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단신

새로운 2,5-디치환된 1,3,4-디아디아졸의 합성: 항경련 활성에 대한 구조적인 관계 연구

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Synthesis of Novel 2,5-Disubstituted 1,3,4-Thiadiazoles: Structural Requirements Necessary for Anticonvulsant Activity

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INTRODUCTION

Epilepsy, a common neurological disorder characterized by the periodic sudden loss or impairment of consciousness, often followed by convulsions. Approximately 60 million people worldwide suffer from epilepsy, making this condition the second leading neurological disorder.[1] Epilepsy also affects about 4% of individuals over their lifetime. Despite the development of several new anticonvulsants, about one third of patients fail to experience seizure control and other do so only at the expense of significant dose-related toxicity and peculiar adverse effects.[2] Thus there is an enormous need for the development of more effective and safer antiepileptic drug.

In the last two decades, aryl semicarbazones has been identified and established as a structurally novel class of compounds with remarkable anticonvulsant activity.[3-5] On the other hand, several investigations have revealed that 1,3,4-thiadiazole analogues possess considerable anticonvulsant activity.[6-8]

A general model for anticonvulsant activity has been proposed as a result of the conformational studies of the clinically active anticonvulsant drugs such as phenytoin, carbamazepine, lamotrigine, rufinamide and phenobarbitone[9,10] These semicarbazones based pharmacophore models are consist of following four essential binding sites: (i) An aryl hydrophobic binding site (A) with halo substituent preferably at para position; (ii) A hydrogen bonding domain (HBD); (iii) An electron donor group (D) and (iv) Another hydrophobic-hydrophilic site controlling the pharmacokinetic properties of the anticonvulsant (C) (*Fig*. 1). In earlier studies on pharmacophore model, our research group confirmed that the presence of aryl group (preferably halogen substituted) near the semicarbazone moiety is one of the indispensable parameters for anticonvulsant activity.[11]

RESULTS AND DISCUSSION

The title compounds were prepared using the synthetic strategy described in *Scheme* 1. 2-Methyl-1*H*-benzimidazole **II** was

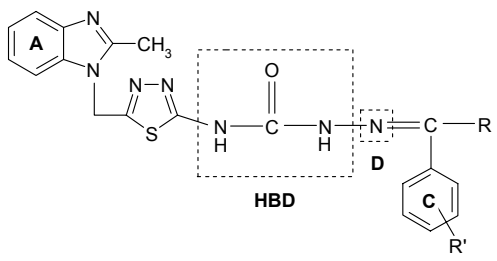
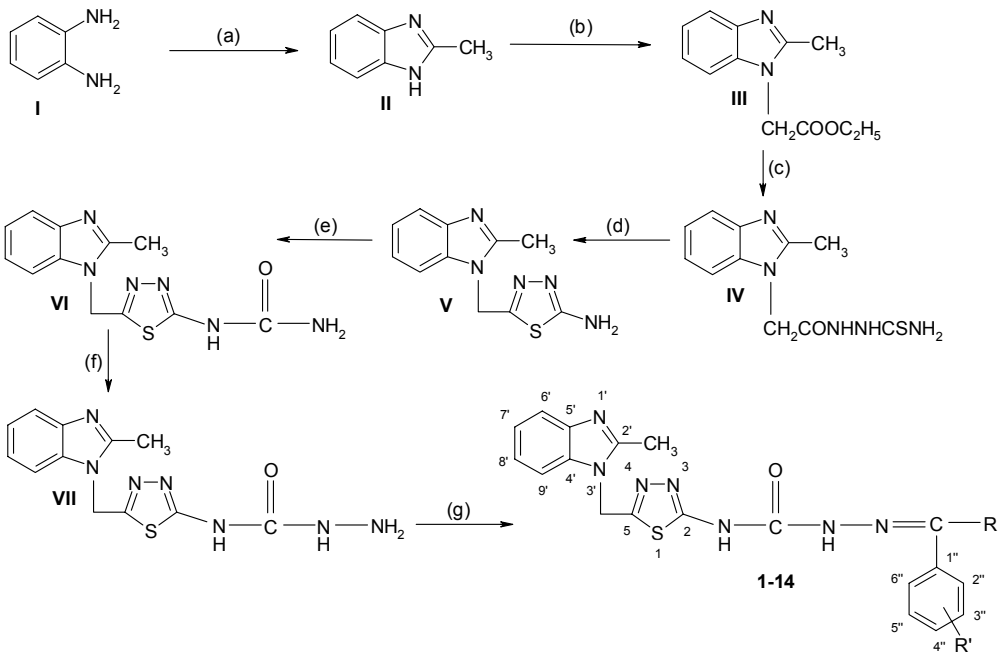


Fig. 1. Pharmacophoric structural features in title compounds: (A) hydrophobic Aryl ring system, (HBD) hydrogen binding domain, (D) electron donor moiety, (C) Distal aryl ring.



