Chapter III

Section A

Sulfonated graphene oxide (SGO) as metal-free efficient carbocatalyst for the synthesis of 3-methyl-4-(hetero) arylmethylene isoxazole-5(4H)-ones

III.A.1. Introduction

Isoxazoles and isoxasolone derivatives are an important class of heterocyclic compounds that display beneficial biological properties such as antitumor [1], antifungal [2], cytotoxic, anti-inflammatory [3], antibacterial, and anti-HIV activities [4-6]. Isoxazole scaffold is considered as a major compound in the combinatorial synthesis and protein kinase inhibitors as well as playing a crucial role in the development of chemotherapeutic agents [7-8]. Moreover, many compounds belonging to this class have also been employed as versatile building blocks of synthetic drug molecules [9], a variety of natural products [10], fungicides, and insecticides [9]. Isoxazoles are beneficial starting materials in various organic synthesis [11] and found application in liquid crystalline material [12], optical storage and nonlinear optical research [13], filter dyes in photographic films [14]. A series of androgen antagonists with isoxazole scaffold are found to have medicinal utility [15] and some of them also exhibit full antagonistic activity towards human metastatic breast cancer cells and human prostate tumor cells [16]. Panathur *et al.* also studied biological activities (in vitro) of some isoxazolone derivatives showing their I12, I17 compounds (Figure III.A.1) with cytotoxicity against cancer cells viz. Human metastatic breast cancer cells (MDA-MB-231), Human breast cancer cells (MCF-7), Human colon adenocarcinoma cells (HT-29) remarkably without affecting the noncancerous cells (HEK-239) [16].

In recent times, one-pot multicomponent reactions (MCR) are emerging as ecologically sustainable processes in pharmaceutical chemistry, drug designing, and have been considered as a powerful tool for the synthesis of biologically active heterocyclic compounds. With increasing demand in green

chemistry, much attention has been paid to MCRs to achieve high yield, high selectivity, and synthetic simplicity in various research fields.

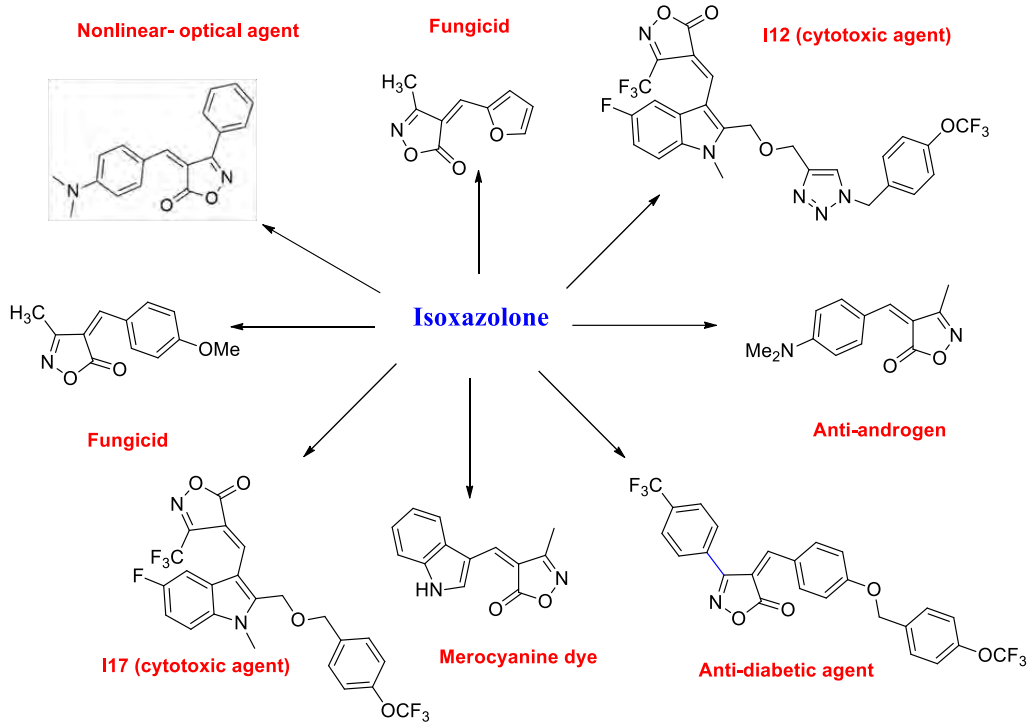


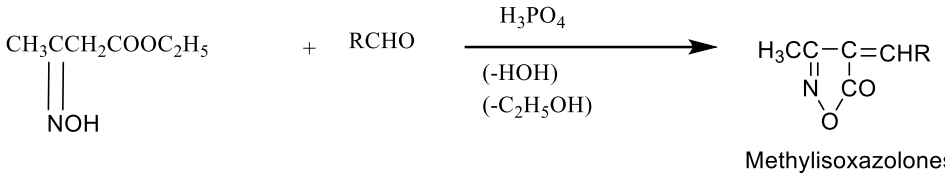
Figure III.A.1. *Some examples of biologically active compounds containing isoxazole moiety.*

III.A.2. Background and objectives

There are several methods for synthesis of isoxazole-5(4*H*)-one derivative, a) cyclization of *O*-propionyl oximes [17], b) condensation between substituted benzaldoximes and 1,3-dicarbonyl compounds [18], c) the reaction of *β*-ketoesters with hydroxylamine and sodium hydroxide followed by the subsequent addition of aqueous HCl under heating condition [19]. The traditional procedure to synthesize 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones involve two consecutive steps viz. a) formation of an oxime from the condensation of ethyl acetoacetate with hydroxylamine hydrochloride followed

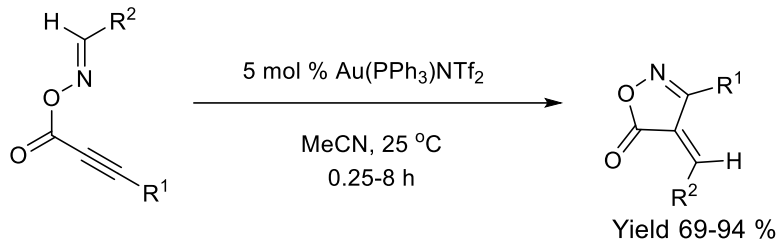
by b) Knoevenagel type reaction with aromatic aldehydes [20]. The convenient methodologies demand solid state grinding, solid state heating [21], microwave heating [22], ultrasonic irradiation [23], application of sodium acetate in presence of visible light in ethanol solvent [24]. It is worth mentioning that different moisture-sensitive reagents like sodium sulphide [25], phthalimide-*N*-oxyl salts [26], sulphated polyborate [27], boric acid [28], sodium azide [29], SnII-montmorillonite [30], potassium sorbate [31] etc [32-35]. However, most of the conditions, suffer from drawbacks such as high temperature, harsh reaction conditions, prolonged reaction time, strongly acidic/basic condition, low yield, use of homogeneous catalyst and suffer from rapid loss of catalytic activity. Although in most of the reported protocols acceptable yield of isoxazolone has been reported using toxic metal catalysts, costly reagents [27, 29] as well as people suffered tedious reaction conditions and work up process [24, 29, 30]. To avoid these drawbacks it is imperative to develop a high-yielding greener, radiation, and metal-free efficient method for its synthesis with a broad range of substrate applicability.

In 1928-1929 Minunni *et al.* investigated the reaction between acetoacetic ester oxime with various aromatic aldehydes in presence of acid (Scheme III.A.1) [36]. The striking similarity of the product obtained by this procedure to those obtained by R. Schiff and M. Betti [37] may lead to an assumption that the products were isoxazolones. The probable mechanism of this reaction was discussed and it was found that the reactions are feasible in presence of strong acids.



Scheme III.A.1. *The reaction of acetoacetic ester oxime with an aromatic aldehyde.*

Nakamura *et al.* demonstrated gold-catalyzed cyclizations of *O*-propioloyl oximes to 4-arylideneisoxazol-5(4*H*)-ones in good to excellent yields via C-N bond formation followed by arylidene group transfer (Scheme III.A.2) [17]. As a representative reaction, (*E*)-benzaldehyde *O*-3-phenylpropioloyl oxime was reacted in acetonitrile in the presence of $Au(PPh_3)NTf_2$ (5 mol %) at 25 °C temperature to give 4-benzylidene-3-phenylisoxazol-5(4*H*)-one with excellent yield (90%). Crossover experiments showed the arylidene "migration" proceeded through an intermolecular manner.

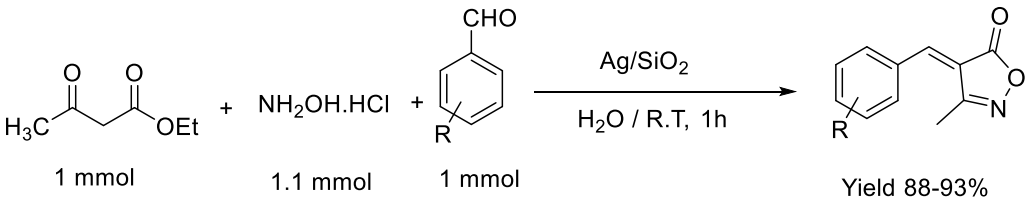


R^1 = Ph, *p*-tolyl, *p*-anisyl, *p*-$CF_3C_6H_4$, *n*-Pr, Cy, *t*-Bu
R^2 = Ph, *p*-tolyl, *p*-anisyl, *p*-$CF_3C_6H_4$, *p*-ClC_6H_4, *p*-$iPrC_6H_4$

Scheme III.A.2. *Au-catalyzed synthesis of 4-arylideneisoxazol-5(4H)-ones.*

Maddila *et al.* described the one-pot synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-ones in a water medium using Ag/SiO_2 as heterogeneous catalyst (Scheme III.A.3) [34]. Interestingly, different aromatic aldehydes with several electron-withdrawing and electron-donating substrates in

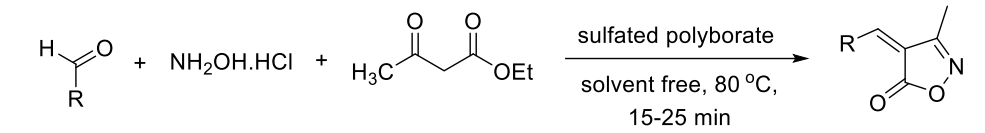
ortho, meta, and para positions have also contributed positively to produce the desired substituted isoxazoles in good to excellent yield. All the synthesized products were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra.



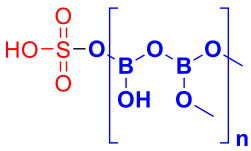
R = H, 4-OH, 4-OMe, 4-$N(Me)_2$, 2,5-$(OH)_2$, 3,4-$(OH)_2$,
3-OH, 2,3-$(OMe)_2$, 2,5-$(OMe)_2$, 2,4,6-$(OMe)_3$, 2,4-$(Me)_2$, 4-Et

Scheme III.A.3. *Ag/SiO_2 catalyzed green synthesis of 3-methyl-4-(phenyl)methylene-isoxazole5(4H)-ones.*

Patil *et al.* developed a mild and rapid synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones via an eco-benign protocol involving a new heterogeneous catalyst sulfated polyborate (Scheme III.A.4). The boric acid was dehydrated at 200 ^{o}C and converted into polymeric Lewis acid form and then sulfonated to induce the Bronsted acid character into the polymerized form [38]. Several electron-withdrawing and donating groups on the aromatic nucleus showed no significant change in the yield of the product. The main advantage of this method was a solvent-free approach, easy work-up, recyclable catalyst, and short reaction time.



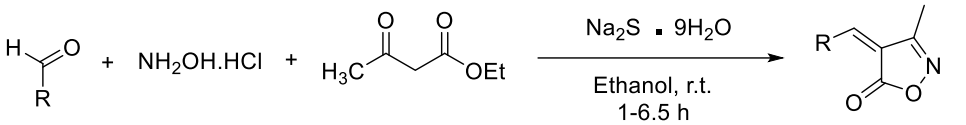
R = C_6H_5, 2-OH-C_6H_4, 2-NO_2-C_6H_4, 3-Cl-C_6H_4,3-Br-C_6H_4
4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-OH-C_6H_4
4-NO_2-C_6H_4, 2-Thienyl, 5-Methyl furan-2-yl, Indol-3-yl



Sulfated ployeborate

Scheme III.A.4. *Sulfated polyborate catalyzed synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones.*

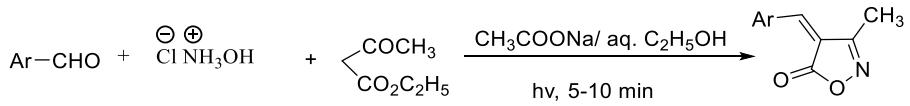
Liu *et al.* described the one-pot three component synthesis of isoxazolones using ethyl acetoacetate, hydroxylamine hydrochloride, and aromatic aldehydes in presence of sodium sulfide as catalyst (Scheme III.A.5) [39]. Probably, sodium sulfide is one of the oldest and widely used industrial chemicals that has been used as an effective catalyst in some reactions [40]. The electron-donating group containing aromatic aldehydes afforded the target products in high yield in a short time while aromatic aldehydes with electron-withdrawing groups were failed to convert to the target products. Although, the heterocyclic aldehydes and *α,β*- unsaturated aldehydes exerted the corresponding isoxazolones with moderate to high yield.



R = C_6H_5, 2-Furyl, 4-$CH_3OC_6H_4$, 2-OHC_6H_4,
Vaniline, C_6H_5CH=CH, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$

Scheme III.A.5. *The one-pot synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones catalyzed by sodium sulfide.*

Photochemical reactions in presence of visible light in eco-friendly solvents are particularly useful and are considered an extremely green and clean procedure. The photo activation of the substrates minimizes the chance of the byproduct formation and requires much less time than the thermal procedure (Scheme III.A.6) [41]. Saikh *et al.* reported an eco-friendly synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4*H*)-ones induced by visible light in the aqueous-ethanol solvent [42]. However, it was observed from the reaction that the electron-donating group containing aromatic aldehydes smoothly participate whereas, the electron-withdrawing group containing aromatic aldehydes (nitro or chloro) failed to produce the target product.

