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Article

# Nano $Fe_2O_3$, Clinoptilolite and $H_3PW_{12}O_{40}$ as Efficient Catalysts for Solvent-Free Synthesis of 5(4*H*)-Isoxazolone under Microwave Irradiation Conditions

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Uma abordagem rápida e sem solvente envolvendo a exposição de reagentes puros a radiação de micro-ondas em conjunto com o uso dos catalisadores clinopetilolita, $H_3PW_{12}O_{40}$ e nanopartículas de $Fe_2O_3$ é descrita. Neste trabalho, a condensação de cloridrato de hidroxilamina, acetato de sódio, acetoacetato ou benzoilacetato de etila e aldeídos apropriados pelo emprego dos catalisadores forneceu 5(4*H*)-isoxazolona em etapa única. A quantidade de catalisador, efeito de temperatura e reutilização dos catalisadores foram monitorados. Entre os catalisadores, o catalisador de nanopartículas de $Fe_2O_3$ apresentou melhor desempenho que os demais do ponto de vista de rendimento e tempo de reação. Os presentes protocolos oferecem várias vantagens, tais como tempo de reação curto, rendimento razoável, condição de reação suave e fácil reciclagem dos catalisadores.

A quick and solvent-free approach involving the exposure of neat reactants to microwave irradiation in conjunction with the use of clinoptilolite, $H_3PW_{12}O_{40}$ and $Fe_2O_3$ nanoparticle catalysts is described. In this work, condensation of hydroxylamine hydrochloride, sodium acetate, acetoacetic or benzoyl acetic ethyl ester and appropriate aldehydes by employing catalysts gave 5(4*H*)-isoxazolone only in one step. Catalyst amount, temperature effects and catalysts reusability were monitored. Among the catalysts, $Fe_2O_3$ nanoparticles had better performance than other catalysts from viewpoint of yield and reaction time. The present protocol offers several advantages, such as short reaction time, reasonable yield, mild reaction condition and recycling catalysts with a very easy workup.

**Keywords:** $Fe_2O_3$ nanoparticles, clinoptilolite, HPA, 5(4*H*)-isoxazolone, multicomponent reactions

## Introduction

Heterocyclic compounds are acquiring more importance in recent years due to their pharmacological activities.[1] Nitrogen, sulfur, oxygen containing five/six membered heterocyclic compounds have occupied enormous significance in the field of medicinal chemistry.[2,3] Oxazoles play very important role in the manufacturing process of various biologically active drugs as anti-cancer,[4] anti-microbial, anti-diabetic and anti-obesity.[5,6]

5-Isoxazolone derivatives have been associated with diverse pharmacological activities and they have been used in the dye chemistry.[7-10] Recently, heterogeneous catalysts have attracted the attention of researchers due to their economic and industrial significance and published reports indicate that they scored over homogeneous catalysts. Amongst various heterogeneous catalysts, heteropolyacids (HPAs), zeolites and nanoscale catalysts are the most attractive ones.[11]

Heteropolyacids are very interesting solid acid catalysts and they can act as green and ecofriendly catalysts.[12] Catalysis by HPAs and related compounds is a field of increasing importance in worldwide. The reactions, in which they can

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be used from dehydration, cyclization and esterification up to amine oxidation or olefin epoxidation, may find wide applications in the field of industrial chemical productions, such as fragrances, pharmaceuticals and foods.[13-19] Clinoptilolite $[(Na,K,Ca)_3Al_3(Al,Si)_2Si_{13}O_{36}\text{-}12H_2O]$ is one of the most useful natural zeolites. Clinoptilolite is a aluminosilicate framework, whose structure is characterized by cavities and channels, where exchangeable cations and water molecules are hosted.[20] These structural features are responsible for the wide industrial applications of zeolites as catalysts and selective absorbers.[21-25] They are used in many applications such as chemical sieves,[26] gas absorbers[27] and feed additives,[28] odor control agents and as water filters for municipal and residential drinking water and aquariums.[29] They can easily absorb ammonia and other toxic gases from air and water, and thus can be used as filters, for health reasons and for odor removal.[30] Metal oxide promoted reactions at heterogeneous conditions is a proficient field of chemistry which is highlighted by the use of various nanosized catalysts.[31-33] Metal oxide surfaces exhibit both acid and base properties. These dualities make metal oxides excellent adsorbents and activators of organic compounds. The promising factors which govern the catalytic activity of metal oxides are their metal cation nature, morphology, particle size and surface area. Recent developments on the nanoscience have provided great opportunity for the surface modification and chemical composition of nanosized metal oxides.[34-37]

$H_3PW_{12}O_{40}$, clinoptilolite and $Fe_2O_3$ nanoparticles were selected as catalysts because there are no reports on their use for multicomponent synthesis of 5(4*H*) isoxazolone.

## Experimental

### Material and methods

Melting points were obtained on a Gallenkamp melting point apparatus. Infrared (IR) spectra were recorded on a Mattson 1000 FT-IR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker DRX-500 Avance spectrometer using tetramethylsilan (TMS) as an internal standard. Mass spectra were obtained by Shimadzu QP 1100EX. The microanalyses for C, H and N were performed on a Perkin-Elmer elemental analyzer. The used commercial microwave reactor was an Ethos 1600 Microwave Lab Station (Italy). All reagents and solvents were purchased from Merck Chemical Company except for γ-$Fe_2O_3$ which was bought from Nano Pars Lima Company. All materials were used without further purification. The size and structure of γ-$Fe_2O_3$ were also evaluated using transmission electron microscopy (Zeiss EM10 C Germany). TEM image shows that nanoparticle size is 40 nm with spherical morphology (Figure 1).

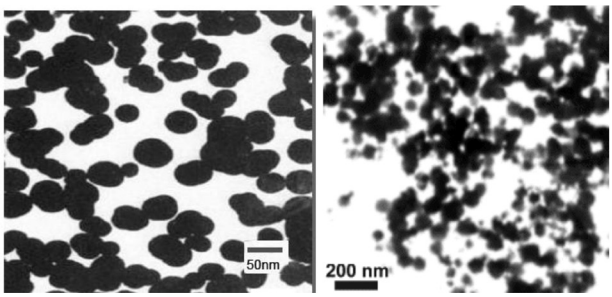



**Figure 1**. TEM image of γ-$Fe_2O_3$.

### Method A: synthesis of 5(4*H*)-isoxazolone, using $H_3PW_{12}O_{40}$

Hydroxylamine hydrochloride (1 mmol), sodium acetate (1 mmol), acetoacetic ester or benzoyl acetic ester (1 mmol), appropriate aldehydes (1 mmol) and $H_3PW_{12}O_{40}$ (5 mol%) were all poured into a beaker, the obtained suspension was irradiated by a microwave oven at a power output of 300 W for an appropriate time. After irradiation, the mixture was cooled down to room temperature, washed with cold water and filtered. Filtrate was evaporated under reduced pressure, and then the solid catalyst was collected, dried and reused. The filtered crud product was recrystallized from ethanol (96%).

