Quantum Mechanical Modeling of N^4-(2, 5-Disubstituted phenyl) Semicarbazones: Synthesis and Anticonvulsant Activity of N^4-(2, 5-dimethylphenyl/ -2-fluoro-5-methyl phenyl) Semicarbazones

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Abstract: Two new series of N^4-(2, 5-disubstitutedphenyl) semicarbazones were synthesized and evaluated for the anticonvulsant activity in various animal models of seizures. Quantum mechanical modeling was carried out on these compounds to understand the structural features essential for activity. The higher the difference in HOMO and LUMO energy levels the greater was the activity profile. Substitution with fluoro group on the ortho position of the aryl ring was found to decrease the reactivity and hence the activity profile of aryl semicarbazones, which has been justified with the molecular orbital surface analysis of the synthesized compounds.

Key Words: Aryl semicarbazones, Anticonvulsant, HOMO and LUMO energy, HOMO surfaces.

INTRODUCTION

Worldwide approximately 40-50 million people (~ 0.5-1% of the population), suffers from epilepsy, a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes, in which there is disturbance of movement, sensation and/or consciousness [1]. We have recently been investigating various aryl-substituted semicarbazones as potential anticonvulsant agents [2-8]. The rationale behind the development of semicarbazones is their structural dissimilarity to exciting antiepileptic drugs, so it was hoped that such novel compounds would lack the side effects seen with many of the currently available medications [9]. Aryl semicarbazones have also shown to possess excellent anticonvulsant activity in the maximal electroshock screen (MES) in both mice and rats and also against clonic seizures induced by pentylenetetrazole (PTZ) in mice, being more active than some conventional antiepileptic drugs, beside their low neurotoxicity.

While fitting semicarbazones to the binding site hypothesis, it is likely that two electron donor atoms in semicarbazones group and aryl ring align at the complimentary area on a macromolecular complex with the receptor *in vivo* [7]. Our analysis of the distance relationship showed that aryl semicarbazones fulfill the essential demands of the pharmacophore when compared with the phenytoin, carbamazepine, denzinamide, and remacemide [6, 7].

Various studies depicted the importance of methyl group substituted at various position of the aryl ring, in which *o*-methyl group was found to be more beneficial for anticonvulsant activity [4, 10]. Recently we reported a series of 2,6-dimethylphenyl semicarbazones [7] as potential anticonvulsant agents. In continuation of our work on disubstituted aryl semicarbazones, the present work focuses on the synthesis and anticonvulsant evaluation of new 2,5-dimethylphenyl semicarbazones and 2-fluoro-5-methylphenyl semicarbazones towards exploring the importance of *o*-methyl substitution on anticonvulsant activity of aryl semicarbazones.

CHEMISTRY

The synthesis of 2,5-dimethylphenyl/2-fluoro-5-methylphenyl semicarbazones was accomplished as presented in Scheme **1**. The 2,5-dimethyl/2-fluoro-5-methyl substituted aniline was treated with sodium cyanate in the presence of glacial acetic acid according to the previously known urea preparation method [2-3], to yield 2,5-dimethyl/2-fluoro-5-methyl-substituted phenyl urea. The urea derivatives on condensation with hydrazine hydrate in ethanol in presence of sodium hydroxide gave the 2,5-dimethyl/2-fluoro-5-methyl-substituted phenyl semicarbazide. The 2,5-dimethylphenyl semicarbazone derivatives (**1-19**) were prepared by reaction of the appropriate aryl/alkyl/cycloalkyl aldehyde or ketone with the corresponding semicarbazide by irradiation in an unmodified domestic microwave oven at power setting of 80% with 30 seconds/cycle. The number of cycle in turn depended on the completion of the reaction, which was checked by thin layer chromatography (TLC). The reaction timing varied from 6 to 8 minutes. The 2-fluoro-5-methylphenyl semicarbazones (**20-46**) were synthesized by reaction of the appropriate aryl/alkyl/cycloalkyl aldehyde or ketone or isatin with the corresponding semicarbazide hydrochloride salt by stirring at room temperature in presence of sodium acetate. Thin layer chromatography (TLC) was run throughout the reactions to optimize the reactions for purity and completion. All the synthesized compounds were character-