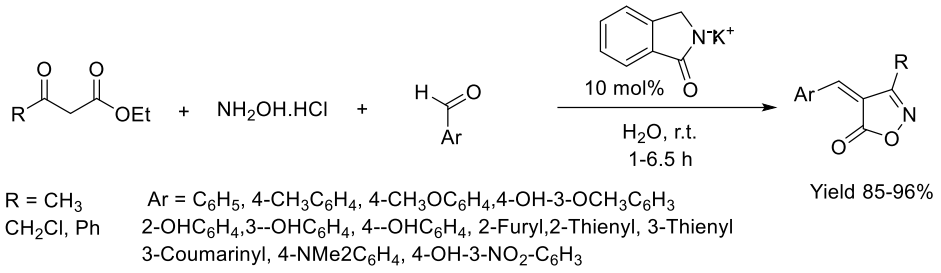


Ar = C_6H_5, 4-OHC_6H_4, 4-$OCH_3C_6H_4$, 2,4-$(OCH_3)_2C_6H_3$
3,4-$(OCH_3)_2C_6H_3$, benzodioxole, 2-Thiophenyl, Indole

Yield 56-89 %

Scheme III.A.6. *Synthesis of 3-methyl-4-arylmethylene-isoxazole5(4H)-ones induced by visible light in an aqueous-ethanol solvent.*

Kiyani *et al.* developed an environmentally benign protocol for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones at room temperature using Potassium phthalimide (PPI) as an efficient and effective basic organocatalyst (Scheme III.A.7) [43]. Potassium phthalimide (PPI) is a mild, inexpensive, commercially available basic recyclable catalyst, and also a stable reagent.



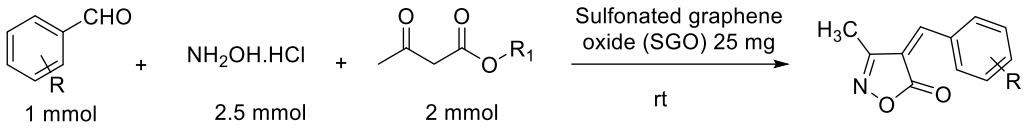
Scheme III.A.7. *Synthesis of 3,4-disubstituted isoxazol-5(4H)-ones catalyzed by Potassium phthalimide (PPI) in water at room temperature.*

This reagent (PPI) has been widely used in the synthesis of primary amines by the Gabriel method [44], particularly used for the synthesis of phthalimide derivatives [45, 46] and the preparation of cyanohydrin trimethylsilyl ethers [47].

As an alternative to non-metal for organic synthesis, carbonaceous nanomaterials have been received considerable attention due to their sustainability and affordability [48]. Graphene oxide (GO), a 2D unique nanomaterial, contains a variety of oxygen-containing functional groups (e.g. alcohols, carboxylates, epoxides, sulphate groups), the presence of these extrinsic functionalities provides moderate acidic properties (pH = 4.2) to GO and its high surface area males it an efficient catalyst for several organic transformation reactions. In addition to this, its derivative sulfonated graphene oxide (SGO) possesses BrØnsted acid properties in organic reactions. The use of GO and SGO as heterogeneous catalysts has been attracted consideration owing to their acidic property, thermal stability in reaction, high surface area, and easy recovery of the catalyst [49-52].

III.A.3. Present work: Result and discussion

Over the past decades, as an alternative of nonmetal carbonaceous nanomaterials have received considerable attention owing to their sustainability and affordability in organic transformation [53-55]. Herein, we report a simple and unprecedented transformative protocol to furnish a wide variety of biologically active substituted 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones using aldehyde, ethyl acetoacetate, and hydroxylamine hydrochloride in presence of sulfonated graphene oxide (SGO) at room temperature (Scheme II.A.8). The catalyst SGO was characterized by different spectroscopic techniques and reused up to the 5th run without a significant drop in its catalytic activity.



R = H, 4-OMe, 4-NO_2, 4-Me, 4-Cl, 3-NO_2, 2-Furyl, 2-Thienyl, 2-Napthyl, 4-OH, 4-Br, 4-NMe_2, 2-OH, 3-Me, Indole-3-carbaldehyde, Cinnamaldehyde

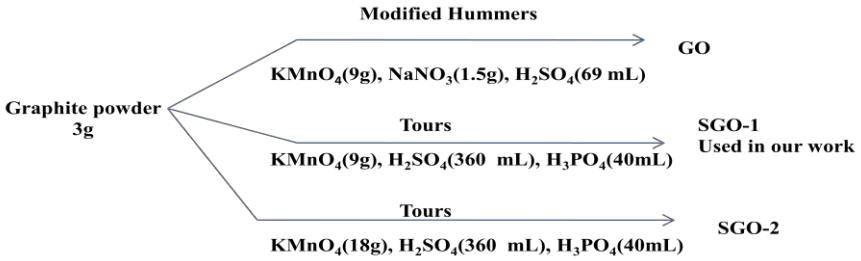
R_1= -Me, Et

Yield 64-93 %

Scheme III.A.8. *One-pot three-component synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones using SGO as a catalyst.*

III.A.3.1.Synthesis of the catalyst

We have assessed the catalytic activity of SGO as an acid catalyst in the promotion of isoxazole synthesis. SGO was synthesized by the Tours method shown in scheme III.A.9 and was extensively purified to remove any metal impurity.

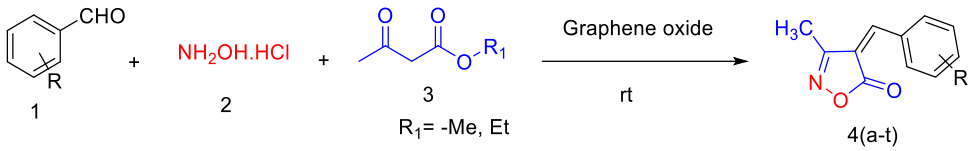


Scheme III.A.9. *Synthesis of SGO using different method.*

III.A.3.2. Optimization of the reaction conditions

For screening the reaction condition, benzaldehyde, ethyl acetoacetate, and hydroxylamine hydrochloride were selected for the model reaction. The effects of the reaction parameters such as solvent, temperature, amount of the catalyst are discussed briefly in Table III.A.1. It was noticed that except toluene other solvents produced the desired product in moderate to good yield. Further investigation revealed that solvent-free stirring yielded the corresponding products with an excellent yield at room temperature (Table III.A.1). Inspired by this expectancy, we altered the amount of the catalyst SGO under solvent-free conditions to achieve the optimal condition of the reaction. Depending upon the time, yield and temperature, 25 mg SGO-1 displayed the best result (Table III.A.1, entry 8) and was opted as the optimum quantity for the promotion of the reaction (Table III.A.1). To show catalytic efficiency, SGO-1 was also compared with GO and SGO-2 (Table III.A.1, entry 9 and10) and results revealed that SGO-1 exerted the desired product with a high yield.

Table III.A.1. Optimization of reaction parameters for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones based on the result of the following combination intheprotocol[a]



Entry	Catalyst (SGO-1) mg	Solvent	Temperature ° C	Time(h)	Yield (%)[b]
1.	None	Water	Rt	8	Trace
2.	50	Water	Rt	2	82%
3.	50[d]	Water	100	1	84%
4.	50	Ethanol	rt	2	74%
5.	50	MeCN	rt	2	52%
6.	50	Neat	rt	2	91%
7.	50	Toluene	rt	2	NR
8.	**25**	**Neat**	**rt**	**1**	**90%**
9.	25 (GO)	Neat	rt	1	84%[e]
10	25 (SGO-2)	Neat	rt	1	87%[f]
11.	25	Neat	rt	12	86%
12.	15	Neat	rt	4	60%
13.	10	Neat	rt	12	49%
14.	100[g]	Neat	rt	4	81%

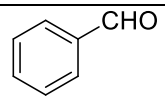
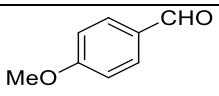
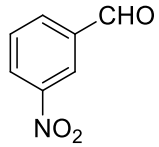
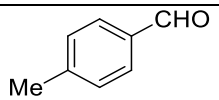
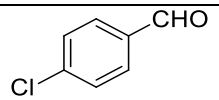
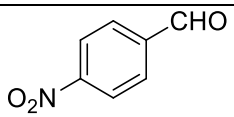
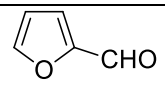
[a]Reaction of benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), hydroxylamine hydrochloride (2.5 mmol) at room temperature (rt).
[b]Isolated yield after purification through column chromatography on silica gel.
[c]No sulfonated graphene oxide (SGO) was added.
[d]Temperature of the reaction 100 °C.
[e]GO was used as catalyst,
[f]SGO-2 was used as a catalyst.
[g]The reactants are used 5 mmol each.

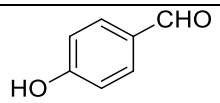
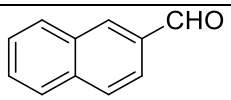
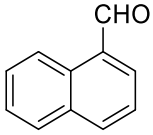
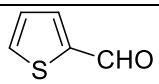
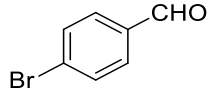
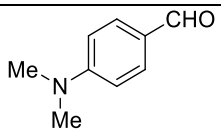
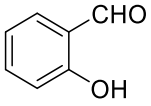
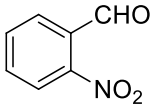
To test the water tolerance of the catalyst, we have also carried out the reaction in an aqueous medium (Table III.A.1, entry 2). Upto 82% yield of the entry suggested that there is no chance of poisoning the catalyst by water. To

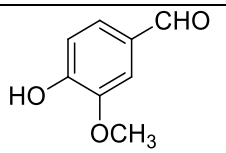
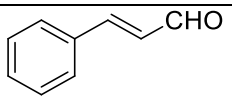
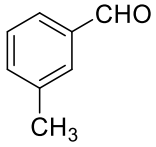
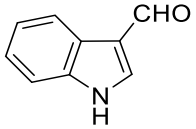
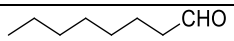
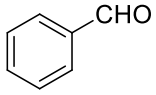
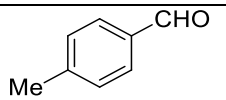
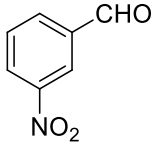
reconfirm the anticipation, after the 1st run the recovered catalyst was dried in a rotary evaporator at 50 °C and reused under the identical condition and in each case, we observed almost identical yield up to the 3rd run.

After achieving the optimized condition, we used some substituted aromatic aldehydes to get different substituted 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones. The study also indicated that various aromatic aldehydes afforded the corresponding products with high yields (except 2-nitro and 4-nitrobenzaldehyde). Aldehydes with electron-donating groups considerably increase the nucleophilicity on carbonyl oxygen, thereby efficiently yielding the desired product with excellent yield (Table III.A.2, entries 2, 4, 8, 13, 18, and 22), whereas, the aldehydes with electron-withdrawing groups affording relatively poor yield of the product. 2-Napthaldehyde (Table III.A.2, entry 9) gave moderate yield whereas 1-Naphthaldehyde (Table III.A.2, entry 10) did not respond to reaction and the reason may be due to the hindrance offered by steric factor. Again, we examined the reaction in the case of aliphatic aldehyde also (Table III.A.2, entry 20) which gave a trace amount of product. The generality of the reaction was further extended in the case of heterocyclic and α,β-unsaturated aldehydes which also afforded the corresponding product with good yield (Table III.A.2, entries 7, 11, and 17, 19). The versatility of the reaction was further tested by using methyl acetoacetate instead of ethyl acetoacetate. As expected we get the same product and with an almost identical yield (Table III.A.2, entry 21, 22, 23).

Table III.A.2. SGO catalyzed synthesis of different substituted 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones[a]

Entry	Aldehyde	R	Product	Time	Yield (%)[b]	Mp (°C)	
						Found	Reported
1.		Et	4a	1	90	141-142	141-143
2.		Et	4b	1.5	89	176-178	174-176
3.		Et	4c	1.5	80	141-143	142-144
4.		Et	4d	1.5	87	135-136	135-136
5.		Et	4e	2	84	119-121	118-120
6.		Et	4f	4	Trace	-	-
7.		Et	4g	1.5	91	237-239	238-241

8.		Et	4h	1.5	84	215-216	214-216
9.		Et	4i	3	64	165-166	-
10.		Et	4j	8	NR	-	-
11.		Et	4k	1.5	90	144-146	146-147
12.		Et	4l	2.5	82	122-125	120-122
13.		Et	4m	1	93	225-227	227-228
14.		Et	4n	2	82	200-202	198-201
15.		Et	4o	8	Trace	-	-

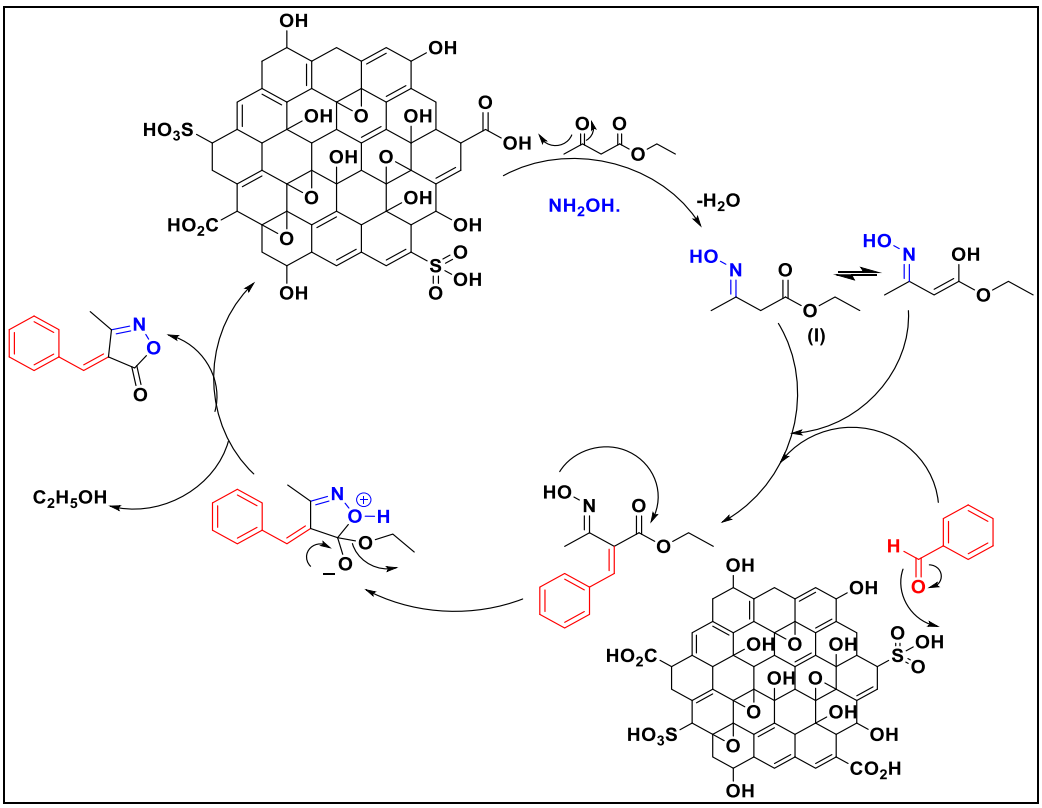
16.		Et	4p	2.5	90	214-216	211-214
17.		Et	4q	2	84	172-174	171-173
18.		Et	4r	2.5	87	108-110	-
19.		Et	4s	2.5	86	239-240	240-242
20.		Et	4t	8	Trace	-	-
21.		Me	4a	2	84	141-142	141-143
22.		Me	4d	2	86	135-136	135-136
23.		Me	4c	2	78	141-143	142-144

[a]Reaction of aldehyde (1 mmol), ethyl acetoacetate (2 mmol), hydroxylamine hydrochloride (2.5 mmol), SGO (25mg) at room temperature.