### Method B: synthesis of 5(4*H*)-isoxazolone, using clinoptilolite

Hydroxylamine hydrochloride (1 mmol), sodium acetate (1 mmol), acetoacetic ester or benzoyl acetic ester (1 mmol), appropriate aldehydes (1 mmol) and clinoptilolite (2.5 mol%) were all irradiated by a microwave oven (300 W) for an appropriate time. After irradiation, the mixture was washed three times with chloroform and filtered. The filtrate was evaporated under reduced pressure to give isoxazolone which was then recrystallized from ethanol 96%. The filtered catalyst was repeatedly washed with chloroform and reused.

### Method C: synthesis of 5(4*H*)-isoxazolone, using nano $Fe_2O_3$

Nano $Fe_2O_3$ (1 mol%) was added to a mixture of hydroxylamine hydrochloride (1 mmol), sodium acetate (1 mmol), acetoacetic ester or benzoyl acetic ester (1 mmol) and appropriate aldehydes (1 mmol). The resulting mixture was then reacted in an orbital shaker incubator for the appropriate reaction time. After the reaction completion, as indicated by thin layer chromatography (TLC), the reaction mixture was diluted using ethanol 96% and then heated. Nanoparticles were separated from hot ethanol by filtration. The filtrate was cooled to give 5(4*H*)-isoxazolone. The crud product was then recrystallized from ethanol

96%. Filtered nanoparticles were washed twice with dichloromethane, dried and reused without any significant deactivation even after five runs.

3-Methyl-4-(1-phenylmethylidene)-5-isoxazolone (**3a**, $C_{11}H_9NO_2$)

Yellow crystal; mp 144-145 ºC; IR (KBr) ν/cm$^{-1}$ 1753, 1636; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.32 (s, 3H, $CH_3$); 7.47 (s, 1H, vinyl); 7.53 (dd, 2H, *J* 7.6, 7.4 Hz, ArH); 7.61 (dd, 1H, *J* 7.4, 7.4 Hz, ArH); 8.37 (d, 2H, *J* 7.5 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 12.0, 120.0, 129.4, 132.7, 134.2, 134.4, 150.5, 161.7, 168.3; MS *m/z* 187 (68%, M$^+$), 186 (100%), 128 (85%), 90 (65%).

4-{1-[4-(Dimethylamino)phenyl]methylidene}-3-methyl-5-isoxazolone (**3b**, $C_{13}H_{14}N_2O_2$)

Red crystal; mp 208-209 ºC; IR (KBr) ν/cm$^{-1}$ 1729, 1636; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.26 (s, 3H, $CH_3$); 3.17 (s, 6H, $2CH_3$); 6.73 (d, 2H, *J* 9.2 Hz, ArH); 7.23 (s, 1H, vinyl); 8.42 (d, 2H, *J* 8.5 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 12.1, 40.5, 111.6, 111.9, 121.9, 138.0, 149.6, 154.7, 162.0, 170.5; MS *m/z* 230 (100%, M$^+$), 215 (6%), 172 (11%), 144 (31%); CHN ($C_{13}H_{14}N_2O_2$) calc. (%) C (67.84), H (6.08), N (12.17); found (%) C (67.71), H (5.94), N (12.33).

4-[1-(4-Methoxyphenyl)methylidene]-3-methyl-5-isoxazolone(**3c**, $C_{12}H_{11}NO_3$)

Yellow crystal; mp 160-161 ºC; IR (KBr) ν/cm$^{-1}$ 1753, 1612; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.32 (s, 3H, $CH_3$); 3.96 (s, 3H, $OCH_3$); 7.05 (d, 2H, *J* 9 Hz, ArH); 7.38 (s, 1H, vinyl); 8.47 (d, 2H, *J* 9 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 12.1, 56.1, 115.1 116.8, 126.3, 137.4, 149.7, 161.7, 165.0, 169.2; MS *m/z* 217 (100%, M$^+$), 202 (8%), 159 (28%).

3-Methyl-4-[1-(4-methylphenyl)methylidene]-5-isoxazolone(**3d**, $C_{12}H_{11}NO_2$)

Yellow crystal; mp 132-133 ºC; IR (KBr) ν/cm$^{-1}$ 1753, 1636; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.32 (s, 3H, $CH_3$); 2.49 (s, 3H, $CH_3$); 7.35 (d, 2H, *J* 8.1 Hz, ArH); 7.43 (s, 1H, vinyl); 8.32 (d, 2H, *J* 8.2 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 12.0, 22.5, 118.9, 130.3, 130.4, 134.6, 146.1, 150.3, 161.6, 168.6; MS *m/z* 201(100%, M$^+$), 186 (67%), 145 (50%), 128 (81%); CHN ($C_{12}H_{11}NO_2$) calc. (%) C (71.66), H (5.47), N (6.96); found (%) C (71.78), H (5.46), N (6.81).

3-Methyl-4-[1-(2-thienyl) methylidene]-5-isoxazolone (**3e**, $C_9H_7NO_2S$)

Yellow brown crystal; mp 148-149 ºC; IR (KBr) ν/cm$^{-1}$ 1753, 1612; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.32 (s, 3H, $CH_3$); 7.29 (dd, 1H, *J* 4.9, 3.9 Hz, thienyl); 7.66 (s, 1H, vinyl); 7.96 (d, 1H, *J* 5 Hz, ArH); 8.13 (d, 1H, *J* 8.5 Hz, thienyl); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 11.9, 115.0, 129.3, 136.9, 139.6, 140.0, 141.9, 161.1, 169.1; MS *m/z* 193 (100%, M$^+$), 135 (32%), 108 (18%); CHN ($C_9H_7NO_2S$) calc. (%) C (55.96), H (3.62), N (7.25); found (%) C (55.85), H (3.57), N (7.39).

4-[1-(4-Fluorophenyl)methylidene]-3-methyl-5-isoxazolone (**3f**, $C_{11}H_8NO_2F$)

Yellow crystal; mp 139-140 ºC; IR (KBr) ν/cm$^{-1}$ 1727, 1623; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.31 (s, 3H, $CH_3$); 7.24 (dd, 2H, *J* 8.5, 8.5 Hz, ArH); 7.42 (s, 1H, vinyl); 8.47 (dd, 2H, *J* 8.38, 5.58 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 12.0, (116.8, 117.0 $^2J_{CF}$ 22.01 Hz), 119.6, 129.29, 137.1, 137.2, 148.7, 161.5, (167.4, 168.4 $^1J_{CF}$ 131.05 Hz); MS *m/z* 205 (100%, M$^+$), 146 (78%), 147 (54%), 108 (39%), 120 (35%); CHN ($C_{11}H_8NO_2F$) calc. (%) C (64.41), H (3.90), N (6.83); found (%) C (64.28), H (3.85), N (6.75).

3-Phenyl-4-(1-phenylmethylidene)-5-isoxazolone (**3g**, $C_{16}H_{11}NO_2$)

Yellow crystal; mp 193-194 ºC; IR (KBr) ν/cm$^{-1}$ 1753, 1636; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.29 (dd, 2H, *J* 7.7, 7.5 Hz, ArH); 7.76-7.66 (m, 7H, vinyl, ArH), 8.37 (d, 2H, *J* 7.6 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 119.2, 127.8, 129.2, 129.4, 129.7, 131.5, 132.8, 134.4, 134.6, 153.2, 164.4, 168.5; MS *m/z* 249 (100%, M$^+$), 205 (57%), 191 (65%), 102 (100%).

