonvulsant activity. The structures of all the synthesized compounds were confirmed by means of spectral and elemental analysis. All the compounds were evaluated for their anticonvulsant activity by maximal electroshock seizures (MES) test, subcutaneous pentylenetetrazole (scPTZ) screen, subcutaneous strychnine (scSTY) pattern test and subcutaneous picrotoxin (scPIC) seizure threshold test along with the behavioral, and neurotoxicity evaluation. A number of *N*-(3-methylpyridin-2-yl) semicarbazone derivatives exhibited significant protection after intraperitoneal administration at the dose of 100 and 300 mg/kg. Compound N^1-(3-methylpyridin-2-yl)-N^4-(isatin) semicarbazone (**19**) emerged as the most active analogue of the series, being more effective in most of the test models than ethosuximide and sodium valporate.

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Introduction.

About 2 million people in the United States are affected by epilepsy [1]; the term "epilepsy" encompasses a number of different syndromes whose cardinal feature is a predisposition to recurrent unprovoked seizures. It has afflicted many historical figures, and an enormous collection of research has been performed in an effort to understand the many facets of the disease. More than half of a century has elapsed since the anticonvulsant properties of phenytoin [2] was first evidenced in the laboratory animal models with the successful therapeutic administration in epileptic patients [3]. Today in addition to phenytoin; several AEDs (antiepileptic drugs) are widely utilized in the treatment of various forms of epilepsy [4]. Some of the other conventional drugs include carbamazepine, phenobarbital, ethosuximide, valproic acid and various benzodiazepines, in addition several new agents are in human clinical experimentation. Unfortunately, current medications are ineffective for more than one third of the patients with epilepsy [1]. Many continue to have seizures, while others experience disturbing side effects (*e.g.*, drowsiness, dizziness, nausea, liver damage) [5]. Current therapies have failed to adequately control this disorder, documenting the need for new agents with different mechanisms of action.

In recent years, the field of AED development is quite dynamic, affording many promising research opportunities. The chemical diversity and various mechanisms of action of anticonvulsants, make it difficult to identify the common pharmacophore. Unverferth *et al*. [6], suggested a pharmacophoric model by the conformational analysis of the older generation clinically active anticonvulsants drugs such as hydantoin, succinimides, glutarimides, oxazolidine-2,4-diones, pyrimidine-2,6-diones and barbituric acids, comprising aromatic rings or their equivalent in a favored orientation, electron donor moiety and a third region usually, a cyclic ureide, containing a number of hydrogen bond forming functional groups. Recently Dimmock [7-10], Pandeya [11-13], Yogeeswari [13-18] and coworkers have evaluated various aryl semicarbazones as candidate anticonvulsants. Our interest in developing semicarbazones rests upon the structural dissimilarity to existing antiepileptic drugs, so it was hoped that such novel compounds would lack the side effects seen with many of the currently available medications [7]. For the aryl semicarbazones the aryl ring and the semicarbazono group ($H_2NCONHN=$) were considered to interact at both an aryl binding site and a hydrogen bonding area, respectively [9-10], and an additional hydrophobic binding area has also been proposed. The analysis of the distance relationship

showed that aryl semicarbazones fulfill the essential demands of the pharmacophore when compared with conventional antiepileptic drugs [16,17].

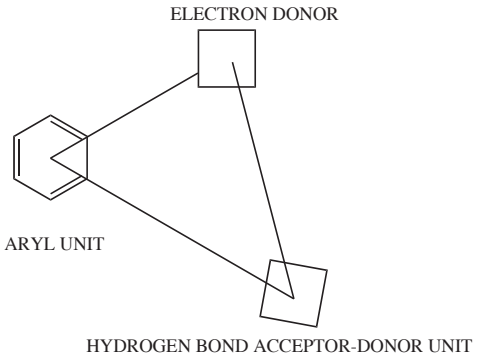


Figure 1. Pharmacophore model for anticonvulsants.