[b]Isolated yield after purification through column chromatography on silica gel.

III.A.3.3. Mechanism

A probable mechanism for the synthesis of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones by SGO is depicted below (Scheme III.A.10). It is suggested that acid-catalyzed oxime (I) formation initiated the reaction. The oxime so formed subsequently guided the Knoevenegal condensation between aromatic aldehyde and intermediate (I). This will be followed by successive cyclization along with the elimination of ethanol to yield the desired product.



Scheme III.A.10. *Possible route for SGO catalyzed synthesis of 3-methyl-4-(hetero) arylmethylene isoxazole-5(4H)-ones.*

III.A.3.4. HR-TEM and SEM analysis

A morphological study of graphene oxide (SGO) and SGO after the 5th run was carried out by HR-TEM microscopy to investigate the disintegration of SGO sheets due to the reactions (Figure III.A.2). After reuse SGO sheets appear to have disintegrated along with slight aggregation. The possible explanation may be put forward that, after catalysis, its reduction to rGO leads to disintegration into smaller sheets. Furthermore, the morphological study (SEM images) confirms the formation of multiple SGO sheets (Figure III.A.3). Thus, from the above, it may be included that SGO has taken part in the reaction.

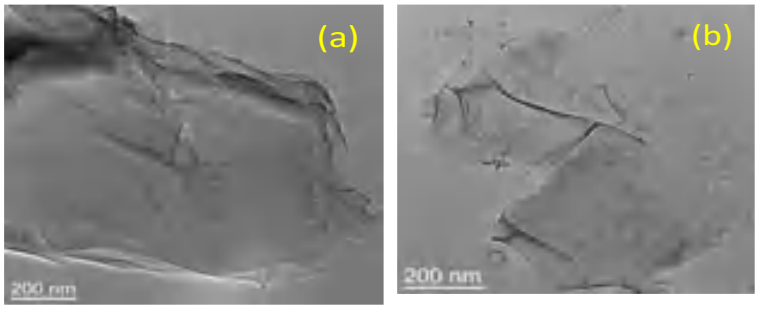


Figure III.A.2. *HR-TEM images of (a) SGO and (b) SGO after 5th run.*

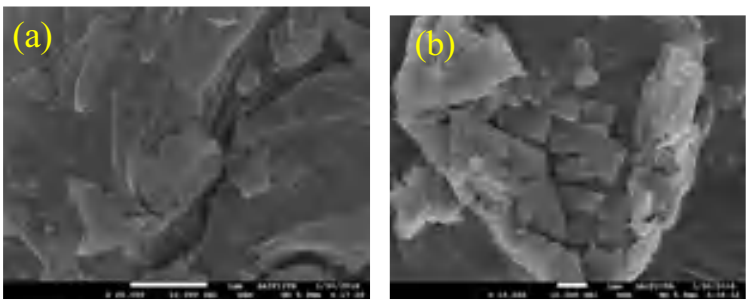
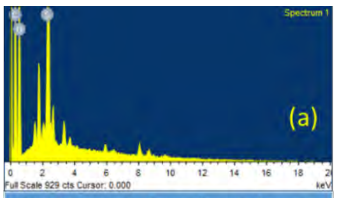


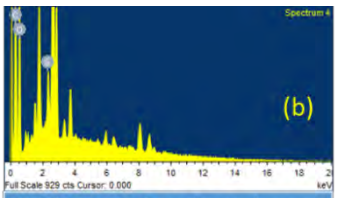
Figure III.A.3. *SEM images of (a)SGO and (b) SGO after the 5th run.*

The S content in fresh SGO and the residue left after the 5th run was 3.12 and 0.68 wt% respectively (Figure III.A.4). The decreased percentage of S in

SGO after the 5th run reveals that the functional groups containing sulfur have had participated in the reaction.



Weight percent of constituent elements	
C	50.41
O	46.47
S	3.12



Weight percent of constituent elements	
C	53.7
O	45.62
S	0.68

Figure III.A.4. *EDX spectra of (a) SGO and (b) SGO after 5th run.*

III.A.3.5. XRD and Raman spectra analysis

For structural studies, XRD spectra of the synthesized catalyst SGO, and that of it after the 5th run are shown in Figure III.A.5.

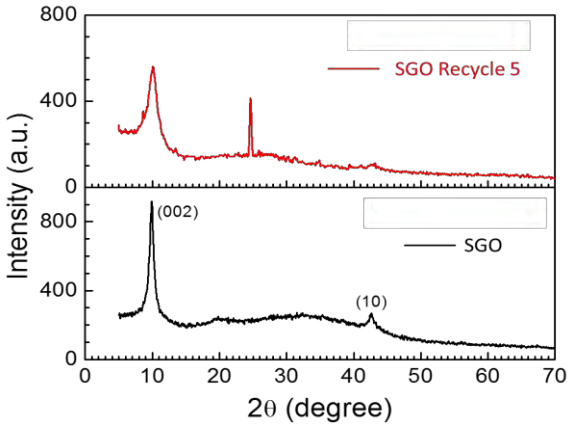


Figure III.A.5. *XRD spectra of synthesized SGO and SGO catalyst after 5th recycle.*

A comparison indicates a reduction in the intensity of the first peak (2Θ=9.98) which is a characteristic peak of sulfonated graphene oxide. After the 5th cycle, a new peak appears at 2Θ=24.64, which indicates the partial formation of rGO. These results show a proportional reduction of the content of functional groups on SGO during the reaction.

The Raman spectra of both SGO and used SGO after the 5th run showed a characteristic D peak at 1346 cm^{-1} and G peak at 1582cm^{-1} (Figure III.A.6). The ratio of intensities of D and G band (I_D/I_G) of SGO and used SGO after 5th run displayed 0.91 and 0.93 respectively. However, the slight increased (I_D/I_G) ratio suggested that during successive runs partial formation of rGO has occurred through the restoration of some C=C bonds.

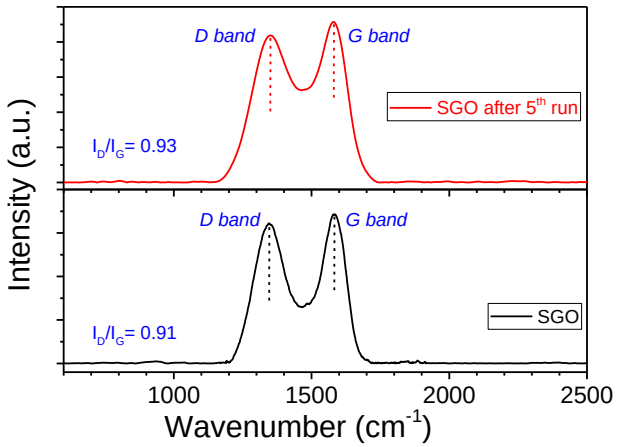


Figure III.A.6. *Raman spectra of SGO and SGO after 5th run.*

III.A.3.6. Recyclability experiment

To check the recyclability of the catalyst SGO, a model reaction between benzaldehyde, ethylacetoacetate, and hydroxylamine hydrochloride in presence of 100 mg of SGO was carried out. After the completion of the reaction, ethyl

acetate (20 ml) was added into the reaction mixture and centrifuged at 4000 rpm for 5 minutes. The supernatant liquid containing the product was decanted off and the process was repeated thrice.The recovered catalyst was then washed with water and acetone repeatedly to obtain dry SGO.

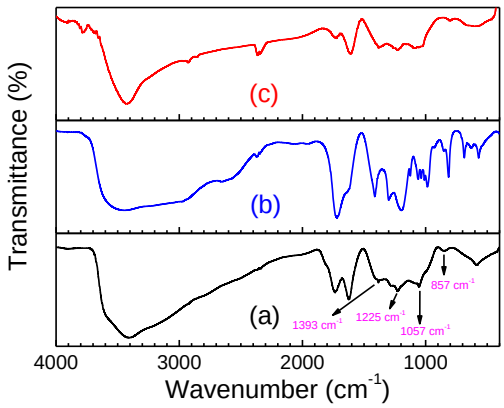


Figure III.A.7. *FTIR spectra of SGO (a) fresh (b) after 2nd run (c) after 5th run.*

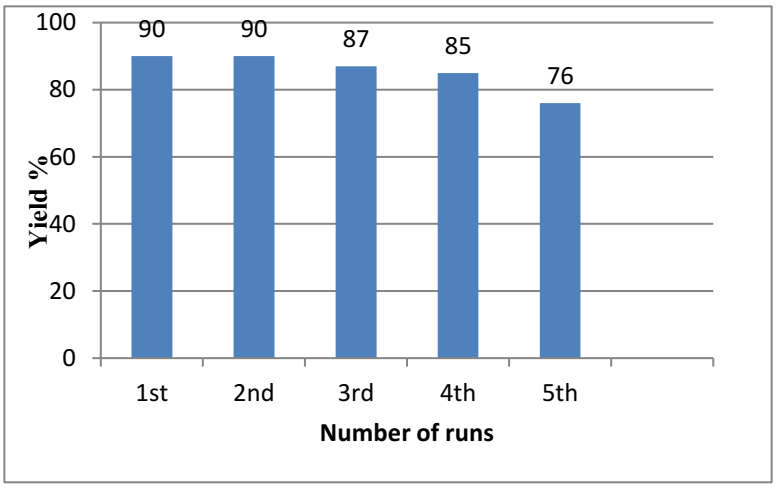


Figure III.A.8. *Recyclability experiment of catalyst SGO.*

The SGO catalyst could easily be separated from the reaction mixture by simple centrifugation and was found to retain its acidic property, even after 5 runs (Figure III.A.8). This was further supported by comparing the FTIR data of fresh SGO and recovered catalyst (Figure III.A.7). This may be attributed that the involvement of the nucleophilic oxo groups in SGO during the reaction may reduce the catalytic activity of SGO after the 5th run.

III.A.4. Conclusion

In conclusion, a green and efficient methodology for the synthesis of a variety of isoxazoles from commercially available aldehydes has been established. We have unfolded a new role of sulfonated graphene oxide as an efficient and heterogeneous carbocatalyst. SGO, itself is capable of furnishing the desired 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones with excellent yield. It can be envisioned that such a cheap and robust solid acid catalyst SGO holds great potential for a wide range of acid-catalysed reactions.

III.A.5. Experimental section

III.A.5.1. General information

The reactions were monitored by TLC [carried out on Merck silica gel (60 F_{254}) by using UV light as the visualizing agent]. The HR-TEM characterization was performed on a JEM 2100F Jeol TEM. The PXRD data and Raman spectra were obtained from Bruker D8 Advanced X-ray Powder Diffractometer (Cu Kα radiation, λ = 1.54 Å) and Enspectr R532 (laser used 532 nm). NMR spectra of all the products were taken in $CDCl_3$/DMSO-d_6 (TMS as an internal standard) using a Bruker AV-300 spectrometer operating for ^1H at 300 MHz and ^{13}C at 75 MHz. ^1H NMR spectroscopic data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d= doublet, t = triplet, dd

= doublet of doublets, m = multiplet, brs = broad), integration, coupling constants in Hertz (Hz). ^{13}C NMR spectroscopic data are reported in ppm. Coupling constants were reported as J values in Hertz (Hz). The chemicals and reagents were purchased from Merck, Spectrochem, and Sigma-Aldrich.

III.A.5.2. General procedure for the preparation of the catalyst

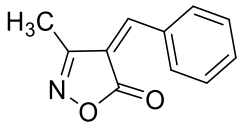
SGO-1 and SGO-2 were prepared by the Tours method according to the literature [55]. In brief, a 9:1 mixture of concentrated H_2SO_4/ H_3PO_4 (360:40 ml) was taken in a beaker, after that graphite powder (3.0 g) was added slowly to it taking the whole system in an ice bath to keep the temperature below 20 °C. $KMnO_4$ (9.0 g) was then added slowly in portions to the solutions. Afterward, the reaction mixture was heated to 50 °C and stirred for 12 h. After the reaction, the mixture was centrifuged (5000 rpm for 30 min), and the supernatant was decanted away. The remaining solid material was then washed with water successively, 30% HCl and ethanol to remove the remaining salt. The solid obtained was then dried to obtain the powdered graphene oxide [55] In SGO-2 9.0 g $KMnO_4$ is only replace by 18 g.

III.A.5.3. General procedure for the synthesis of 3-methyl-4 arylmethylene isoxazole-5(4*H*)-ones

25-ml RB was charged with benzaldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol), hydroxylamine hydrochloride (2.5 mmol), and 25mg of SGO. The mixture was allowed to stir at room temperature for adequate time (Table III.A.1) and the extent of the reaction was governed by thin-layer chromatography (TLC). The reaction mixture was extracted by ethyl acetate after completion of the reaction and further purified by Column Chromatography using silica gel 60-120 mesh to get the desired product.

III.A.5.4. Spectral data of compounds mentioned in Table III.A.2

4a. 4-benzylidene-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 1) [28]

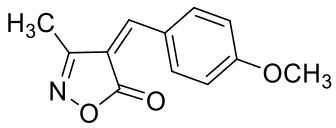


^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.21 (s, 3H), 7.36 (s, 1H), 7.39-7.52 (m, 3H), 8.25-8.27 (d, 2H, *J*=7.5Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 11.67, 119.54, 128.95, 129.05, 130.55, 132.28, 133.86, 134.08, 150.23, 161.31, 167.96;

IR (KBr, cm^{-1}) bands 3431, 1741, 1590, 1347, 1218, 1107, 681.

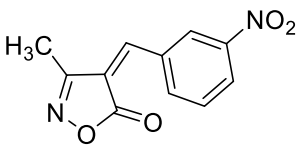
4b. 4-(4-methoxybenzylidene)-3- methylisoxazol-5(4*H*)-one (Table III.A.2, entry 2) [28]



^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.212 (s, 3H), 3.84 (s, 3H), 6.92-6.95 (d, 2H, *J*=8.1Hz), 7.27 (s, 1H), 8.35-8.38 (d, 2H, *J*= 8.4Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 11.75, 56.02, 114.11, 116.30, 117.14, 125.50, 132.08, 147.96, 152.33, 154.38, 162.74, 169.48.

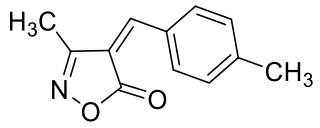
4c. 4-(3-nitrobenzylidene)-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 3) [36]



^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.24 (s, 3H), 8.20-8.26 (t, 1H, *J*=8.1Hz), 2.57-2.59 (d, 1H, *J*=7.5Hz), 8.73-8.76 (d, 1H, *J*=7.8Hz), 8.86 (s, 1H), 8.95 (s, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.53, 121.79, 124.65, 125.04, 125,65, 130.24, 131.06, 133.31, 135.92, 149.12, 162.21.