4-{1-[4-(Dimethylamino)phenyl]methylidene}-3-phenyl-5-isoxazolone (**3h**, $C_{18}H_{16}N_2O_2$)

Red crystal; mp 142-143 ºC IR (KBr) ν/cm$^{-1}$ 1729, 1636; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 3.19 (s, 6H, $2CH_3$); 6.74 (d, 2H, *J* 9.2 Hz, ArH); 7.41 (s, 1H, vinyl); 7.57-7.63 (m, 5H, ArH), 8.42 (d, 2H, *J* 8.1 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 40.6, 110.4, 111.9, 122.2, 129.1, 129.3, 129.4, 130.7, 138.4, 152.1, 154.9, 165.2, 170.8; MS *m/z* 292 (100%, M$^+$), 234 (5%), 144 (18%), 117 (30%).

4-[1-(4-Methoxyphenyl)methylidene]-3-phenyl-5-isoxazolone (**3i,** $C_{17}H_{13}NO_3$)

Yellow crystal; mp 166-167 ºC; IR (KBr) ν/cm$^{-1}$ 1753, 1612; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 3.96 (s, 3H, $OCH_3$); 7.04 (d, 2H, *J* 8.9 Hz, ArH); 7.56 (s, 1H, vinyl); 7.70-7.64 (m, 5H, ArH), 8.45 (d, 2H, *J* 8.9 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 56.2, 115.1, 115.8, 126.4, 128.2, 129.2, 129.6, 131.2, 137.7, 152.5, 164.8 165.3, 169.4; MS *m/z* 279 (100%, M$^+$), 221 (14%), 132 (16%).

4-[1-(4-Methylphenyl)methylidene]-3-phenyl-5-isoxazolone (**3j,** $C_{17}H_{13}NO_2$)

Yellow crystal; mp 181-182 ºC; IR (KBr) ν/cm$^{-1}$ 1753, 1636; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.49 (s, 3H, $CH_3$); 7.36 (d, 2H, *J* 8.2 Hz, ArH); 7.59-7.65 (m, 6H, vinyl, ArH), 8.30 (d, 2H, *J* 8.2 Hz, ArH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 2.5, 118.0, 128.0, 129.2, 129.7, 130.3, 130.5, 131.4, 134.8, 146.4, 153.2, 164.6, 168.8; MS *m/z* 263 (100%, $M^+$), 248 (44%), 219 (49%), 205 (44%), 116 (68%).

3-Phenyl-4-[1-(2-thienyl)methylidene]-5-isoxazolone (**3k**, $C_{14}H_9NO_2S$)

Yellow crystal; mp 189-190 ºC; IR (KBr) ν/cm$^{-1}$ 1753, 1612; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.31 (dd, 1H, *J* 4.6, *J* 4.5 Hz, thienyl); 7.59-7.66 (m, 5H, ArH ), 7.83 (s, 1H, vinyl); 8.01 (d, 1H, *J* 5 Hz, thienyl); 8.11 (d, 1H, *J* 3.7 Hz, thienyl); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 113.9, 128.0, 128.9, 129.3, 129.8, 131.4, 137.1, 140.6, 142.0, 142.5, 163.8, 169.4; MS *m/z* 255 (100%), 211 (42%), 105 (97%).

## Results and Discussion

In this work, it is reported good catalytic activities for HPA, clinoptilolite and nano $Fe_2O_3$ for the synthesis of 5(4H) isoxazolone by microwave irradiation using a commercial microwave reactor. Initially, the reaction of benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), sodium acetate (1 mmol) and acetoacetic ester (1 mmol) was chosen as a model of reaction for the optimization of catalyst amount (Table 1). Results summarized in Table 1 show the influence of the catalyst concentration on the reaction process. 5 mol% HPA, 2.5 mol% clinoptilolite and 1 mol% nano $Fe_2O_3$ gave maximum yields. It is noteworthy to mention that in the absence of the catalyst, only small amounts of the product were obtained and the microwave irradiation decreased just the reaction time. These results indicate that the catalysts exhibit a high catalytic activity in this transformation.

During the optimization of the reaction conditions, the effect of temperature was monitored. The product yields were not good even after 5 h under thermal heating condition but the yields were excellent by microwave irradiation. Thus, microwave irradiation has been employed to reduce the reaction time and rate enhancement, and to increase yields (Table 2). Reusability of the catalysts was examined under identical reaction conditions. The recycled catalysts were used five times to obtain 5(4*H*)-isoxazolone without appreciable decreasing in yields (Table 3).

**Table 1**. Influence of the catalyst concentration on the synthesis of **3a**

| entry | Catalyst / mol% | Yield / % (a/b/c) |
|---|---|---|
| 1 | 1 | 48/44/75 |
| 2 | 2.5 | 56/60/71 |
| 3 | 5 | 63/52/64 |
| 4 | 10 | 60/56/61 |
| 5 | 15 | 55/51/50 |
| 6 | no catalyst | 14 |

Reactions were performed using: hydroxylamine hydrochloride (1 mmol), sodium acetate (1 mmol), acetoacetic ester (1 mmol ), benzaldehyde (1 mmol). a: $H_3PW_{12}O_{40}$ (5 mol%); b: clinotilolite (2.5 mol% ); c: nano $Fe_2O_3$ (1 mol%) under microwave irradiation at a power output of 300 W.

**Table 2.** Influence of the temperature on the synthesis of **3a**

| entry | Temperature / °C | Yield / % (a/b/c) |
|---|---|---|
| 1 | 25 | 20/10/25 |
| 2 | 40 | 23/15/33 |
| 3 | 60 | 34/22/52 |
| 4 | 90 | 45/36/55 |
| 5 | microwave (reaction time: Table 1) | 63/60/75 |

Reactions were performed using: hydroxylamine hydrochloride (1 mmol), sodium acetate (1 mmol), acetoacetic ester (1 mmol ), benzaldehyde (1 mmol). a: $H_3PW_{12}O_{40}$ (5 mol%); b: clinoptilolite (2.5 mol%); c: nano $Fe_2O_3$ (1 mol%) under thermal heating condition for 5h and microwave irradiation at a power output of 300 W.

**Table 3**. Reusability of catalysts for synthesis of **3a**

| Run | Yield / % (a/b/c) |
|---|---|
| 1 | 63/60/75 |
| 2 | 63/60/75 |
| 3 | 62/58/75 |
| 4 | 62/57/74 |
| 5 | 62/56/72 |

Reactions were performed using: hydroxylamine hydrochloride (1 mmol), sodium acetate (1 mmol), acetoacetic ester (1 mmol), aldehydes (1 mmol). a: $H_3PW_{12}O_{40}$ (5 mol%); b: clinoptilolite (2.5 mol%); c: nano $Fe_2O_3$ (1 mol%) under microwave irradiation at a power output of 300 W.