Compound Code	R	R'	Compound Code	R	R'	Compound Code	R	R'
1	H	H	6	H	4-Cl	11	C_6H_5	H
2	H	4-NO_2	7	CH_3	4-OH	12	C_6H_5	4-OH
3	H	4-OH	8	CH_3	4-OCH_3	13	C_6H_5	4-NO_2
4	H	4-CH_3	9	CH_3	4-NO_2	14	C_6H_5	4-OCH_3
5	H	4-OCH_3	10	CH_3	4-Cl			

Scheme 1. **Synthesis of 2,5-disubstituted-1,3,4-thiadiazole derivatives 1-14. Reagents and conditions** (a) CH_3COOH, distilled water, 1 h reflux, Conc. NH_3; (b) $ClCH_2COOC_2H_5$, anhydrous K_2CO_3, dry acetone; (c) $NH_2NHCSNH_2$, 1,4-dioxane, 7 h reflux; (d) Conc. H_2SO_4, overnight, rt, NH_3; (e) NaOCN, CH_3COOH, 4-5 h, rt; (f) $NH_2NH_2.H_2O$, NaOH, ethanol, 2-8 h reflux; (g) Aldehyde or ketone, ethanol, 2-3 h reflux.

prepared according to the reported method.[12] Compound **II** on N-ethoxylation with ethylchloroacetate in the presence of anhydrous K_2CO_3 in dry acetone gave ethyl (2-methyl-1*H*-benzimidazol-1-yl)acetate **III** which on treatment with thiosemicarbazide resulted in the formation of 2-[(2-methyl-1*H*-benzimidazol-1-yl)acetyl]-hydrazinecarbothioamide **IV**. Dehydrated annulation of compound **IV** with conc. H_2SO_4 followed by NH_3 treatment yielded 5-[(2-methyl-1*H*-benzimidazol-1-yl)-methyl]-1,3,4-thiadiazol-2-amine **V**.[13] Compound **V** was treated with sodium cyanate in the presence of glacial acetic acid, to yield 1-[5-{(2-methyl-1*H*-benzimidazol-1-yl)methyl}-1,3,4-thiadiazol-2-yl]-urea **VI**. N-[5-{(2-Methyl-1*H*-benzimidazol-1-yl)methyl}-1,3,4-thiadiazol-2-yl]-hydrazine carboxamide **VII** was prepared by reaction of **VI** with hydrazine hydrate in the presence of sodium hydroxide. Title compounds **1-14** were prepared by reaction of the appropriate aldehyde or ketone with compound **VII**.

All the compounds were screened for their anticonvulsant potential through maximal electroshock seizure (MES) and subcutaneous pentylenetrtrazole (scPTZ) models in doses of 30, 100, 300 mg/kg by *i.p.* injection. The data indicates that 64% of the compounds were active in the MES screening as compared to 28% in the ScPTZ test. Thus the compounds exhibited some MES selectivity. The majority of the compounds showed activity after 4 h, indicating that the synthesized compounds are slow acting anticonvulsants. In the neurotoxicity screen, compounds **7** and **10** did not showed any neurotoxicity at the maximum administered dose (300 mg/kg). On the other hand, compounds **2**, **3**, **9**, **11** and **12** were neurotoxic at the anticonvulsant dose. Compounds **6** and **8** exhibited neither anticonvulsant activity nor neurotoxicity. The compound N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-nitrophenyl) (phenyl) methanone]-semicarbazone **13** emerged out as the most potent compound, showing considerable activity in maximal electroshock seizure (at 100 mg/kg after 0.5 h and at 300 mg/kg after 4.0 h) and subcutaneous pentylenetrtrazole model (at 300 mg/kg after 4.0 h) without any neurotoxicity (up to 300 mg/kg after 4.0 h) (*Table* 1). Some of the

selected compounds with appreciable biological activity were evaluated for anticonvulsant activity and neurotoxicity studies after oral administration in rats. The promising results shown by compounds **13** in mice after *i.p.* administration were again confirmed in these studies (*Table* 2).

In general, compounds bearing the groups like nitro, hydroxy on distant phenyl ring showed high potency in MES and scPTZ tests. Whereas replacement of these groups with methoxy and chloro groups on the distant phenyl ring has resulted in compounds with decrease in anticonvulsant activity. Replacement of the proton on the carbimino carbon atom by methyl group *i.e.*, **7** to **10** or phenyl ring *i.e.*, **11** to **14** has demonstrated variation in activity due to increase in the dimension of the group at this position of the molecule. Compounds with phenyl ring were found to possess considerable activity in comparison to methyl group. The increase in the anticonvulsant activity with phenyl substitution might be due to additional van der Waals bonding to the binding site. In the present studies, we have designed and synthesized the title compounds with keeping a fact in mind that a number of clinically active anticonvulsants possess a nitrogen hetero atomic system with one or two phenyl rings and at least one carbonyl group in their structure. The structure of the title compounds fulfilled all the pharmacophore structural requirements *i.e.*, presence of [5-{(2-Methyl-1*H*-benzimidazol-1-yl)methyl}-1,3,4-thiadiazol-2-yl] moiety as hydrophobic portion, N as electron donor system and another hydrophobic distal aryl ring responsible for metabolism.