4d. 3-methyl-4-(4-methylbenzylidene)isoxazol-5(4*H*)-one (Table III.A.2, entry 4) [28]

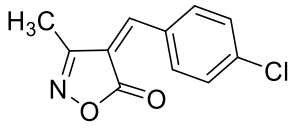


^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.34 (s, 3H), 2.50 (s, 3H), 7.35-7.37 (d, 2H, *J*=9.2Hz), 7.80 (s, 1H), 8.27-8.29 (d, 2H, *J*= 8.4 Hz);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.82, 21.62, 116.12, 119.25, 128.79, 130.05, 135.92, 152.01, 162.78, 168.47;

IR (KBr, cm^{-1}) bands 3415, 1730, 1585, 1356, 1203, 1109, 685.

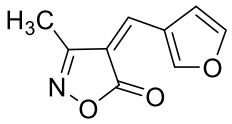
4e. 4-(4-chlorobenzylidene)-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 5) [36]



^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.50 (s, 3H), 6.93-6.96 (d, 2H, *J*=7.5Hz), 7.57 (s, 1H), 8.20-8.23 (d, 2H, *J*=8.1Hz);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.71, 116.27, 116.91, 119.57, 119.94, 125.19, 132.42, 137.21, 145.52, 160.08, 162.62.

4g. 3-methyl-4-(furan-3-ylmethylene)isoxazol-5(4*H*)-one (Table III.A.2, entry 7) [4]

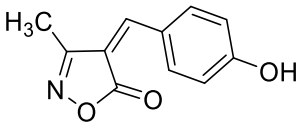


^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.23 (s, 3H), 6.90-6.93 (d, 2H, *J*=8.4Hz), 7.07 (s, 1H), 8.39-8.41 (d, 2H, *J*=8.4Hz);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.70, 114.31, 116.59, 125.02, 137.99, 151.84, 162.64, 164.28, 169.25;

IR (KBr, cm^{-1}) bands 3402, 1730, 1553, 1388, 1295, 1177

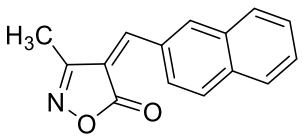
4h. 4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 8) [36]



^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.20 (s, 3H), 6.90-6.93 (d, 2H, *J*=8.4Hz), 7.70 (s, 1H), 8.31-8.41 (d, 2H, *J*=8.4Hz), 11.07 (s, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.75, 114.11, 116.30, 125.50, 132.08, 147.96, 154.38, 162.74, 168.48.

4i. 3-methyl-4-(naphthalen-2-ylmethylene)isoxazol-5(4*H*)-one (Table III.A.2, entry 9) [56]

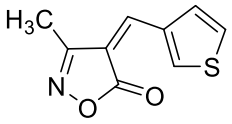


^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.31 (s, 3H), 7.65-7.70 (m, 2H), 8.02-8.07 (t, 3H), 8.55-8.58 (d, 2H, *J*=8.1Hz), 8.90 (s, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.80, 119.19, 127.73, 128.24, 128.55, 128.79, 130.09, 130.79, 132.65, 135.49, 137.06, 146.18 151.95, 162.75, 168.45;

IR (KBr, cm^{-1}) bands 3431, 1732, 1558, 1388, 1290, 1107; HRMS-ESI (m/z) calcd for $C_{15}H_{11}NO_2$ $[M+H]^+$ 238.0878 found 238.0856.

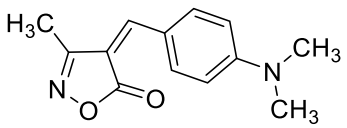
4k. 3-methyl-4-(thiophen-3-ylmethylene)isoxazol-5(4*H*)-one (Table III.A.2, entry 11) [36]



^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H), 7.38-7.40 (t, 1H, *J*=4.4 Hz), 8.22-8.23 (d, 1H, *J*=3.6 Hz), 8.27 (s, 1H), 8.31-8.33 (d, 1H, *J*=4.8 Hz);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.59, 113.54, 129.50, 136.66, 141.69, 142.17, 143.57, 162.15, 169.01.

4m. 4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 13) [30]

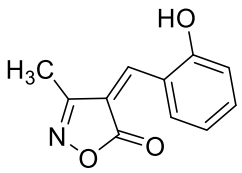


^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.20 (s, 3H), 3.16 (s, 3H), 3.35 (s, 3H), 6.83-6.86 (d, 2H, *J*=8.7Hz), 7.60 (s, 1H), 8.43-8.46 (d, 2H, *J*=8.1Hz);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.70, 52.41, 109.46, 112.09, 121.43, 135.04, 150.35, 154.51, 162.59, 170.29;

IR (KBr, cm^{-1}) bands 3444, 1715, 1558, 1382, 1203, 994, 668

4n. 4-(2-hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 14) [36]

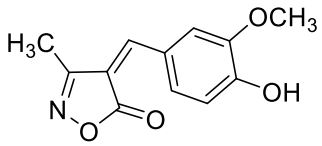


^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.21 (s, 3H), 6.91-7.02 (m, 2H), 7.44-7.57 (m, 1H), 8.09 (s, 1H), 8.72-8.74 (d, 1H, *J*=8.1Hz), 9.96 (s, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.68, 116.61, 116.91, 119.57, 119.94, 132.77, 137.22, 145.51, 160.10, 162.53, 168.45;

IR (KBr, cm-1) bands 3431, 1730, 1564, 1284, 1089, 776

4p. 4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 16) [24]

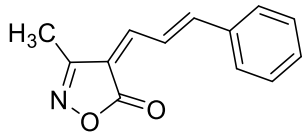


^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.23 (s, 3H), 3.83 (s, 3H), 6.95 (s, 1H), 7.57-7.89 (m, 2H), 8.50 (s, 1H), 10.41 (s, 1H);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.71, 56.02, 114.17, 116.27, 117.19, 125.51, 132.42, 147.95, 152.30, 154.31, 162.73, 169.41;

IR (KBr, cm^{-1}) bands 3416, 1730, 1557, 1284, 1023, 685

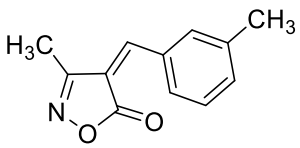
4q. 3-methyl-4-((E)-3-phenylallylidene)isoxazol-5(4*H*)-one (Table III.A.2, entry 17) [36]



^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.248 (s, 3H), 6.924-7.014 (m, 4H), 7.484-7.505 (d, 2H, *J*=6.3Hz), 8.079 (s, 1H), 8.706-8.733 (d, 1H, *J*=8.1Hz);

^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 11.66, 116.61, 116.91, 119.57, 119.94, 125.19, 132.76, 137.21, 145.52, 160.04, 162.62, 168.73.

4r. 3-methyl-4-(3-methylbenzylidene)-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 18)

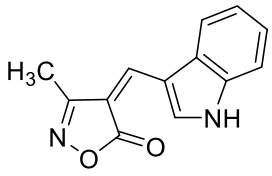


^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.26 (s, 3H), 2.34-2.36 (s, 3H), 7.45-7.47 (m, 2H), 7.90 (s, 1H), 8.19 (s, 1H), 8.23-8.25 (m, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 11.74, 21.31, 119.10, 128.84, 130.18, 132.94, 135.58, 135.13, 138.60, 152.29, 162.69, 168.30;

HRMS-ESI (m/z) calcd for $C_{12}H_{11}NO_2$ $[M+H]^+$ 202.0878 found 202.0825.

4s. 4-((1H-indol-3-yl)methylene)-3-methylisoxazol-5(4*H*)-one (Table III.A.2, entry 19) [36]

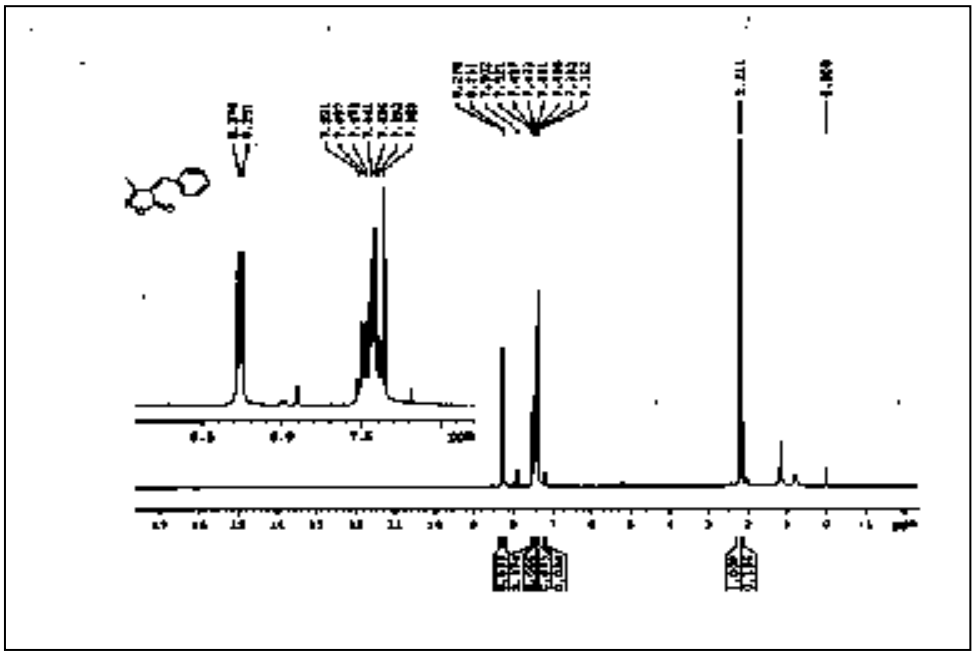


^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.31 (s, 3H), 7.29-7.32 (m, 2H), 7.56-7-59 (m, 1H), 8.12-8.16 (m, 2H), 9.48-9.49 (d, 2H, *J*=3.2Hz), 12.77 (br, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 11.66, 109.32, 113.13, 113.59, 119.30, 123.04, 124.42, 128.43, 136.84, 138.96, 140.93, 162.17, 170.86.

III.A.5.5. Scanned copies of ^{1}H, ^{13}C NMR and HRMS spectra of synthesized compounds

Figure III.A.9. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 4-benzylidene-3-methylisoxazol-5(4H)-one.*



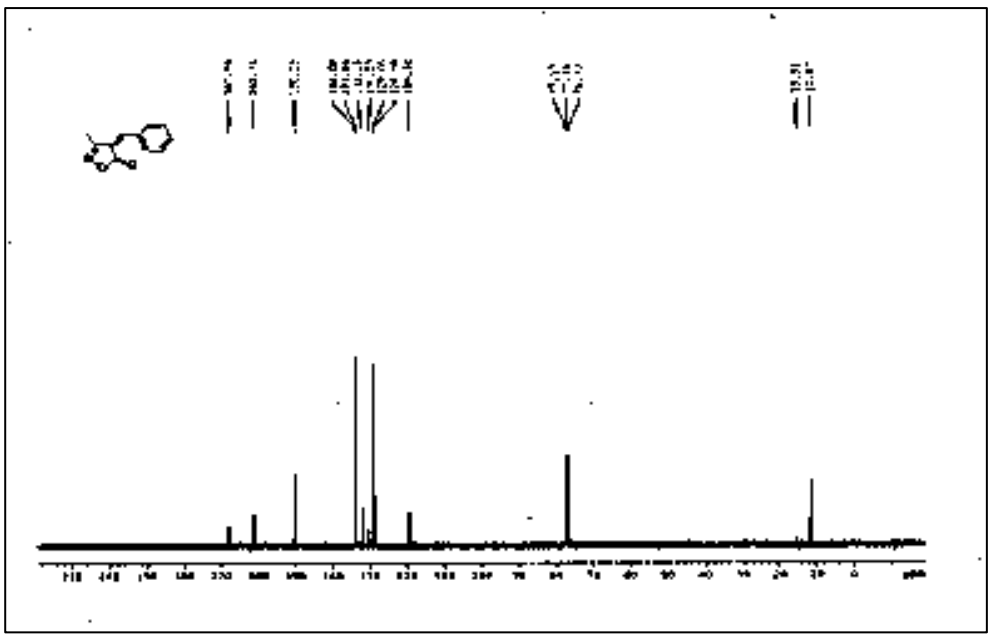
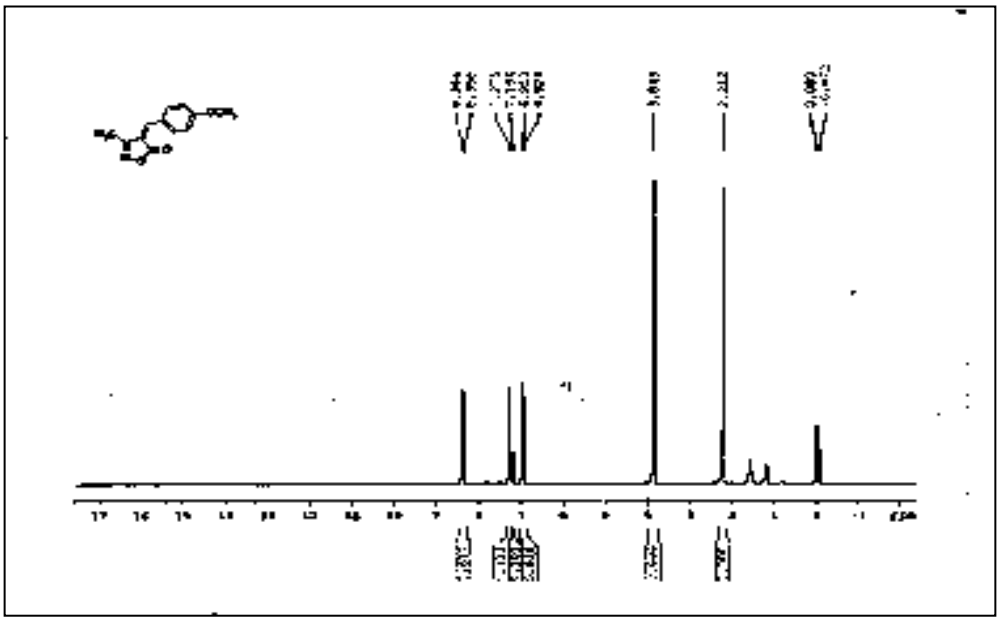


Figure III.A.10. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 4-(4-methoxybenzylidene)-3- methylisoxazol-5(4H)-one.*