The results presented in Table 4 show the scope and generality of the methods (Scheme 1). One of the salient features of these methods is that electron poor or rich aldehydes give good yields and purities. These catalysts are the most attractive ones because of their flexibility in modifying the acid strength, environmental compatibility, low toxicity and experimental simplicity. From these, $Fe_2O_3$ nanoparticle is the most promising catalyst because of its ease of handling, ease of recovery and high catalytic activities. This catalyst is highly preferred as it offers

**Table 4.** One-pot synthesis of 5(4*H*)-isoxazolone under microwave irradiation

| entry | R | R' | time / s a/b/c (d[38]/e[39]) | Yield / % a/b/c (d[38]/e[39]) | mp / °C |
|---|---|---|---|---|---|
| **3a** | $CH_3$ | $C_6H_5$ | 180/300/90 (–/12h) | 63/60/75 (–/65) | 144-145 (146-147)[39] |
| **3b** | $CH_3$ | $N,N(CH_3)_2$-$C_6H_4$ | 30/60/30 (–/–) | 89/80/90 (–/–) | 208-209 |
| **3c** | $CH_3$ | 4-$CH_3O$-$C_6H_4$ | 60/120/90 (–/–) | 88/77/90 (–/75) | 160-161 (180-181)[39] |
| **3d** | $CH_3$ | 4-$CH_3$- $C_6H_4$ | 90/180/ 90 (–/–) | 79/70 /63 (–/–) | 132-133 |
| **3e** | $CH_3$ | $C_4H_3S$ | 60/120/90 (–/–) | 85/76/72 (–/–) | 148-149 |
| **3f** | $CH_3$ | 4-F-$C_6H_4$ | 120/150/100 (–/–) | 89/81/97(–/–) | 139-140 |
| **3g** | Ph | $C_6H_5$ | 300/350/80 (70 min /3 h) | 57/45/61 (72/48) | 193-194 (193-194)[39] |
| **3h** | Ph | $N,N(CH_3)_2$-$C_6H_4$ | 60/90/60 (40 min/–) | 85/74/88 (87/–) | 179-180 (194-196)[38] |
| **3i** | Ph | 4-$CH_3O$-$C_6H_4$ | 60/90/90 (60 min/3 h) | 80/70/62 (77/60) | 166-167 (168-169)[39] |
| **3j** | Ph | 4-$CH_3$-$C_6H_4$ | 90/180/100 (50 min /–) | 65/57/75 (74/–) | 181-182 (189-191)[38] |
| **3k** | Ph | $C_4H_3S$ | 90/180/90 (80 min/–) | 78/68/67 (61/–) | 189-190 (226-228)[38] |

Reactions were performed using: hydroxylamine hydrochloride (1 mmol), sodium acetate (1 mmol), acetoacetic ester or benzoyl acetic ester (1 mmol), aldehydes (1 mmol). a: $H_3PW_{12}O_{40}$ (5 mol%); b: Clinoptilolite (2.5 mol% ); c: nano $Fe_2O_3$ (1 mol%) under microwave irradiation at a power output of 300 W; d: presented method in reference 38; e: presented method in reference 39.

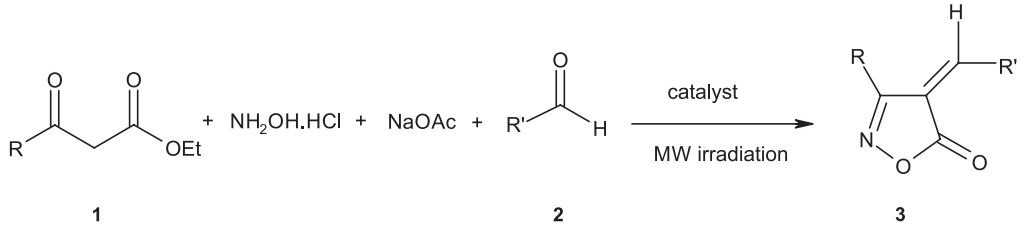
high surface area and low-coordinated sites which are responsible for the higher catalytic activities.

Further, a comparison to illustrate between our work and other methods for synthesis of 4-arylidene-5(4*H*)-isoxazolones in terms of yield and reaction rate is made. Recently Ablajan *et al.*[38] prepared some 4-arylidene-5(4*H*)-isoxazolone derivatives in the presence of pyridine just in one step. Yields are similar to ours but our reaction time is shorter. Donleavy *et al.*[39] also reported the synthesis of 4-arylidene-5(4*H*)-isoxazolone derivatives in two steps. The reaction takes longer time to be complete and yields are lower than ours (Table 4).

Plausible mechanism for the synthesis of 5(4*H*)-isoxazolone has been proposed in Scheme 2. The acetoacetic ester or benzoyl acetic ester was first activated in the presence of the catalysts. The reaction between this intermediate and hydroxylamine produced oxime (A). Activation of oxime by the catalyst and intramolecular reaction provided (B). This, in effect on subsequent reaction and activated aldehyde in the presence of the catalyst, produced the 5(4*H*) isoxazolone. These three catalysts accelerate the reaction by carbonyl group activation. This idea is supported by performing the reaction in the absence of catalysts. Without any catalyst, only small amounts of the product were obtained even after long period of time.

## Conclusions

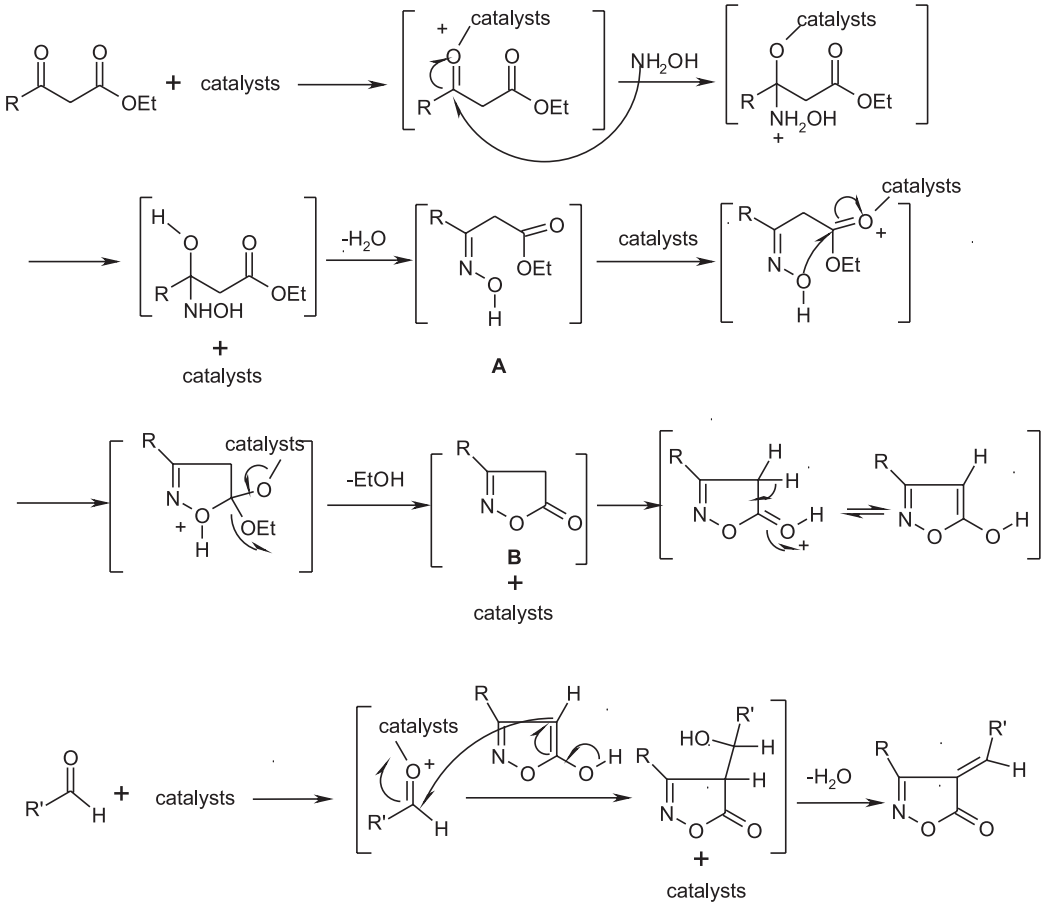
This procedure offers several advantages including mild reaction conditions, cleaner reaction, and satisfactory yields of products, as well as simple experimental and isolating procedures, which in effect make them useful and attractive protocols for the synthesis of these compounds. The salient features are short reaction times, good conversions, solvent-free conditions, and the use of easily recyclable catalysts without the loss of considerable catalytic activity. This method is also applicable for a wide range of substrates.




