Chapter I

Section B

Graphene oxide (GO) catalyzed one-pot synthesis of 3,5-disubstituted 1,2,4-oxadiazoles

I.B.1. Introduction

Nitrogen-containing heterocyclic compounds are valuable due to their potential application as a key intermediate in the synthesis of numerous drugs [1]. 3,5-disubstituted 1,2,4-oxadiazoles are remarkably an important class of nitrogen-containing heterocyclic scaffold as it is widely used as pharmacophores, bioactive molecules, and functional materials [1-2]. Among the oxadiazole derivatives, the 1,2,4-oxadiazole motif has received interest due to its application as a stable bioisostere in place of an amide, ester, or urea functionality [3]. The 1,2,4-oxadiazole moiety is generally found in many drugs including potent S1P1 agonist I [4] and the metabotropic glutamate subtype 5 (mGlu5) receptor antagonist II for the treatment of Alzheimer's disease [5]. In previous literature, 1,2,4-oxadiazoles have shown good affinities for serotonin and norepinephrine transporters [6]. These compounds when selectively functionalized, have performed as various muscarinic agonists [7], benzodiazepine receptor partial agonists [8], serotonergic (5-HT_3) antagonists [9], dopamine transporters [10], antischistosomal drug [11], G-quadruplex ligands for probing DNA superstructure in antitumor research (Figure I.B.1) [12-13].

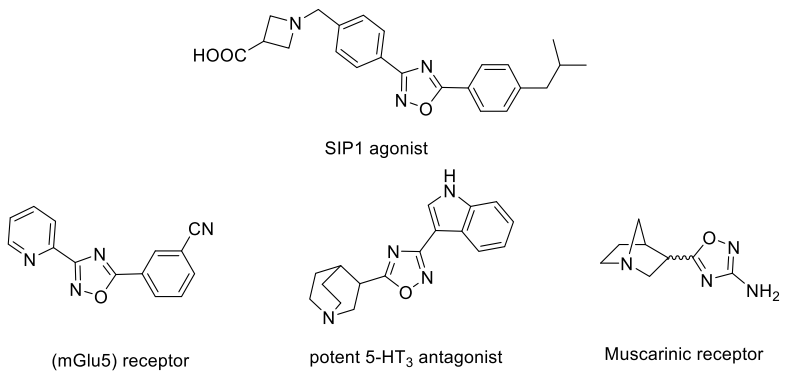


Figure I.B.1. *Some biologically active 1,2,4-oxadiazoles.*

I.B.2. Background and objectives

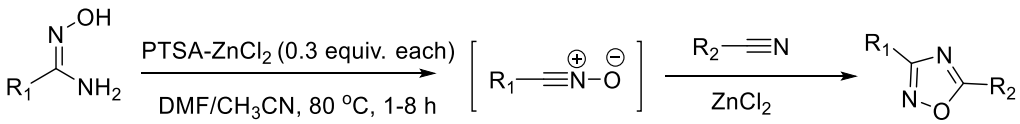
In the past decade, Multicomponent reactions (MCRs) have been accounted as very elegant and efficient methods to form complex structures in a single synthetic pathway from three or more reactants. The great synthetic efficiency, High atom economy, and procedural convenience in the construction of new multiple bonds in a one-pot procedure are the advantages of multicomponent reactions (MCRs) [14, 15]. The development of new MCRs and the improvement of known MCRs are popular research areas in current synthetic organic chemistry.

It is noteworthy that, in the last decade many efficient protocols have been developed to synthesize significant heterocyclic moieties 1,2,4-oxadiazoles. Among the known synthetic strategies of 1,2,4-oxadiazoles, the most conventional approach involves the use of amidoximes as starting materials or intermediates. Other common approaches involve i) *O*-Acylation of amidoximes by an activated carboxylic acid derivative, followed by cyclodehydration [16], ii) the 1,3-dipolar cycloaddition of nitrile oxide to nitriles [17], iii) intermolecular cyclodehydration reaction of amidoximes (as starting material) with aldehydes to give 4,5-dihydro 1,2,4-oxadiazoles followed by oxidative dehydrogenation [18], iv) formation of amidoxime intermediate through the reaction of nitrile with hydroxylamine which further reacts with aldehyde to provide 4,5-dihydro 1,2,4-oxadiazoles and oxidative dehydrogenation give 3,5-disubstituted 1,2,4-oxadiazoles [19]. Besides this, base-mediated one-pot synthesis and microwave-assisted efficient synthesis of oxadiazoles using PTSA and $ZnCl_2$ have also been reported [17, 19-20]. However, all the methods mentioned above are efficient enough but most of the methods suffer from the use of harsh conditions (microwave irradiation, the

addition of strong acid/ strong base or strong dehydrate, high reaction temperature) and unavailable starting materials.

I.B.2.1. Synthesis 3,5-disubstituted 1,2,4-oxadiazoles from amidoxime

Augustine *et al*. developed p-toluenesulfonic acid (PTSA) mediated zinc chloride ($ZnCl_2$) catalyzed synthesis of 3,5-disubstituted 1,2,4-oxadiazoles (Scheme I.B.1) using amidoximes and organic nitriles [17]. They examined the reaction of various amidoximes with acetonitrile and interestingly all the reactions were complete within 1-2 h to provide 3-substituted 5-methyl-1,2,4-oxadiazoles. The strained cycloalkyl amidoximes were successfully reacted with different aromatic and aliphatic nitriles in DMF solvent and resulted in the corresponding product with a good yield. The mechanism of the reaction was explained through the initial activation of amidoxime by PTSA-$ZnCl_2$ resulting in the formation of nitrile oxide and 1,3-Dipolar cycloaddition of nitrile oxide to nitriles resulted in the formation of 1,2,4-oxadiazoles.



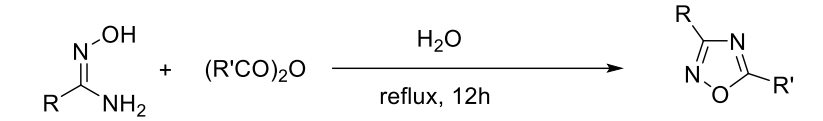
R_1= alkyl, aryl
R_2= alkyl aryl

Yield 77-95 %

Scheme I.B.1. (PTSA) mediated zinc chloride ($ZnCl_2$) catalyzed synthesis of 3,5-disubstituted 1,2,4-oxadiazoles.

The formation of *O*-acyl amidoxime from the reaction of an amidoxime with an acyl chloride is the most difficult and time-consuming step and generally requires a long reaction time and sealed tube condition. Kaboudin *et al.* reported a new efficient method for the synthesis of 1,2,4-oxadiazoles via the reaction of amidoximes with anhydrides under mild, catalyst-free conditions (Scheme I.B.2) in aqueous media [16]. They observed that under the reaction conditions benzoyl

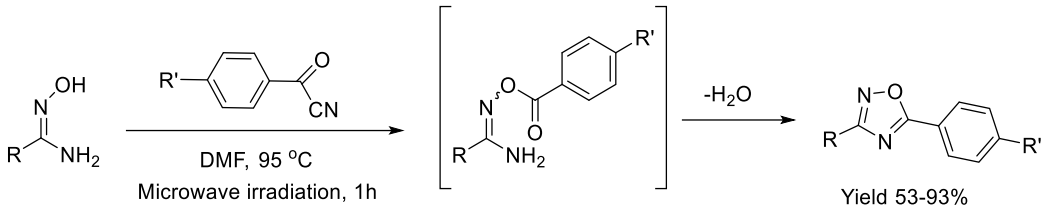
chloride (PhCOCl) is not much effective as benzoic anhydride and provides a very low yield of the product. Substituted benzamidoximes and aliphatic amidoximes afforded 1,2,4-oxadiazoles in presence of benzoic anhydride in good yields. However, the reaction of aliphatic anhydride, with various amidoximes gave the corresponding products in lower yields which may be due to the electronic effect.



R= C_6H_5, *p*-Cl-C_6H_4, *p*-Br-C_6H_4, 2,4-$Cl_2C_6H_3$
m-ClC_6H_4, *p*-$MeOC_6H_5$, Cyclohexyl
R'= C_6H_5, *p*-$CH_3C_6H_5$, n-C_5H_{11}

Scheme I.B.2. The synthesis of 1,2,4-oxadiazoles via the reaction of amidoximes with anhydrides under mild and catalyst-free conditions.

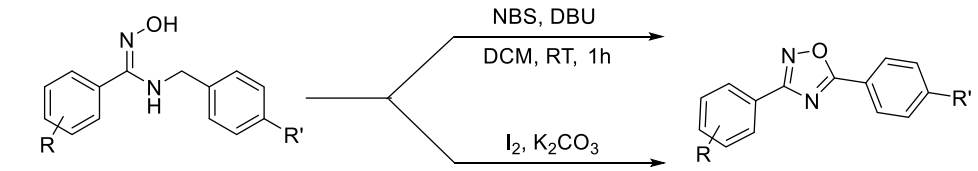
Kandre *et al*. evaluated microwave-assisted one-pot synthesis of 1,2,4-oxadiazoles from amidoximes and commercially available benzoyl cyanides (Scheme I.B.3). Generally, microwave heating reduced the reaction time as well as improved the yield over conventional heating [20]. It was assumed that the higher temperature in microwave irradiation, aids in the cyclization of *O*-carboxyaryl amidoxime intermediate. Among the solvents, DMF was found to be suitable for conducting the reaction at 95 °C for 1h. However, the yield was reduced at elevated temperatures due to the formation of side products. Here, the reactivity of the electron donating group containing phenyl amidoxime is higher than that of the phenyl amidoxime bearing electron-withdrawing groups.



R= Phenyl, 2-Methoxyphenyl, 3-Methoxyphenyl,
4-Methoxyphenyl, 2-Nitrophenyl, 3-Nitrophenyl,
4-Nitrophenyl, Cyclohexyl, Adamantyl
R'= H,-F,-CH_3

Scheme I.B.3. The one-pot synthesis of 1,2,4-oxadiazoles from amidoximes and commercially available benzoyl cyanides.

Lade *et al.* reported the synthesis of 1,2,4-oxadiazoles from *N*-benzyl amidoximes using oxidizers such as *N*-bromosuccinimide (NBS)-1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and I_2-K_2CO_3 at room temperature (Scheme I.B.4) [21]. The use of 1 equiv. of NBS oxidant and 1 equiv. of DBU base was found to be the best-optimized condition of the product conversion at room temperature in 1h. In absence of both oxidant and base, the reaction could not occur, indicating the vital role of oxidant and base during the reaction. Oxidative cyclization of amidoxime with electron-donating substituents offered a moderate yield of the product whereas, amidoximes with electron-withdrawing substituents underwent this oxidative pathway with high reactivity. The higher yield may be due to the formation of a more stable imine bond.

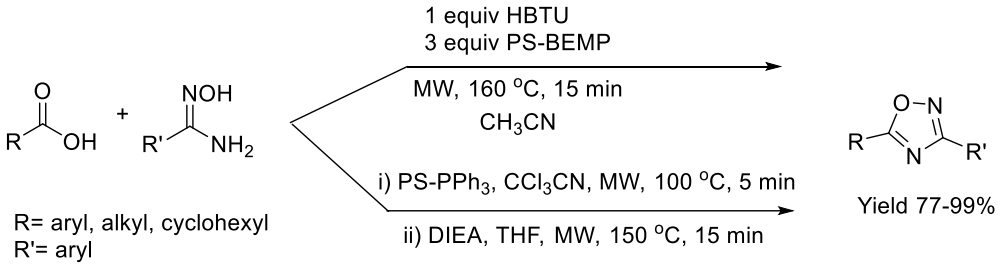


R= H, Cl, F, Br, OMe, OPh, Me, NO_2, CN
R'= H, OMe, F

Scheme I.B.4. The synthesis of 1,2,4-oxadiazoles from *N*-benzyl amidoximes.

Wang *et al*. developed a polymer-assisted solution-phase synthesis of 1,2,4-oxadiazoles using amidoxime and carboxylic acids in presence of a coupling reagent. They began their investigation to synthesize 1,2,4-oxadiazoles in presence of HBTU and *N,N*-diisopropylethylamine (DIEA) [22]. But the conversion was low under microwave irradiation at a higher temperature. The use of polymer-supported bases MP-carbonate and PS-BEMP showed much higher reactivity than DIEA. The use of HBTU/PS-BEMP in this protocol worked well for a wide range of amidoximes and afforded the corresponding oxadiazoles in good to excellent yield (Scheme I.B.5). Among many reported procedures, the use of PS-PPh_3/CCl_3CN is attractive, because it converts carboxylic acids to the corresponding carboxylic acid chloride in situ. After the generation of carboxylic acid chloride DIEA was added and heated in MW at 150 ^oC for 15 min.

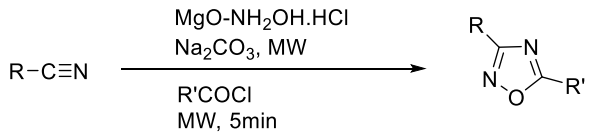
The most common method for the synthesis of 1,2,4-oxadiazoles through cyclization of *O*-acyl amidoximes obtained from the acylation of amidoximes and carboxylic acids or acid chlorides have some drawbacks. The acid chlorides are very hard to handle and store, on the other hand, carboxylic acids require a long reaction time along with a coupling reagent such as TBTU, DCC, EDC, HOBt to react with amidoxime [23, 24].



Scheme I.B.5. Polymer-assisted solution-phase synthesis of 1,2,4-oxadiazoles.

I.B.2.2. Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from nitriles

Kaboudin *et al*. reported the one-pot synthesis of 1,2,4-oxadiazoles through the solvent-free reaction of nitriles with hydroxylamine hydrochloride ($NH_2OH.HCl$) in the presence of magnesia-supported sodium carbonate (Scheme I.B.6) followed by reaction with acyl halides under microwave irradiation [25]. Other bases were also employed in this reaction but they were not much effective as Na_2CO_3. Different substituted benzonitriles reacted with hydroxylamine hydrochloride under the same reaction condition followed by the addition of acyl halide and afforded the product with a good yield.