Previous studies revealed that substitution with the methyl group on the aryl binding ring of semicarbazones led to an increase in the anticonvulsant activity when the compounds were administered by the intraperitoneal route to mice [19-22]. Earlier, various methyl substituted pyridyl derivatives were found to possess antiepileptic properties [23]. With this as background, the present work focuses on the synthesis and anticonvulsant evaluation of *N*-(3-methylpyridin-2-yl) semicarbazones, towards exploring the effect of replacement of the aryl ring with heteroaryl ring *i.e.* pyridyl ring, in combination with methyl substituent on anticonvulsant activity of semicarbazones.

Results and Discussion.

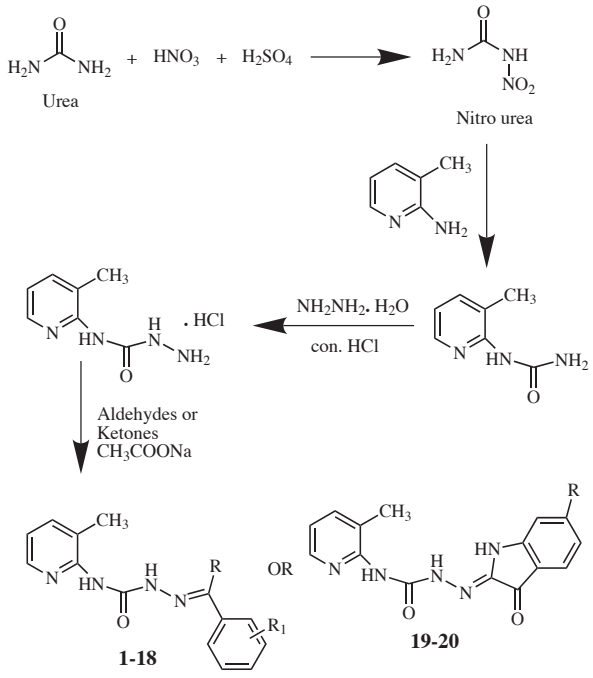
Chemistry.

In the present investigation, a series of *N*-(3-methylpyridin-2-yl) semicarbazones was synthesized and evaluated for their anticonvulsant activity. The preparation of the pyridyl semicarbazones was achieved as depicted in Scheme. Substituted pyridyl amine *i.e.* 2-amino-3-methyl pyridine, was treated with nitrourea, which led to the synthesis of 1-(3-methylpyrin-2-yl)urea. The urea derivatives on condensation with hydrazine hydrate in ethanol gave substituted semicarbazides, which further on reaction with appropriate aldehydes and ketones gave the semicarbazone derivatives *i.e.*, *N*-(3-methylpyridin-2-yl)semicarbazones (**1-20**). All the synthesized compounds were characterized by physical, analytical and spectral data. In general the IR spectra showed the C=N peak at 1620-1590 cm^{-1} and the NH stretching vibrations at 3450 cm^{-1}, amide bond at 3300-3200 cm^{-1} and 1710-1680 cm^{-1}. The ^{1}H-NMR spectrum revealed that the hydrazino proton (=N-NH) showed a singlet at δ 9.56-10.28 and the aryl NH at 8.28-9.26 both of which were D_2O exchangeable.

Pharmacology.

The synthesized compounds (**1-20**) were evaluated at dose levels of 30, 100 and 300 mg/kg intraperitoneally in mice for anticonvulsant activity by following the standard anticonvulsant drug development (ADD) program protocols [24-26]. Table 1 lists the results obtained from the initial anticonvulsant evaluation of the synthesized compounds compared to the clinically proven anti-epileptics such as phenytoin, ethosuximide and sodium valporate. The tests included one electrical and three chemoshock tests *i.e.* maximal electroshock seizure test (MES), subcutaneous pentylenetetrazole (scPTZ) seizure threshold test, subcutaneous strychnine (scSTY) pattern test and subcutaneous picrotoxin (scPIC) seizure threshold test. The acute neurological toxicity was determined by the rotorod test. Nine compounds showed activity in the preliminary MES screen, indicative of their ability to prevent seizure spread. Compounds **7**, **16**, and **19** showed protection at 100 mg/kg (0.5h) and other active compounds showed protection at 300 mg/kg dose. Compounds **2**, **12**, **15**, and **16** exhibited shorter duration of action (*i.e.* activity at 0.5 h interval only) whereas compound **1** showed late onset of action. Other compounds showed activity at both 0.5 h and 4 h intervals. In the subcutaneous pentylenetetrazole (scPTZ) screen, a test used to identify compounds that elevates seizures threshold, nine compounds (**1**, **2**, **4**, **7**, **10-12**, **15**, and **16**) showed protection. The compounds **1**, **10**, and **16** showed protection at 100mg/kg up to 0.5 h time period.