1 2 3

Catalysts: $H_3PW_{12}O_{40}$, clinotilolite, nano $Fe_2O_3$

**Scheme 1**. Synthesis of 5(4*H*)-isoxazolone by using $H_3PW_{12}O_{40}$, clinotilolite and nano $Fe_2O_3$ under microwave irradiation.




**Scheme 2**. Plausible mechanism for synthesis of 5(4*H*)-isoxazolone.

## Supplementary Information

Supplementary information (spectra of synthesized compounds) is available free of charge at http://jbcs.sbq.org.br as a PDF file.

## Acknowledgements

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# *Supplementary Information*

## Nano $Fe_2O_3$, Clinoptilolite and $H_3PW_{12}O_{40}$ as Efficient Catalysts for Solvent-Free Synthesis of 5(4*H*)-Isoxazolone under Microwave Irradiation Conditions

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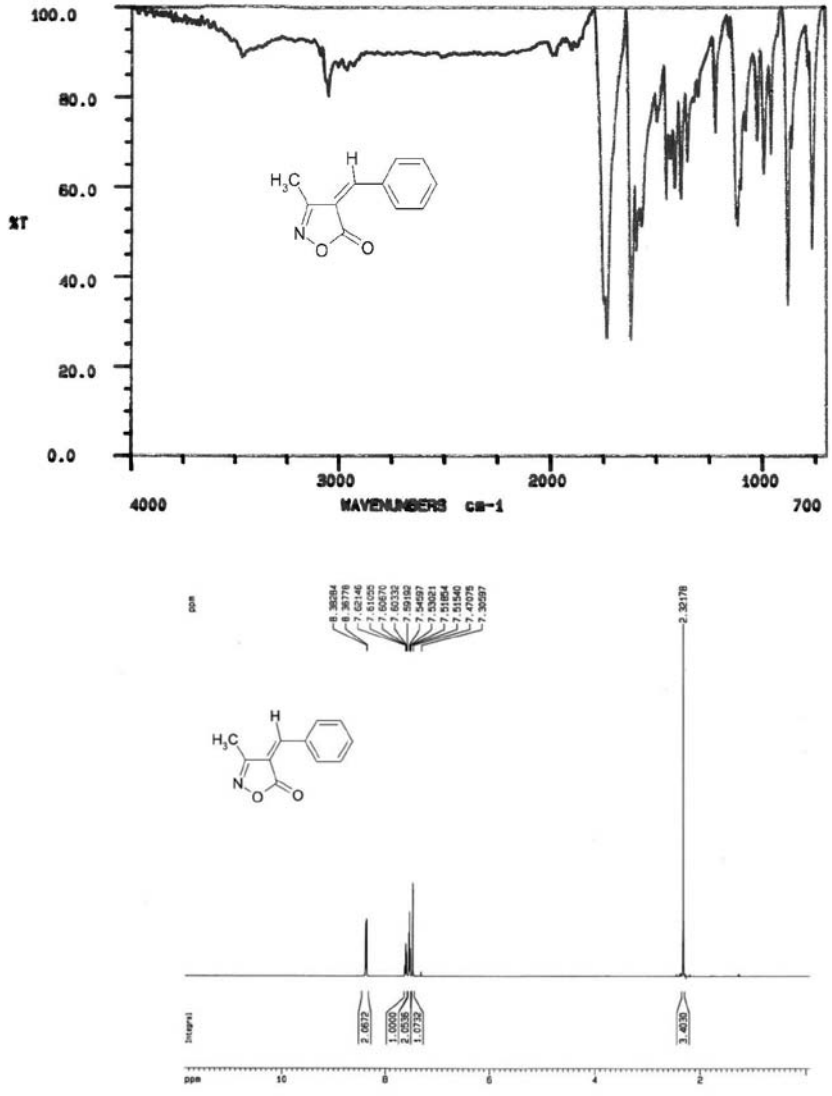