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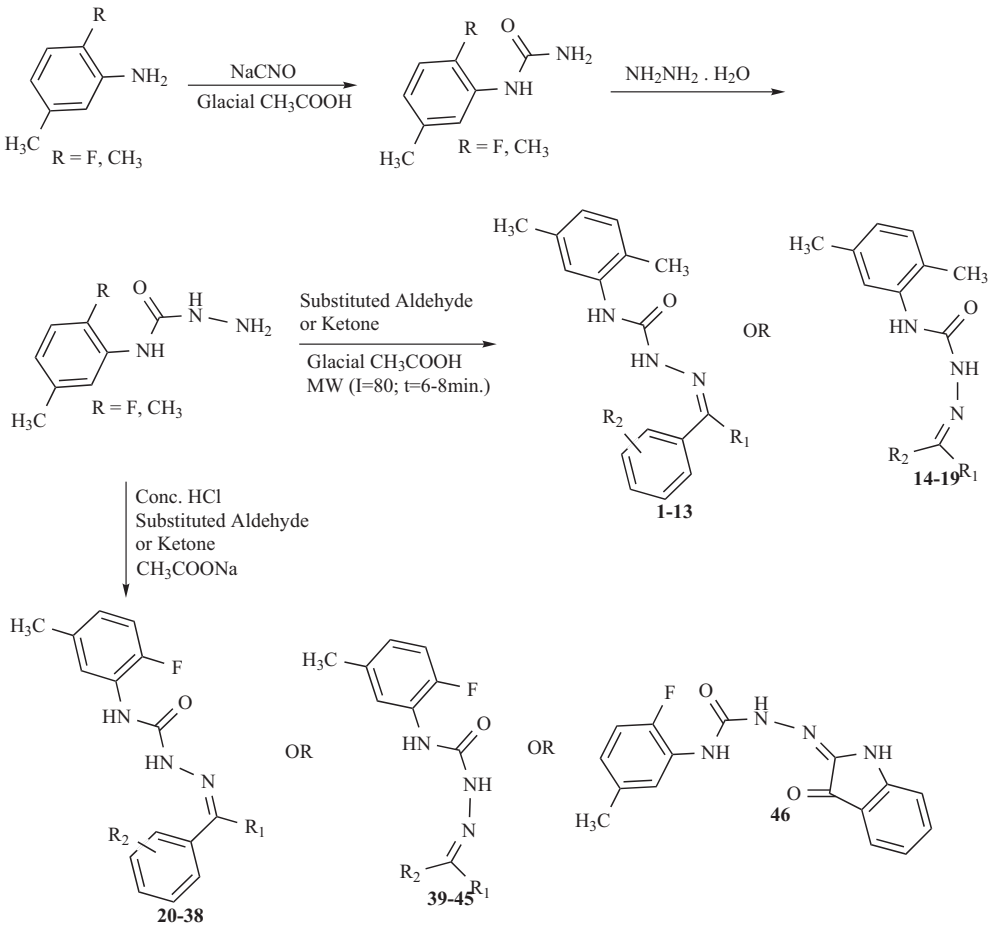

Scheme 1. Synthesis of 2, 5-dimethyl/2-fluoro-5-methyl phenyl semicarbazones.

ized 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}, and 920 $cm^{-1}$and 1320 cm^{-1} characteristics of halogen substituted phenyl ring. The ^{1}H-NMR spectrum revealed that the hydrazino proton (=N-NH) attached to the phenyl ring showed a singlet at δ 9.54-10.80 and the aryl NH at 7.84-8.86 both of which were D_2O exchangeable. The physical and chemical data for the newly synthesized compounds are presented in Table **1**-**2**.

PHARMACOLOGICAL ACTIVITY

The initial anticonvulsant evaluation of the 2,5-dimethylphenyl/2-flouro-5-methylphenyl semicarbazones was established by electrical and chemical tests, using the standard protocol. The electrical test employed was maximal electroshock seizures (MES) pattern test and chemical test was subcutaneous pentylenetetrazole (scPTZ) seizure threshold test. The acute neurological toxicity was determined by the rotorod test. The anticonvulsant and neurotoxicity test results for the titled compounds are reported in the Table **1**-**2**, along with the literature data for the standard drugs. The titled semicarbazones (**1**-**46**) were administered at 30, 100, 300 mg/kg doses intraperitoneally. In the preliminary MES screen, the compounds of 2,5-dimethylphenyl except **2**, **3**, and **12** and five compounds (**20**, **33**, **38**-**39**, and **40**) of 2-fluoro-5-methylphenyl semicarbazones showed protection, indicative of their ability to prevent seizure spread. Compounds that were active at 100 mg/kg include **1**, **10**, **14**, and **39** at 0.5h period, whereas other active compounds showed protection at higher dose (300 mg/kg). Compounds **1**, **9**-**11**, **13**-**15**, **17**-**19**, **20** and **39** were active at both 0.5 h & 4h time periods; hence these compounds exhibited prolonged duration of action. Other compounds showed rapid onset (0.5 h) with shorter duration of action except **33** and **40** which showed activity only at 4h time point (late onset of action).

In the subcutaneous pentylenetetrazole (scPTZ) screen, a test used to identify compounds that elevates seizures threshold, twelve compounds (**4**, **6**-**7**, **14**-**18**, **25**, **35**, **38**, and **39**) showed protection. All the active compounds showed protection at 300 mg/kg except **6** and **7** (100 mg/kg) and the action was for a shorter duration (0.5h) except **7**, **17**-**18** in the pentylenetetrazole seizure model.