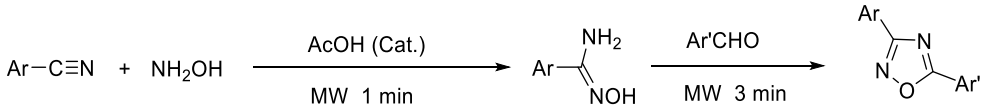


R= C_6H_5, *p*-$ClC_6H_4CH_2$,*p*-ClC_6H_4, 2,4-$Cl_2C_6H_3$, m-ClC_6H_4, Cyclohexyl
R'= C_6H_5, *p*-$CH_3OC_6H_4$, *p*-$NO_2C_6H_4$

Yield 40-70 %

Scheme I.B.6. Magnesia-supported sodium carbonate catalyzed synthesis of oxadiazole.

Adib *et al.* reported a facile one-pot three-component synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from nitriles, hydroxylamine, and aldehydes under solvent-free conditions and microwave irradiation (Scheme I.B.7) [19]. This reaction was carried out in presence of a catalytic amount of acetic acid. After a minute of MW irradiation nearly full conversion of the amidoxime intermediate was observed, then aldehyde was added to the reaction mixture and irradiated for a further 3 min. The formation of the 1,2,4-oxadiazoles in excellent yields was indicated by TLC analysis. Different substituted nitriles and aldehydes were successfully implemented in this protocol to synthesize the corresponding oxadiazoles in excellent yield.

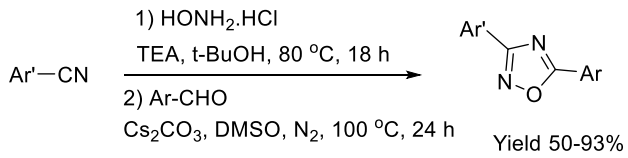


Yield 92-97%

Ar= C_6H_5, 4-$CH_3C_6H_4$, 3-ClC_6H_4
Ar'= C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4

Scheme I.B.7. 3,5-disubstituted 1,2,4-oxadiazoles synthesis from nitriles, hydroxylamine, and aldehydes under solvent-free conditions and microwave irradiation.

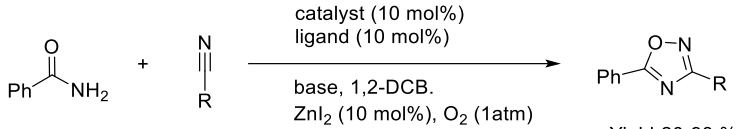
Wang *et al.* developed an efficient base-mediated synthesis of 3,5-disubstituted 1,2,4-oxadiazoles using nitrile, hydroxylamine hydrochloride, and aldehyde (Scheme I.B.8) [26]. Aldehydes are weak oxidants as they take part in self-redox reactions using a concentrated strong alkaline solution. They observed that the formation of oxadiazole was carried out by three sequential steps a) nucleophilic addition of hydroxylamine to produce amidoxime intermediate in the presence of triethylamine (TEA) for 18 h without exclusion of air at 80 °C, b) base mediated cascade coupling and cyclization reaction, c) oxidative dehydrogenation to form the target compound. Two different solvents were used in this reaction, *t*-BuOH was used as the solvent in the 1st step at 80 ºC and DMSO was the best solvent in the 2nd step of the reaction at 100 °C. The electron-donating and electron-withdrawing groups in aromatic nitriles, heterocyclic nitriles, and aromatic aldehydes were successfully capable to afford the corresponding oxadiazoles in moderate to excellent yield. However, the presence of larger steric hindrance in the substituents lowers the yield of the product.



Ar'= C_6H_5, 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$CF_3C_6H_4$, 4-BrC_6H_4
Ar= C_6H_5, 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-ClC_6H_4, napthyl, furyl, thinyl, pyridyl

Scheme I.B.8. An efficient base-mediated synthesis of 3,5-disubstituted 1,2,4-oxadiazoles.

Kuram *et al*. reported a Cu-catalyzed one-step protocol for the synthesis of 1,2,4-oxadiazoles from stable, readily available, and less toxic amides and organic nitriles by an oxidative rare N–O bond formation using oxygen as the sole oxidant (Scheme I.B.9) [27]. The optimized condition was obtained when CuI (10 mol%), bathophenanthroline ligand (10 mol%), K_2CO_3 base (2.0 equiv.), ZnI_2 (10 mol%), were used in 1,2-dichlorobenzene (1,2-DCB) at 130 °C temperature for 24 h. The substrates bearing electron-donating and withdrawing groups at the para position of the benzonitrile afford the corresponding product in good yields. This method showed good tolerance for diverse functional groups and broad substrate scope.

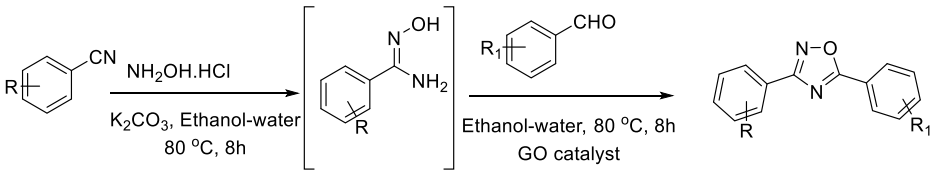


R= (hetero)aryl or alkyl

Scheme I.B.9. Cu-catalyzed one-step protocol for the synthesis of 1,2,4-oxadiazole.

I.B.3. Present work: Result and discussion

Herein we have developed a convenient and efficient process for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles (Scheme I.B.10) using an inexpensive, environmentally benign, metal-free heterogeneous carbocatalyst, graphene oxide (GO). GO plays a dual role of an oxidizing agent and solid acid catalyst for synthesizing 1,2,4-oxadiazoles. This dual catalytic activity of GO is due to the presence of oxygenated functional groups which are distributed on the nanosheets of graphene oxide. A broad scope of substrate applicability and good sustainability is offered in this developed protocol.



R= H, 4-CH_3, 4-OCH_3, 4-pyridinecarbonitrile
R_1= H, 4-CH_3, 4-OCH_3, 4-F, 3-NO_2, 4-$N(CH_3)_2$
1-Napthaldehyde, Furan-2-carbaldehyde,
Thiophene-2-carbaldehyde, Acetaldehyde

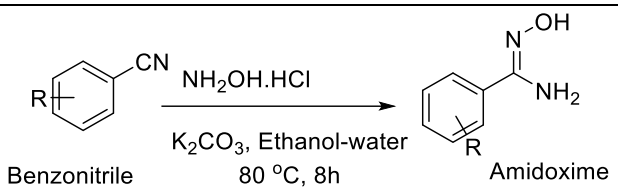
Scheme I.B.10. Synthesis of 1,2,4-oxadiazole using GO as catalyst.

I.B.3.1. Optimization of the reaction condition

For screening the reaction parameter benzonitrile (1.5 mmol), hydroxylamine hydrochloride (1.5 mmol), and base (1.5 mmol) were taken as model substrates to find out suitable conditions for the synthesis of amidoxime (intermediate). To satisfy our curiosity, the reaction was performed in different solvents e.g. polar protic, polar aprotic, and nonpolar. However, in absence of a base, a low yield was obtained (Table 1.B.1, entry 6). Gratifyingly, the reaction results showed (Table 1.B.1) the formation of amidoxime is highly favored in mixed solvent ethanol-water (1:3) using K_2CO_3 as a base. To control the reaction conditions, after completion of the reaction,the solvent was removed by a rotary

evaporator to separate the intermediate. While monitoring the TLC, only one spot was observed other than the reactant. After workup and purification by column chromatography, 91% yield of the intermediate (amidoxime) was obtained (Table I.B.1, entry 7). Although other bases were also employed (Table 1.B.1, entry 2, 5, 9), K_2CO_3 exerted the best result in an ethanol-water solvent. The synthesized amidoxime was characterized by NMR (300 MHz) spectroscopy.

Table I.B.1. Optimization of reaction condition for the synthesis of amidoxime (intermediate)[a]



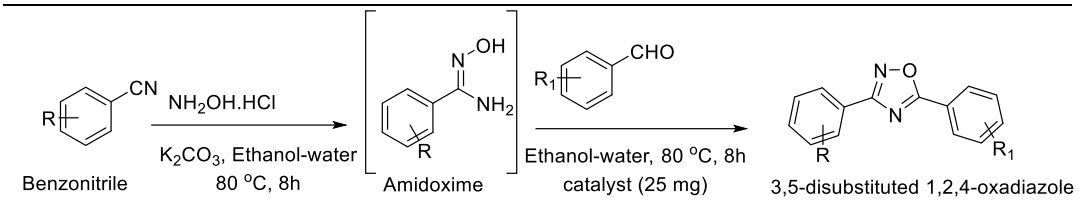
Benzonitrile — Amidoxime

Entry	Solvent	Temp. (°C)	Base	Yield(%)[b]
1	Water	100	K_2CO_3	68
2	Water	100	Cs_2CO_3	72
3	Ethanol	80	K_2CO_3	66
4	Ethanol	80	TEA	70
5	Ethanol-water	80	TEA	80
6	Ethanol-water	80	-	<50[c]
7	**Ethanol-water**	**80**	**K_2CO_3**	**91**
8	Ethanol-water	80	K_2CO_3	94[d]
9	Ethanol-water	80	Cs_2CO_3	93
10	THF	120	K_2CO_3	54
11	Toluene	110	K_2CO_3	<50
12	CH_3CN	82	K_2CO_3	68
13	DMF	120	K_2CO_3	76

[a]Reaction condition: Benzonitrile (1.5 mmol), hydroxylamine hydrochloride (1.5 mmol), base (1.5 mmol) and solvent (5 mL).
[b]Isolated yield.
[c]No base was added.
[d]The reaction was carried out for 24 hrs.

In the second step of the reaction, benzaldehyde (1 mmol) and the catalyst were added to the synthesized amidoxime in ethanol-water solvent to prioritize the synthesis of 3,5-disubstituted 1,2,4-oxadiazole. In presence of a small amount of GO, 73% yield of the product was obtained at 80 ^{o}C temperature (Table I.B.2, entry 2). Further increase in the amount of GO, proved to be favorable in the formation of 1,2,4-oxadiazole. No product was obtained when the reaction was carried out in absence of GO (Table I.B.2, entry 1). High yield of the product was observed in aqueous ethanolic solution with a ratio ethanol-water (1:3). The outstanding catalytic activity of GO in ethanol-water (1:3) is revealed due to its better dispersibility. To establish the catalytic activity of GO, few controlled experiments were carried out using various catalysts. Other carbonaceous nanomaterials e.g. powdered graphite, reduced graphene oxide (rGO) showed less catalytic activity than GO because they do not contain as many hydroxyl and carboxylic groups, indicating oxygen-containing functional groups in graphene oxide have a profound effect in catalyzing the synthesis of 3,5-disubstituted 1,2,4-oxadiazole. The reaction was also carried out in presence of GO and an oxidant H_2O_2, the reason for the low yield may be due to the oxidation of benzaldehyde to benzoic acid in presence of H_2O_2 (Table I.B.2, entry 12). The yield was not improved when only an H_2O_2 oxidant was used (Table I.B.2, entry 13). These control experiments infer the significant catalytic role of GO in the reaction.

Table I.B.2. Optimization of reaction condition for the synthesis of 3,5-disubstituted 1,2,4-oxadiazole from amidoxime[a]



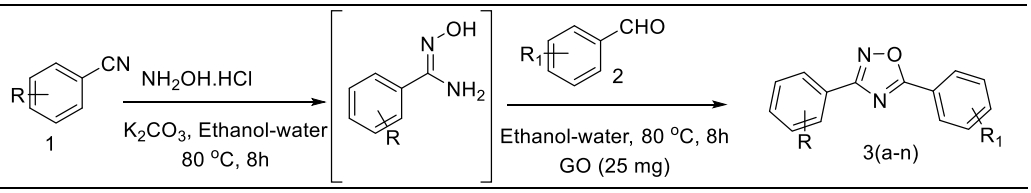
Entry	Catalyst (mg)	Solvent	Temp. (°C)	Time (h)	Yield%
1	-	Ethanol	80	12	Trace
2	15 (GO)	Ethanol	80	12	73
3	15 (GO)	Water	100	12	77
4	15 (GO)	DMF	100	12	60
5	15 (GO)	Ethanol-water	80	12	79
6	15 (GO)	Ethanol-water	80	24	83
7	25 (GO)	Ethanol-water	80	12	89
8	**25 (GO)**	**Ethanol-water**	**80**	**8**	**88**
9	25 (GO)	Ethanol-water	rt	12	52
10	25 (Graphite)	Ethanol-water	80	8	40[b]
11	25 (rGO)	Ethanol-water	80	8	45[c]
12	25 (GO)/Oxidant	Ethanol-water	80	8	67[d]
13	Oxidant	Ethanol-water	80	8	<40[e]
14	25 (GO)	Neat	80	8	69
15	25 (GO)	Ethanol-water	80	8	85[f]
16	-	Ethanol-water	80	8	Nil[f]

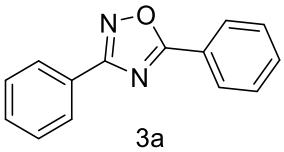
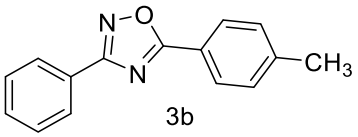
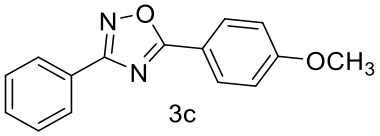
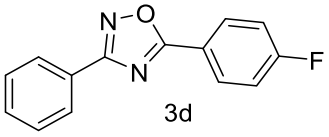
[a]Reaction condition: Benzaldehyde (1 mmol), amidoxime (1 mmol) and Ethanol-water (5 mL), pristine GO (25 mg).
[b]Graphite powder was used.
[c]Reduced graphene oxide (rGO).
[d]GO and extra oxidant 30 % H_2O_2 (1 mmol) were used.
[e]Only H_2O_2 was used.
[f]Under inert atmospheric condition.