**Figure S1**. IR spectrum and $^1$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3a**.

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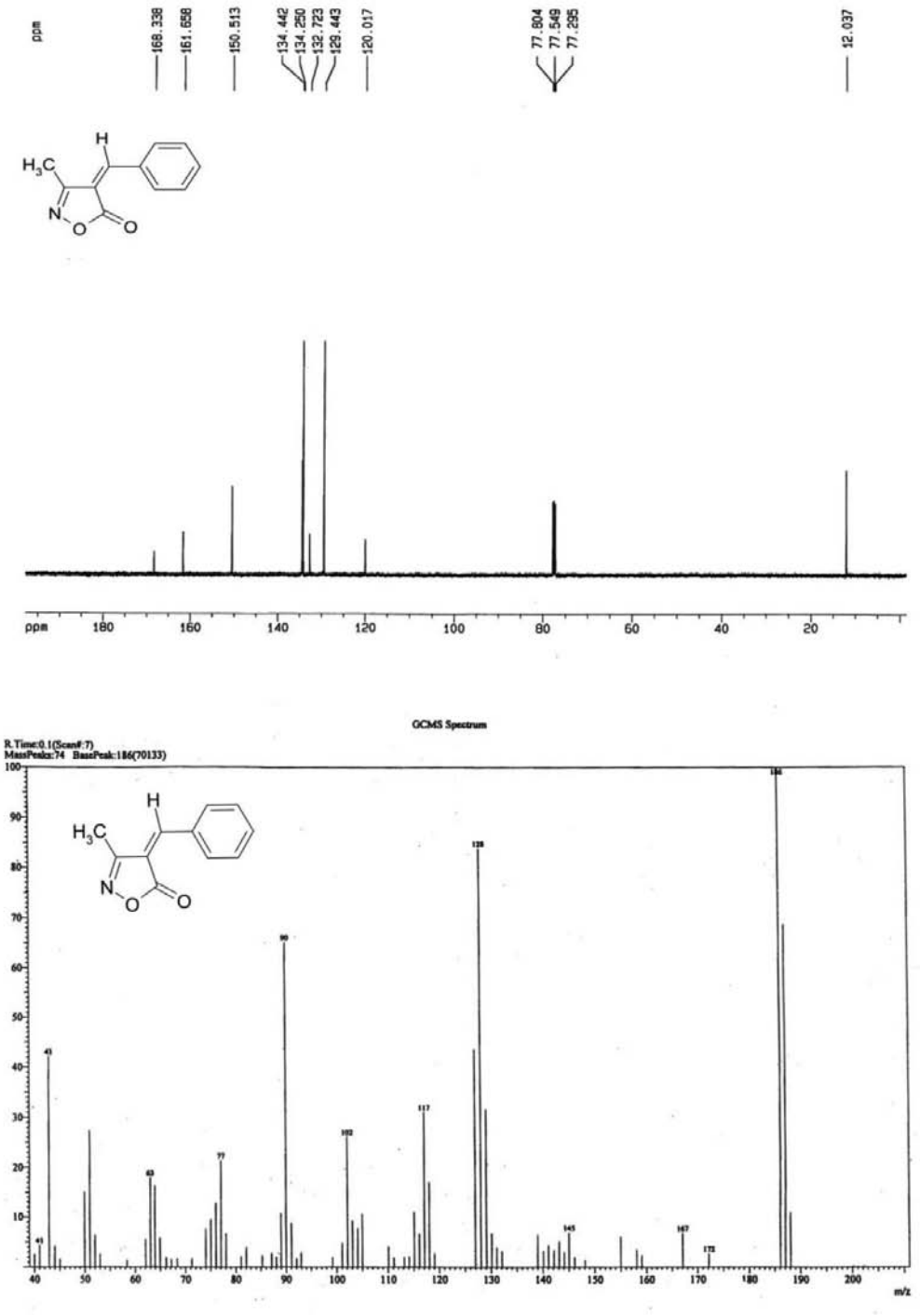
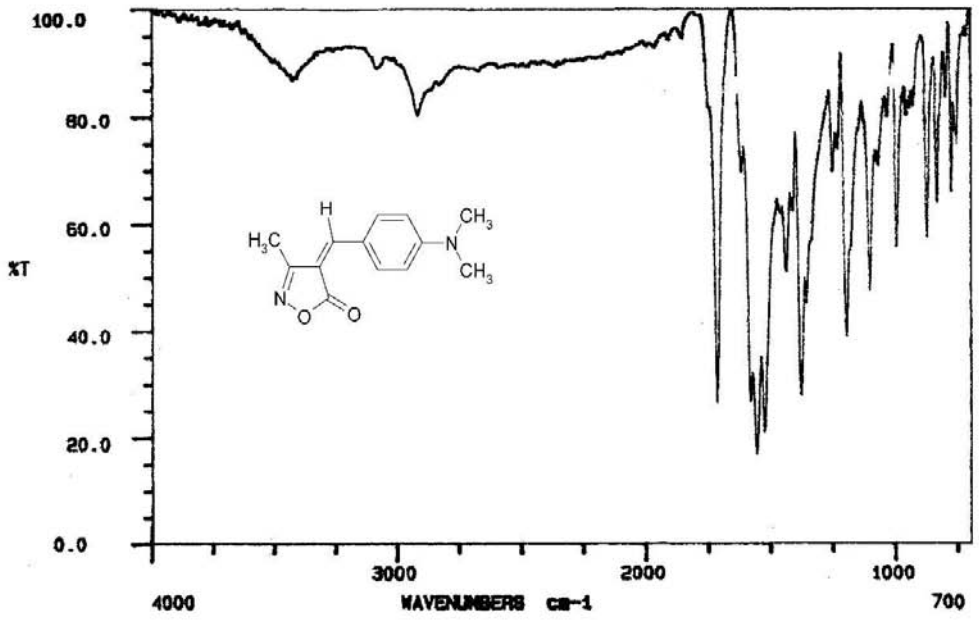