Table 1. Anticonvulsant activity and minimal motor impairment of 2,5-disubstituted 1,3,4-thiadiazoles

Compound	Intraperitoneal injection in mice[a]					
	MES Screening		scPTZ Screening		NT Screening	
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
1	-	-	-	-	100	-
2	-	300	-	-	-	300
3	-	300	-	-	-	300
4	-	300	-	-	100	100
5	-	-	300	-	300	-
6	-	-	-	-	-	-
7	-	300	-	300	-	-
8	-	-	-	-	-	-
9	100	300	-	-	-	300
10	-	-	-	300	-	-
11	-	300	-	-	300	-
12	100	300	-	-	-	300
13	100	300	-	300	-	-
14	-	300	-	-	300	-
Phenytoin	30	30	-	-	100	100
Carbamazepine	30	100	100	300	100	300
Na valproate	300	-	300	-	-	-

[a]30, 100 and 300 mg/kg of doses were administered *i.p.* in mice. The data of the table indicates the minimal dose whereby biological activity was demonstrated in half or more of the mice. The activity was measured after 0.5 and 4.0 h of dose administration of test compounds. The sign - (dash) represents an absence of activity at maximum dose administered (300 mg/kg).

CONCLUSIONS

The results obtained showed that the majority of the compounds exhibited anticonvulsant activity. Thus the results confirmed the four binding site hypothesis for semicarbazones. In the present studying 4-NO_2 phenyl substituted semicarbazone came out as the most active compound, showing a broad spectrum of activity without any neurotoxicity. Our results validated that the pharmacophore model with four binding sites is essential for anticonvulsant activity. These new data might be beneficial in the future development of semicarbazones as novel anticonvulsants.

EXPERIMENTAL

General procedure for synthesis of 1-[5-{(2-methyl-1*H*-benzimidazol-1-yl)methyl}-1,3,4-thiadiazol-2-yl]-urea VI: The compound **V** (0.01 mol) was dissolved in 10 ~ 30 mL of glacial acetic acid diluted to 50 mL with distilled water. To this equimolar (0.01 mol) quantity of sodium cyanate in 20 ~ 30 mL of warm water was added with stirring. The reaction mixture was allowed to stand for 4 to 5 h followed by cooling on an ice bath. The precipitates obtained were collected by filtration, washed with cold water and recrystallized from 90% aqueous ethanol. MP 178 ~ 179 ^{o}C; Yield 66%; IR (KBr) 3427.1 (NH str of NH_2), 3345.1 (NH str of amide), 3052.9 (Aromatic C-H str), 1647.5

Table 2. Anticonvulsant evaluation of compounds after oral administration in rats

Compound	Oral administration in rats[a]									
	MES Screening					NT Screening				
	0.25 h	0.5 h	1 h	2 h	4 h	0.25 h	0.5 h	1 h	2 h	4 h
7	0	0	0	1	1	0	0	0	0	1
9	0	1	0	0	1	0	0	0	1	0
12	0	0	1	0	1	0	0	0	1	0
13	0	0	0	1	1	0	0	0	0	0

[a]The compounds were administered in a dose of 30 mg/kg. The data in table indicates the number of rats out of four, which were protected.

(C=N of thiadiazole), 1614.9 (C=N of benzimidazole ring), 1688.5 (C=O str of amide), 738.3 (C-S of thiadiazole nucleus); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 7.2-7.8 (m, 4H, ArH), 6.2 (s, 2H, NH_2), 5.9 (s, 1H, NH), 4.9 (s, 2H, NCH_2), 2.4 (s, 3H, CH_3); ESMS (Methanol) *m/z* 288 (M^+).

General procedure for synthesis of N-[5-(1H-indol-3-yl-methyl)-1,3,4-thiadiazol-2-yl]-hydrazinecarboxamide VII: Required quantity of the compound **VI** (0.01 mol) was dissolved in 30 ~ 40 mL of ethanol. To this was added equimolar solution of hydrazine hydrate in 5 mL of water. The reaction mixture was made alkaline by adding 4 g of sodium hydroxide pellets. The contents were then heated to reflux for 2 ~ 8 h, followed by cooling on an ice bath. The product was filtered and recrystallized from 90% aqueous ethanol. MP 195 ~ 196 °C; Yield 68%; IR (KBr) 3438.5 (NH str of NH_2), 3336.4 (NH str of amide), 3048.2 (Aromatic C-H str), 1679.5 (C=O str of amide), 1643.7 (C=N of thiadiazole), 1609.4 (C=N of benzimidazole ring), 740.4 (C-S of thiadiazole nucleus); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 7.2-7.8 (m, 4H, ArH), 6.2 (t, 1H, N<u>H</u>NH_2), 6.1 (s, 1H, N<u>H</u>CO), 4.9 (s, 2H, NCH_2), 2.6 (d, 2H, NH_2), 2.4 (s, 3H, CH_3),; ESMS (Methanol) *m/z* 303 (M^+).