Scheme 1



Some selected compounds (**1**, **2**, **10**-**12**, **15**-**17**, and **19**) were examined in the scSTY and scPIC animal models. All the tested compounds except **1** and **11** showed protection in the subcutaneous strychnine-induced seizure model. Compound **19** showed activity at 100 mg/kg and other compounds showed activity at 300mg/kg. Only compounds **10**, **16**, and **19** exhibited a longer duration (0.5 h and 4 h) of action. The results are presented in Table 1.

In the acute neurological toxicity screen, the compounds **1**, **10** and **11**, showed activity but no neurotoxicity at the maximum dose administered (300 mg/kg), and compounds **3**, **5**, **6**, **8**, **9**, **13**, **14**, **18**, and **20** did not exhibit anticonvulsant activity as well as neurotoxicity. Compound **19** showed no neurotoxicity at the anticonvulsive dose and compound **2**, **7**, **15-17** exhibited neurotoxicity at the anticonvulsive dose. Compound **4** was found to be more neurotoxic at the anticonvulsive dose.

In the behavioral despair test, compounds except **7**, **13**, and **16**, showed significant decrease in motor activity as indicated by the actophotometer scores. The standard drug phenytoin also showed significant decrease in the locomotor activity *i.e.* possessed behavioural despair side effect. The compound with 4-chloro benzylidene substituents (**7**) showed no motor impairment with the maximum actophotometer score of 308.00±8.00 (0.5 h) and 272.50±5.06 (1 h). The semicarbazones derivatives were also studied for CNS depressant effect by porsolt's forced swim pool test and compared with carbamazepine. Compounds except **1-6**, **8**-**10** and **20**, did not show significant increase in immobility time as compared to the control, indicating significant CNS depressant than the conventional drugs (table 3).

In terms of interaction at the binding site, as proposed previously [6,9,10], the pharmacophoric descriptors were thought to be a lipophilic aryl ring and hydrogen bonding semicarbazone moiety. The distal aryl ring at the carbimino terminal (benzylidene ring) may be essential for the pharmacokinetic properties of the compounds since variation in the substituents at the distal aryl ring was found to affect the biological activity. Among the benzylidene derivatives, 4-methyl (**7**) and 2-chloro (**10**) substituents were found to be most favourable.

Replacement of the proton on the carbimino carbon atom by the methyl (**13-16**) or the phenyl (**17-18**) or the

Table 1

Anticonvulsant and Minimal Motor Impairment of 4-Methyl-substituted-pyridy semicarbazones

Comp.	Intraperitoneal injection in mice[a]									
	MES screen		scPTZ screen		scSTY screen		scPIC screen		Neurotoxicity screen	
	0.5h	4h	0.5h	4h	0.5h	4h	0.5h	4h	0.5h	4h
1	-	300	100	-	-	-	300	300	-	-
2	300	-	300	-	300	-	300	-	300	-
3	-	-	-	-	x	x	x	x	-	-
4	-	-	300	-	x	x	x	x	100	-
5	-	-	-	-	x	x	x	x	-	-
6	-	-	-	-	x	x	x	x	-	-
7	100	300	-	300	x	x	x	x	100	300
8	-	-	-	-	x	x	x	x	-	-
9	-	-	-	-	x	x	x	x	-	-
10	300	300	100	-	300	300	300	300	-	-
11	-	-	300	-	-	-	300	-	-	-
12	300	-	300	-	300	-	300	-	-	300
13	-	-	-	-	x	x	x	x	-	-
14	-	-	-	-	x	x	x	x	-	-
15	300	-	300	-	300	-	100	100	300	-
16	100	-	100	-	300	300	300	300	100	-
17	300	300	-	-	300	-	300	-	300	-
18	-	-	-	-	x	x	x	x	-	-
19	100	300	-	-	100	100	300	300	300	-
20	-	-	-	-	x	x	x	x	-	-
Phenytoin	30	30	-	-	-	-	x	x	100	100
Ethsuximide	-	-	300	-	300	-	-	-	-	-
Sod. valporate	-	300	100	-	100	-	-	-	-	-

[a]Doses of 30, 100 and 300mg/kg were administered. The figures in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The dash (-) indicates an absence of activity at maximum dose administered (300mg/kg). The cross (x) indicates the compounds not tested in the animals.