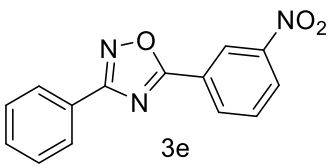
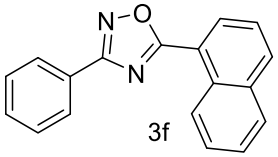
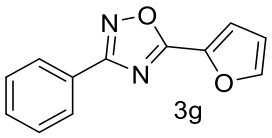
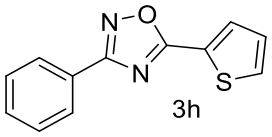
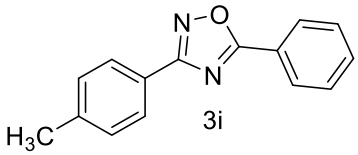
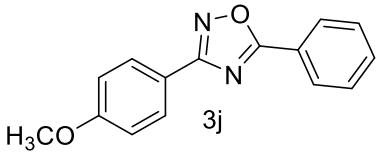
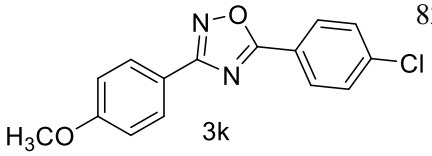
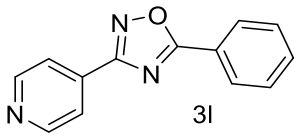
The scope and the substrate applicability of the reaction were also examined and results were summarized in Table I.B.3. With the optimized condition in hand, we have extended the substrate scope in organic

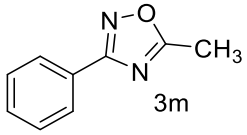
transformations and a series of diversely substituted aldehydes and benzonitriles are subjected to the synthesis of 3,5-disubstituted 1,2,4-oxadiazole (Table I.B.3). Both the electron-donating (Table I.B.3, entries 2-3, 10-11) and electron-withdrawing groups (entries 4-5) in the substituents afforded the corresponding product in good to excellent yield which indicates that the electronic nature of the substituents is not much influential to determine the yield of the reaction. 1-Napthaldehyde offered the product with low yield and the reason may be due to steric hindrance (Table I.B.3, entry 7).

Table 1.B.3. Synthesis of diversely functionalised 3,5-disubstituted 1,2,4-oxadiazole[a]



Entry	R	R_1	Product	Yield (%)[b]
1	4-H	4-H	 3a	83
2	4-H	4-CH_3	 3b	81
3	4-H	4-OCH_3	 3c	80
4	4-H	4-F	 3d	78

5	4-H	3-NO_2	 3e	75
6[c]	4-H	4-$N(CH_3)_2$	No 1,2,4-oxadiazole, only imine formation	-
7	4-H	1-Napthaldehyde	 3f	62
8	4-H	Furan-2-carbaldehyde	 3g	72
9	4-H	Thiophene-2-carbaldehyde	 3h	70
10	4-CH_3	4-H	 3i	80
11	4-OCH_3	4-H	 3j	78
12	4-OCH_3	4Cl	 3k	82
13	4-Pyridinecarbonitrile	4-H	 3l	68

14	4-H	CH_3CHO	 3m	75
15[d]	4-H	Heptaldehyde	NR	-
16[e]	CH_3CN	4-H	NR	-

[a] In the first step, Benzonitrile (1 mmol), hydroxylamine hydrochloride (1.5 mmol), K_2CO_3 (1.5 mmol), and Ethanol-water (5 mL) were stirred for 8 hr and in the 2nd step benzaldehyde (1 mmol) and GO (25 mg) were added in same reaction vessel and stirred for another 8 hr.
[b] Isolated yield after purification through column chromatography.
[c] 4-(dimethylamino)benzaldehyde (1 mmol) was used.
[d] Heptaldehyde was used.
[e] Acetonitrile (1 mmol) was used.

In the case of 4-*N,N*-(dimethylamino)benzaldehyde, the reaction was stopped at amidoxime, no desired oxadiazole is obtained (Table I.B.3, entry 6). The present catalytic condition showed a wide tolerance to heterocyclic aldehydes (Table I.B.3, entries 8, 9) and they were found to be highly effective to afford the corresponding product. The generality of the reaction was examined in the case of aliphatic aldehydes also. Interestingly, acetaldehyde was equally effective to yield the product with excellent quantity (Table I.B.3, entry 14). However, no product was found with increasing the side chain of aliphatic aldehydes (Table I.B.3, entry 15). It was disappointing that acetonitrile did not exert the corresponding product (Table I.B.3, entry 16). Due to the heterogeneous nature of GO, it can be easily isolated from the reaction mixture and reused. The catalytic activity of GO was examined for five consecutive cycles for the synthesis of 3,5-disubstituted 1,2,4-oxadiazole from benzaldehyde and amidoxime under reflux conditions for 8h to ascertain the recyclability potential of graphene oxide. The catalyst was separated after each recycles and washed thoroughly with ethanol and reused. A marginal decrease in the yield of oxadiazole is observed after each cycle which indicates a slight loss of catalytic activity of GO with recycling (Figure I.B.2).

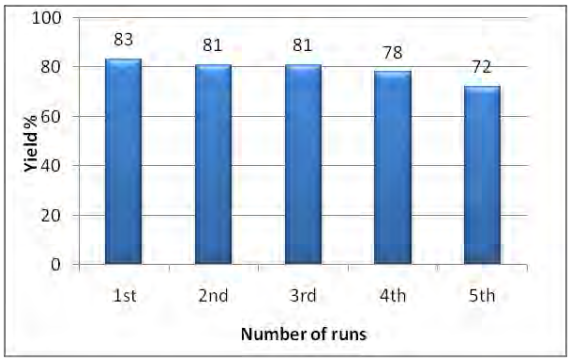


Figure I.B.2. Recyclability study of GO for the synthesis of 3,5-disubstituted 1,2,4-oxadiazole.

The catalytic activity arises some structural changes in GO which were analyzed by FTIR, XRD, SEM, HR-TEM, and EDX analysis. The XRD spectra of fresh GO and recycled catalyst (GO after 3rd run and 5th run) are shown in Figure I.B.3.

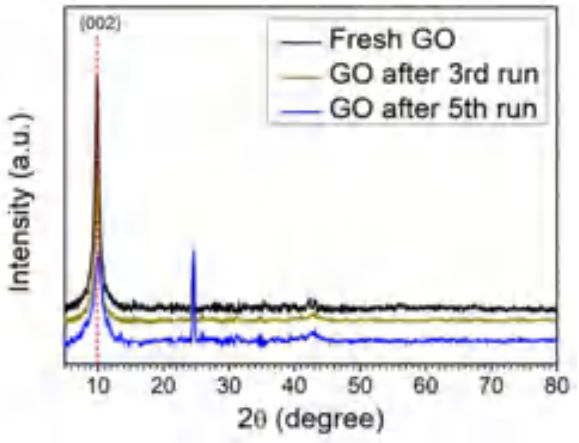


Figure I.B.3. *XRD spectra of fresh GO, after 3rd run and 5th run.*

A comparison of spectra indicates the reduction in the intensity of the first characteristic peak of GO (2Θ = 10.01) and the appearance of a new peak at (2Θ

= 24.62) due to the formation of partially reduced GO/ reduced graphene oxide upon reuse. These results confirm the reduction of the functional groups of GO during the reaction.

The comparison of the FTIR spectra revealed that the peak at 1720 cm^{-1} in fresh GO has completely disappeared after reuse. In addition to this, the peak intensity of the hydroxyl group at 3400 cm^{-1} decreases after reuse. FTIR data strongly support the reduction of GO to rGO in this oxidative cyclization reaction (Figure I.B.4).

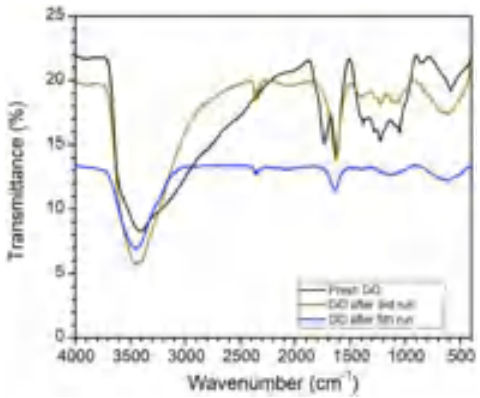


Figure I.B.4. *Comparative FTIR of fresh GO, after 3rd run and 5th run.*

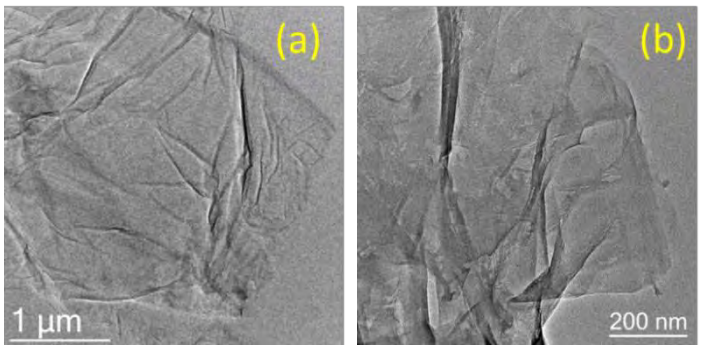


Figure I.B.5. *HR-TEM images of (a) GO and (b) GO after the 5th run.*

A morphological study of GO and GO after the 5th run was carried out using SEM and HR-TEM to investigate the disintegration of graphene oxide sheets after the reaction. In HR-TEM, the graphene oxide sheets are disintegrated into smaller sheets with slight aggregation after recycle (Figure I.B.5).

Moreover, the SEM images (Figure I.B.6) also reveal the formation of multiple small GO sheets after reuse. As GO catalyzes the reaction,its reduction to reduced graphene oxide possibly leads to its disintegration into smaller sheets.

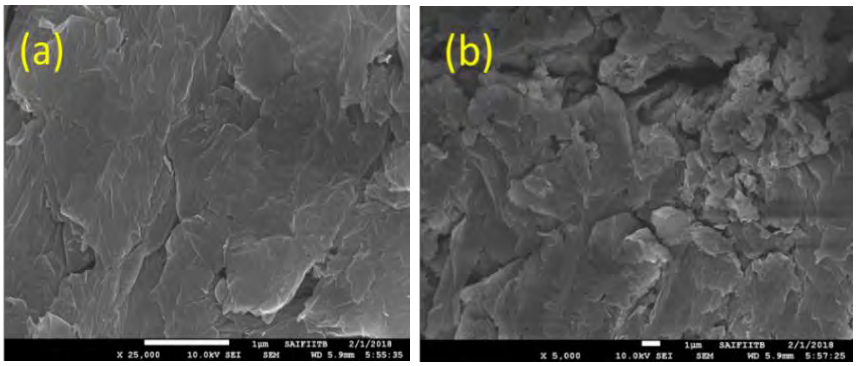
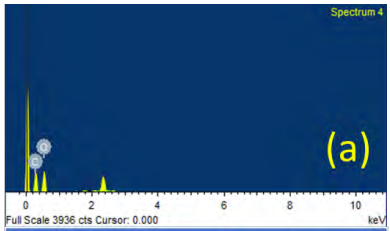
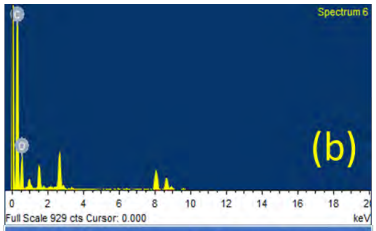


Figure I.B.6. *SEM images of (a) GO and (b) GO after the 5th run.*



Weight percent of constituent elements	
C	52.65
O	47.35



Weight percent of constituent elements	
C	71.79
O	28.21

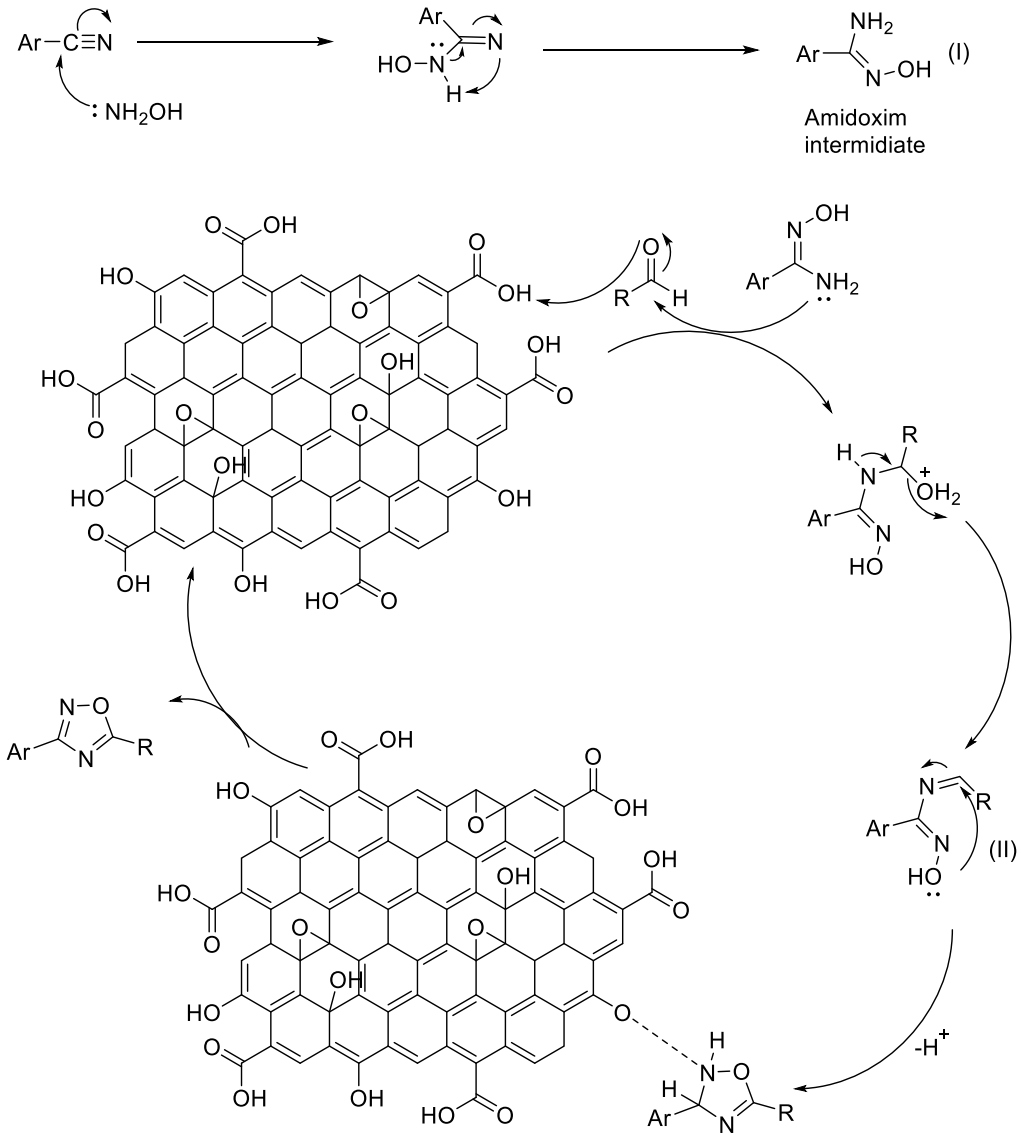
Figure I.B.7. *EDX spectra of (a) GO and (b) GO after the 5th run.*

The contribution of oxygen-containing functionalities during the reaction was further confirmed by the EDX analysis (Figure I.B.7). The carbon content was increased from 52.65% (fresh GO) to 71.79% (GO after 5th run) and the oxygen content was decreased from 47.35% (fresh GO) to 28.21% (GO after 5th run). The decrease in the oxygen content, therefore, indicates the role of GO in this cyclization reaction as an oxidizing agent. The universality and the dual catalytic activity of GO were established by a plausible mechanism (Scheme I.B.11).