In the acute neurological deficit test, compound **2**, **7** **20**-**27**, **29**-**37**, **40**-**46** showed no neurotoxicity at the maximum

Table 1. Physical and Biological Data of 2, 5-dimethylphenyl-semicarbazones

Comp	R_1	R_2	Yield (%)	M.P. (°C)[a]	Rf[b]	Intraperitoneal injection in mice[c]									
						MES screen		scPTZ screen		scSty screen		scPIC screen		Neurotoxicty screen	
						0.5h	4h	0.5h	4h	0.5h	4h	0.5h	4h	0.5h	4h
1	H	H	57	150	0.78	100	300	-	-	300	-	300	300	100	-
2	H	2-NO_2	38	60	0.67	-	-	-	-	300	300	300	300	-	-
3	H	2-OH	67	196	0.77	-	-	-	-	300	300	300	300	300	-
4	H	4-NO_2	70	190	0.45	300[d]	-	300[e]	-	300	300	-	-	300	-
5	H	4-CH_3	56	180	0.50	300[d]	-	-	-	300	300	300	300	300	-
6	H	4-Br	62	172	0.58	300	-	100	-	100	100	100	100	300	-
7	H	4-OCH_3	64	174	0.78	300	-	100	300	100	100	100	100	-	-
8	H	4-OH 3-OCH_3	51	175	0.62	300	-	-	-	300	300	300	300	300	-
9	CH_3	3-NH_2	52	165	0.52	300	300	-	-	300	-	100	100	300	-
10	CH_3	4-OH	47	175	0.38	100	300	-	-	300	300	300	-	300	300
11	CH_3	4-NH_2	95	145	0.52	300[d]	300	-	-	300	300	300	-	300	-
12	C_6H_5	H	72	153	0.58	-	-	-	-	300	-	300	-	100	-
13	C_6H_5	4-Br	91	165	0.77	300	300	-	-	300	300	300	-	300	-
14	CH_3	CH_3	63	185	0.52	100	300	300	-	100	100	100	100	300	-
15	CH_3	C_2H_5	72	184	0.44	300[d]	300	300[e]	-	300	300	300	-	300	-
16	CH_3	CH_2COCH_3	46	195	0.58	300[d]	-	300	-	-	-	300	-	300	-
17	CH_3	C_5H_{11}	54	185	0.56	300[d]	300	300[e]	300	-	-	-	-	300	-
18	Cyclopentylene		51	165	0.77	300[d]	300	300[e]	300	100	100	300	300	300	300
19	Cyclohexylene		56	185	0.79	300	300	-	-	300	300	-	-	300	300
Phenytoin			-	-	-	30	30	-	-	-	-	-	-	100	100
Ethosuximide			-	-	-	-	-	300	-	-	-	-	-	-	-

[a]Elemental analyses for C, H, N were with in ± 0.4 % of the theoretical values. [b]Mobile phase $CHCl_3$: CH_3OH (9:1). [c]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). [d]In the MES screen at the dose of 100mg/kg, compounds **4**, **5**, **11**, **15**, **16**, **18** (1/3, 0.25h), **17** (1/3, 0.5h) showed protection. [e]In the ScPTZ screen, at the dose of 100 mg/kg, compounds that showed protection were **4**, **15** (1/5, 0.5h), **17**, **18** (1/3, 0.5h).

Table 2. Physical and Biological Data of 2-fluoro-5-methylphenyl-semicarbazones

Comp	R_1	R_2	Yield (%)[a]	M.P. (°C)[b]	R_f[c]	Intraperitoneal injection in mice[d]			
						MES screen		ScPTZ screen	Toxicity screen
						0.5h	4h	0.5h	0.5h
20	H	H	59	100	0.62	300	300	-	-
21	H	2-NO_2	67	200	0.78	-	-	-	-
22	H	2-Cl	72	178	0.60	-	-	-	-
23	H	2-CH_3	65	132	0.82	-	-	-	-

(Table 2. Contd….)

Comp	R_1	R_2	Yield (%)[a]	M.P. (°C)[b]	R_f[c]	Intraperitoneal injection in mice[d]			
						MES screen		ScPTZ screen	Toxicity screen
						0.5h	4h	0.5h	0.5h
24	H	3-NO_2	63	178	0.70	-	-	-	-
25	H	4-NO_2	82	>260	0.63	-	-	300	-
26	H	4-OH	88	210	0.66	-	-	-	-
27	H	4-OCH_3	61	205	0.74	-	-	-	-
28	H	4-Br	64	225	0.73	-	-	-	300
29	H	4-CH_3	62	134	0.78	-	-	-	-
30	H	4-$N(CH_3)_2$	74	198	0.80	-	-	-	-
31	H	3-OCH_3 4-OH	60	165	0.81	-	-	-	-
32	CH_3	H	71	160	0.70	-	-	-	-
33	CH_3	3-NH_2	68	182	0.82	-	300	-	-
34	CH_3	4-NH_2	60	190	0.84	-	-	-	-
35	CH_3	4-NO_2	62	238	0.71	-	-	300	-
36	CH_3	4-OH	55	>260	0.80	-	-	-	-
37	CH_3	4-CH_3	60	158	0.78	-	-	-	-
38	C_6H_5	4-Br	80	200	0.74	300	-	300	300
39	CH_3	CH_3	52	163	0.75	100	300	300	300
40	CH_3	C_2H_5	54	175	0.66	-	300	-	-
41	CH_3	CH_2COCH_3	52	144	0.75	-	-	-	-
42	CH_3	$CH_2CH(CH_3)_2$	56	135	0.59	-	-	-	-
43	CH_3	C_5H_{11}	50	100	0.67	-	-	-	-
44	CRR_1= Cylopentylene		51	184	2.09	-	-	-	-
45	CRR_1= Cylohexylene		48	190	2.68	-	-	-	-
46	H		68	215	0.68	-	-	-	-
Phenytoin						-	300	-	-
Ethsuximide						30	30	-	100

[a]Elemental analyses for C, H, N were with in ± 0.4 % of the theoretical values. [b]Melting points of the compounds at their decomposition. [c]Mobile phase $CHCl_3$: CH_3OH (9:1). [d]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 animals.

dose administered (300mg/kg) and compounds **10**, **14, 20**, **25**, **27**, **33**, **35**, **39** and **40**, did not exhibited any neurotoxicity at the anticonvulsive dose. Only compound **12** was found to be more neurotoxic at the anticonvulsive dose.