General procedure for synthesis of title compounds 1-14: Equimolar quantities of compound **VII** (0.01 mol) and carbonyl compound (0.01 mol) were dissolved in 20 ~ 30 mL of ethanol. To this 5 mL of water was added. The turbidity if appeared was removed by adding ethanol with adequate stirring of the reaction mixture. The pH of the reaction mixture was adjusted between 4 and 5, by adding glacial acetic acid. The reaction mixture was refluxed for a period of time ranging from 2 ~ 3 h. Thereafter reaction mixture was cooled on an ice bath and the crystallized product so obtained was filtered under vacuum. The crude product was recrystallized from 90% aqueous ethanol.

The anticonvulsant screening[14,15] was performed using male albino mice (swiss, 18 ~ 25 g) and rat (wistar 100 ~ 150 g). The anticonvulsant activity of the test compounds was evaluated by two models namely, maximal electroshock seizure (MES) and subcutaneous pentylenetrtrazole (scPTZ) models. The MES-induced convulsions represent grandmal type of epilepsy while chemo-convulsions due to pentylenetetrazole produce clonic-type of convulsion resemble petit mal type of epilepsy. The maximal electroshock seizure were elicited with a 60 cycle altering current of 50 mA intensity delivered for 0.25 s *via* ear clip electrodes. The maximal seizure usually consists of a short period of tonic extension of the hind limbs and a final clonic episode. After 30 min and 4 h of drug administration electroshock was applied *via* corneal electrodes. Disappearance of the hind limb tonic extensor component of convulsion was considered as positive criteria. The scPTZ test was performed by administering PTZ dissolved in 0.9% sodium chloride solution in the posterior midline of the animals. A minimal time of 30 min consequent to administration of PTZ was used for seizure detection. Protection was referred to as the failure to observe an episode of clonic convulsions of at least 5 s duration during this time period. Acute neurological toxicity was determined in the rotorod test.[16] The mice were trained to stay on an accelerating rotorod of diameter 3.2 cm that rotates at 6 revolutions per min. Only those animals which have demonstrated their capability to remain on the revolving rod for at least 1 min were considered for the test. Previously trained mice were given test compounds *i.p.* in doses of 30, 100 and 300 mg/kg. 30 min after *i.p.* administration the mice are placed on the rotating rod. Neurotoxicity was indicated by the failure of the animal to sustain equilibrium on the rod for at least 1 min in each of three trials. Procedures employed for evaluation of anticonvulsant activity and neurotoxicity were reviewed and approved by the University Animal Ethical Committee.

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-(benzaldehyde)-semicarbazone 1: MP 162 °C; Yield 54%; IR (cm^{-1}) (KBr) 3435.8 (N-H str of amide), 3048.2 (Aromatic C-H str), 1680.5 (C=O str of amide), 1644.8 (C=N of 1,3,4-thiadiazole nucleus), 1614.9 (C=N group), 1602.5 & 1504.7 (Aromatic C-C str), 743.1 (C-S of 1,3,4-thiadiazole nucleus); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.4 (C-2), 157.3 (NH<u>C</u>ONHNCH), 156.5 (C-5), 154.8 (NHCONHN<u>C</u>H), 141.3 (C-2'), 137.6 (C-4' & C-5'), 131.3 (C-1"), 130.8 (C-4"), 129.1 (C-2" & C-6"), 128.7 (C-3" & C-5"), 122.7 (C-7' & C-8'), 115.3 (C-6' & C-9'), 46.4 (<u>C</u>H_2), 9.3 (<u>C</u>H_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.5 (s, 1H, NHCON<u>H</u>), 6.8-7.6 (m, 9H, ArH), 6.9 (s, 1H, imine H), 6.1 (s, 1H, N<u>H</u>CONH), 5.1 (s, 2H, CH_2), 2.5 (s, 3H, CH_3); ESMS (Methanol) *m/z* 391 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-(4-nitrobenzaldehyde)-semicarbazone 2: MP 174 °C; Yield 62%; IR (cm^{-1}) (KBr) 3427.2 (N-H str of amide), 3044.3 (Aromatic C-H str), 1683.8 (C=O str of amide), 1644.6 (C=N of 1,3,4-thiadiazole nucleus), 1613.7 (C=N group), 1603.6 & 1505.8 (Aromatic C-C str), 1522.5 & 1353.6 (N=O str of Ar-NO_2 group), 745.2 (C-S of 1,3,4-thiadiazole nucleus); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.6 (C-2), 157.5 (NH<u>C</u>ONHNCH), 156.4 (C-5), 154.7 (NHCONHN<u>C</u>H), 150.8 (C-4"), 141.5 (C-2'), 137.8 (C-4' & C-5'), 137.4 (C-1"), 129.8 (C-2" & C-6"), 123.6 (C-3" & C-5"), 122.8 (C-7' & C-8'), 115.4 (C-6' & C-9'), 46.4 (<u>C</u>H_2), 9.4 (<u>C</u>H_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.4 (s, 1H, NHCON<u>H</u>), 7.2-8.2 (m, 8H, ArH), 6.8 (s, 1H, imine H), 6.2 (s, 1H, N<u>H</u>CONH), 5.0 (s, 2H, CH_2), 2.4 (s, 3H, CH_3); ESMS (Methanol) *m/z* 436 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)1,3,4-thiadiazol-