I.B.3.2. Mechanism

A plausible mechanism of GO catalyzed synthesis of 3,5-disubstituted 1,2,4-oxadiazole has been proposed (Scheme I.B.11) based on literature reports [28] and our controlled experiments (Table I.B.2). Now, we propose the formation of amidoxime intermediate (I) from benzonitrile and hydroxylamine hydrochloride. However, in the first step, a base is required to neutralize hydroxylamine hydrochloride. In the 2nd step, protonation of aldehyde, oxygen occurs and subsequently, a nucleophilic attack by amidoxime occurs at the electrophilic center of aldehyde. After that, the intermediate (II) undergoes an oxidative cyclization in presence of GO to produce 1,2,4-oxadiazoles. This mechanism is in good agreement with the control experiments as described in table I.B.2. However, in presence of only H_2O_2 oxidant the yield of the reaction was diminished (Table I.B.2, entry 13). The role of GO as an acid catalyst and an oxidant was confirmed as its absence did not lead to the oxadiazole product (Table I.B.2, entry 1). The oxygen containing functional groups of GO are consumed during the reaction and the activity of GO gradually decreases. The activity of recycled GO is lower than that of the pristine GO. Good yield of the

product was obtained even under an inert atmosphere which strongly establish (Table I.B.2, entry 15), the prime role of GO in absence of atmospheric oxygen.



Scheme I.B.11. *A plausible route to the synthesis of 3,5-disubstituted 1,2,4-oxadiazole.*

I.B.4. Conclusion

In conclusion, carbocatalyst based metal-free catalytic pathway for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles has been established. The solid acid catalyst, GO facilitates the synthesis of oxadiazoles with good yield, easy recovery, and under mild reaction conditions. The dual catalytic activity of GO has been demonstrated without any undesired by-product under benign conditions. The present protocol gives a clean strategy to provide a wide variety of substituted oxadiazoles .

I.B.5. Experimental section

I.B.5.1. General experimental procedure

All the chemicals and reagents were purchased from Sigma–Aldrich, Spectrochem, TCI and were used without further purification. The solvents were purchased from commercial suppliers and were used after proper distillation. The progress of the reaction was monitored by Merck TLC plates which are coated with silica gel (60 F_{254}) and UV light was used as visualizing agent. NMR spectra of all the synthesized compounds were carried out in $CDCl_3$/DMSO-d_6 solvent and TMS was used as an internal standard. All the NMR spectroscopic data are recorded in BrukerAvance FT-NMR operating for 1H at 300/400 MHz. The ^{1}H NMR data are represented by chemical shift δ (ppm), multiplicity (s = singlet, d= doublet, t = triplet, m = multiplet), integration, coupling constants (Jvalues) in Hertz (Hz). The ^{13}C NMR spectroscopic data are also reported in ppm as ^{1}H NMR spectra.

I.B.5.2. General procedure for the preparation of (GO) catalyst

There are several methods for the preparation of graphene oxide (GO). Herein, Graphene oxide (GO) was synthesized by the Tours method using

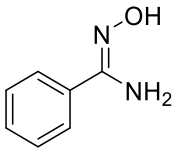
graphite powder as starting material [29]. At first, 9:1 volume ratio of (180 mL) sulfuric acid (H_2SO_4) and (20 mL) phosphoric acid (H_3PO_4) were taken in a 500 ml conical flask, and then 1.5 g of graphite powder was added to it under stirring condition. The temperature of the whole mixture was kept below 10 ^oC using an ice bath and 9g of potassium permanganate ($KMnO_4$) was added very slowly into it as the addition of $KMnO_4$ evolves heat. Then the reaction mixture was stirred for 12 hrs and after that hydrogen peroxide (H_2O_2) was added drops wise to eliminate excess $KMnO_4$. After that, 30-40 mL hydrochloric acid (HCl) (strength 30%) was added to this mixture followed by the addition of 200 mL of deionized water. Then the mixture was centrifuged at 5000 rpm for 20 minutes. After that, the supernatant liquid was decanted away and the residual was dried at 90 ^oC rotary evaporator to get dry graphene oxide (GO) with pH (4.2 at 0.1 mg/mL).

I.B.5.3. General procedure for the synthesis of 3,5-disubstituted 1,2,4 oxadiazoles

50-mL of RB was charged with benzonitrile (1.5 mmol), hydroxylamine hydrochloride (1.5 mmol), K_2CO_3 (1.5 mmol), and Ethanol-water (5 mL), and then the reaction mixture was stirred at 80 ^oC for 8 hrs. After 8 hrs, benzaldehyde (1 mmol) and 25 mg of GO were added to it and the reaction was carried out for another 8 hrs. The progress of the reaction was governed by thin-layer chromatography (TLC). After completion of the reaction, the solvent was evaporated by a rotary evaporator. The reaction mixture was extracted by ethyl acetate and the catalyst was separated by a simple filtration procedure. After workup, ethyl acetate extract was concentrated in a water bath and further purified by column chromatography using silica gel 60-120 mesh.

I.B.5.4. ^{1}H and ^{13}C NMR data of various 3,5-disubstituted 1,2,4 oxadiazoles

***N'*-Hydroxybenzenecarboximidamide (Table I.B.1, entry 7) [26]**



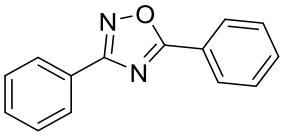
White solid;

MP: 72-74 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.07 (bs, 2H), 7.32-7.42 (m, 3H), 7.55-7.59 (m, 2H), 8.79 (bs, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 126.00, 128.67, 130.01, 132.38, 158.88 .

3,5-diphenyl-1,2,4-oxadiazole (Table I.B.3, entry 1) [28]



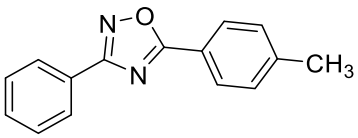
White solid;

MP: 103-104 °C;

^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm) 7.42-7.51 (m, 6H), 8.15-8.20 (m, 4H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 126.96, 127.52, 128.16, 128.84, 129.09, 131.17, 132.72, 133.90, 168.04, 173.96.

3-phenyl-5-(p-tolyl)-1,2,4-oxadiazole (Table I.B.3, entry 2) [28]



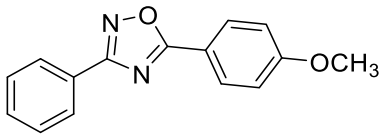
White solid;

MP: 110-112 ºC;

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.89 (s, 3H), 7.06-7.20 (m, 2H). 7.49-7.54 (m, 3H), 7.80-7.90 (m, 4H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 54.76, 126.98, 127.55, 128.19, 128.88, 129.13, 131.22, 132.77, 150.49, 168.76, 174.91.

5-(4-methoxyphenyl)-3-phenyl-1,2,4-oxadiazole (Table I.B.3, entry 3) [28]



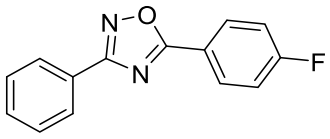
White solid;

MP: 100-101 ºC;

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 3.89 (s, 3H), 7.04 (d, 2H, *J*= 8.7Hz), 7.50-7.52 (t, 3H), 8.15-8.18 (m, 4H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.07, 122.80, 126.71, 127.41, 128.09, 129.63, 130.62, 131.90, 133.93, 168.09, 174.91.

5-(4-fluorophenyl)-3-phenyl-1,2,4-oxadiazole (Table I.B.3, entry 4) [28]



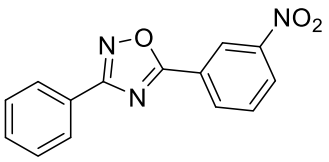
White solid;

MP: 118-119 ºC;

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (d, 2H, *J*= 8.1 Hz), 7.52-7.57 (m, 3H), 8.21-8.47 (m, 4H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 120.80, 126.21, 127.10, 127.98, 128.77, 130.58, 130.74, 133.80, 169.05, 175.57.

5-(3-nitrophenyl)-3-phenyl-1,2,4-oxadiazole (Table I.B.3, entry 5) [29]



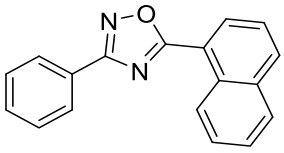
White solid;

MP: 140-142 °C;

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.75-7.89 (m, 3H), 8.14-8.31 (m, 5H), 8.62 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 123.57, 126.25, 126.71, 127.41, 127.93, 129.34, 130.83, 131.93, 133.90, 149.04, 169.67, 173.91.

5-(naphthalen-1-yl)-3-phenyl-1,2,4-oxadiazole (Table I.B.3, entry 7) [28]



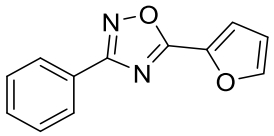
White solid;

MP: 99-101 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63-7.73 (m, 5H), 8.02-8.14 (m, 5H), 8.60 (d, 1H, *J* = 8.4 Hz), 8.93 (d, 1H, *J* =8.4 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 122.77, 126.77, 127.27, 127.53, 128.89, 129.15, 129.46, 129.53, 129.74, 130.89, 131.31, 131.79, 139.20, 169.06, 174.81.

5-(furan-2-yl)-3-phenyl-1,2,4-oxadiazole (Table I.B.3, entry 8) [28]



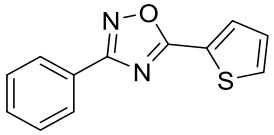
Yellow solid;

MP: 100-101 °C;

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25-7.33 (t, 1H), 7.52-8.03 (m, 4H), 8.09 (d, 2H, J = 7.2 Hz), 8.18 (d, 2H, J = 6.9 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 112.85, 116.69, 126.76, 127.91, 129.42, 131.68, 140.43, 147.05, 167.91, 168.99.

3-phenyl-5-(thiophen-2-yl)-1,2,4-oxadiazole (Table I.B.3, entry 9) [28]



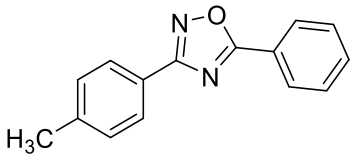
White solid;

MP: 107-108 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.23-7.29 (m, 1H), 7.54-7.68 (m, 4H), 7.98 (s, 1H), 8.17-8.24 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 127.58, 128.17, 128.51, 129.11, 131.26, 131.74, 132.88, 168.85, 171.36.

5-phenyl-3-(p-tolyl)-1,2,4-oxadiazole (Table I.B.3, entry 10) [28]



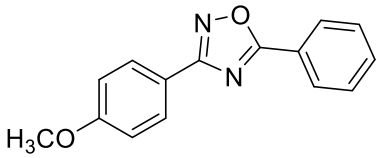
White solid;

MP: 100-102 ^{o}C;

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.43 (s, 3H), 7.53-7.61 (m, 3H), 8.00 (d, 2H, *J* = 6.9 Hz), 8.12 (d, 2H, *J* = 8.1 Hz), 8.59-8.78 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.61, 124.10, 127.95, 128.57, 128.92, 129.07, 129.39, 132.67, 141.50, 168.95, 174.10.

3-(4-methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (Table I.B.3, entry 11) [28]



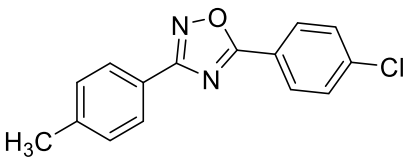
White solid;

MP: 101-102 ^{o}C;

^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm) 3.88 (s, 3H), 7.02 (d, 2H, *J* = 8.7 Hz), 7.52-7.63 (m, 3H), 8.10-8.23 (m, 4H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 54.87, 113.759, 118.99, 123.97, 127.64, 128.54, 128.63, 132.09, 161.46, 168.18, 174.94.

5-(4-chlorophenyl)-3-(p-tolyl)-1,2,4-oxadiazole (Table I.B.3, entry 12) [28]



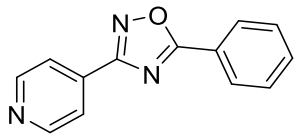
White solid;

MP: 132-134 ºC;

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.43 (s, 3H), 7.31 (d, 2H, *J* = 7.8 Hz), 7.51-7.54 (t, 2H), 8.04 (d, 2H, *J* = 8.1 Hz), 8.15 (d, 2H, *J* = 8.7 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.124, 122.329, 123.418, 126.418, 126.943, 128.945, 129.002, 129.105, 138.612, 141.162, 168.552, 174.135.

5-phenyl-3-(pyridin-4-yl)-1,2,4-oxadiazole (Table I.B.3, entry 13) [28]



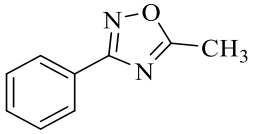
White solid;

MP: 145-146 ºC;

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47-7.64 (m, 3H), 8.07-8.08 (t, 1H), 8.13-8.20 (m, 2H). 8.21-8.85 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 121.044, 123.294, 127.744, 129.460, 132.399, 134.321, 149.758, 166.834, 176.054.