Overall the 2,5-dimethylphenyl semicarbazones were more effective than 2-fluoro-5-methylphenyl semicarbazones. Hence the compounds **1**-**19** were carried onto the second phase of study that involved anticonvulsant evaluation in subcutaneous strychnine (scSTY) and subcutaneous picrotoxin (scPIC)-induced seizure threshold tests. All of the compounds except **16** and **17** showed protection against scSTY model. Compounds **6**, **7**, **14** and **18** showed protection at 100mg/kg (0.5 and 4h) and other compounds showed activity at 300mg/kg. Except compounds **1**, **9**, and **12**, all the active compounds exhibited a longer duration (4h) of action. The results suggest that these compounds have the possibility of interacting in the glycine pathway. In the scPIC screen,

compounds except **4, 17** and **19** exhibited protection from seizures and death, which implicated that semicarbazones could also act through GABA (γ-aminobutyric acid)–mediation as reported earlier [3]. Compounds **6-7**, **9**, and **14** showed protection at 100 mg/kg and other compounds exhibited protection at 300 mg/kg. Except compounds **10**, **11-13**, and **15-17,** all other compounds showed protection in both 0.5h and 4h intervals.

In this paper, it is clear that N^4-(2,5-dimethylphenyl) 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. Five compounds (**6**, **7**, **14-15**, and **18**) had shown activity in all the screens (MES, scPTZ, scSty, scPIC), exhibiting a broad spectrum of anticonvulsant activity.

QUANTUM MECHANICAL MODELING STUDIES

Quantum Mechanical (QM) modeling methods predict the behavior of electrons. They are thus the most fundamental and accurate theoretical tool available to predict molecular properties. In theory, QM methods enable completely accurate prediction of any property; there are some important classes of property (notably reactivity, electronic, magnetic, and optical behavior) that can only be modeled using QM methods, because they are determined by electronic behavior that cannot be approximated well using other methods.

In the present study the titled compounds were geometry optimized by semi-empirical PM3 QM method and subjected to single-point energy calculation to determine their HOMO (Highest occupied molecular orbital) and LUMO (Lowest unoccupied molecular orbital) energies (E_{HOMO} and E_{LUMO}). The greater E_{HOMO} is, the greater the electron-donating capability; conversely, the smaller E_{LUMO} is, the smaller the resistance to accept electrons. Compounds that present larger values of E_{HOMO} are more electron donor and the compounds that present smaller values of E_{LUMO} are more electron acceptor. These variables are interpreted as measures of molecular reactivity and stability. As E_{HOMO} increases (relative to other molecules), the molecule is less stable and more reactive. For E_{LUMO}, the situation is the opposite [11]. The higher energy values (E_{HOMO} and E_{LUMO}) for alkyl ketone compounds when compared to aryl aldehyde/ketone compounds could be due to the absence of resonance stability which is seen with the latter. The difference (ΔE) in E_{HOMO} and E_{LUMO} was also determined and presented in Table **3**. Higher the ΔE, higher was the anticonvulsant activity as seen with compounds **14** and **39**.

Analysis of the molecular orbital surfaces also reveals the extent of conjugation, and elucidates the nature of extended pi-systems in particular. Electron-rich and electron-poor species tend to reveal the localization or delocalization of the partial or full charge by the shape of the HOMO or LUMO. Molecular orbitals, when viewed in a qualitative graphical

Table 3. HOMO, LUMO and ΔE Energy Values for 2,5-dimethyl/2-fluro-5-methylphenyl Semicarbazones

R_1	R_2	2, 5-Dimethylphenyl-semicarbazones			2-Fluoro-5-methylphenyl-semicarbazones		
		E_{HOMO} (eigenvalues)	E_{LUMO} (eigenvalues)	ΔE	HOMO energy (eigenvalues)	LUMO energy (eigenvalues)	ΔE
H	H	-0.310	-0.033	-0.277	-0.316	-0.041	-0.275
H	2-NO_2	-0.317	-0.144	-0.174	-0.327	-0.147	-0.180
H	4-NO_2	-0.317	-0.056	-0.261	-0.325	-0.157	-0.278
H	4-OCH_3	-0.305	-0.041	-0.264	-0.310	-0.044	-0.266
H	4-CH_3	-0.303	-0.039	-0.263	-0.307	-0.042	-0.265
H	4-OH 3-OCH_3	-0.283	-0.050	-0.233	-0.311	-0.048	-0.263
CH_3	3-NH_2	-0.289	-0.043	-0.247	-0.291	-0.042	-0.249
CH_3	4-NH_2	-0.279	-0.044	-0.235	-0.286	-0.042	-0.244
CH_3	4-OH	-0.304	-0.034	-0.270	-0.291	-0.053	-0.237
CH_3	CH_3	-0.305	-0.009	-0.300	-0.325	-0.013	-0.312
CH_3	C_2H_5	-0.301	-0.005	-0.294	-0.320	-0.011	-0.309
CH_3	CH_2COCH_3	-0.306	-0.027	-0.279	-0.324	-0.037	-0.288
CH_3	C_5H_{11}	-0.304	-0.011	-0.294	-0.321	-0.013	-0.308
Cyclopentylene		-0.304	-0.006	-0.295	-0.321	-0.021	-0.301
Cyclohexylene		-0.300	-0.008	-0.292	-0.319	-0.020	-0.299