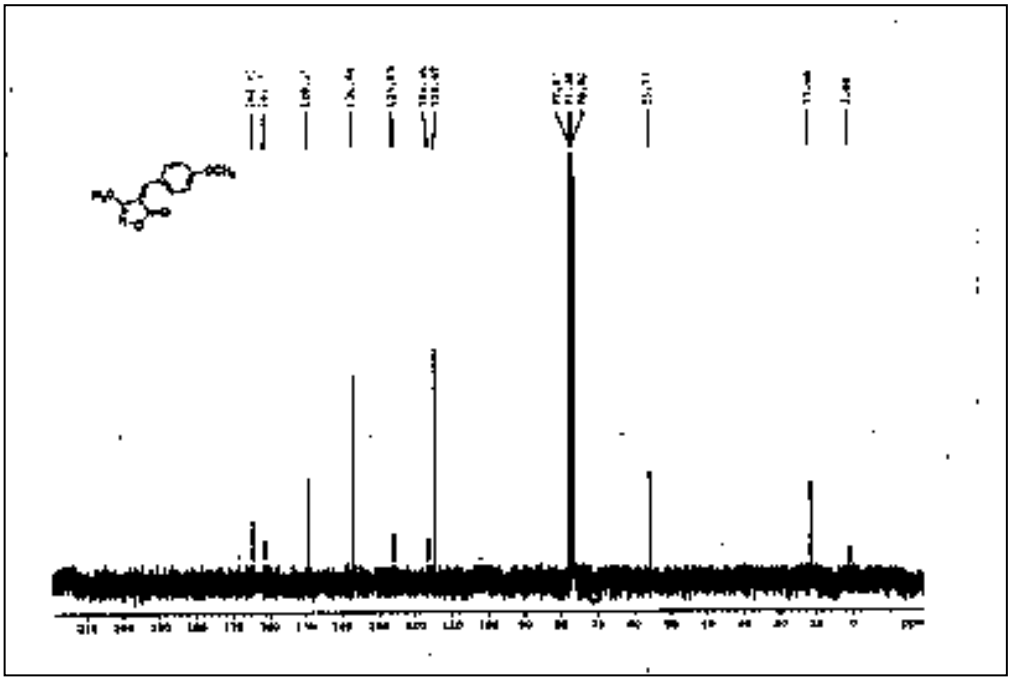
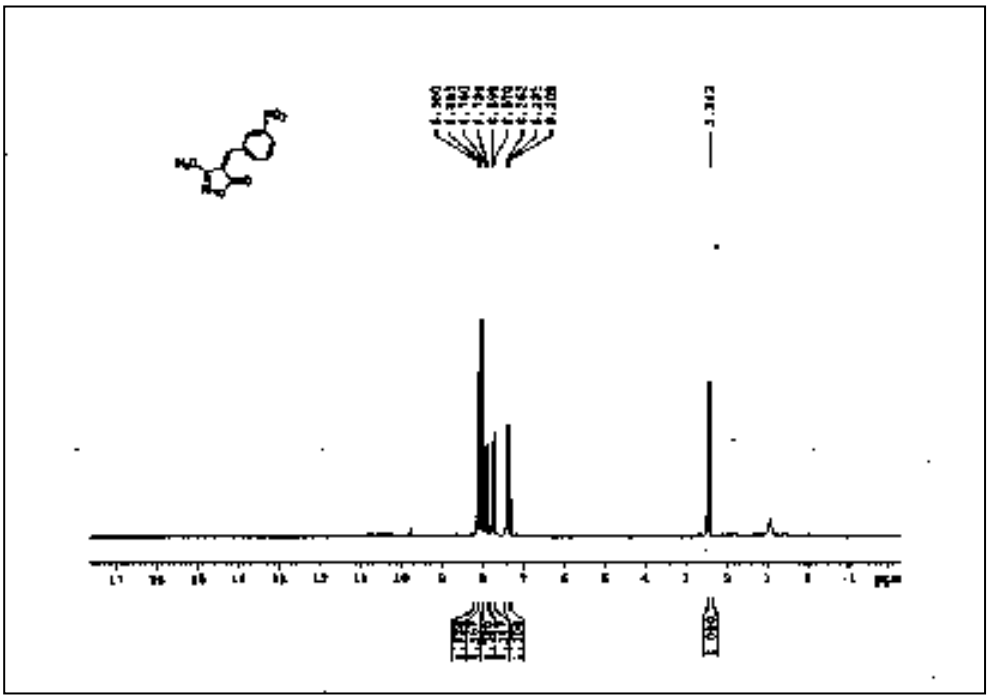


Figure III.A.11. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 4-(3-nitrobenzylidene)-3-methylisoxazol-5(4H)-one.*



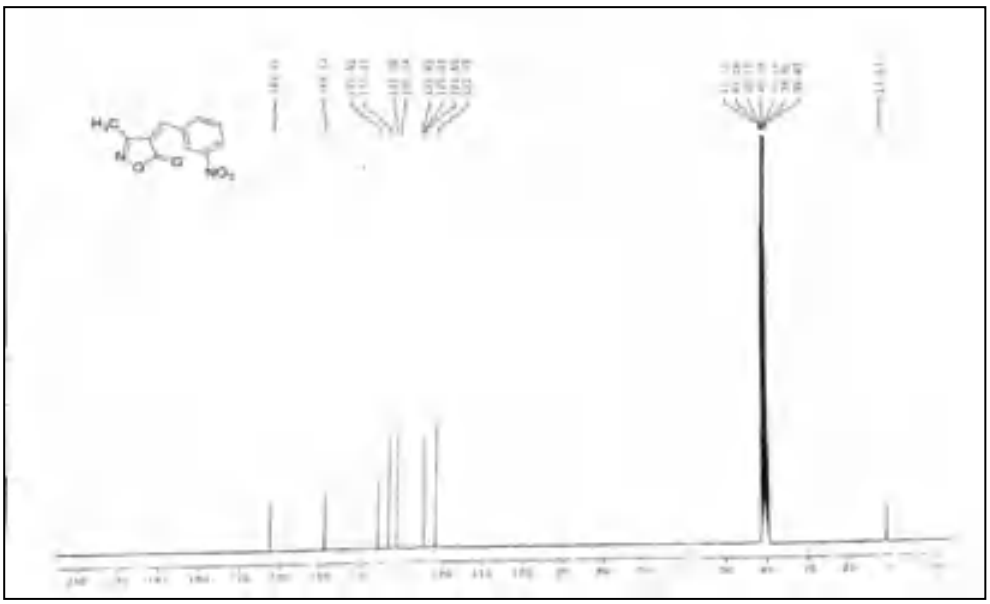
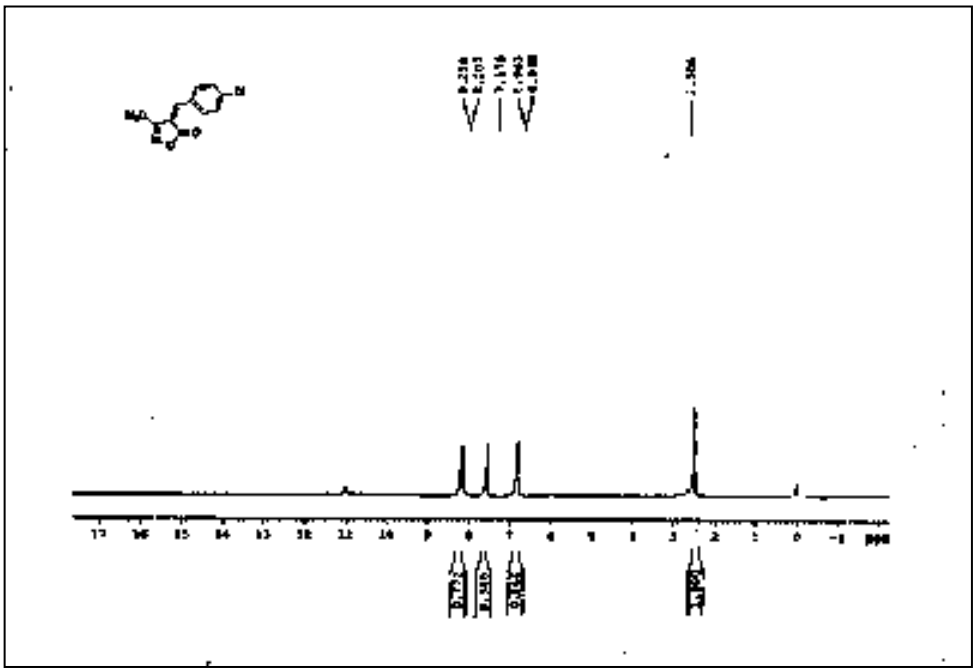


Figure III.A.12. *Scanned copy of ^{1}H and ^{13}C NMR spectra of . 4-(4-chlorobenzylidene)-3-methylisoxazol-5(4H)-one.*



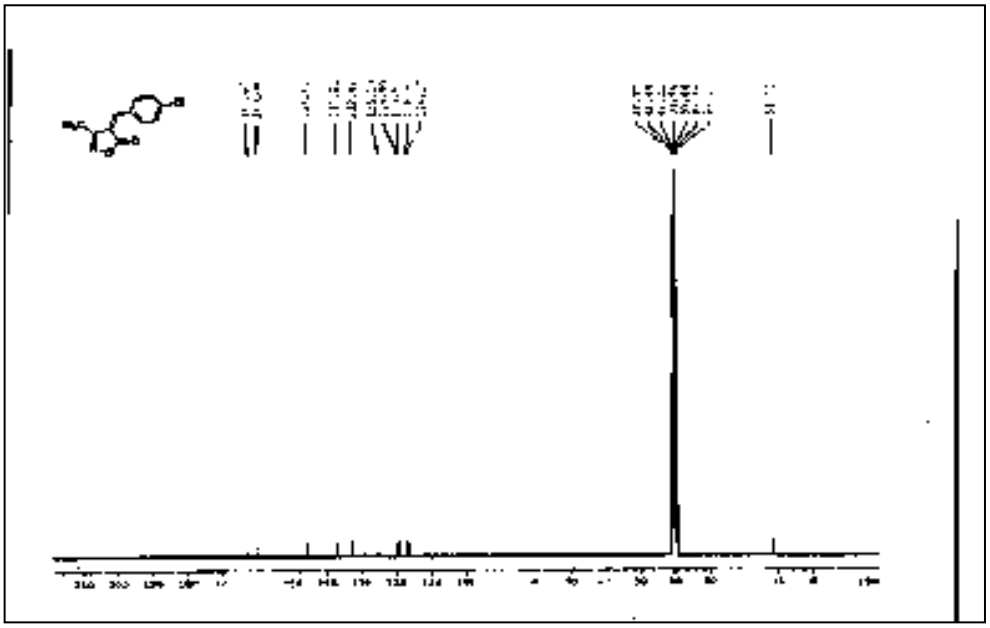
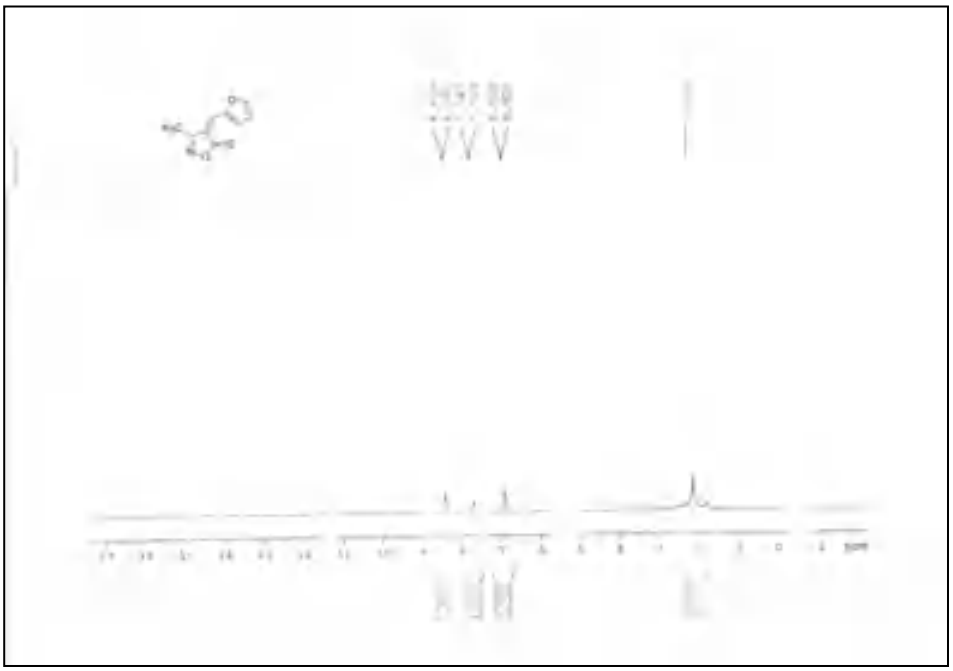


Figure III.A.13. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-methyl-4-(furan-3-ylmethylene)isoxazol-5(4H)-one.*



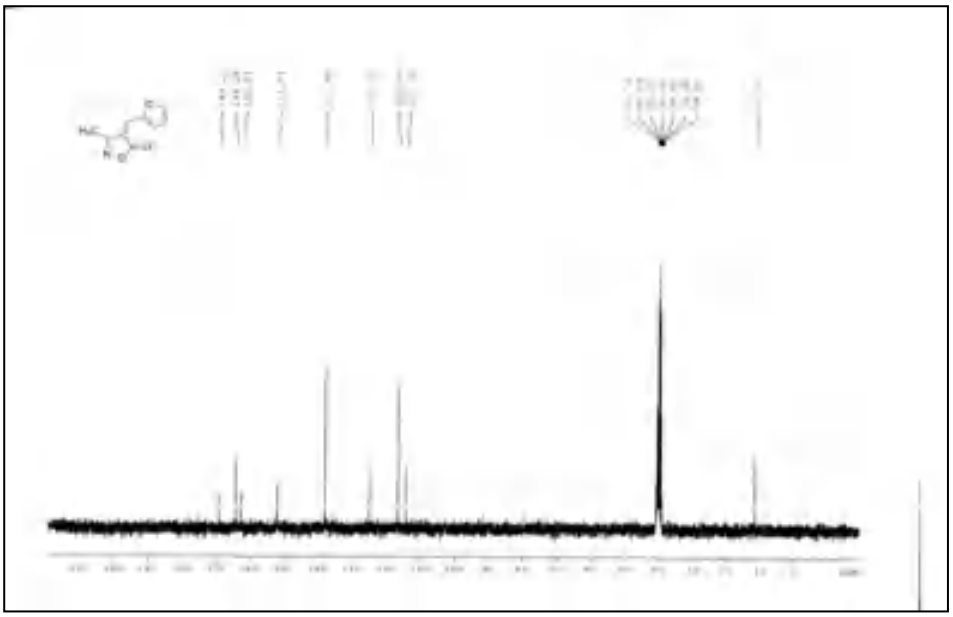
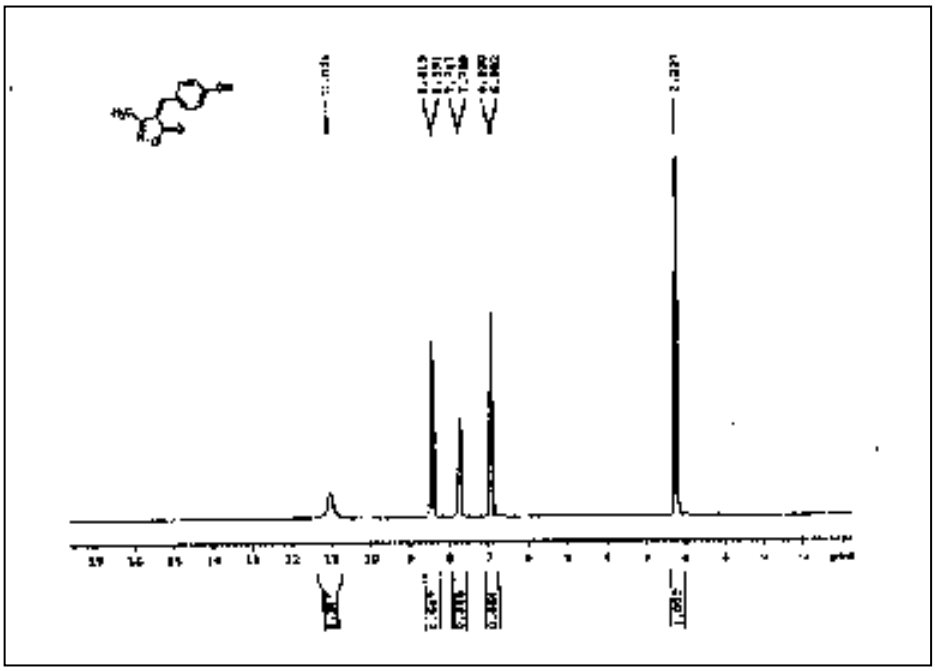