5-methyl-3-phenyl-1,2,4-oxadiazole (Table I.B.3, entry 14) [28,30]



Colourless liquid;

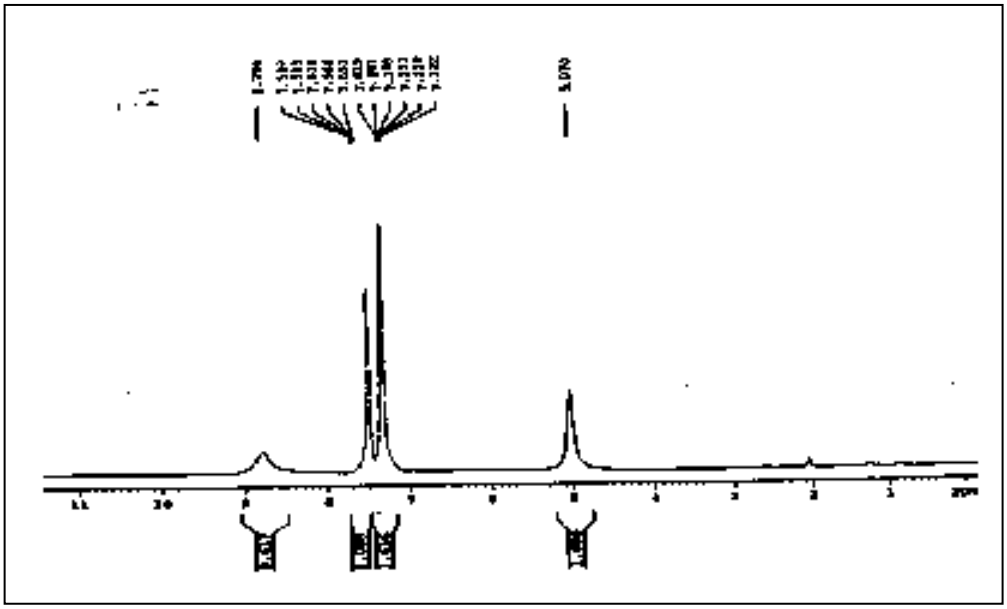
BP>200 ºC;

^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm) 2.57 (s, 3H), 7.36-7.38 (m, 3H), 7.95-7.98 (m, 2H);

^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 12.36, 126.82, 127.33, 128.84, 131.11, 168.35, 177.28; LCMS (ESI-APCI) $C_9H_8N_2O$ for: 161$[M+H]^+$, Anal. Calcd for $C_9H_8N_2O$: C= 67.39, H= 5.09, N= 17.49.

I.B.5.5. Scanned copies of ^{1}H and ^{13}C NMR spectra of synthesized compounds

Figure I.B.8. *Scanned copy of ^{1}H and ^{13}C NMR spectra of N'-Hydroxybenzenecarboximidamide*



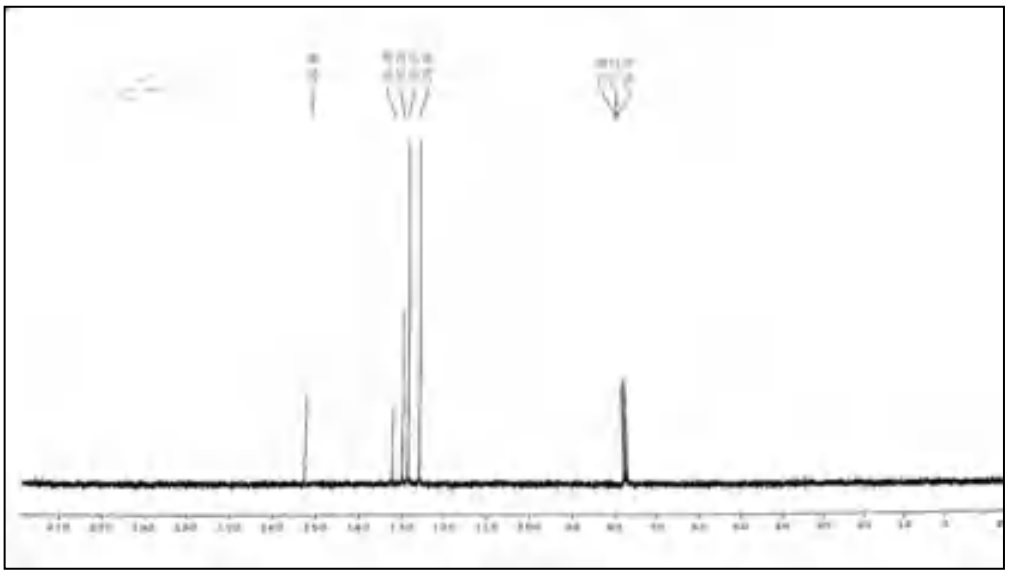
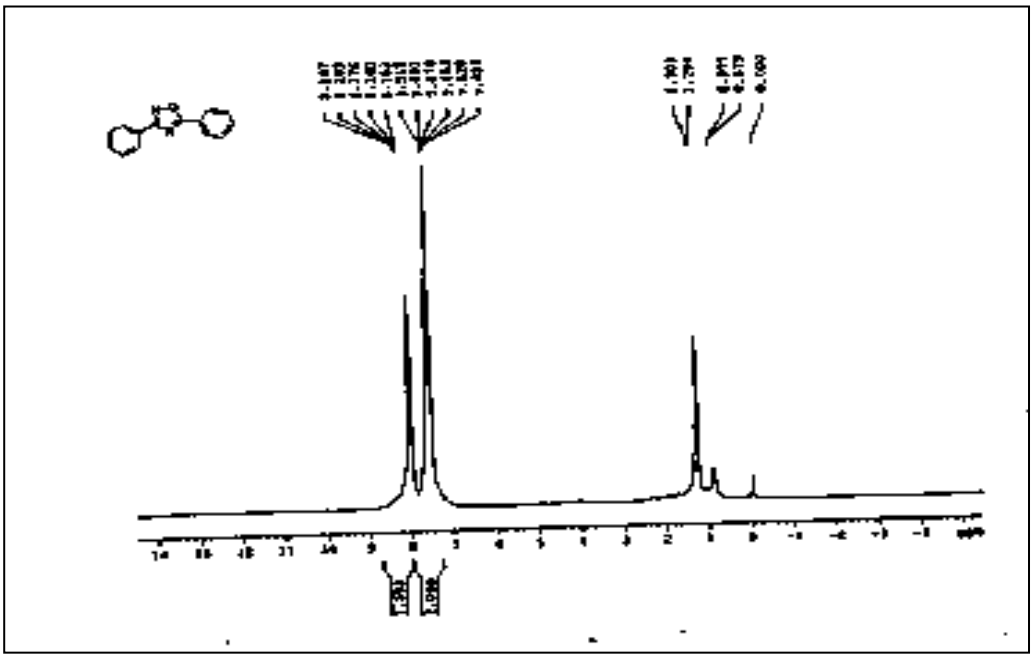


Figure I.B.9. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3,5-diphenyl-1,2,4-oxadiazole*



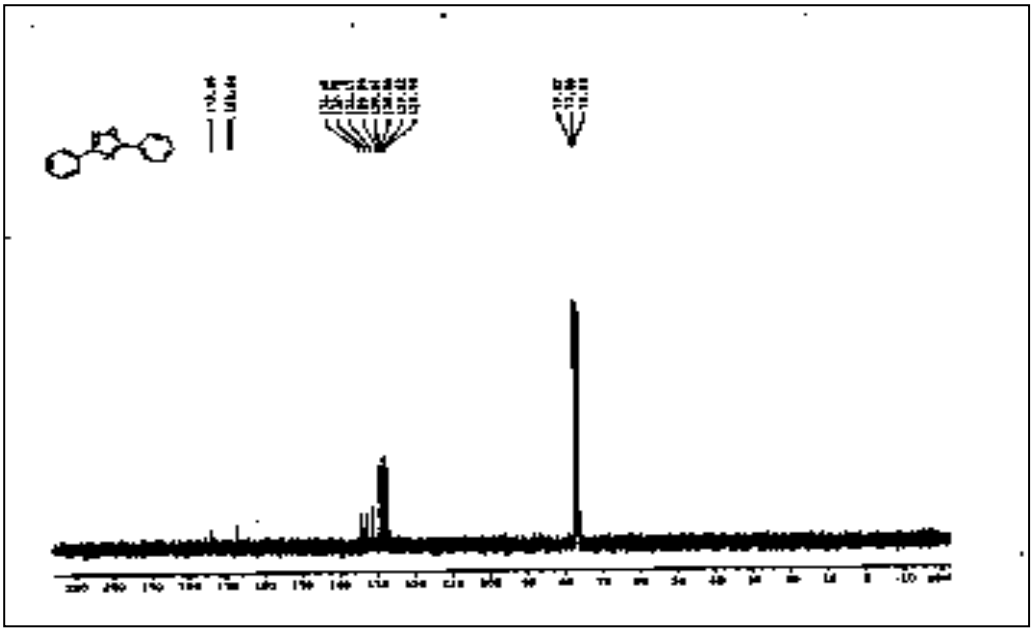
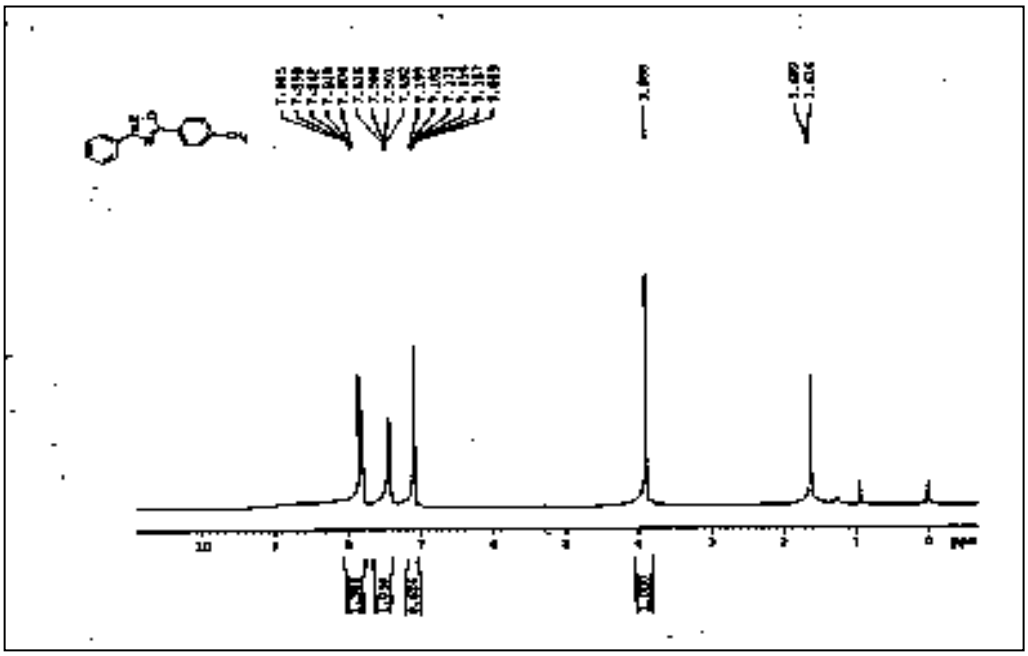


Figure I.B.10. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-phenyl-5-(p-tolyl)-1,2,4-oxadiazole*



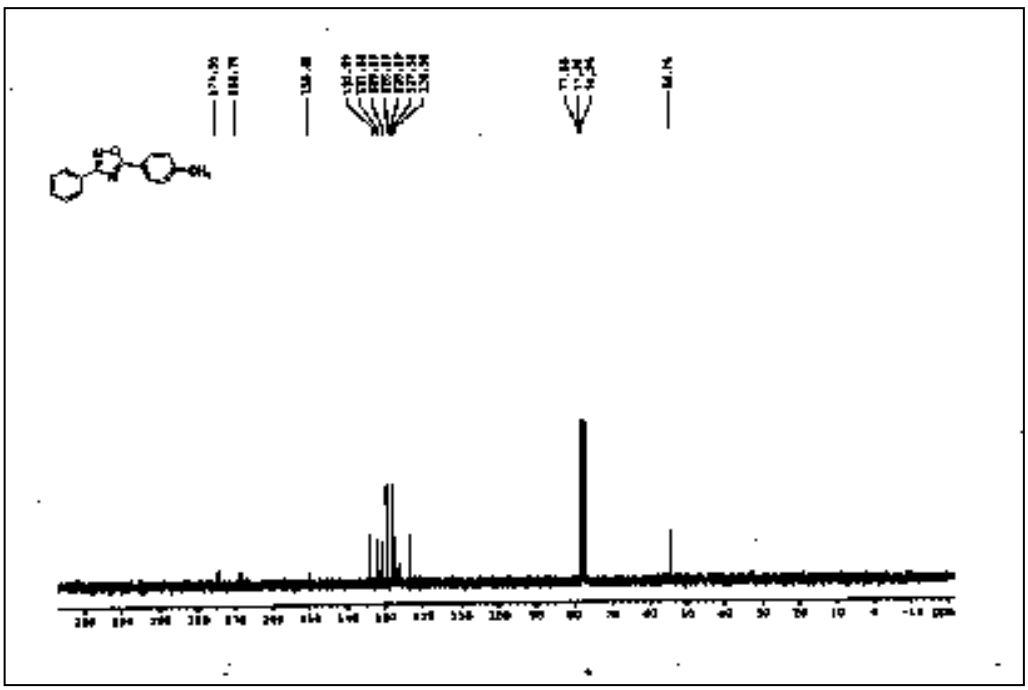
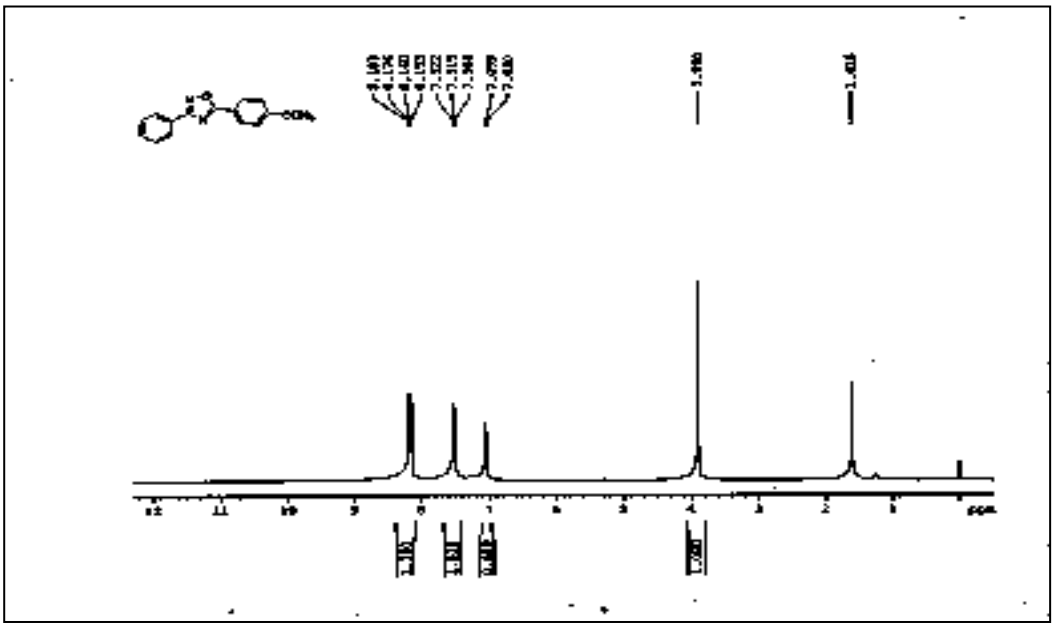