representation, can provide insight into the nature of reactivity, and some of the structural and physical properties of molecules. Well known concepts such as conjugation, aromaticity and lone pairs are well illustrated by molecular orbitals.

In the present study the HOMO surface was visualized for both the series for comparison and the following observations were made. As proposed earlier, the anticonvulsant pharmacophore requirement for aryl semicarbazones include an aryl ring, a hydrogen-bonding domain and an electron donor system. The HOMO surface analysis also confirmed this hypothesis wherein with compounds **5** and **7** showed a delocalized orbital surface over an aryl ring, imine group (electron donor), and the amide moiety (hydrogen acceptor-donor unit) (Fig. **1**). Similar surfaces were observed with all active compounds. Compound **2** which did not comply with this hypothesis was found to be inactive. Another observation made with compound **2** is that the electron cloud of the carbimino aryl ring is shifted to the 2,5-dimethylphenyl ring due to the presence of deactivating nitro group. Undelocalized or splitting of electron cloud on the aryl ring was found to be not favorable for activity as represented in figure for compound **27** and **29**. It was also seen that unsymmetrical molecular orbital surfaces resulted in decrease in activity. This observation was made with other less active and inactive compounds of 2-fluoro-5-methylphenyl semicarbazones. The fluorine group because of electron withdrawing nature might deactivate the ring when compared to the *ortho*-methyl group in 2,5-dimethylphenyl semicarbazones. The exceptionally active acetone derivatives **14** and **39** also showed HOMO surface in accord to the pharmacophore hypothesis with an aryl binding site contributed by the disubstituted phenyl ring, electron donor unit (imine group), hydrogen donor-acceptor unit (amidic hydrogen and lone pair in nitrogen). Similar observations were made with the compounds **15** and **40**. This is a preliminary report on quantum mechanical modeling on aryl semicarbazones. In future further studies on other well-known aryl semicarbazones have to be dealt in detail.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR-spectra were recorded on a JASCO IR Report 100 spectrometer in KBr. ^{1}H-NMR spectra were recorded on a JEOL Fx 90Q Fourier Transform-NMR spectrometer employing TMS as the internal standard. Elemental analyses were performed on a Perkin Elmer Model 240C analyser. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) on silica-G (Merck) coated glass plates, visualized by iodine vapour. The quantum mechanical modeling was carried out using Argus Lab 4.0.1 version.

Synthesis of 2,5-disubstituted Phenyl Urea

The 2,5-dimethyl and 2-fluoro-5-methylphenyl ureas were synthesized according to the procedures reported earlier [2-3]. Briefly the 2,5-dimethyl or 2-fluoro-5-methyl aniline was dissolved in 20 ml of glacial acetic acid and 10 ml of water. To this, equimolar amount of sodium cyanate in 80 ml of warm water was added with stirring. Allowed to stand for 30 min, then cooled in ice and filtered with suction and dried. Recrystallized from boiling water to yield the respective phenyl ureas.

2,5-Dimethylphenyl Urea

M.p. 172°C; Yield: 60%; IR-KBR pellets (cm^{-1}) 3400, 1700, 780, 750, ^{1}H-NMR (DMSO-d_6,, ppm, 300 MHz) 2.4 (s,