Table 2

Physical data of 3-Methyl-substituted-pyridyl-semicarbazones

#	R	R_1	Yield (%)	M.P. (°C)	Molecular Formula[b]	Mol. Weight	R_f[c]	CLog P[d]
1	H	H	57	150	$C_{14}H_{14}N_4O$	254	0.75	2.39
2	H	2-NO_2	38	60	$C_{14}H_{13}N_5O_3$	299	0.64	1.60
3	H	3-NO_2	49	145	$C_{14}H_{13}N_5O_3$	299	0.76	1.29
4	H	4-NO_2	58	95	$C_{14}H_{13}N_5O_3$	299	0.62	1.55
5	H	2-OH	62	185	$C_{14}H_{14}N_4O_2$	270	0.54	0.78
6	H	2-CH_3	67	90	$C_{15}H_{16}N_4O$	268	0.66	2.36
7	H	4-CH_3	48	220	$C_{15}H_{16}N_4O$	268	0.63	2.58
8	H	4-OCH_3	64	185	$C_{15}H_{16}N_4O_2$	284	0.64	2.45
9	H	4-$N(CH_3)_2$	58	125	$C_{16}H_{19}N_5O$	297	0.52	1.96
10	H	2-Cl	56	210	$C_{14}H_{13}N_4OCl$	288	0.66	2.60
11	H	4-Cl	65	135	$C_{14}H_{13}N_4OCl$	288	0.78	3.08
12	H	4-OH 3-OCH_3	44	250	$C_{15}H_{16}N_4O_3$	300	0.70	1.71
13	CH_3	H	72	115	$C_{15}H_{16}N_4O$	268	0.50	2.08
14	CH_3	4-OH	40	130	$C_{15}H_{16}N_4O_2$	284	0.67	1.51
15	CH_3	4-NH_2	54	72	$C_{15}H_{17}N_5O$	283	0.70	0.91
16	CH_3	4-CH_3	73	184	$C_{16}H_{18}N_4O$	282	0.84	2.34
17	C_6H_5	H	72	85	$C_{20}H_{18}N_4O$	330	0.59	3.19
18	C_6H_5	4-Br	61	65	$C_{20}H_{17}N_4OBr$	409	0.73	3.69
19	H	-	48	180	$C_{15}H_{13}N_5O_2$	295	0.62	1.04
20	F	-	78	135	$C_{15}H_{12}N_5O_2.F$	313	0.66	2.97

[a]Melting points of the compounds at their decomposition. [b]Elemental analyses for C, H, N were with in ± 0.4 % of the theoretical values. [c]Mobile phase $CHCl_3$: CH_3OH (9:1). [d]Log P was generated using Alkemey 2000 and SciLog P softwares