Figure I.B.11. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 5-(4-methoxyphenyl)-3-phenyl-1,2,4-oxadiazole*



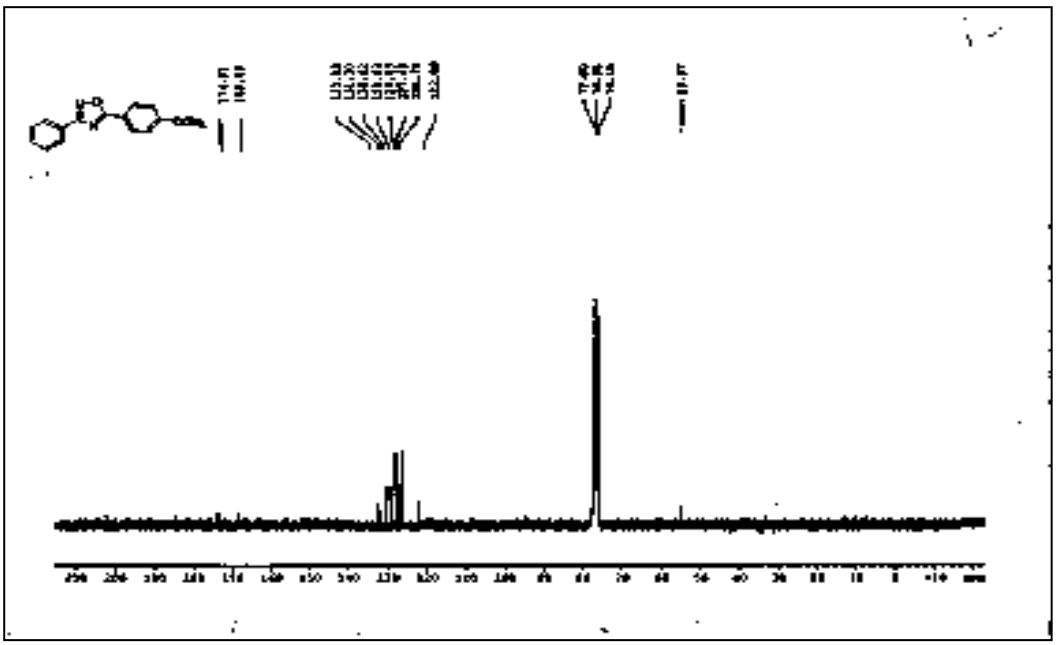
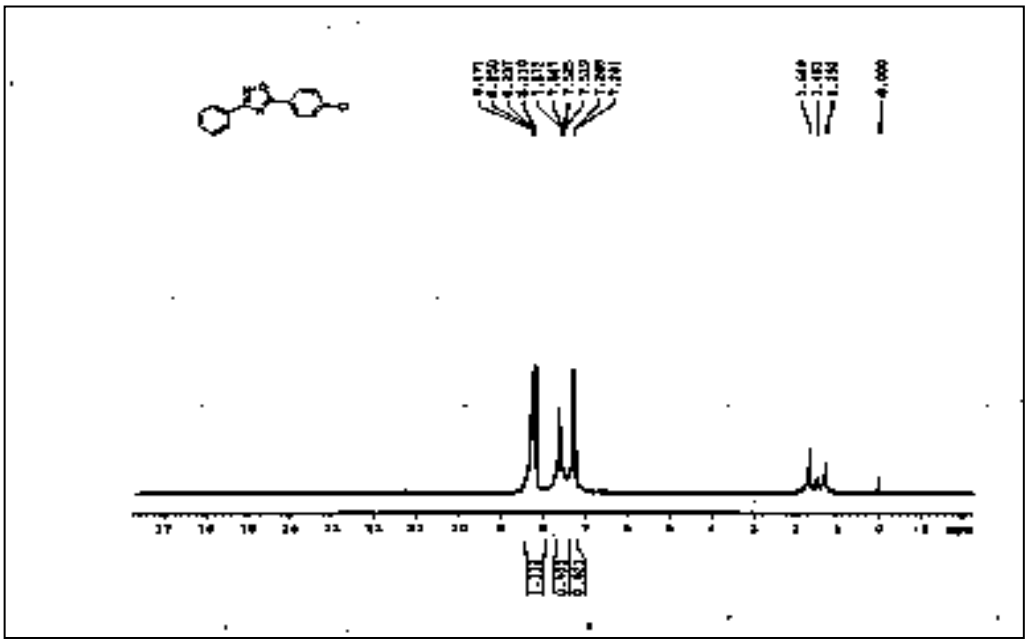


Figure I.B.12. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 5-(4-fluorophenyl)-3-phenyl-1,2,4-oxadiazole*



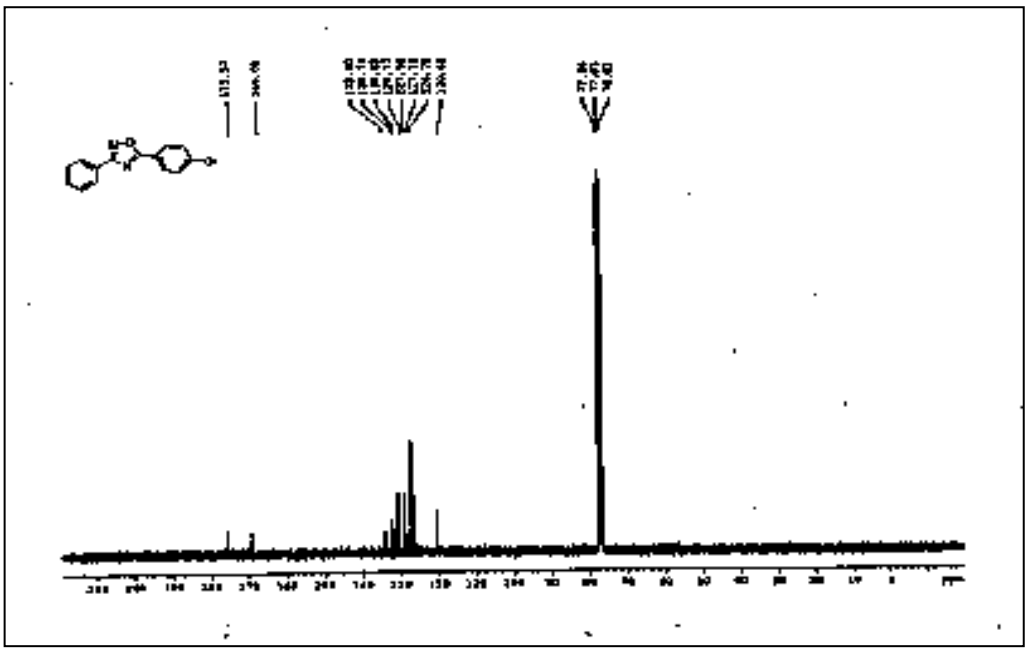
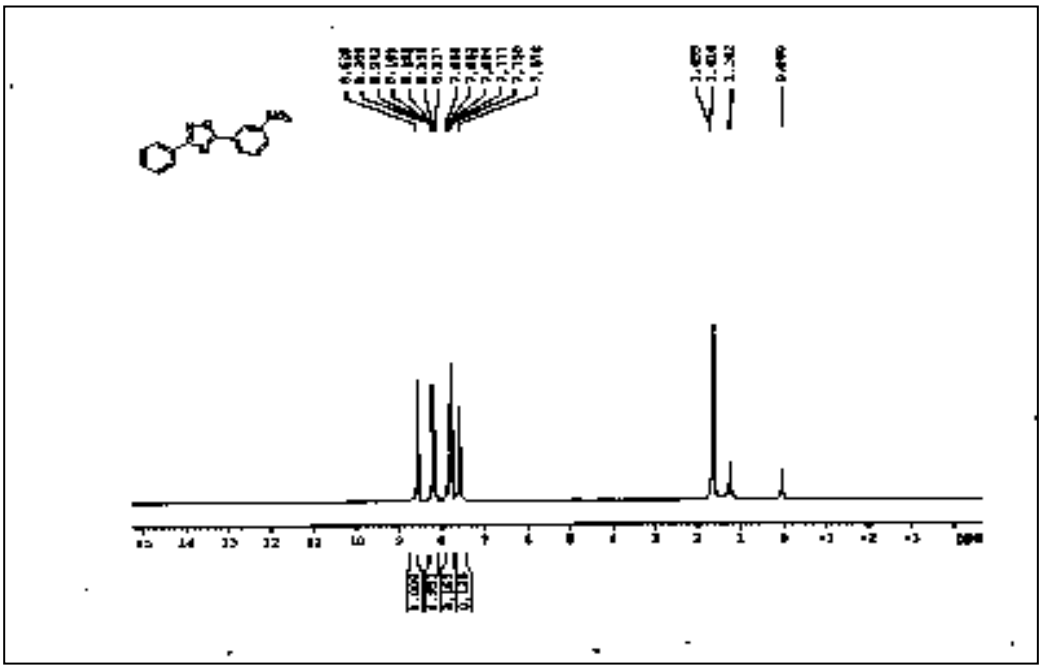


Figure I.B.13. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 5-(3-nitrophenyl)-3-phenyl-1,2,4-oxadiazole*



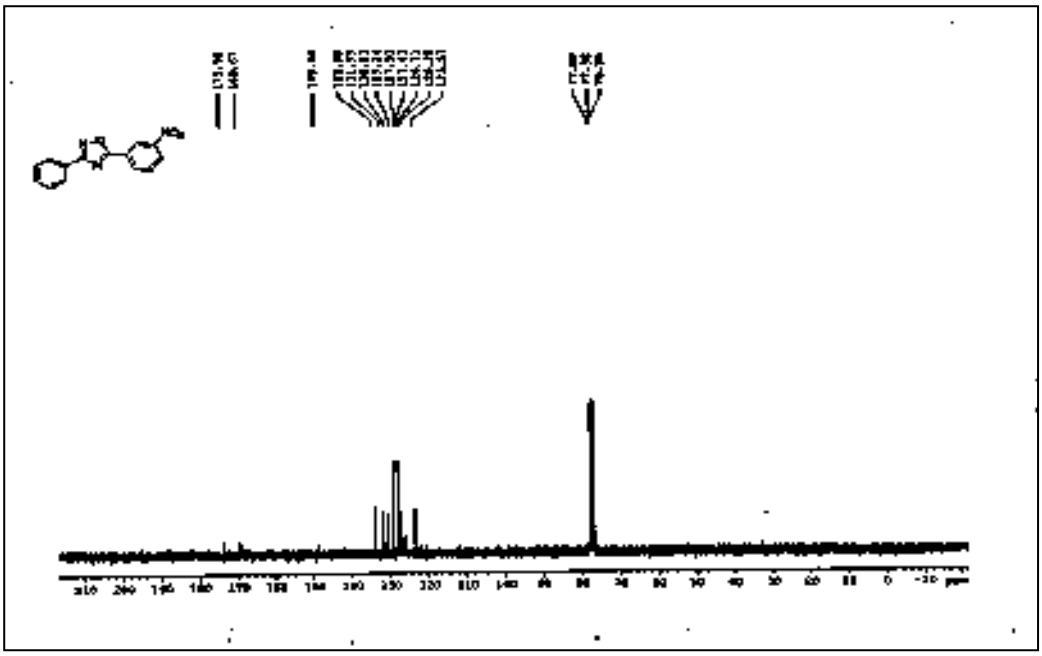
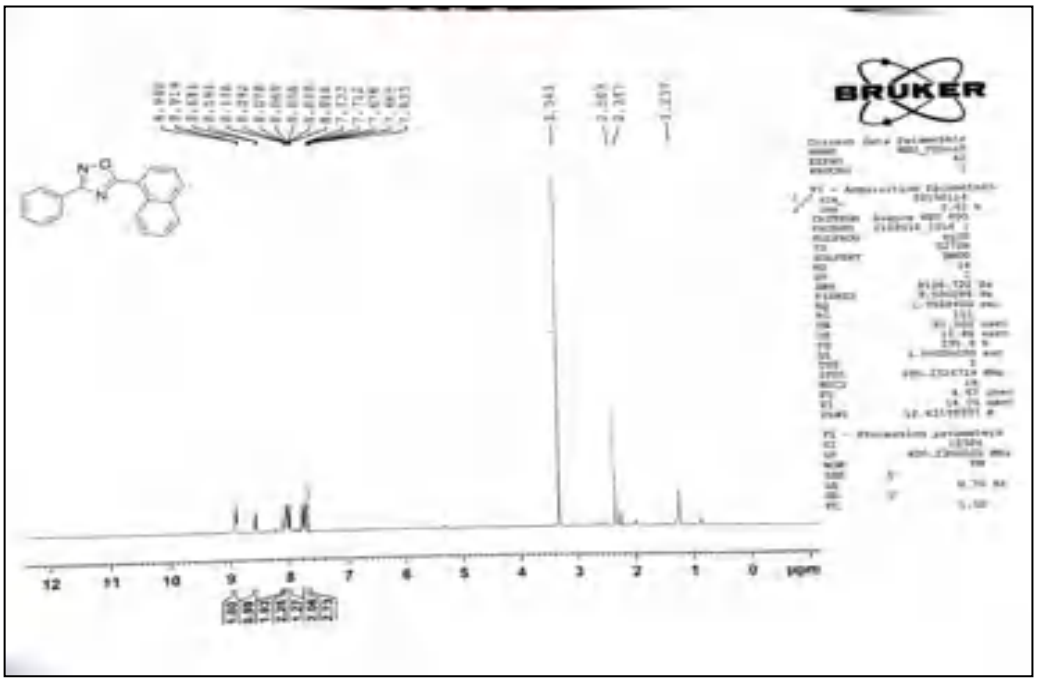


Figure I.B.14. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 5-(naphthalen-1-yl)-3-phenyl-1,2,4-oxadiazole*