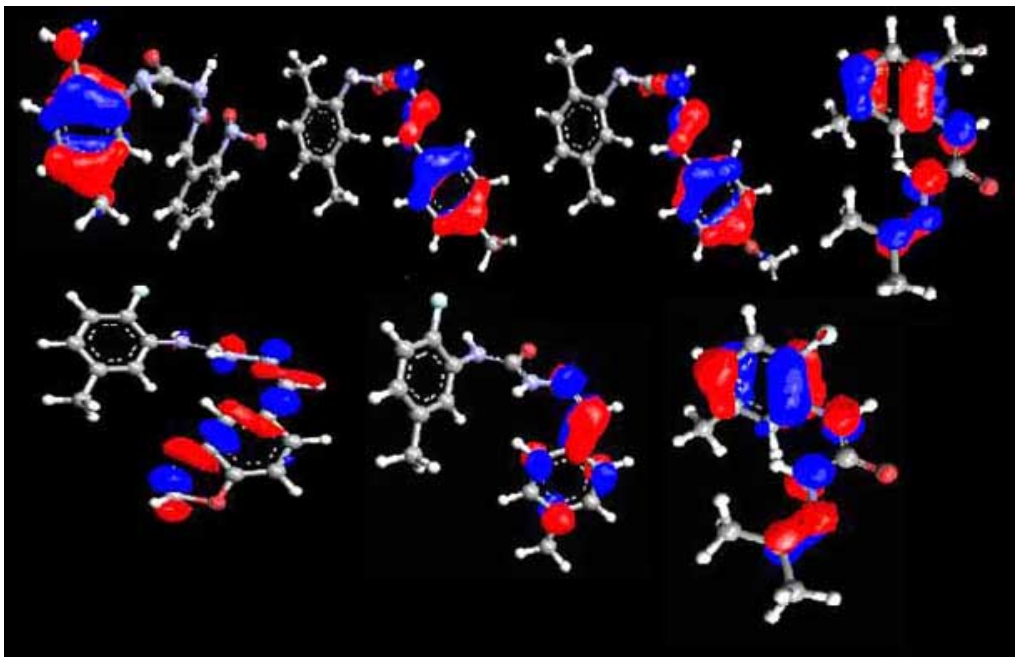

Fig. (1). HOMO surface visualization (Contour value = 0.05) of some representative compounds (Top from left 2, 5, 7, 14; Bottom from left 27, 29, 34) in opaque mode. The colors indicate the phase of the orbital in space (blue for positive and red for negative).

3H, $ArCH_3$), 2.24 (s, 3H, $ArCH_3$), 7.3-7.5 (m, 3H, ArH), 7.98 (s, 1H, ArNH, D_2O exchangeable), 9.88 (s, 2H, NH_2, D_2O exchangeable); ($C_9H_{12}N_2O$) C, H, N.

2-Fluoro-5-methylphenyl Urea

M.p. 148°C; Yield: 62%; IR-KBR pellets (cm^{-1}) 3380, 1740, 780 , 720 , ^{1}H-NMR (DMSO-d_6,, ppm, 300 MHz) 2.4 (s, 3H, $ArCH_3$), 7.3-7.5 (m, 3H, ArH), 7.98 (s, 1H, ArNH, D_2O exchangeable), 9.88 (s, 2H, $CONH_2$, D_2O exchangeable); ($C_8H_9N_2OF$) C, H, N.

Synthesis of 2,5-disubstituted Phenyl Semicarbazide

The 2,5-dimethyl and 2-fluoro-5-methylphenyl semicarbazides were prepared according to the procedure reported earlier [2-3]. Following the similar procedure, the 2,5-dimethyl and 2-fluoro-5-methylphenyl semicarbazides were prepared by treating equimolar quantities of the phenyl urea and hydrazine hydrate in ethanol under reflux for 24h with stirring. The two-third volume of alcohol was distilled by vacuum distillation unit and then poured into ice. The resultant precipitate was filtered, washed with water and dried. The solid phenyl semicarbazide obtained was recrystallized from 50ml of 90% alcohol

2,5-Dimethylphenyl Semicarbazide

M.p. 192°C; Yield: 65%; IR-KBR pellets (cm^{-1}) 3400, 3280,1640, 760, ^{1}H-NMR (DMSO-d_6,, ppm, 300 MHz) 2.18 (s, 3H, $ArCH_3$), 2.26 (s, 3H, $ArCH_3$), 7.4-7.5 (m, 3H, ArH), 5.60 (s, 2H, NH_2, D_2O exchangeable), 7.92 (s, 1H, ArNH, D_2O exchangeable), 9.94 (s, 1H, CONH, D_2O exchangeable); ($C_9H_{13}N_3O$) C, H, N.

2-Fluoro-5-methylphenyl Semicarbazide

M.p. 178°C; Yield: 68%; IR-KBR pellets (cm^{-1}) 3370, 3300, 1620, 810, ^{1}H-NMR (DMSO-d_6, ppm, 300 MHz) 2.18 (s, 3H, $ArCH_3$), 7.4-7.5 (m, 3H, ArH), 5.60 (s, 2H, NH_2, D_2O exchangeable), 7.92 (s, 1H, ArNH, D_2O exchangeable), 9.94 (s, 1H, CONH, D_2O exchangeable); ($C_8H_{10}N_3OF$) C, H, N.

General Method for Synthesis of 2,5-dimethylphenyl Semicarbazones (1-19)

The conversion of 2,5-dimethylphenyl semicarbazide to semicarbazones was carried by microwave irradiation using a domestic microwave oven Matrix LG input 220V- 50 Hz, 980 W, 4.7 A, frequency 2450 MHz, as per the reported procedure. To a solution of 2,5-dimethylphenyl semicarbazide (0.003 mol), in ethanol was added an equimolar quantity of appropriate aldehyde or ketone. The pH of the reaction mixture was adjusted to 5-6 by adding glacial acetic acid, to facilitate the nucleophilic substitution. The reaction mixture was exposed to microwave irradiation for 6-8 mins (I = 80). The products (**1-19**) obtained after cooling was filtered and recrystallized from 95% ethanol. The physical data of the semicarbazones are given in Table **1**. The IR spectra of the semicarbazone derivatives were identical in the following aspects; IR-KBR pellets (cm^{-1}) 3450, 3300-3250, 1650, 1595, 840. ^{1}H-NMR (300 MHz, δ, DMSO d_6) spectra of some representative compounds are as follows:

3: 2.20 (s, 3H, $ArCH_3$), 2.22 (s, 3H, $ArCH_3$) 6.74-7.62 (m, 7H, ArH), 7.76 (s, 1H, imine H), 8.64 (s, 1H, ArNH, D_2O exchangeable), 9.47 (s, 1H, ArOH, D_2O exchangeable), 9.88 (s, 1H, CONH, D_2O exchangeable).