Table 3

CNS Study of 3-Methyl-substituted-pyridyl-semicarbazones

Compd No[a]	Actophotometer (Locomotor activity score)[b]		Immobility Time (Sec)[c]	
	0.5h	1h	Control	Test (After 1 h)
Control	318.00±13.68	288.50±11.31		
1	184.67±3.13	142.50±5.18	102.00±4.13	144.50±5.65
2	182.00±4.16	145.00±4.14	158.00±4.04	196.00±7.14
3	159.01±4.88	160.50±5.11	158.00±5.56	182.00±8.12 **
4	198.50±3.35	196.00±7.04	162.00±5.26	195.00±5.16 *
5	201.56±4.02	150.00±6.18	148.00±.4.49	168.50±2.78 *
6	231.50±5.98	192.00±4.72	154.00±5.03	166.00±2.73 **
7	308.00±8.00 NS	272.50±5.06 NS	192.00±8.58	206.50±7.64 NS
8	209.50±6.34	188.33±4.42	120.00±7.93	165.00±9.34 *
9	188.50±5.54	156.00±3.84	160.00±3.48	193.00±7.69 *
10	272.00±5.06 *	170.50±4.86	184.00±6.47	206.00±6.42 **
11	200.00±7.42	179.00±6.18	161.50±8.03	171.00±10.15NS
12	216.00±5.34	150.00±3.92	194.00±15.98	232.00±6.94 NS
13	286.53±12.64 NS	271.00±12.00 NS	198.00±11.73	207.50±6.58 NS
14	188.17±4.93	205.50±6.90	179.00±4.12	179.50±3.94 NS
15	184.00±12.43	167.00±8.64	100.50±18.12	141.50±9.49 NS
16	295.00±6.78 NS	268.00±8.48 NS	179.00±4.12	179.50±3.94 NS
17	281.33±11.42NS	194.20±8.55	205.00±5.13	212.50±4.16 NS
18	207.33±4.35	200.50±7.49	128.50±16.21	131.00±15.29 NS
19	272.50±4.84 *	212.00±4.59	100.50±18.12	111.50±9.58 NS
20	217.00±8.16	187.00±5.11	139.00±14.36	186.83±5.16 *
Phenytoin[d]	104.11±14.56	106.23±12.44	-	-
Carbamazepine[d]	-	-	131.50±9.32	207.33±08.49

[a] The compounds were tested at the dose level of 100mg/kg. [b] Each value represents the mean ± SEM of six mice significantly different from the control at $p < 0.0005$ and * $p < 0.05$. [c] Each value represents the mean ± SEM of six mice significantly different from the control at $p < 0.0005$, *$p < 0.005$ and **$p < 0.05$ Student t' test). [d] The compounds were tested at the dose level of 30mg/kg.

Table 4

Elemental Analysis of 3-Methyl-substituted-pyridyl-semicarbazones

Compound	Molecular Formula	Mol.wt	Analytical (%)			Experimental (%)		
			C	H	N	C	N	H
1	$C_{14}H_{14}N_4O$	254	66.13	5.55	22.03	66.23	5.43	22.26
2	$C_{14}H_{13}N_5O_3$	299	56.18	4.38	23.40	57.03	4.58	23.14
3	$C_{14}H_{13}N_5O_3$	299	56.18	4.38	23.40	56.96	4.56	22.98
4	$C_{14}H_{13}N_5O_3$	299	56.18	4.38	23.40	56.67	4.88	23.85
5	$C_{14}H_{14}N_4O_2$	270	62.21	5.22	20.73	62.21	5.22	20.73
6	$C_{15}H_{16}N_4O$	268	67.15	6.01	20.88	67.46	6.89	21.46
7	$C_{15}H_{16}N_4O$	268	67.15	6.01	20.88	67.78	6.34	21.32
8	$C_{15}H_{16}N_4O_2$	284	63.37	5.67	19.71	63.65	5.87	19.98
9	$C_{16}H_{19}N_5O$	297	64.63	6.44	23.55	64.42	6.93	23.85
10	$C_{14}H_{13}N_4OCl$	288	58.24	4.54	19.40	58.78	4.84	19.49
11	$C_{14}H_{13}N_4OCl$	288	58.24	4.54	19.40	59.04	5.02	19.32
12	$C_{15}H_{16}N_4O_3$	300	59.99	5.37	18.66	59.69	5.68	18.09
13	$C_{15}H_{16}N_4O$	268	67.15	6.01	20.88	67.31	6.42	21.32
14	$C_{15}H_{16}N_4O_2$	284	63.37	5.67	19.71	63.64	5.87	19.89
15	$C_{15}H_{17}N_5O$	283	63.59	6.05	24.72	63.17	6.17	24.01
16	$C_{16}H_{18}N_4O$	282	68.06	6.43	19.84	68.28	6.14	20.24
17	$C_{20}H_{18}N_4O$	330	72.71	5.49	16.96	72.03	5.23	16.45
18	$C_{20}H_{17}N_4OBr$	409	58.69	4.19	13.69	58.31	4.38	14.01
19	$C_{15}H_{13}N_5O_2$	295	61.01	4.44	23.72	61.27	4.26	23.32
20	$C_{15}H_{12}N_5O_2.F$	313	57.51	3.86	22.35	57.02	3.62	21.97