**Figure S2**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3a**.



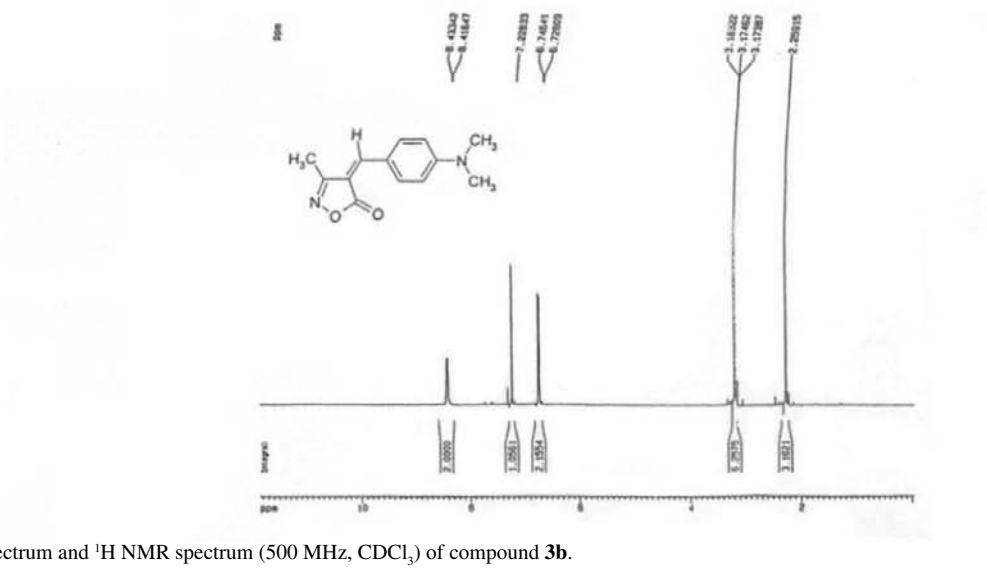




**Figure S3**. IR spectrum and $^1$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3b**.

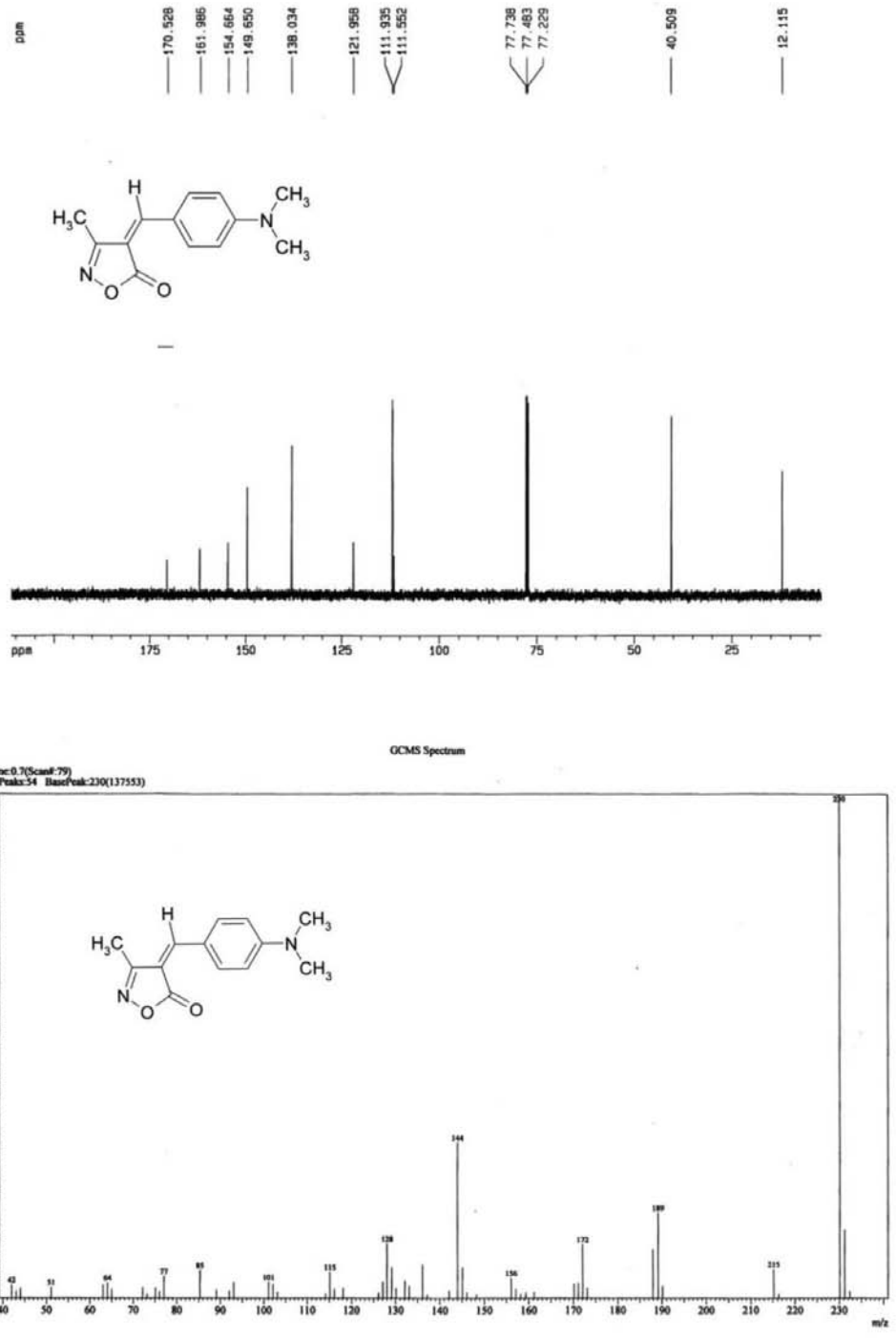
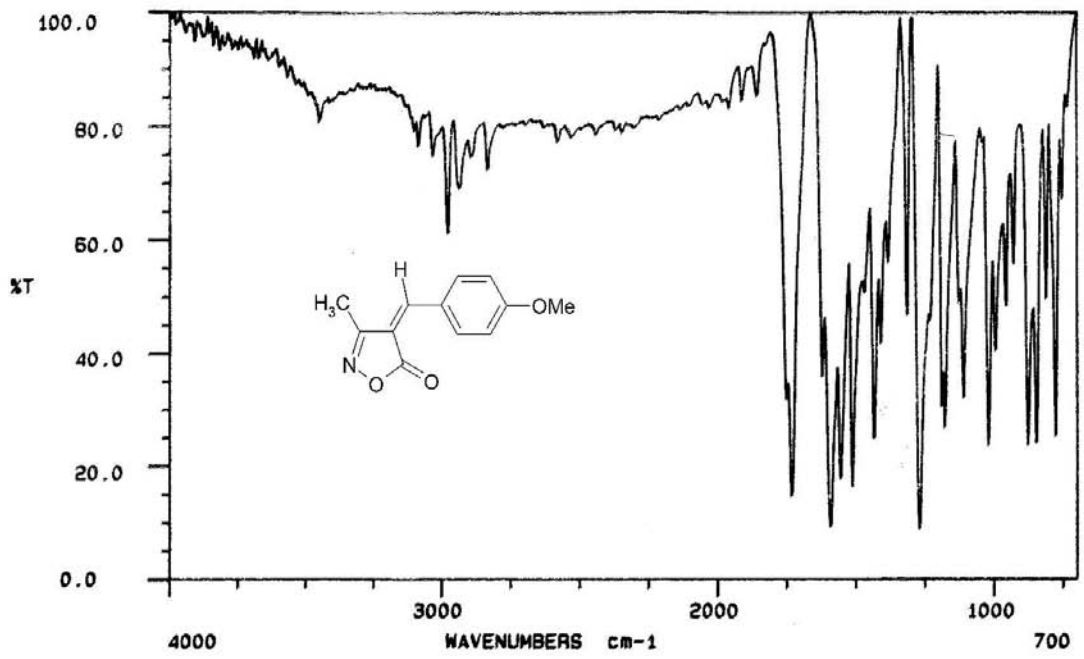