4: 2.20 (s, 3H, $ArCH_3$), 2.22 (s, 3H, $ArCH_3$) 6.58-7.58 (m, 7H, ArH), 7.78 (s, 1H, imine H), 8.60 (s, 1H, ArNH, D_2O exchangeable), 10.20(s, 1H, CONH, D_2O exchangeable).

5: 2.18 (s, 3H, $ArCH_3$), 2.22 (s, 6H, 2-$ArCH_3$) 6.87-8.16 (m, 7H, ArH), 8.06 (s, 1H, imine H), 8.54 (s, 1H, ArNH, D_2O exchangeable), 10.05 (s, 1H, CONH, D_2O exchangeable).

7: 2.18 (s, 3H, $ArCH_3$), 2.20 (s, 3H, $ArCH_3$), 3.75 (s, 3H, OCH_3) 6.85-7.74 (m, 7H, ArH), 7.82 (s, 1H, imine H), 8.58 (s, 1H, ArNH, D_2O exchangeable), 10.40 (s, 1H, CONH, D_2O exchangeable).

8: 2.18 (s, 3H, $ArCH_3$), 2.24 (s, 3H, $ArCH_3$) 3.88 (s, 3H, OCH_3), 7.08-7.26 (m, 3H, ArH) 6.78-7.53 (M, 3H, ArH), 7.78 (s, 1H, imine H), 7.84 (s, 1H, ArNH, D_2O exchangeable), 10.08 (s, 1H, CONH, D_2O exchangeable), 10.17(s, 1H, OH, D_2O exchangeable).

9: 2.02 (s, 3H,CH_3), 2.10 (s, 3H, $ArCH_3$), 2.24 (s, 3H, $ArCH_3$), 5.32 (s, 2H, NH_2, D_2O exchangeable), 7.14-7.64 (m, 7H, ArH), 8.36 (s, 1H, ArNH, D_2O exchangeable), 9.68 (s, 1H, CONH, D_2O exchangeable).

10: 1.96 (s, 3H, CH_3), 2.12 (s, 3H, $ArCH_3$), 2.20 (s, 3H, $ArCH_3$), 7.12 (m, 7H, ArH), 8.16 (s, 1H, ArNH, D_2O exchangeable), 9.64 (s, 1H, CONH, D_2O exchangeable), 10.14 (s, 1H, OH, D_2O exchangeable).

14: 1.82 (s, 3H,CH_3), 1.98 (s, 3H,CH_3), 2.20 (s, 3H, $ArCH_3$), 2.28 (s, 3H, $ArCH_3$), 6.80-7.12 (m, 3H, ArH), 8.31 (s, 1H, ArNH, D_2O exchangeable), 10.54 (s, 1H, CONH, D_2O exchangeable).

15: 1.46-1.50 (t, 3H, CH_3), 1.90-1.94 (q, 2H, CH_2), 1.98 (s, 3H, CH_3), 2.20 (s, 6H, 2-$ArCH_3$) 7.19-7.26 (m, 3H, ArH), 8.46 (s, 1H, ArNH, D_2O exchangeable), 9.54 (s, 1H, CONH, D_2O exchangeable).

17: 1.50-1.52 (t, 3H, CH_3), 1.84-1.88 (m, 8H, CH_2), 2.02 (s, 3H, CH_3), 2.12 (s, 6H, 2-$ArCH_3$) 7.19-7.24 (m, 3H, ArH), 8.36 (s, 1H, ArNH, D_2O exchangeable), 9.68 (s, 1H, CONH, D_2O exchangeable).

General Method for Synthesis of 2-fluoro-5-methylphenyl Semicarbazones (20-46)

The 2-flouro-5-methylphenyl semicarbazones were synthesized from the corresponding semicarbazide hydrochloride salt i.e. by the addition of conc. hydrochloric acid to the solution of semicarbazide in ethanol. To a solution of 2-flouro-5-methylphenyl semicarbazide hydrochloride salt (0.001 mol) in 25 ml of methanol was added sodium acetate solution in water (0.0005 mol in 2 ml of water). This solution mixture was added to appropriate aldehyde or ketone in alcohol, with stirring. The reaction was carried out for 5-10-mins. Solid product was filtered, dried and recrystallized from hot alcohol (Table **2**). The IR spectra of the semicarba-

zone derivatives were identical in the following aspects; IR-KBR pellets (cm^{-1}) 3380, 3090, 2895, 2880, 1680, 1580-1540, 1340, 1210. ^{1}H-NMR (300 MHz, δ, DMSO d_6), spectra of some representative compounds are as follows:

23: 2.20 (s, 6H, 2-$ArCH_3$), 6.66- 7.82 (m, 7 H, ArH), 7.94 (s, 1H, imine H), 8.63 (s, 1H, ArNH, D_2O exchangeable), 10.80 (s, 1H, CONH, D_2O exchangeable).