Figure III.A.14. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one.*



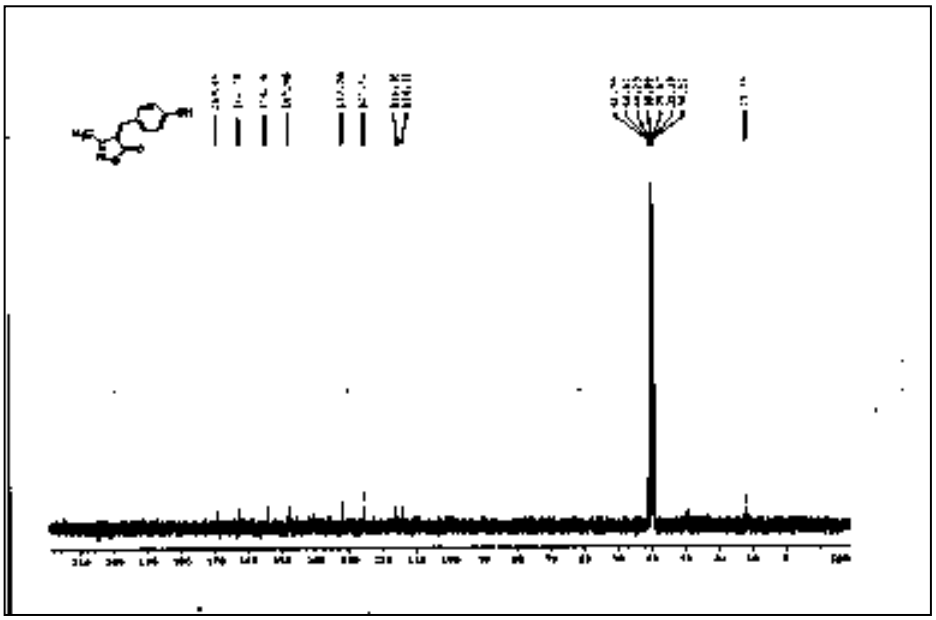
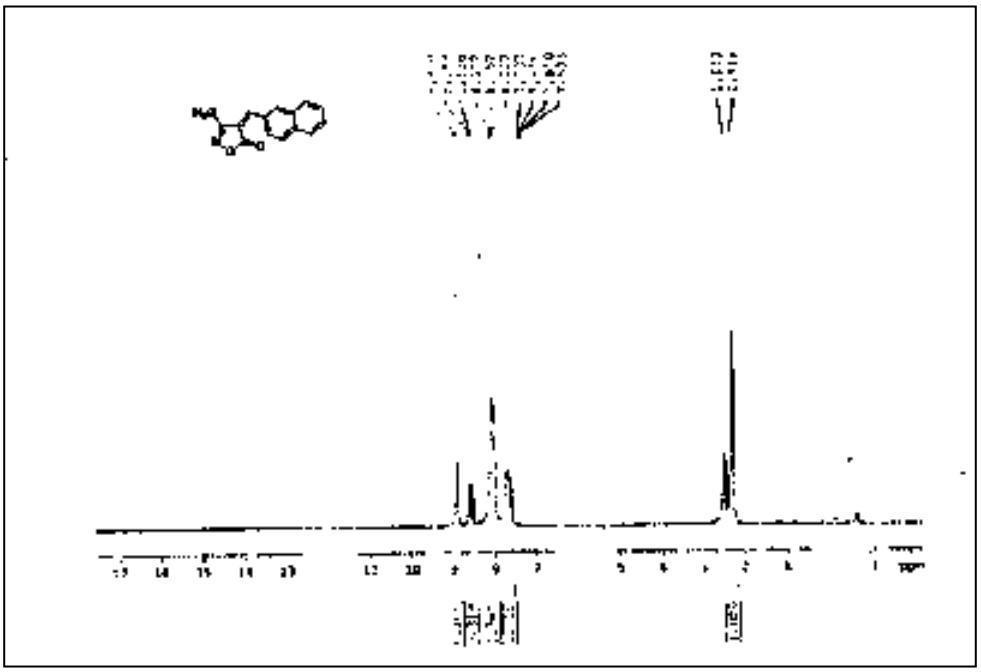


Figure III.A.15. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-methyl-4-(naphthalen-2-ylmethylene)isoxazol-5(4H)-one.*



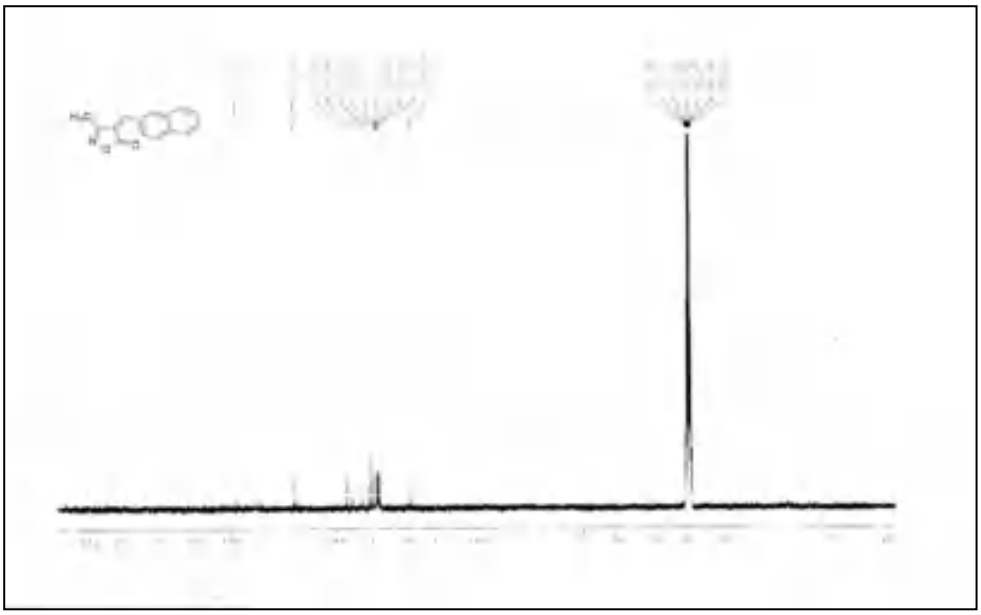


Figure III.A.16. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-methyl-4-(naphthalen-2-ylmethylene)isoxazol-5(4H)-one.*

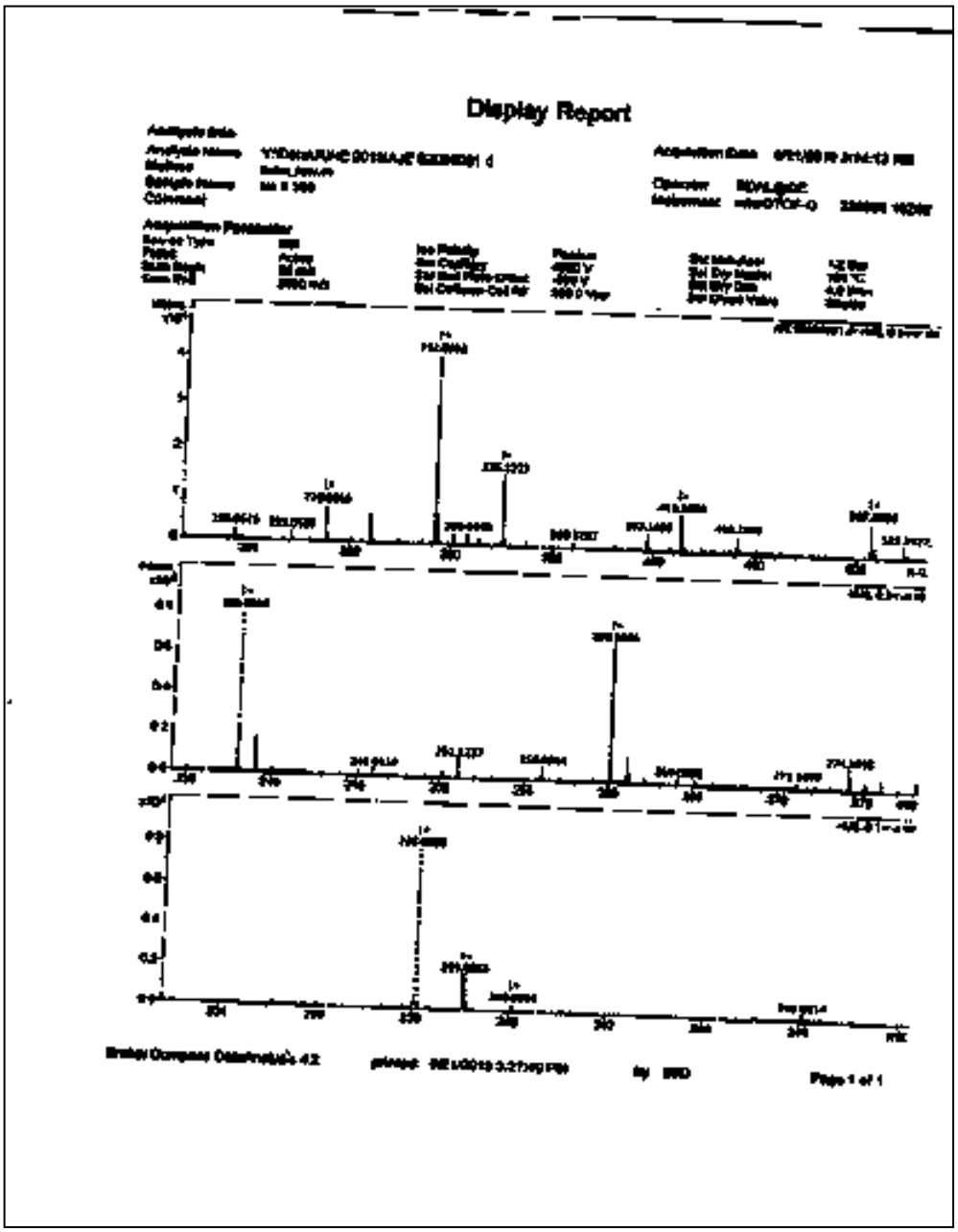
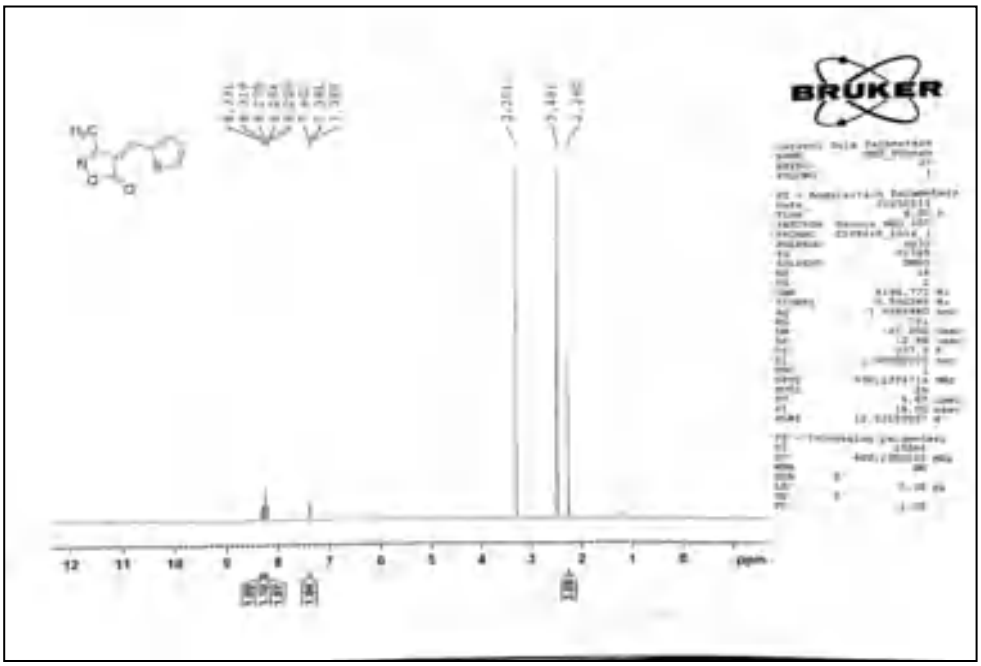


Figure III.A.17. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-methyl-4-(thiophen-3-ylmethylene)isoxazol-5(4H)-one.*