isatinimino ring (**19-20**) leading to increase in the size of the distal aryl binding groups has shown variation in activity, due to additional Vander Waals bonding or alternatively steric impedance to alignment at the binding site. Among the acetophenone derivatives, amino and methyl groups when substituted at the 4-position (**15**, **16**), exhibited anticonvulsant activity in all four animal models. Subsequently the bulkier phenyl ring with bromo substitution (**18**) led to complete loss of activity whereas the unsubstituted compound (**17**) retained activity in three animal models of seizure. Similarly the unsubstituted isatinimino derivative (**19**) was found to show better activity profile than the fluoro substituted compound (**20**) and emerged as the most effective when compared to the benzylidene and acetophenone derivatives.

The MES and scPTZ have become the most widely employed seizures models for the early identification and high-throughput screening of investigational antiepileptic drugs and only a very few standard anticonvulsants exhibit a broad spectrum of activity in all the threshold models. In this respect, it is clear that *N*-(3-methylpyridin-2-yl) semicarbazones have the potential to treat a wide range of seizure types by their multiple mechanism of action as indicated by their activity in four animal models of seizures, *viz.* MES, scPTZ, scSTY, and scPIC tests. Five compounds had shown activity in all the four screens, exhibiting a broad spectrum of anticonvulsant activity. The compounds were found to be equipotent or more potent as compared to some of the conventional AED *i.e* phenytoin, ethosuximde, sodium valporate, in one or other anticonvulsant screens.

In conclusion, the present work indicates that the aryl ring of the semicarbazones can be replaced by other lipophilic heteroaryl ring *i.e*. pyridine ring, which led to a series of compounds with broad spectrum of activity in the anticonvulsants screens with lesser neurotoxicity. In accordance with our previous work, methyl substitution has been found to be favorable for the anticonvulsant activity. Compound with isatinimino substitution (**19**) emerged as the most effective compound with broad spectrum of activity and lesser neurotoxicity.

EXPERIMENTAL

Chemistry.

Melting points were determined in one end open capillary tubes using Buchi 530 melting point apparatus and are uncorrected. The homogeneity of the compounds was monitored by TLC, on silica gel G (Merck) coated aluminium plates, using chloroform: methanol (9:1) as solvent system. Elemental analyses (C, H, and N) were undertaken with Perkin-Elmer model 240C analyzer. Infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded for the compounds on Jasco IR report 100 (KBr) and Brucker Avance (300 MHz) instruments respectively. Chemical shifts are reported in parts per million (ppm) using tetra-methylsilane as internal standard. All exchangeable protons were confirmed by the addition of D_2O. Log P values were calculated using Alkemy-2000 and Scilog P software (Tripos Co.).

Preparation of 1-(3-Methylpyrin-2-yl)urea.

1-(3-Methylpyrin-2-yl)urea was prepared by following the nitro urea method [9]. Addition of a saturated aqueous solution of nitrourea to equimolar quantity of 2-amino-3methyl-pyridine in room temperature, gave an immediate white precipitate which was washed and dried at room temperature; IR (Potassium bromide): 3400 (Ar C-H def), 3340 (Secondary -NH), 1700 (O=C), 1320 (Ar-NH), 750 (subs. Ar), ^{1}H NMR (DMSO-d_6, ppm, 300 MHz): δ 2.08 (s, 3H, Pyridyl-CH_3), 7.21-7.58 (m, 3H,

Pyridyl-H), 8.12 (s, 1H, Pyridyl-NH, D_2O exchangeable), 10.08 (s, 2H, CONH, D_2O exchangeable).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.62: H, 16.00: N, 27.80: O, 10.58. Found: C, 54.92: H, 16.08 N, 33.98: O, 9.58.

Synthesis of *N*-(3-Methylpyridin-2-yl) semicarbazide.

1-(3-Methylpyrin-2-yl)urea (0.05 mol) and excess of hydrazine hydrate (0.1 mol) in ethanol were refluxed for 24 hrs. The two third volume of alcohol was distilled by vacuum distillation unit and poured into ice. The resultant precipitate was collected by filtration, washed with water and dried. The solid was recrystallised with 90% alcohol; IR (Potassium bromide): 3400 (Ar C-H def), 3280 (Sec. O=C-NH), 1640 (O=C), 760 (subs. Ar); ^{1}H NMR (DMSO-d_6, ppm, 300 MHz): δ 2.18 (s, 3H, Pyridyl-CH_3), 7.14-7.60 (m, 3H, Pyridyl-H), 5.68 (s, 2H, NH_2, D_2O exchangeable), 8.04 (s, 1H, Pyridyl-NH, D_2O exchangeable), 9.94 (s, 1H, CONH, D_2O exchangeable).