2-yl}-N^4-(4-hydroxybenzaldehyde)-semicarbazone 3: MP 193 ^oC; Yield 55%; IR (cm^{-1}) (KBr) 3461.9 (O-H str of alcoholic group), 3425.1 (N-H str of amide), 3035.8 (Aromatic C-H str), 1674.7 (C=O str of amide), 1640.4 (C=N of 1,3,4-thiadiazole nucleus), 1615.0 (C=N group), 1603.6 & 1502.1 (Aromatic C-C str), 1164.6 (C-O str of alcoholic group), 821.7 (C-H def disubstituted benzene ring), 743.5 (C-S of 1,3,4-thiadiazole nucleus); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.3 (C-2), 159.8 (C-4"), 157.5 (NHCONHNCH), 156.4 (C-5), 154.7 (NHCONHNCH), 141.4 (C-2'), 137.8 (C-4' & C-5'), 130.4 (C-2" & C-6"), 123.8 (C-1"), 122.8 (C-7' & C-8'), 115.9 (C-3" & C-5"), 115.5 (C-6' & C-9'), 46.4 (CH_2), 9.2 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.5 (s, 1H, NHCONH), 6.8 (s, 1H, imine H), 6.8-7.7 (m, 8H, ArH), 6.2 (s, 1H, NHCONH), 5.3 (ArOH), 5.0 (s, 2H, CH_2), 2.5 (s, 3H, CH_3); ESMS (Methanol) *m/z* 407 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-(4-methylbenzaldehyde)-semicarbazone 4: MP 168 ^oC; Yield 57%; IR (cm^{-1}) (KBr) 3429.4 (N-H str of amide), 3042.8 (Aromatic C-H str), 2909.2 (aliphatic C-H str), 1672.7 (C=O str of amide), 1646.4 (C=N of 1,3,4-thiadiazole nucleus), 1619.3 (C=N group), 1605.8 & 1502.5 (Aromatic C-C str), 1445.1 (aliphatic C-H def), 826.4 (C-H def disubstituted benzene ring), 743.7 (C-S of 1,3,4-thiadiazole nucleus); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.5 (C-2), 156.5 (C-5), 157.2 (NHCONHNCH), 154.7 (NHCONHNCH), 141.5 (C-2'), 140.1 (C-4"), 137.8 (C-4' & C-5'), 129.4 (C-3" & C-5"), 128.9 (C-2" & C-6"), 128.3 (C-1"), 122.8 (C-7' & C-8'), 115.3 (C-6' & C-9'), 46.4 (CH_2), 21.0 ($CH_3C_6H_5$), 9.5 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.6 (s, 1H, NHCONH), 6.9-7.7 (m, 8H, ArH), 6.8 (s, 1H, imine H), 6.0 (s, 1H, NHCONH), 5.1 (s, 2H, CH_2), 2.4 (s, 3H, CH_3), 2.3 ($ArCH_3$); ESMS (Methanol) *m/z* 405 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)1,3,4-thiadiazol-2-yl}-N^4-(4-methoxybenzaldehyde)-semicarbazone 5: MP 198 ^oC; Yield 58%; IR (cm^{-1}) (KBr) 3424.2 (N-H str of amide), 3040.8 (Aromatic C-H str), 1683.7 (C=O str of amide), 1645.0 (C=N of 1,3,4-thiadiazole nucleus), 1616.5 (C=N group), 1606.9 & 1502.1 (Aromatic C-C str), 1266.4 (C-O of OCH_3 group), 825.3 (C-H def disubstituted benzene ring), 744.6 (C-S of 1,3,4-thiadiazole nucleus); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.4 (C-2), 164.3 (C-4"), 157.4 (NHCONHNCH), 156.7 (C-5), 154.6 (NHCONHNCH), 141.3 (C-2'), 137.7 (C-4' & C-5'), 129.9 (C-2" & C-6"), 122.9 (C-7' & C-8'), 123.4 (C-1"), 115.3 (C-6' & C-9'), 114.5 (C-3" & C-5"), 56.1 ($OCH_3C_6H_5$), 46.4 (CH_2), 9.3 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.6 (s, 1H, NHCONH), 6.8-7.8 (m, 8H, ArH), 6.8 (s, 1H, imine H), 6.2 (s, 1H, NHCONH), 5.1 (s, 2H, CH_2), 3.8 ($ArOCH_3$); 2.4 (s, 3H, CH_3); ESMS (Methanol) *m/z* 421 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-(4-chlorobenzaldehyde)-semicarbazone 6: MP 212 ^oC; Yield 62%; IR (cm^{-1}) (KBr) 3423.2 (N-H str of amide), 3036.3 (Aromatic C-H str), 2911.7 (aliphatic C-H str), 1693.6 (C=O str of amide), 1639.9 (C=N of 1,3,4-thiadiazole nucleus), 1605.3 & 1505.6 (Aromatic C-C str), 1604.4 (C=N group), 1443.7 (aliphatic C-H def), 826.1 (C-H def disubstituted benzene ring), 750.5 (C-S of 1,3,4-thiadiazole nucleus), 719.4 (C-Cl str); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.5 (C-2), 157.5 (NHCONHNCH), 156.3 (C-5), 154.9 (NHCONHNCH), 141.4 (C-2'), 137.8 (C-4' & C-5'), 136.2 (C-4"), 130.3 (C-2" & C-6"), 129.2 (C-1"), 128.9 (C-3" & C-5"), 122.9 (C-7' & C-8'), 115.3 (C-6' & C-9'), 46.4 (CH_2), 9.4 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 6.9-9.5 (s, 1H, NHCONH), 7.7 (m, 8H, ArH), 6.8 (s, 1H, imine H), 6.0 (s, 1H, NHCONH), 5.0 (s, 2H, CH_2), 2.5 (s, 3H, CH_3); ESMS (Methanol) *m/z* 426 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-hydroxyphenyl) ethanone]-semicarbazone 7: MP 205 ^oC; Yield 60%; IR (cm^{-1}) (KBr) 3442.8 (O-H str of alcoholic group), 3424.8 (N-H str of amide), 3040.7 (Aromatic C-H str), 1683.1 (C=O str of amide), 1642.6 (C=N of 1,3,4-thiadiazole nucleus), 1607.2 (C=N group), 1606.1 & 1506.0 (Aromatic C-C str), 1144.9 (C-O str of alcoholic group), 826.0 (C-H def disubstituted benzene ring), 745.8 (C-S of 1,3,4-thiadiazole nucleus); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.6 (C-2), 159.8 (C-4"), 157.3 (NHCONHNCCH$_3$), 155.7 (NHCONHNCCH$_3$), 141.4 (C-2'), 137.8 (C-4' & C-5'), 130.5 (C-2" & C-6"), 123.6 (C-1"), 122.8 (C-7' & C-8'), 115.7 (C-3" & C-5"), 115.5 (C-6' & C-9'), 46.4 (CH_2), 11.4 (NHCONHNCCH$_3$), 9.4 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.6 (s, 1H, NHCONH), 6.8-7.8 (m, 8H, ArH), 6.1 (s, 1H, NHCONH), 5.4 (ArOH), 5.1 (s, 2H, CH_2), 2.4 (s, 3H, CH_3), 1.1 (s, 3H, Carbimino CH_3); ESMS (Methanol) *m/z* 421 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-methoxyphenyl) ethanone]-semicarbazone 8: MP 173 ^oC; Yield 62%; IR (cm^{-1}) (KBr) 3432.1 (N-H str of amide), 3043.0 (Aromatic C-H str), 2913.7 (aliphatic C-H str), 1683.5 (C=O str of amide), 1642.6 (C=N of 1,3,4-thiadiazole nucleus), 1618.3 (C=N group), 1604.4 & 1501.6 (Aromatic C-C str), 1444.0 (aliphatic C-H def), 1271.8 (C-O of OCH_3 group), 819.5 (C-H def disubstituted benzene ring), 739.2 (C-S of 1,3,4-thiadiazole nucleus); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.5 (C-4"), 164.3 (C-2), 157.4 (NHCONHNCCH$_3$), 156.4 (C-5), 155.8 (NHCONHNCCH$_3$), 141.5 (C-2'), 137.9 (C-4' & C-5'), 130.3 (C-2" & C-6"), 123.6 (C-1"), 122.8 (C-7' & C-8'), 115.4 (C-6' & C-9'), 114.3 (C-3" & C-5"), 56.1 ($OCH_3C_6H_5$), 46.4 (CH_2), 11.4 (NHCONHNCCH$_3$), 9.2 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ

ppm): 9.8 (s, 1H, NHCONH), 6.8-7.8 (m, 8H, ArH), 6.1 (s, 1H, NHCONH), 5.0 (s, 2H, CH_2), 3.8 ($ArOCH_3$), 2.5 (s, 3H, CH_3), 1.1 (s, 3H, Carbimino CH_3); ESMS (Methanol) *m/z* 436 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-nitrophenyl)ethanone]-semicarbazone 9: MP 219 °C; Yield 57%; IR (cm^{-1}) (KBr) 3430.3 (N-H str of amide), 3044.6 (Aromatic C-H str), 2911.7 (aliphatic C-H str), 1685.9 (C=O str of amide), 1643.6 (C=N of 1,3,4-thiadiazole nucleus), 1617.6 (C=N group), 1604.6 & 1503.7 (Aromatic C-C str), 1531.5 & 1359.1 (N=O str of Ar-NO_2 group), 1439.3 (aliphatic C-H def), 829.0 (C-H def disubstituted benzene ring), 740.8 (C-S of 1,3,4-thiadiazole nucleus); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.4 (C-2), 157.6 ($NHCONHNCCH_3$), 156.3 (C-5), 155.8 ($NHCONHNCCH_3$), 150.6 (C-4''), 141.6 (C-2'), 138.0 (C-4' & C-5'), 137.5 (C-1''), 130.0 (C-2'' & C-6''), 123.8 (C-3'' & C-5''), 122.8 (C-7' & C-8'), 115.5 (C-6' & C-9'), 46.4 (CH_2), 11.3 ($NHCONHNCCH_3$), 9.4 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.7 (s, 1H, NHCONH), 7.2-8.2 (m, 8H, ArH), 6.2 (s, 1H, NHCONH), 5.0 (s, 2H, CH_2), 2.4 (s, 3H, CH_3), 1.1 (s, 3H, Carbimino CH_3); ESMS (Methanol) *m/z* 450 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-chlorophenyl) ethanone]-semicarbazone 10: MP 188 °C; Yield 60%; IR (cm^{-1}) (KBr) 3426.4 (N-H str of amide), 2909.1 (aliphatic C-H str), 3040.4 (Aromatic C-H str), 1683.6 (C=O str of amide), 1649.7 (C=N of 1,3,4-thiadiazole nucleus), 1619.7 (C=N group), 1606.2 & 1501.6 (Aromatic C-C str), 1442.0 (aliphatic C-H def), 825.9 (C-H def disubstituted benzene ring), 746.3 (C-S of 1,3,4-thiadiazole nucleus), 718.4 (C-Cl str); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.5 (C-2), 157.3 ($NHCONHNCCH_3$), 156.4 (C-5), 155.7 ($NHCONHNCCH_3$), 141.7 (C-2'), 137.8 (C-4' & C-5'), 136.2 (C-4''), 130.4 (C-2'' & C-6''), 129.5 (C-1''), 129.2 (C-3'' & C-5''), 122.7 (C-7' & C-8'), 115.5 (C-6' & C-9'), 46.4 (CH_2), 11.4 ($NHCONHNCCH_3$), 9.3 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.8 (s, 1H, NHCONH), 7.2-7.9 (m, 8H, ArH), 6.3 (s, 1H, NHCONH), 5.1 (s, 2H, CH_2), 2.5 (s, 3H, CH_3), 1.2 (s, 3H, Carbimino CH_3); ESMS (Methanol) *m/z* 440 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(diphenyl) methanone]-semicarbazone 11: MP 241 °C; Yield 55%; IR (cm^{-1}) (KBr) 3427.0 (N-H str of amide), 3035.7 (Aromatic C-H str), 1670.7 (C=O str of amide), 1645.2 (C=N of 1,3,4-thiadiazole nucleus), 1627.9 (C=N group), 1605.2 & 1504.4 (Aromatic C-C str), 743.1 (C-S of 1,3,4-thiadiazole nucleus), 709.1 & 765.5 (C-H def monosubstituted benzene ring); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.4 (C-2), 157.5 ($NHCONHNCC_6H_5$), 156.5 (C-5), 155.6 ($NHCONHNCC_6H_5$), 141.5 (C-2'), 137.9 (C-4' & C-5'), 131.3 (C-1''), 131.3 (C-1'''), 130.9 (C-4''), 130.9 (C-4'''), 129.1 (C-2'' & C-6''), 129.1 (C-2''' & C-6'''), 128.6 (C-3'' & C-5''), 128.6 (C-3''' & C-5'''), 122.7 (C-7' & C-8'), 115.6 (C-6' & C-9'), 46.4 (CH_2), 9.3 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.7 (s, 1H, NHCONH), 7.2-7.9 (m, 14H, ArH), 6.2 (s, 1H, NHCONH), 2.5 (s, 3H, CH_3), 5.0 (s, 2H, CH_2); ESMS (Methanol) *m/z* 468 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-hydroxyphenyl) (phenyl) methanone]-semicarbazone 12: MP 227 °C; Yield 59%; IR (cm^{-1}) (KBr) 3474.8 (O-H str of alcoholic group), 3443.9 (N-H str of amide), 3040.6 (Aromatic C-H str), 1680.2 (C=O str of amide), 1642.8 (C=N of 1,3,4-thiadiazole nucleus), 1619.5 (C=N group), 1603.5 & 1507.0 (Aromatic C-C str), 1159.7 (C-O str of alcoholic group), 823.1 (C-H def disubstituted benzene ring), 746.9 (C-S of 1,3,4-thiadiazole nucleus), 708.6 & 762.2 (C-H def monosubstituted benzene ring); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.3 (C-2), 159.7 (C-4''), 157.2 ($NHCONHNCC_6H_5$), 156.4 (C-5), 155.8 ($NHCONHNCC_6H_5$), 141.7 (C-2'), 137.9 (C-4' & C-5'), 131.3 (C-1'''), 130.9 (C-4'''), 130.6 (C-2'' & C-6''), 129.0 (C-2''' & C-6'''), 128.6 (C-3''' & C-5'''), 123.6 (C-1''), 122.8 (C-7' & C-8'), 115.9 (C-3'' & C-5''), 115.2 (C-6' & C-9'), 46.4 (CH_2), 9.5 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.8 (s, 1H, NHCONH), 6.8-7.9 (m, 13H, ArH), 6.2 (s, 1H, NHCONH), 5.3 (ArOH), 5.1 (s, 2H, CH_2), 2.4 (s, 3H, CH_3); ESMS (Methanol) *m/z* 484 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-nitrophenyl) (phenyl) methanone]-semicarbazone 13: MP 186 °C; Yield 60%; IR (cm^{-1}) (KBr) 3425.8 (N-H str of amide), 3041.4 (Aromatic C-H str), 1680.1 (C=O str of amide), 1648.2 (C=N of 1,3,4-thiadiazole nucleus), 1619.9 (C=N group), 1604.6 & 1510.5 (Aromatic C-C str), 1520.8 & 1351.7 (N=O str of Ar-NO_2 group), 824.7 (C-H def disubstituted benzene ring), 760.9 (C-S of 1,3,4-thiadiazole nucleus), 707.8 & 766.0 (C-H def monosubstituted benzene ring); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.5 (C-2), 157.4 ($NHCONHNCC_6H_5$), 156.3 (C-5), 155.7 ($NHCONHNCC_6H_5$), 150.9 (C-4''), 141.8 (C-2'), 137.9 (C-4' & C-5'), 137.5 (C-1''), 131.3 (C-1'''), 130.7 (C-4'''), 130.1 (C-2'' & C-6''), 129.0 (C-2''' & C-6'''), 128.6 (C-3''' & C-5'''), 123.9 (C-3'' & C-5''), 122.9 (C-7' & C-8'), 115.5 (C-6' & C-9'), 46.4 (CH_2), 9.3 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.7 (s, 1H, NHCONH), 7.2-8.2 (m, 13H, ArH), 6.1 (s, 1H, NHCONH), 5.0 (s, 2H, CH_2), 2.3 (s, 3H, CH_3); ESMS (Methanol) *m/z* 513 (M^+).