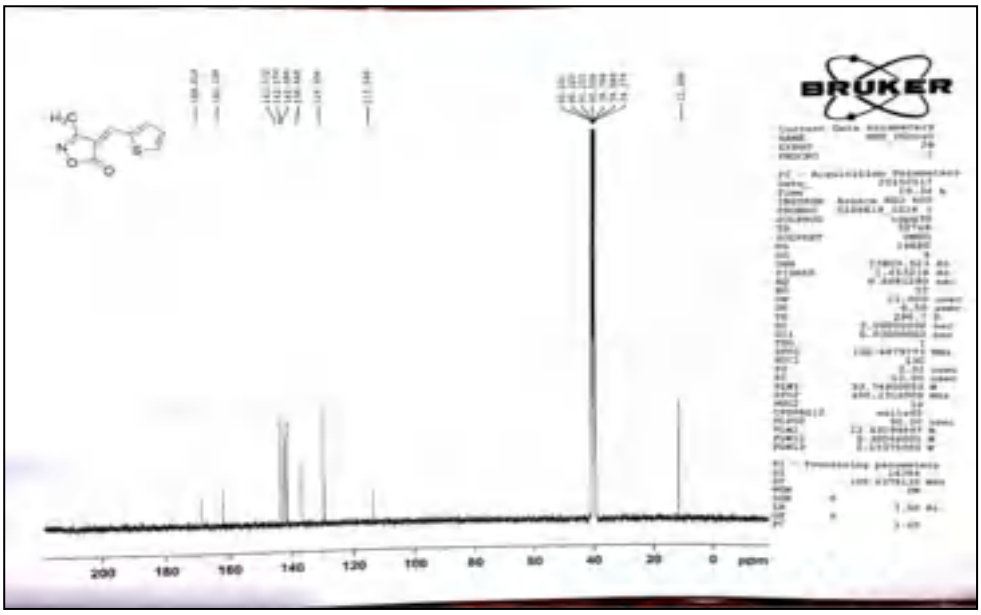
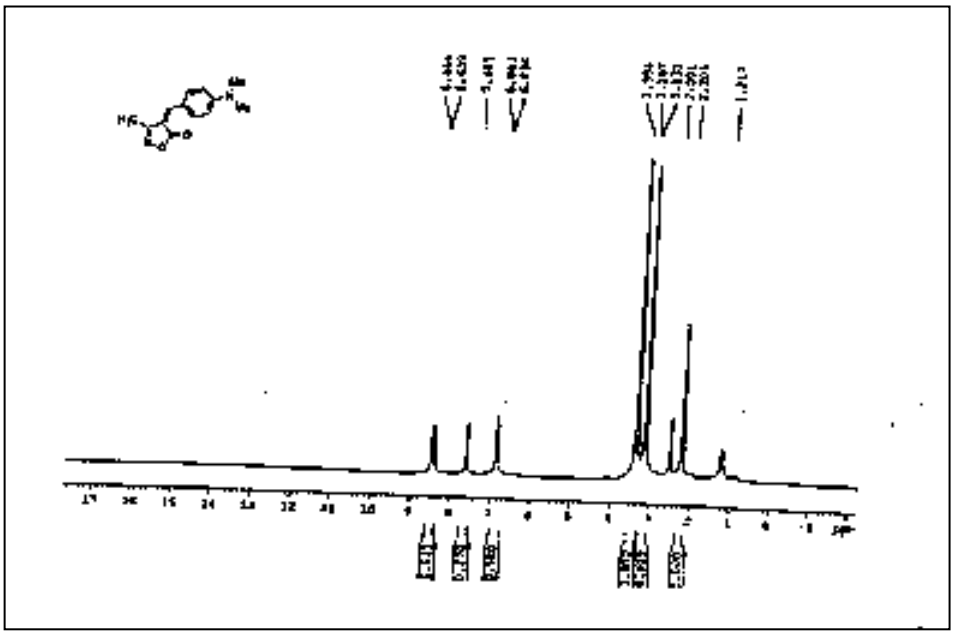


Figure III.A.18. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one.*



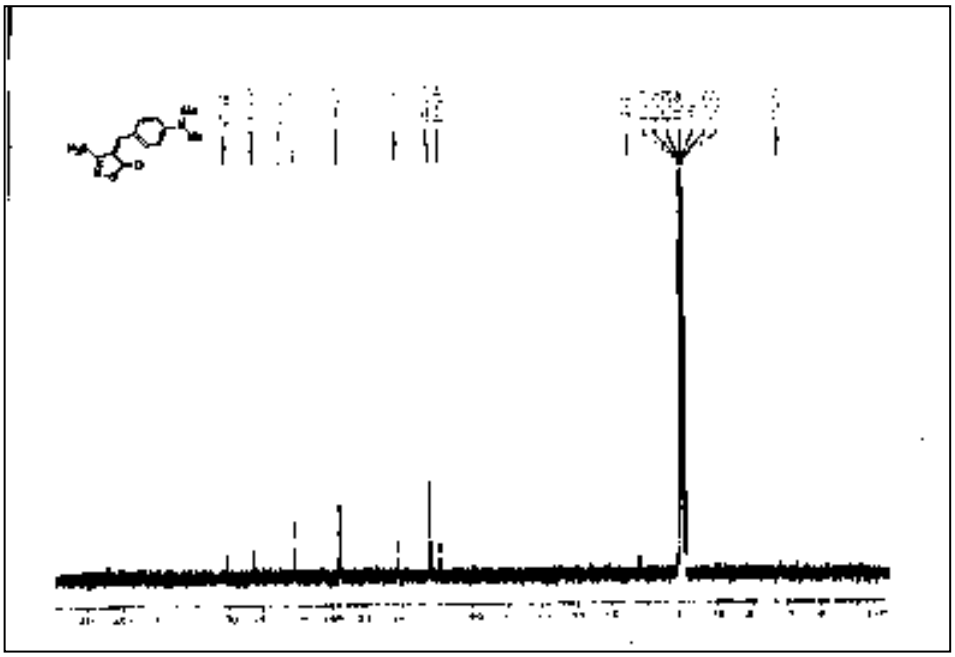
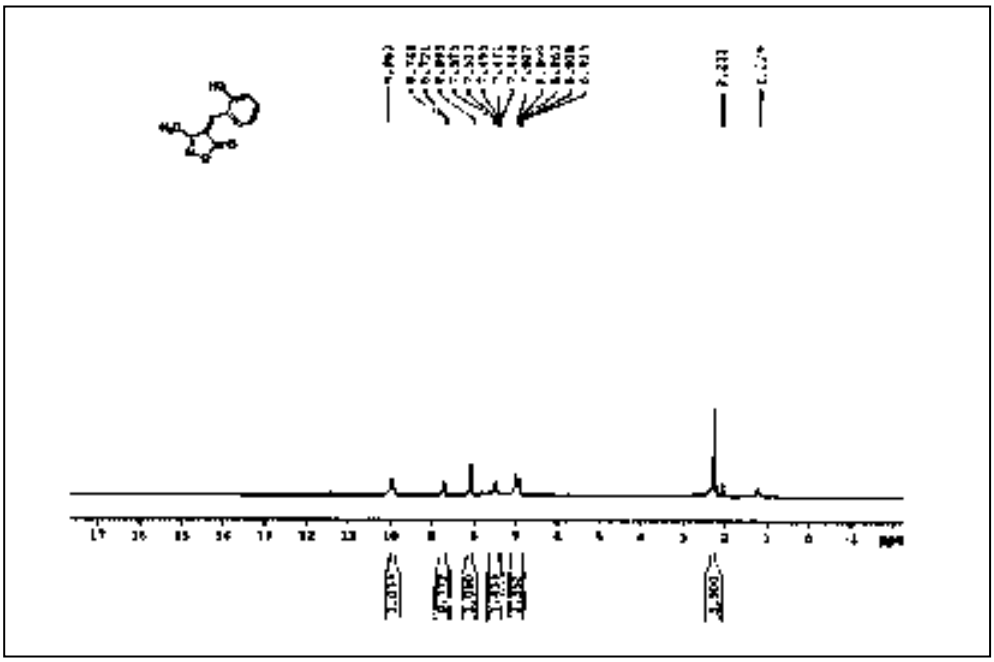


Figure III.A.19. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 4-(2-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one.*



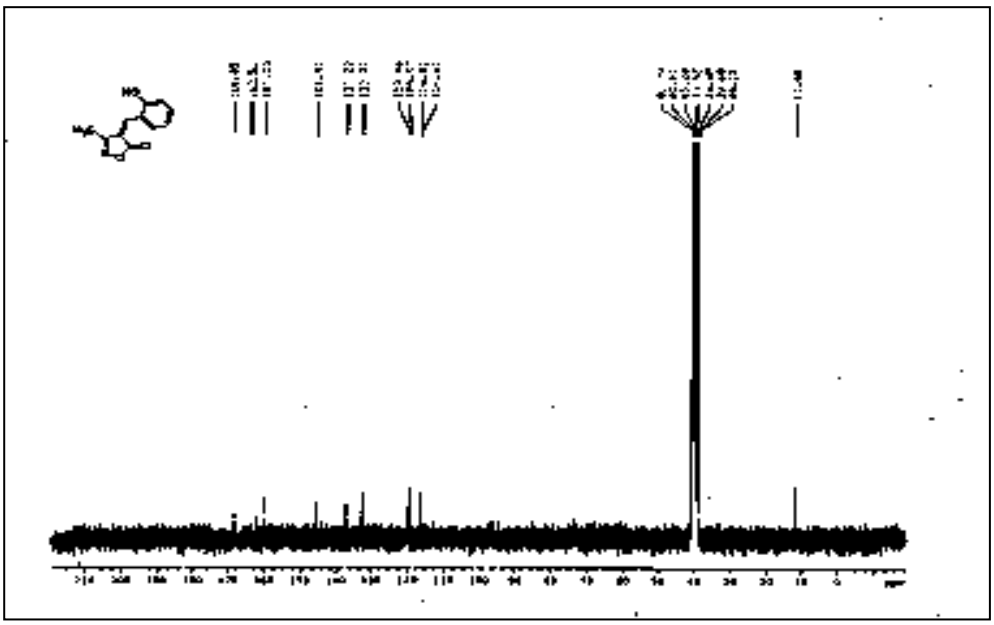
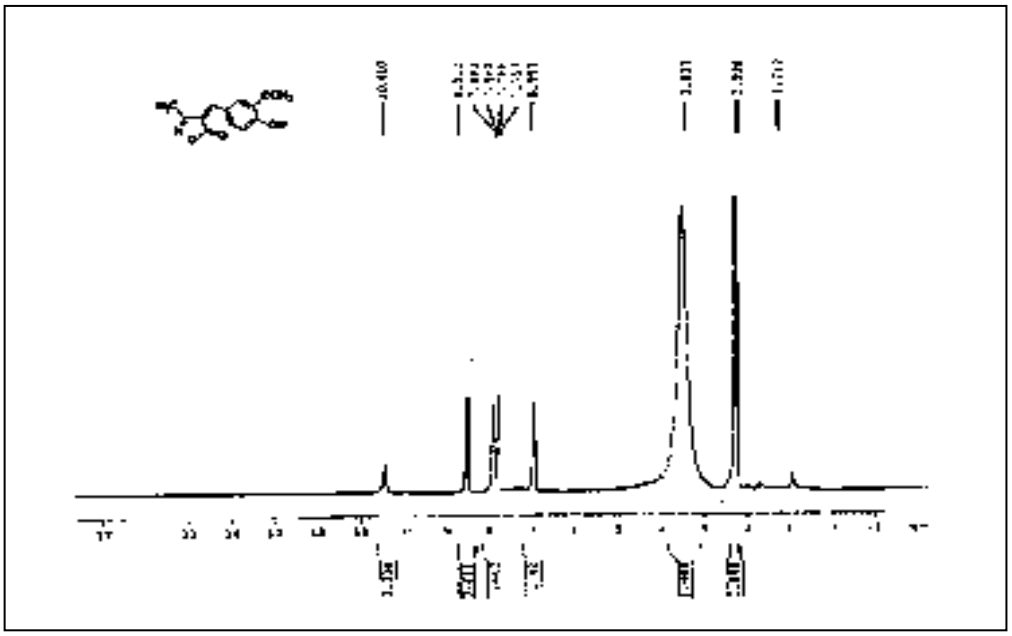


Figure III.A.20. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4H)-one.*



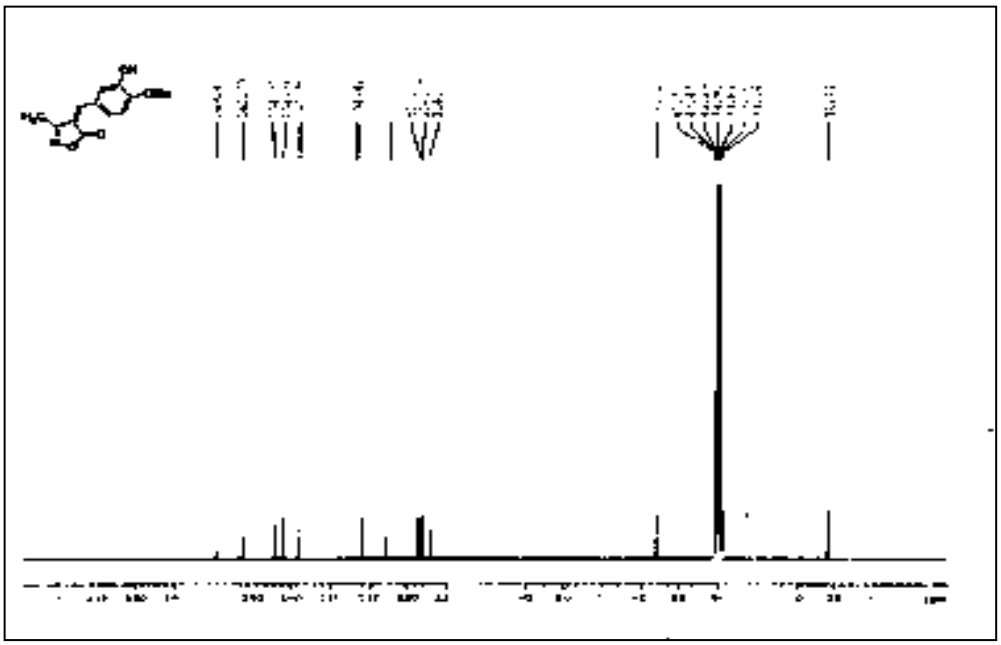
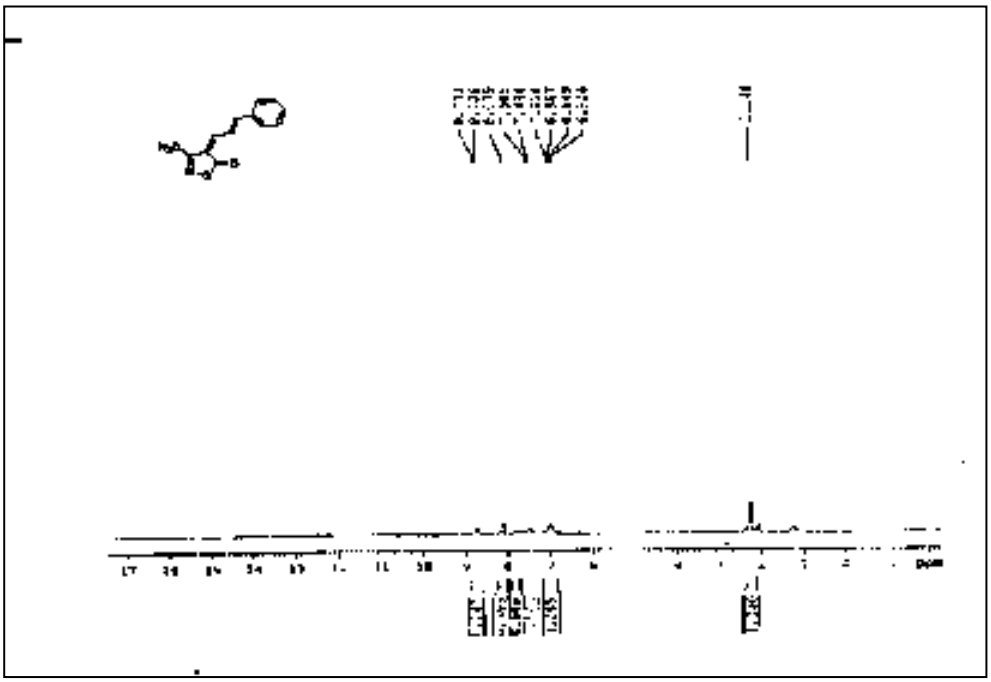