Anal. Calcd for $C_7H_{10}N_4O$: C, 50.59: H, 16.07: N, 33.17: O, 9.63. Found: C, 49.87: H, 15.66: N, 34.08: O, 8.40.

Synthesis of *N*-(3-Methylpyridin-2-yl) semicarbazones.

The *N*-(3-methylpyridin-2-yl) semicarbazones was synthesized from the corresponding semicarbazide hydrochloride salt *i.e.* by the addition of conc. hydrochloric acid to the solution of semicarbazide in ethanol, according to a reported procedure [15]. To the solution of *N*-(3-methylpyridin-2-yl) semicarbazide hydrochloride salt (0.001 mol, 600-800 mg) in 25 ml of methanol was added sodium acetate solution in water (0.06 g in 2 ml of water). This mixture was added to appropriate aldehyde or ketone in alcohol, with stirring. The reaction was carried out for 5-10-mins. The solid product was collected by filtration, dried and recrystallized from hot alcohol. The compounds were mixtures of E/Z isomers. The IR spectra of the semicarbazone derivatives (Table 2) were identical in the following aspects; IR (Potassium bromide): 3380 (Sec. N-H), 3310 (amide-NH), 3090 (Ar-C-H), 1680 (O=C), 1580-1540 (C=N), 740 (Sub. Ar). ^{1}H NMR (300 MHz,) spectra of some representative compounds are as follows:

Benzaldehyde *N*-(3-methylpyridin-2-yl)semicarbazone (**1**).

^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H, Pyridyl-CH_3), 7.20-7.81 (m, 8H, Pyridyl & Ar-H), 8.60 (s, 1H, imine H), 9.24 (s, 1H, Pyridyl-NH, D_2O exchangeable), 9.98 (s, 1H, CONH, D_2O exchangeable).

2-Hydroxybenzaldehyde *N*-(3-methylpyridin-2-yl)semicarbazone (**5**).

^{1}H NMR (DMSO-d_6): δ 2.10 (s, 3H, Pyridyl-CH_3), 6.94-7.86 (m, 7H, Pyridyl & Ar-H), 8.48 (s, 1H, imine H), 9.05(s, 1H, Pyridyl-NH, D_2O exchangeable), 9.56 (s, 1H, CONH, D_2O exchangeable), 10.58 (s, 1H, ArOH, D_2O exchangeable).

4-Methylbenzaldehyde *N*-(3-methylpyridin-2-yl)semicarbazone (**7**).

^{1}H NMR (DMSO-d_6): δ 2.14 (s, 3H, Pyridyl-CH_3), 2.24 (s, 3H, ArCH_3), 6.74-7.96 (m, 7H, Pyridyl & Ar-H), 8.52 (s, 1H, imine H), 8.75 (s, 1H, Pyridyl-NH, D_2O exchangeable), 9.56 (s, 1H, CONH, D_2O exchangeable).

4-Methoxybenzaldehyde *N*-(3-methylpyridin-2-yl)semicarbazone (**8**).

^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, Pyridyl-CH_3), 3.68 (s, 3H, OCH_3), 7.16-8.10 (m, 7H, Pyridyl & Ar-H), 8.24 (s, 1H, imine H), 8.64 (s, 1H, Pyridyl-NH, D_2O exchangeable), 9.14 (s, 1H, CONH, D_2O exchangeable).

4-Hydroxy-3-methoxybenzaldehyde *N*-(3-methylpyridin-2-yl)-semicarbazone (**12**).

^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, Pyridyl-CH_3), 3.64 (s, 3H, OCH_3), 7.14-7.78 (m, 6H, Pyridyl & Ar-H), 8.24 (s, 1H, imine H), 8.42(s, 1H, Pyridyl-NH, D_2O exchangeable), 8.64 (s, 1H, CONH, D_2O exchangeable) 10.28 (s, 1H, ArOH, D_2O exchangeable).