25: 2.20 (s, 3H, $ArCH_3$), 6.66-7.82 (m, 7 H, ArH), 7.94 (s, 1H, imine H), 8.50 (s, 1H, ArNH, D_2O exchangeable), 9.81 (s, 1H, CONH, D_2O exchangeable).

26: 2.28 (s, 3H, $ArCH_3$), 6.68-7.82 (m, 7H, ArH), 7.96 (s, 1H, imine H), 8.82 (s, 1H, ArNH, D_2O exchangeable), 9.38 (s, 1H, ArOH, D_2O exchangeable), 9.96 (s, 1H, CONH, D_2O exchangeable).

29: 2.18 (s, 3H, $ArCH_3$), 2.30 (s, 3H, $ArCH_3$) 6.87-8.10 (m, 7H, ArH), 8.24 (s, 1H, imine H), 8.68 (s, 1H, ArNH, D_2O exchangeable), 10.74 (s, 1H, CONH, D_2O exchangeable).

31: 2.12 (s, 3H, $ArCH_3$), 3.88 (s, 3H, OCH_3), 7.14-7.28 (m, 6H, ArH), 7.70 (s, 1H, imine H), 7.82 (s, 1H, ArNH, D_2O exchangeable), 10.08 (s, 1H, CONH, D_2O exchangeable), 10.14 (s, 1H, OH, D_2O exchangeable).

34: 1.98 (s, 3H, CH_3), 2.14 (s, 3H, $ArCH_3$), 5.32 (s, 2H, NH_2, D_2O exchangeable), 7.04-7.16 (m, 7H, ArH), 8.36 (s, 1H, ArNH, D_2O exchangeable), 9.38 (s, 1H, CONH, D_2O exchangeable).

36: 1.92 (s, 3H, CH_3), 2.10 (s, 3H, $ArCH_3$), 7.30-7.36 (m, 7H, ArH), 8.32 (s, 1H, ArNH, D_2O exchangeable), 9.60 (s, 1H, CONH, D_2O exchangeable), 10.20 (s, 1H, OH, D_2O exchangeable).

39: 1.90 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.14 (s, 3H, $ArCH_3$), 6.80-7.13 (m, 3H, ArH), 8.34 (s, 1H, ArNH, D_2O exchangeable), 9.80 (s, 1H, CONH, D_2O exchangeable).

40: 1.46-1.50 (t, 3H, CH_3,), 1.82-1.88 (q, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.24 (s, 3H, $ArCH_3$), 7.19-7.32 (m, 3 H, ArH), 8.86 (s, 1H, ArNH, D_2O exchangeable), 10.10 (s, 1H, CONH, D_2O exchangeable).

43: 1.60-1.66 (t, 3H, CH_3), 1.78-1.90 (m, 8H, 4-CH_2), 2.08 (s, 3H, CH_3), 2.24 (s, 3H, $ArCH_3$), 7.19-7.26 (m, 3H, ArH), 8.56 (s, 1H, ArNH, D_2O exchangeable), 10.04 (s, 1H, CONH, D_2O exchangeable).

Pharmacological Tests

Male albino mice (CF-1 strain, 18-25g) were used as experimental animals. The semicarbazone derivatives were suspended in 0.5% methylcellulose /water mixture or in polyethylene glycol (PEG). The anticonvulsant evaluation [12, 13] was established by maximal electroshock seizure, subcutaneous pentylenetetrazole seizure threshold, and neurotoxicity screens. Table **1-2** lists the results obtained from the initial anticonvulsant evaluation compared with the clinically proven antiepileptics like Phenytoin, Phenobarbital, Carbamazepine and valproate. The 2,5-dimethylphenyl semicarbazones (**1-19**) were evaluated in the subcutaneous strychnine and picrotoxin-induced seizure models [14, 15]. Rotarod test has been performed to detect the motor deficit in mice. Animals were divided in the groups (4-8) and trained to stay on accelerating rotarod that rotates at 10 revolutions per minute. The rod diameter was 3.2-cm. Trained animal (able to stay on the rotarod for at least 2 consecutive periods of 90 sec) were given an i.p. injection of the test compounds in the doses of 30, 100 and 300 mg/kg. Neurological deficit 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.

Quantum Mechanical Calculations

The quantum mechanical (QM) calculations were carried out using Argus Lab version 4.0.1. The three-dimensional structures of the compounds were geometry optimized using Hamiltonian PM3 (Parameterized Method 3) semi-empirical QM method [16-17]. For the estimation of HOMO and LUMO energy and surfaces, the single-point energy calculation using Hamiltonian ZINDO and RHF-SCF (Restricted Hartree-Fock-Single consistent Field) method (Basis set STO-6G) [18,19] was employed. The HOMO surfaces were visualized using a contour value of 0.05 in opaque mode using blue and red for positive and negative phase of the orbital in space.

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