N^1-{5-[(2-methyl-1*H*-benzimidazol-1-yl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-methoxyphenyl) (phenyl) methanone]-semicarbazone 14: MP 254 °C; Yield 58%; IR (cm^{-1}) (KBr) 3429.0 (N-H str of amide), 3045.9 (Aromatic C-H str), 1688.3 (C=O str of amide), 1647.4 (C=N of 1,3,4-thiadiazole nucleus), 1619.2 (C=N group), 1607.5 & 1502.6 (Aromatic C-C str), 1255.2 (C-O of OCH_3 group), 821.9 (C-H def disubstituted benzene ring),

745.1 (C-S of 1,3,4-thiadiazole nucleus), 709.7 & 767.2 (C-H def monosubstituted benzene ring); ^{13}C-NMR (75 MHz, DMSO-d_6, TMS, δ ppm): 164.6 (C-4''), 164.4 (C-2), 157.3 (NHCONHN-CC_6H_5), 156.6 (C-5), 155.9 (NHCONHNCC_6H_5), 141.5 (C-2'), 137.9 (C-4' & C-5'), 131.4 (C-1'''), 130.8 (C-4'''), 130.3 (C-2'' & C-6''), 129.0 (C-2''' & C-6'''), 128.6 (C-3''' & C-5'''), 123.6 (C-1''), 122.8 (C-7' & C-8'), 115.5 (C-6' & C-9'), 114.5 (C-3'' & C-5''), 56.2 ($OCH_3C_6H_5$), 46.4 (CH_2), 9.4 (CH_3 attached to benzimidazole); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ ppm): 9.8 (s, 1H, NHCONH), 6.8-7.8 (m, 13H, ArH), 6.2 (s, 1H, NHCONH), 3.8 ($ArOCH_3$), 5.0 (s, 2H, CH_2), 2.4 (s, 3H, CH_3); ESMS (Methanol) *m*/*z* 498 (M^+).

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