1-(4-Hydroxyphenyl)ethan-1-one *N*-(3-methylpyridin-2-yl)semicarbazone (**14**).

^{1}H NMR (DMSO-d6): δ 2.02 (s, 3H, CH_3), 2.14 (s, 3H, Pyridyl-CH_3), 7.04-7.86 (m, 7H, Pyridyl & Ar-H), 8.60 (s, 1H, Pyridyl-NH, D_2O exchangeable) 9.26(s, 1H, CONH, D_2O exchangeable), 9.84 (s, 1H, ArOH, D_2O exchangeable).

1-(4-Aminophenyl) ethan-1-one *N*-(3-methylpyridin-2-yl)semicarbazone (**15**).

^{1}H NMR (DMSO-d6): δ 1.98 (s, 3H, CH_3), 2.27 (s, 3H, Pyridyl-CH_3), 5.34 (s, 2H, Ar-NH_2, D_2O exchangeable), 7.18-7.56 (m, 7H, Pyridyl & Ar-H), 8.68 (s, 1H, Pyridyl-NH, D_2O exchangeable), 10.04 (s, 1H, CONH, D_2O exchangeable).

1-(4-Methylphenyl) ethan-1-one *N*-(3-methylpyridin-2-yl)semicarbazone (**16**).

^{1}H NMR, (DMSO-d6): δ 1.92 (s, 3H, CH_3), 2.24 (s, 6H, Pyridyl- & ArCH_3), 7.28- 8.02 (m, 7H, Pyridyl & Ar-H), 8.28 (s, 1H, ArNH, D_2O exchangeable), 10.20 (s, 1H, CONH, D_2O exchangeable).

Diphenylmethanone *N*-(3-methylpyridin-2-yl)semicarbazone (**17**).

^{1}H NMR, (DMSO-d6): δ 2.22 (s, 3H, ArCH_3), 7.18-8.16 (m, 13H, ArH), 8.54 (s, 1H, ArNH, D_2O exchangeable), 10.20 (s, 1H, CONH, D_2O exchangeable).

Pharmacology.

Male albino mice (CF-1 Strain, 18-25g) and male albino rats (Sprague-Dawely, 100-150 g) were used as experimental animals. All the test compounds were suspended in 30 % PEG. The animals were kept at 24 ℃, in the groups of 5 per cage receiving chow pellets and water. The light dark cycle was 12h:12h. Efforts were made in order to avoid any unnecessary distress to the animals. All the animal tests have been performed in accordance with the animal ethics approval of the institute.

Anticonvulsant Screening.

The preliminary anticonvulsant evaluation was done using reported procedures [24-26]. All the test compounds were administered intraperitoneally in a volume of 0.01 ml/g body weights for mice and 0.004 ml/g body weights for rats at doses of 30, 100, and 300 mg/kg to one to four mice. Anticonvulsant activity was assessed after 30 min. and 4 hr after administration. Activity was established using MES, scPTZ, scSTY and scPIC tests and data are presented in the tables 2 & 3.

Neurotoxicity Screen.

Minimal motor impairment was measured in mice by the rotorod test. The mice were trained to stay on an accelerating rotorod that

rotates at 6 revolutions per minute. The rod diameter was 3.2 cm. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. The dose at which the animal was unable to grasp the rotarod, was determined, and presented in Table 1.

Behavioral Test.

The titled compounds (30 mg/kg) were screened for their behavioral effects using actophotometer [27] at 30 min and 1 h after injection. The behavior of animals inside the photocell was recorded as a digital score. Increased scores suggest good behavioral activity. The control animal was administered PEG. The observations are tabulated as Table 3.

CNS – Depressant Study.

The forced swim pool method described earlier was followed [28], Wistar rats were placed in a chamber (diameter: 45 cm, height: 20 cm) containing water up to a height of 15 cm at 25 ± 2°C. Two swim sessions were conducted, an initial 15 min pre-test, followed by a 5 min test session 24 h later. The animals were administered an i.p. injection (30 mg/kg) of the test compounds 30 min before the test session. The period of immobility (passive floating without struggling, making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period were measured. The results are presented in Table 3.

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