Figure III.A.21. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-methyl-4-((E)-3-phenylallylidene)isoxazol-5(4H)-one.*



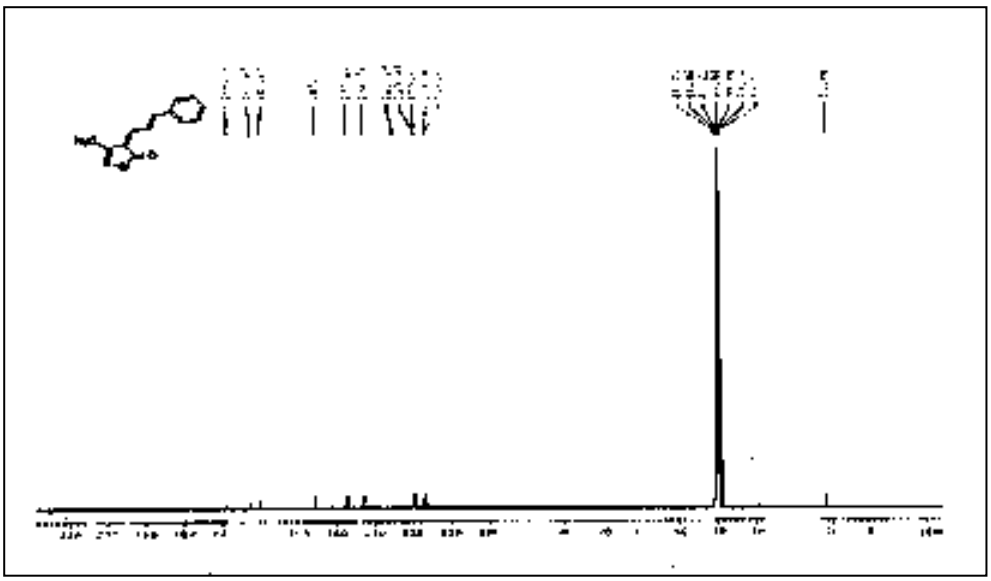


Figure III.A.22. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 3-methyl-4-(3-methylbenzylidene)-3-methylisoxazol-5(4H)-one.*

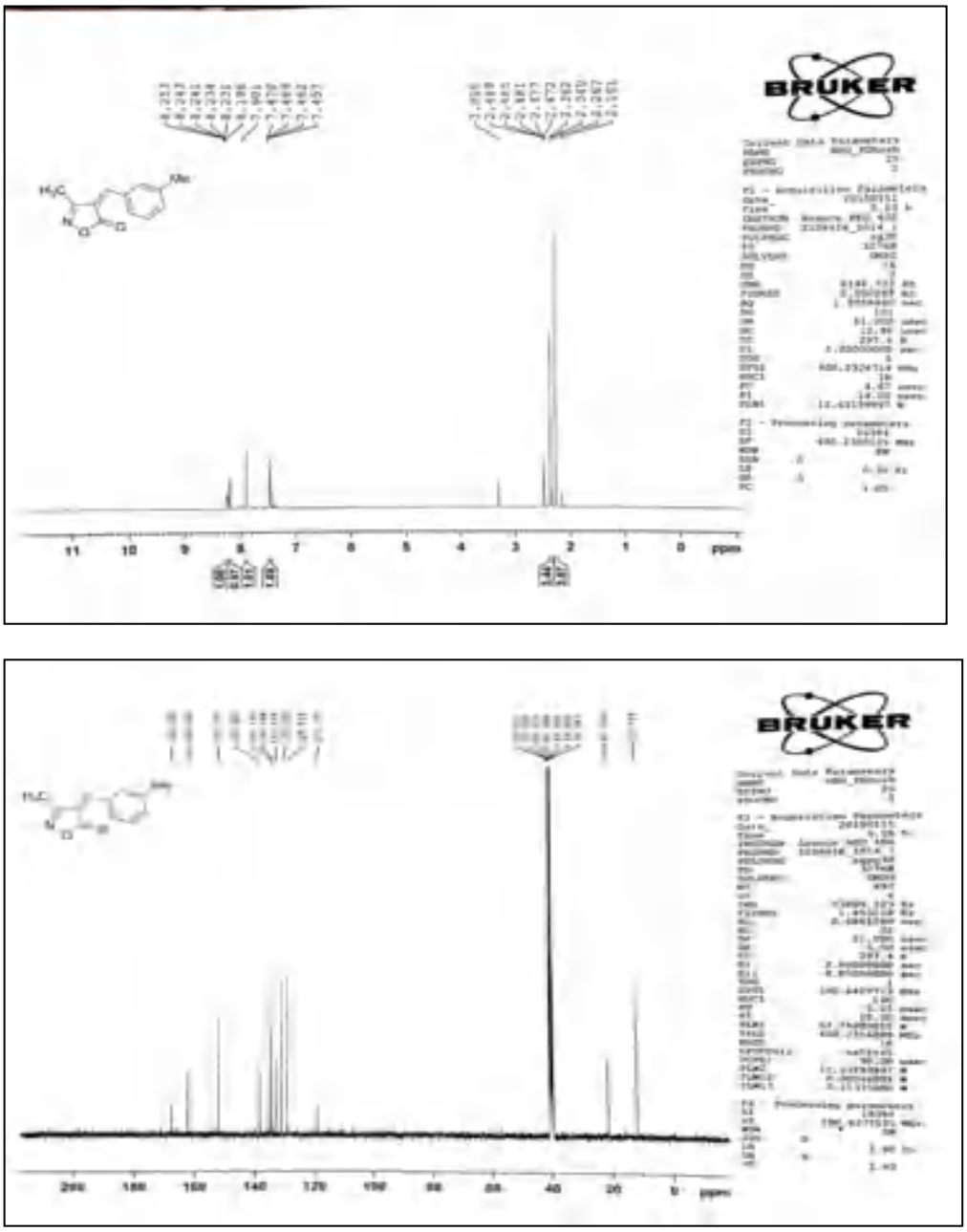


Figure III.A.23. *Scanned copy of [1]HRMS spectra of 3-methyl-4-(3-methylbenzylidene)-3-methylisoxazol-5(4H)-one.*

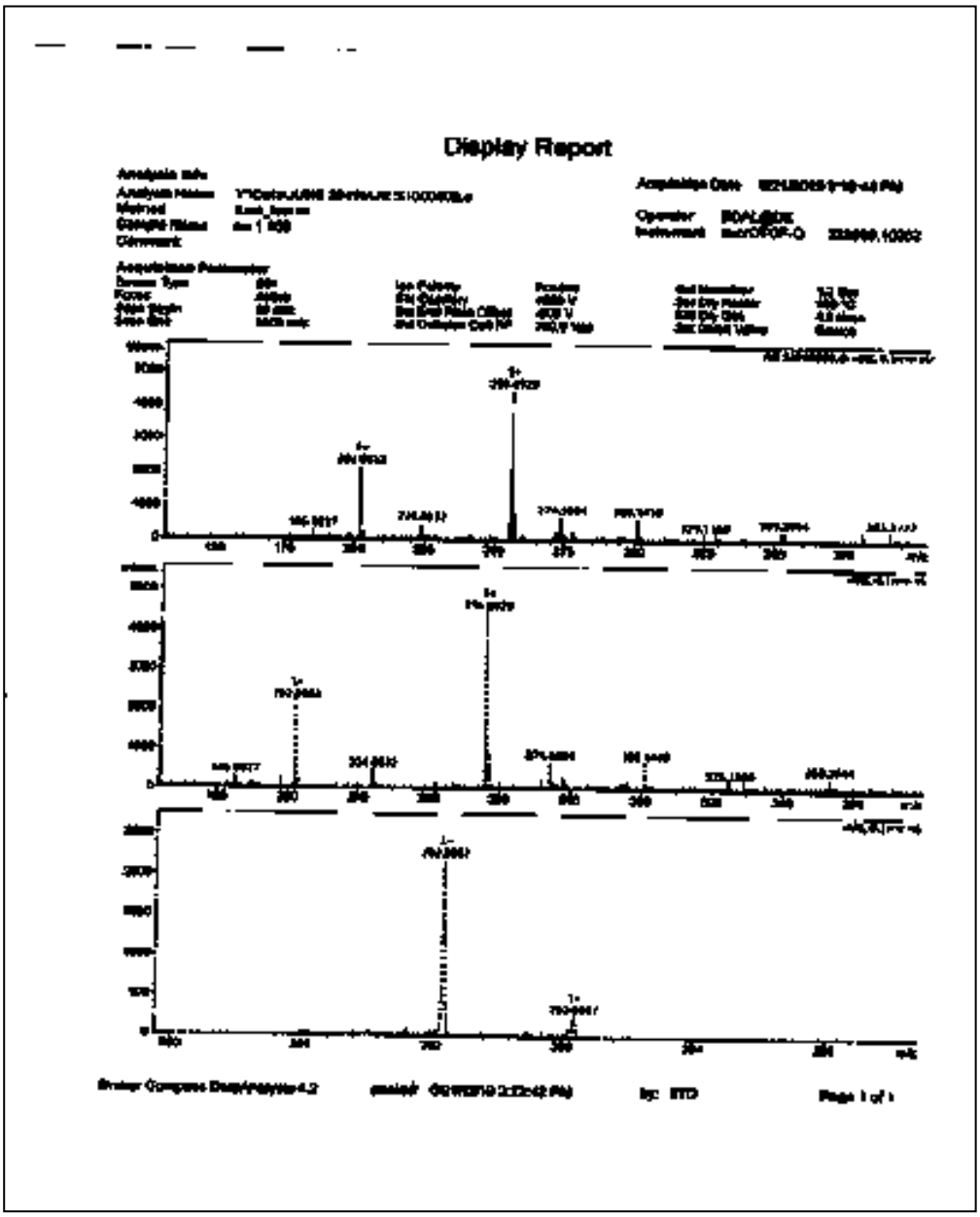
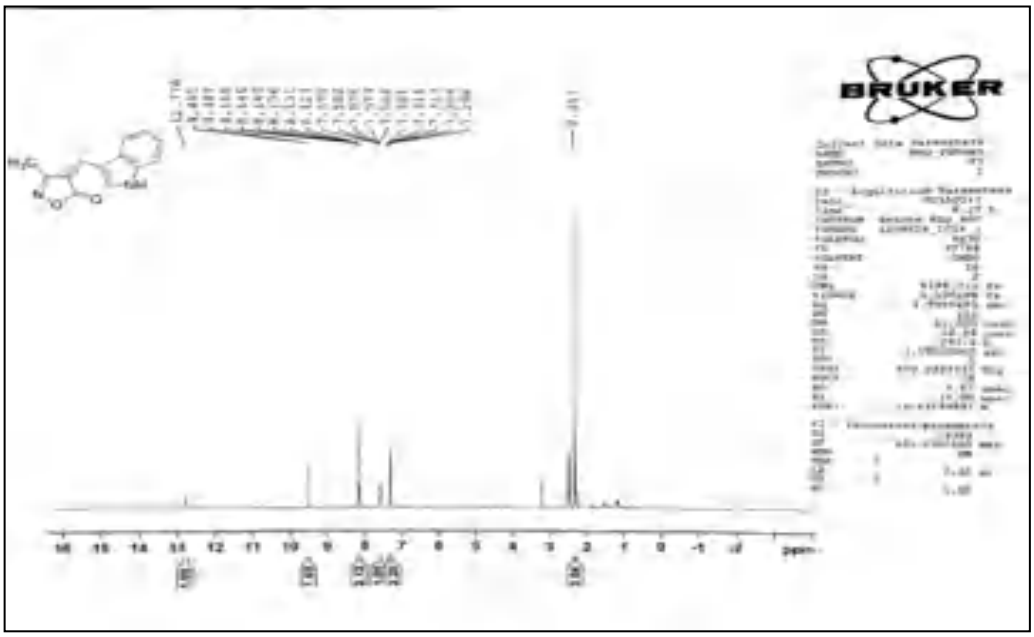
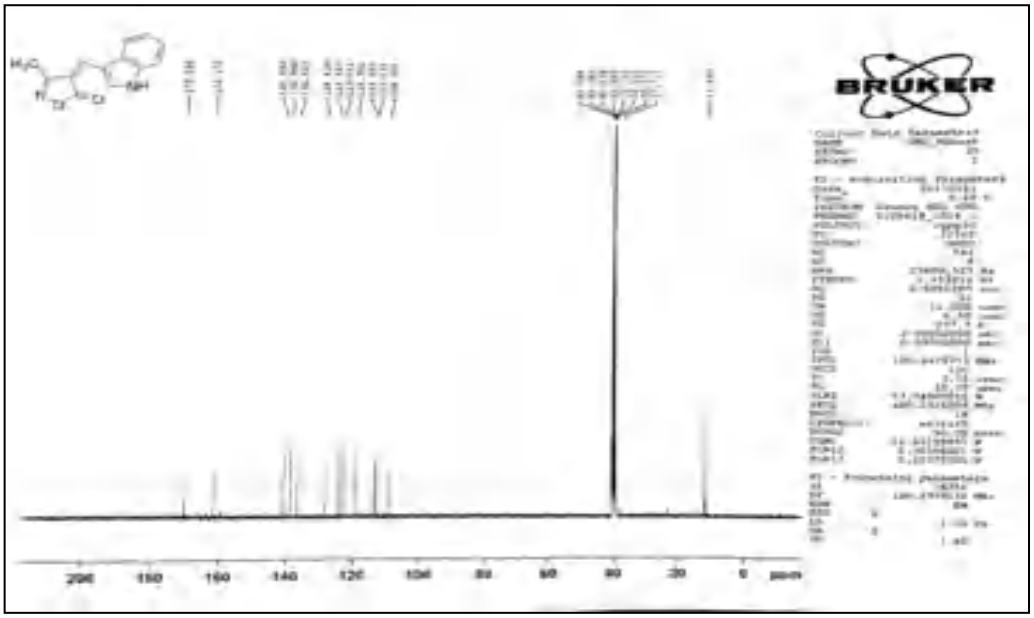


Figure III.A.24. *Scanned copy of ^{1}H and ^{13}C NMR spectra of 4-((1H-indol-3-yl)methylene)-3-methylisoxazol-5(4H)-one.*





III.A.6. References

References are given in Bibliography under Chapter III, Section A