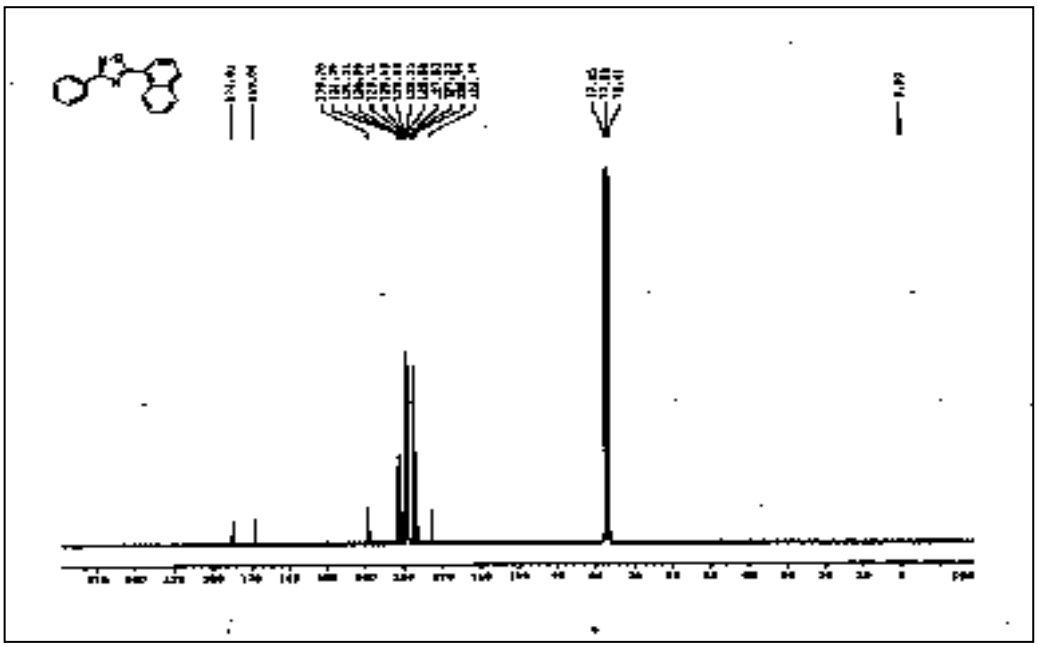
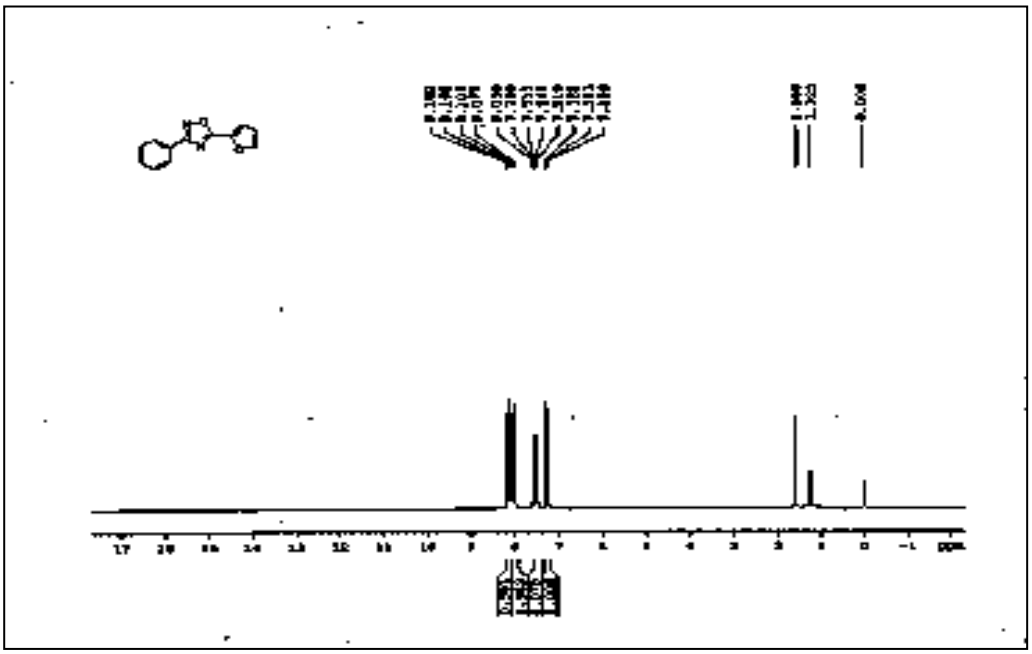


Figure I.B.15. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 5-(furan-2-yl)-3-phenyl-1,2,4-oxadiazole*



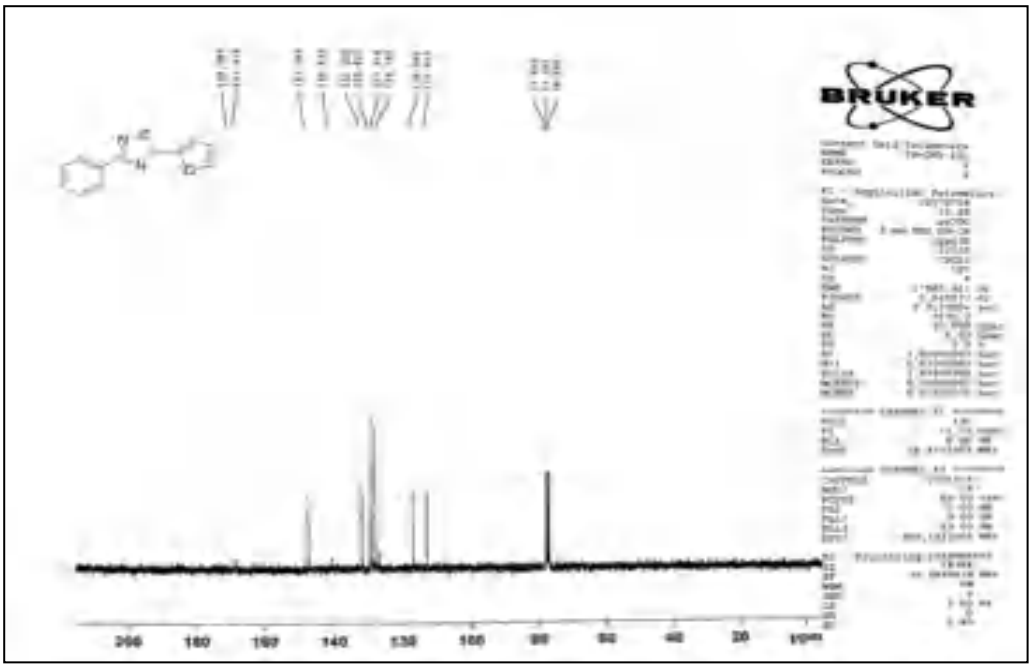
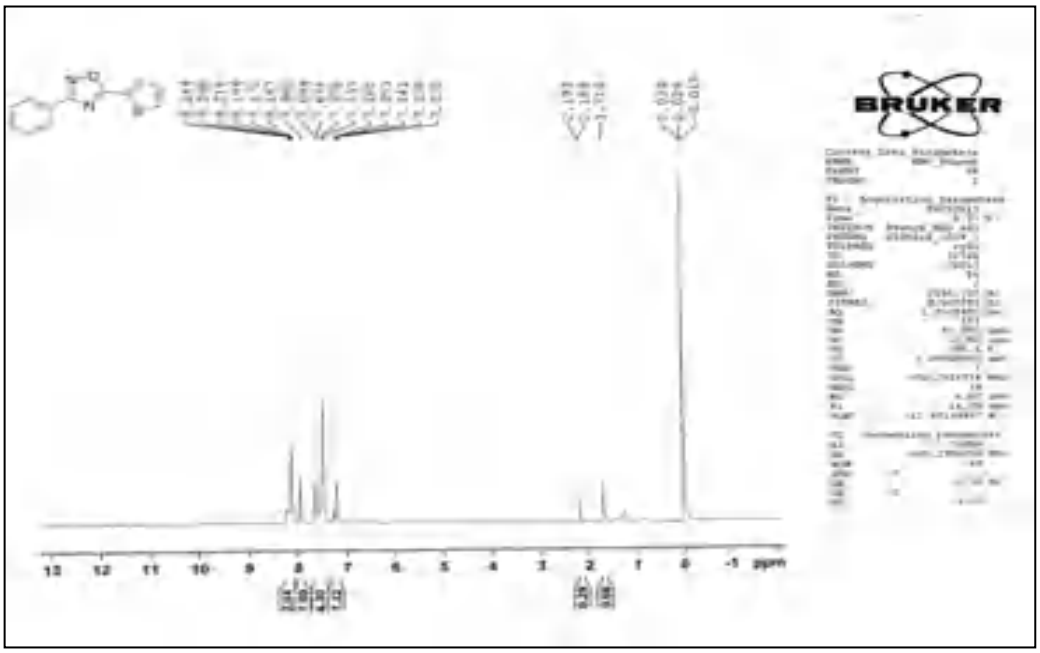


Figure I.B.16. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-phenyl-5-(thiophen-2-yl)-1,2,4-oxadiazole*



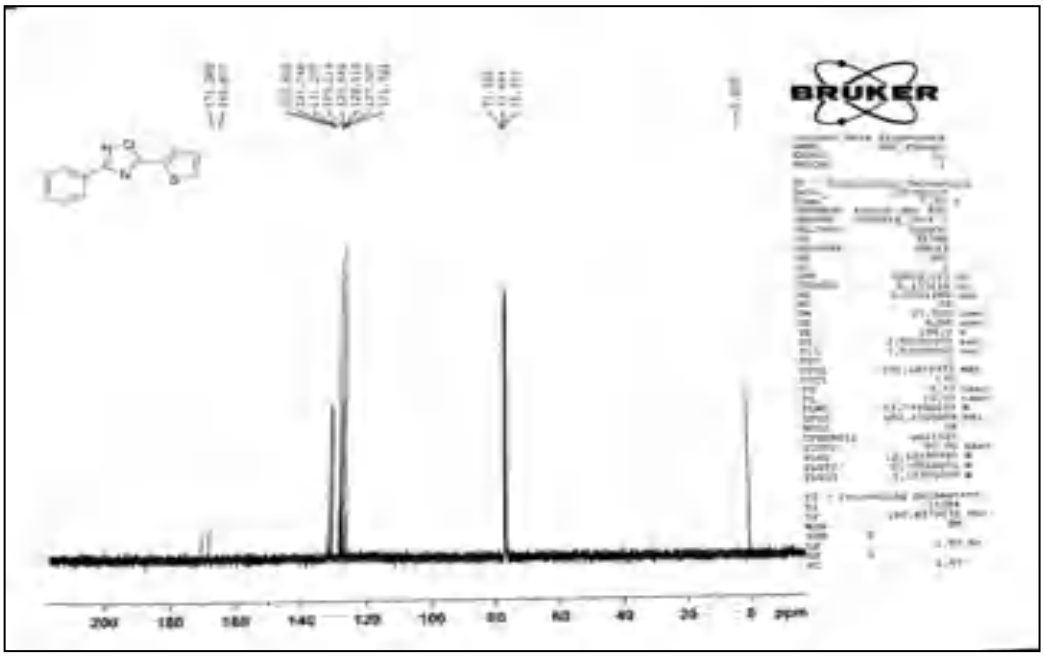
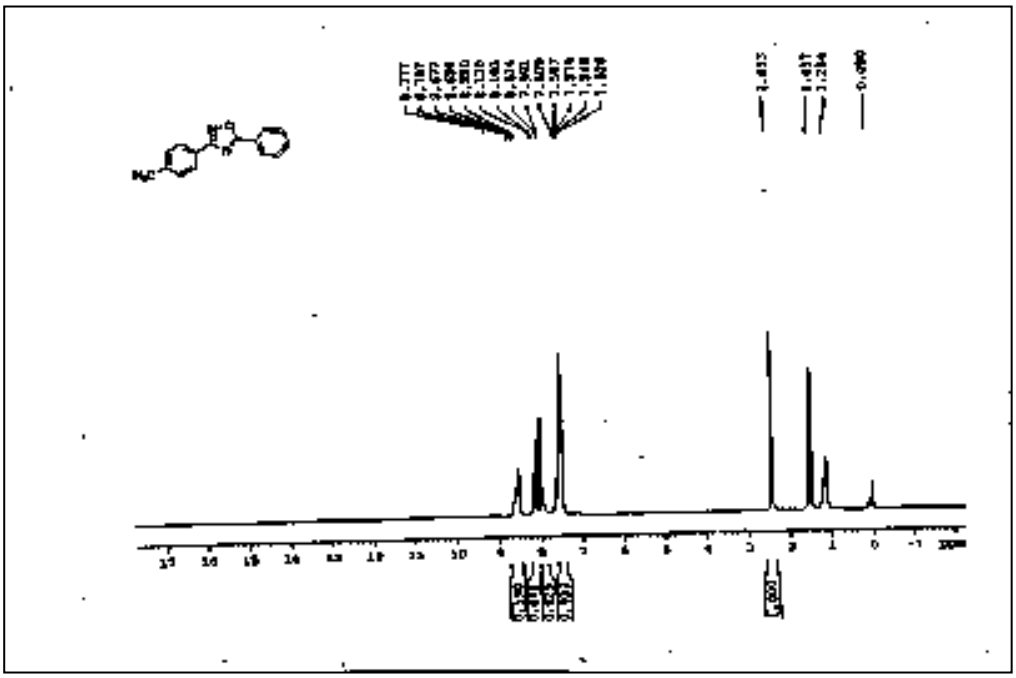


Figure I.B.17. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 5-phenyl-3-(p-tolyl)-1,2,4-oxadiazole*



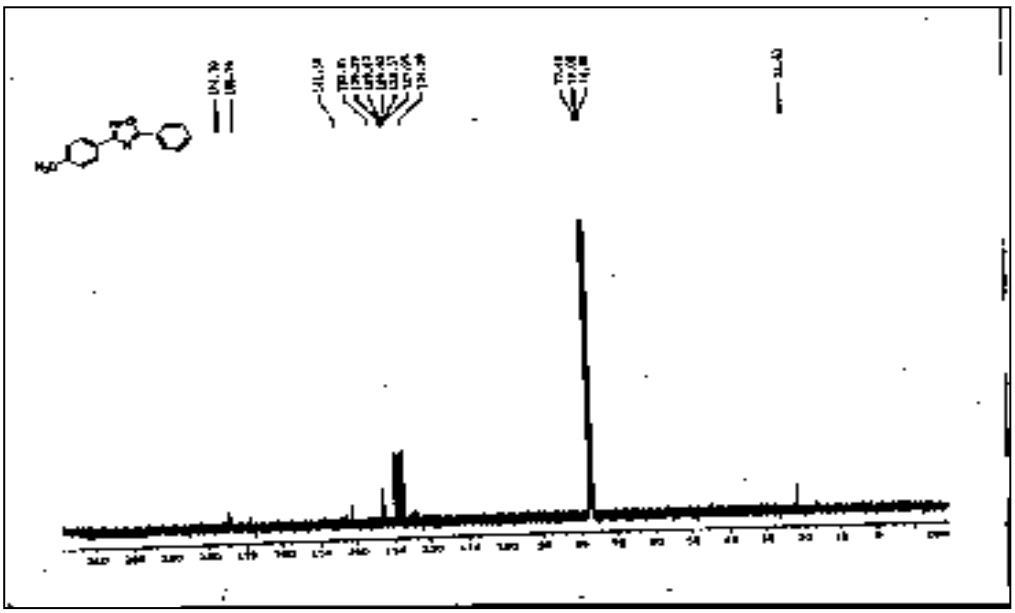
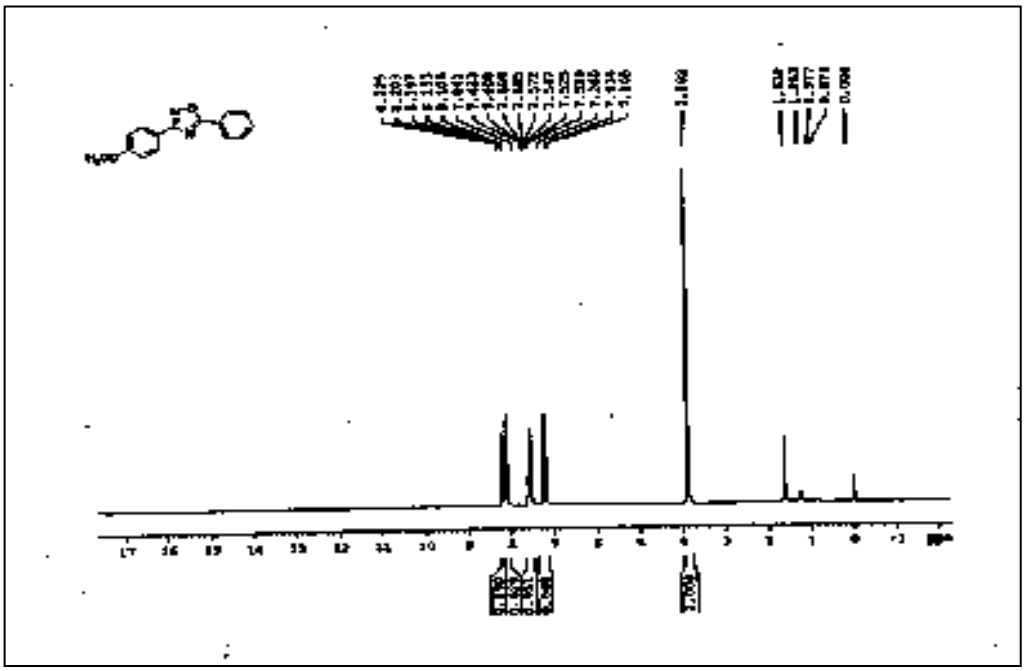


Figure I.B.18. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-(4-methoxyphenyl)-5-phenyl-1,2,4-oxadiazole*



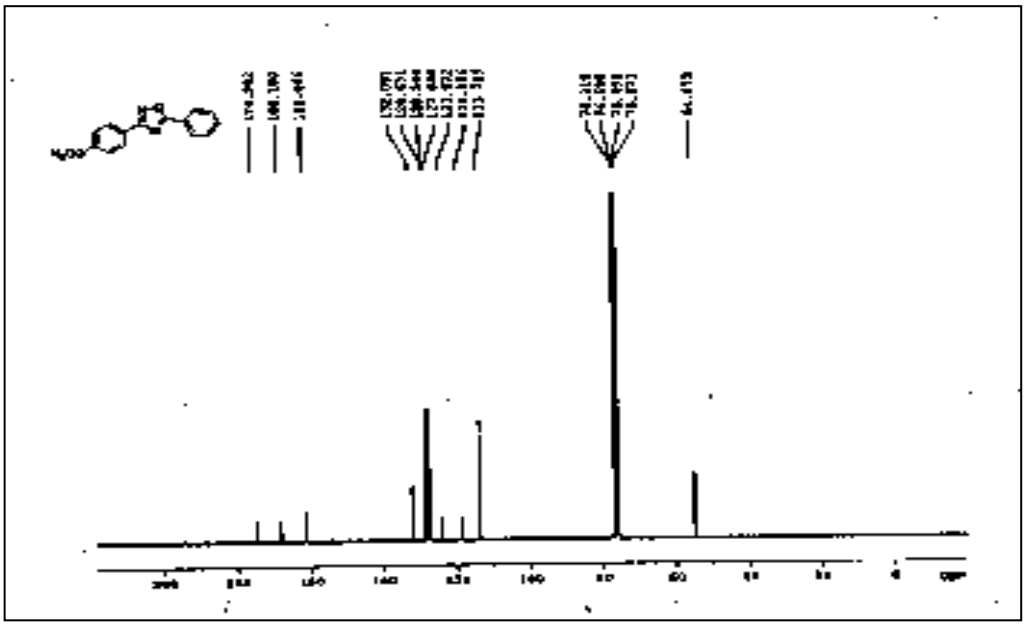
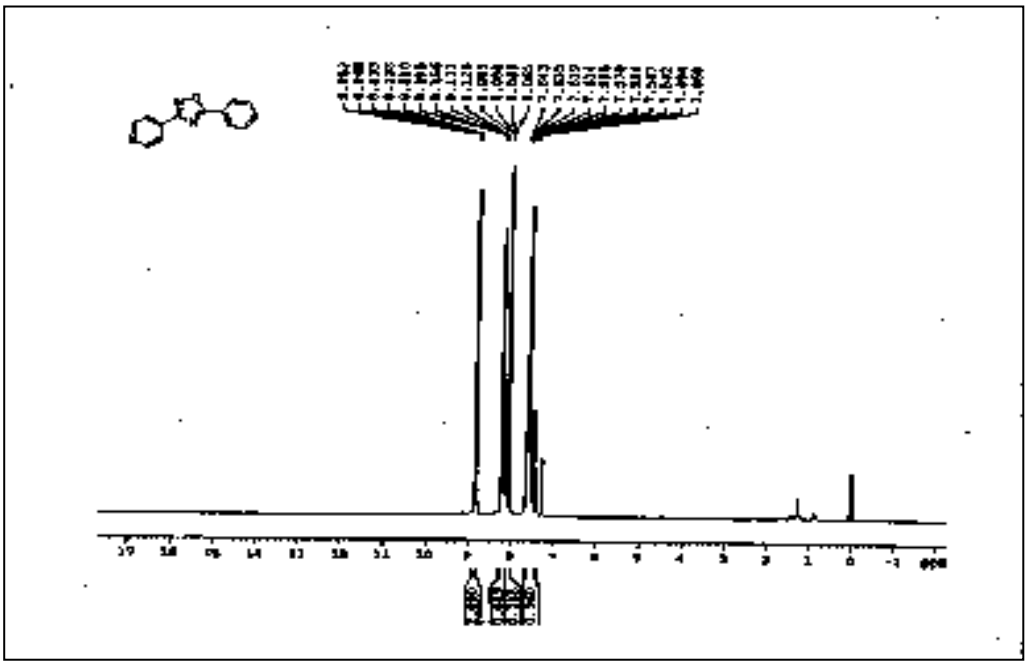


Figure I.B.19. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 5-phenyl-3-(pyridin-4-yl)-1,2,4-oxadiazole*



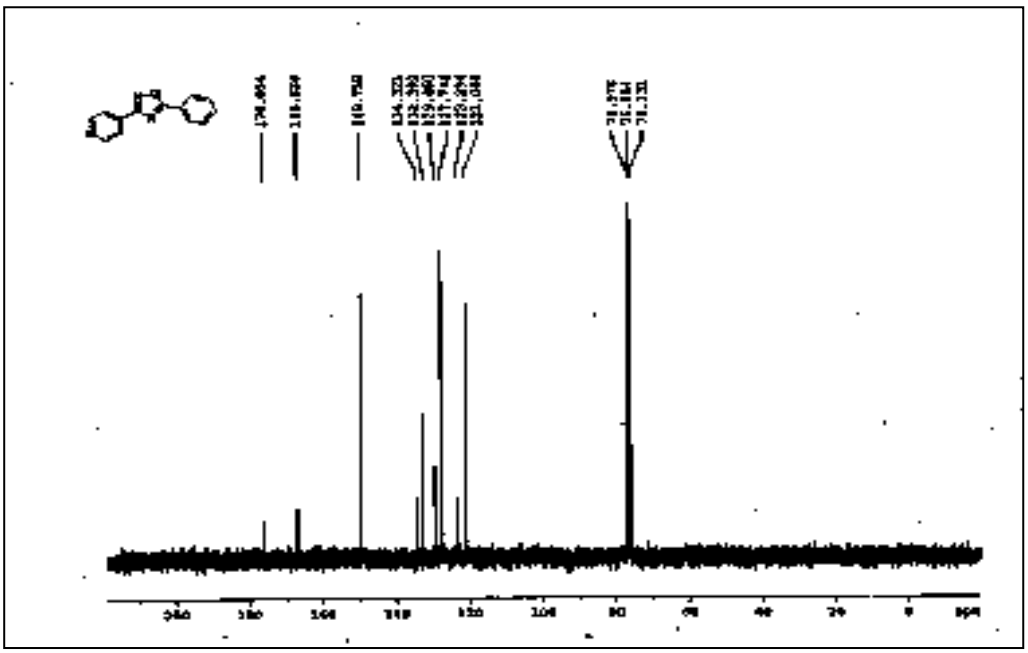
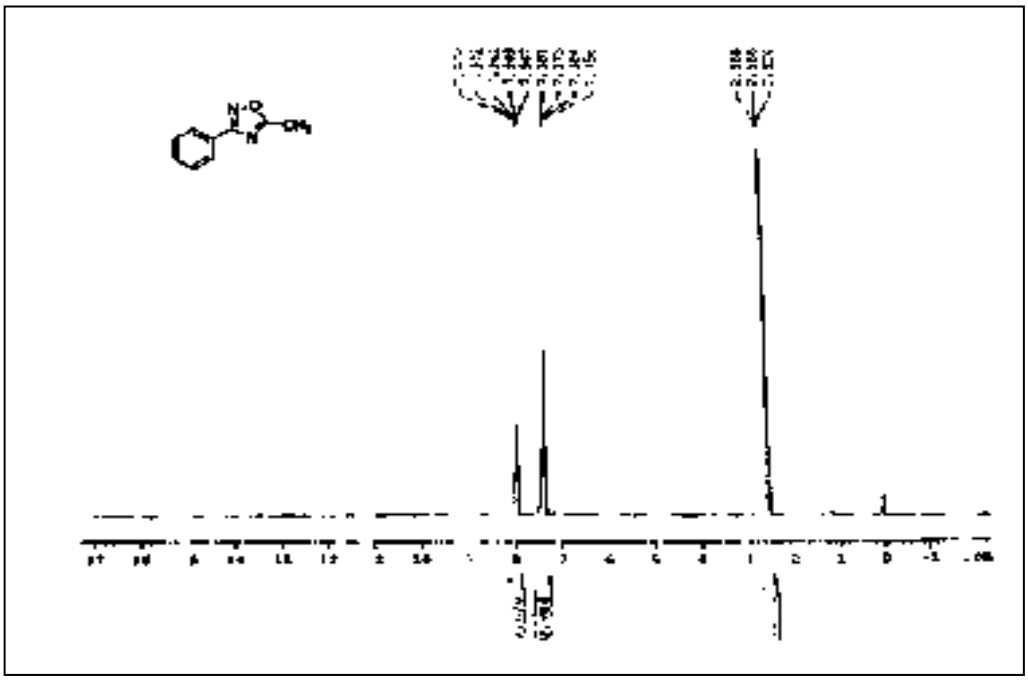
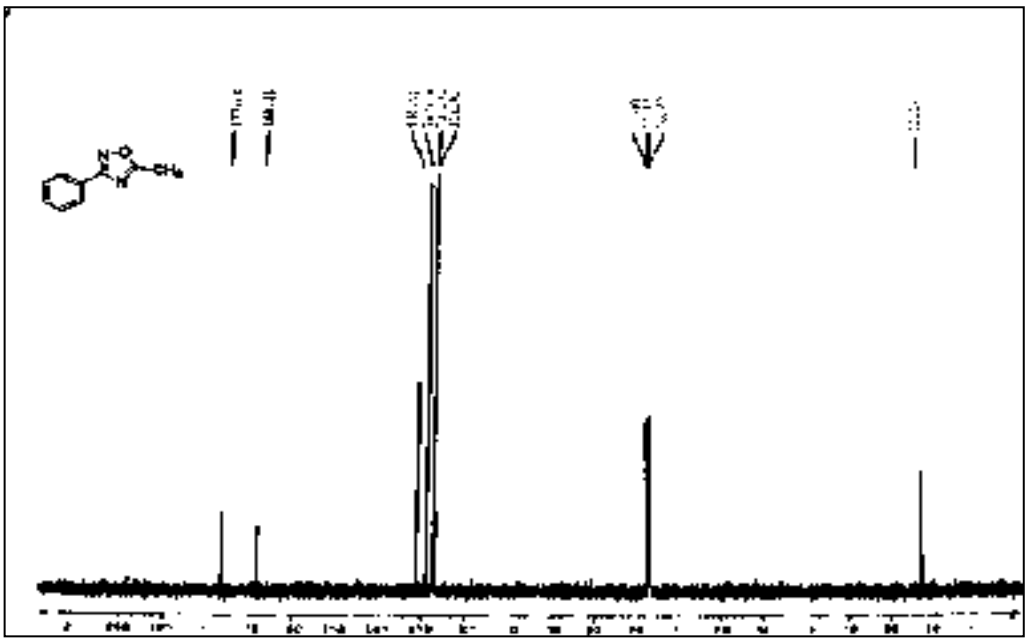


Figure I.B.20. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 5-phenyl-3-(pyridin-4-yl)-1,2,4-oxadiazole*





I.B.6. References

References are given in Bibliography under Chapter I, Section B