**Figure S4**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3b**.



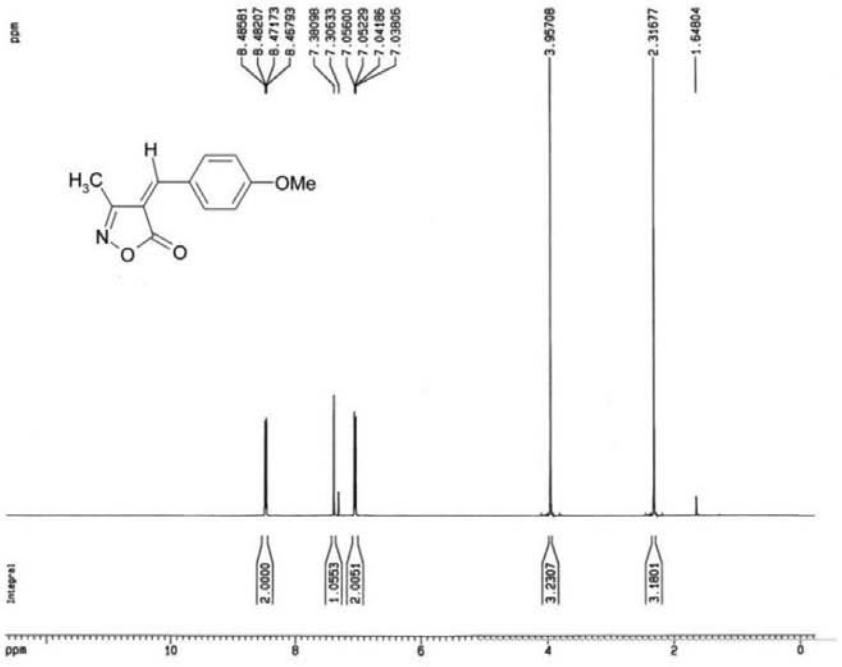




**Figure S5**. IR spectrum and $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3c**.

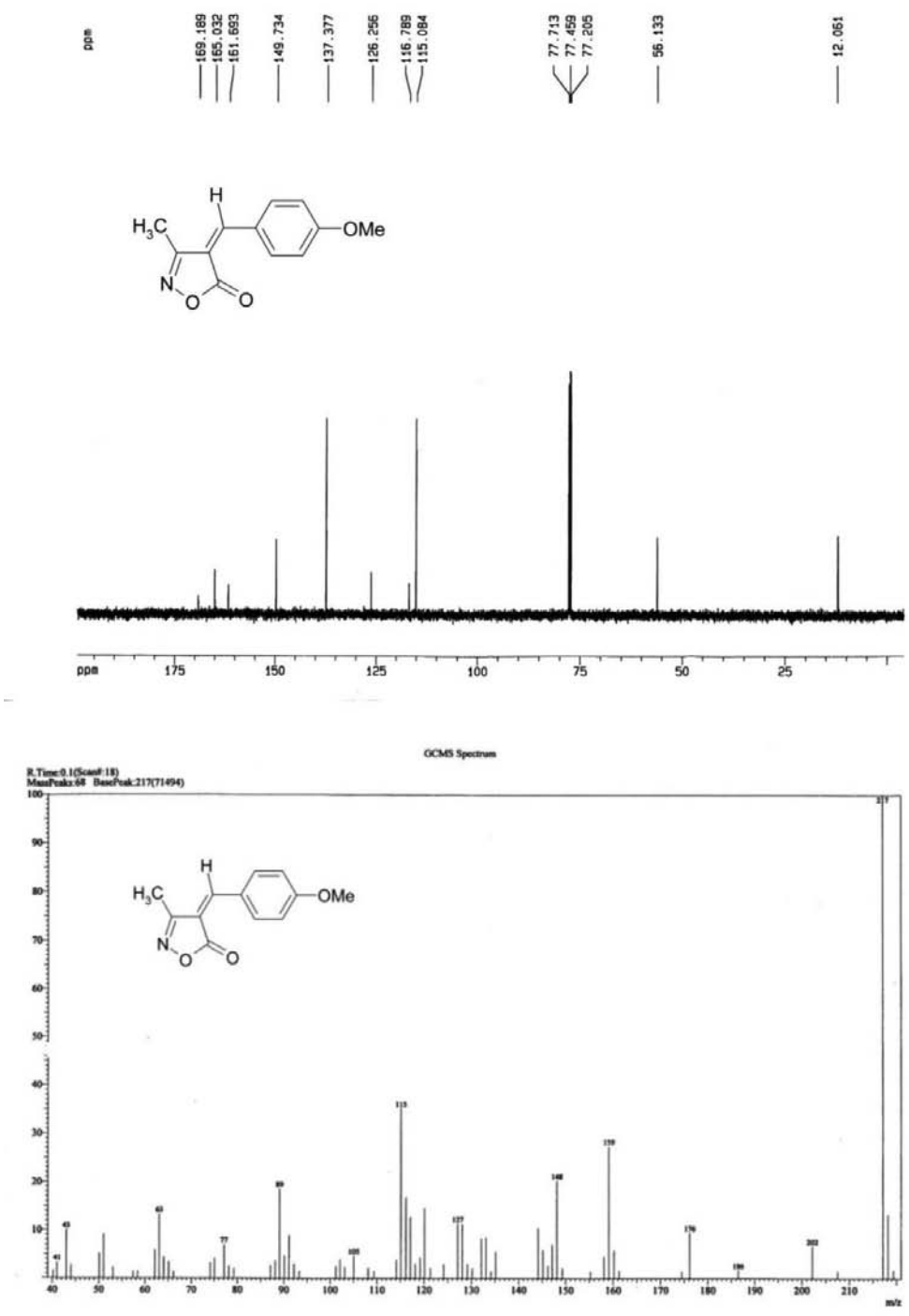



**Figure S6**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3c**.

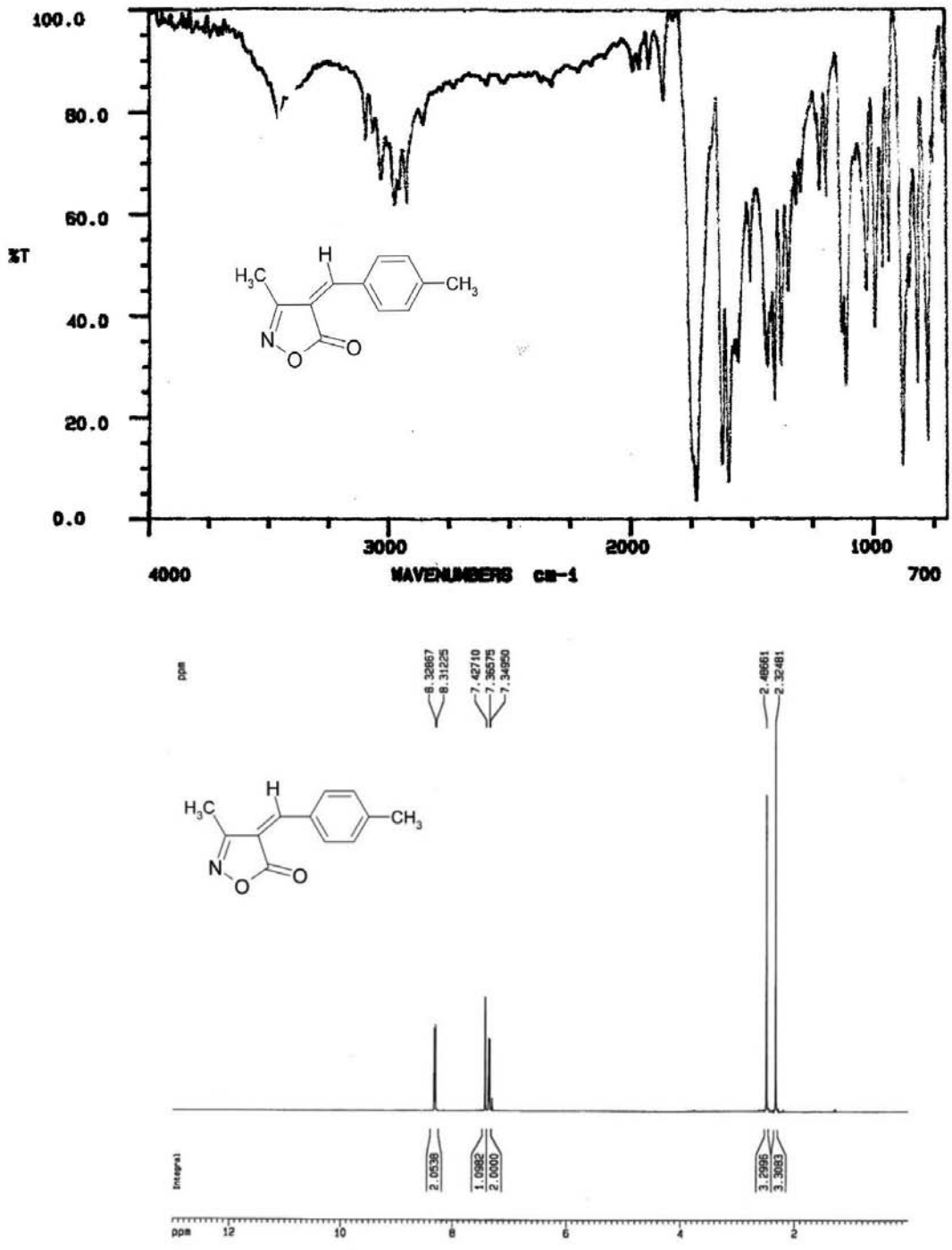



**Figure S7**. IR spectrum and $^1$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3d**.

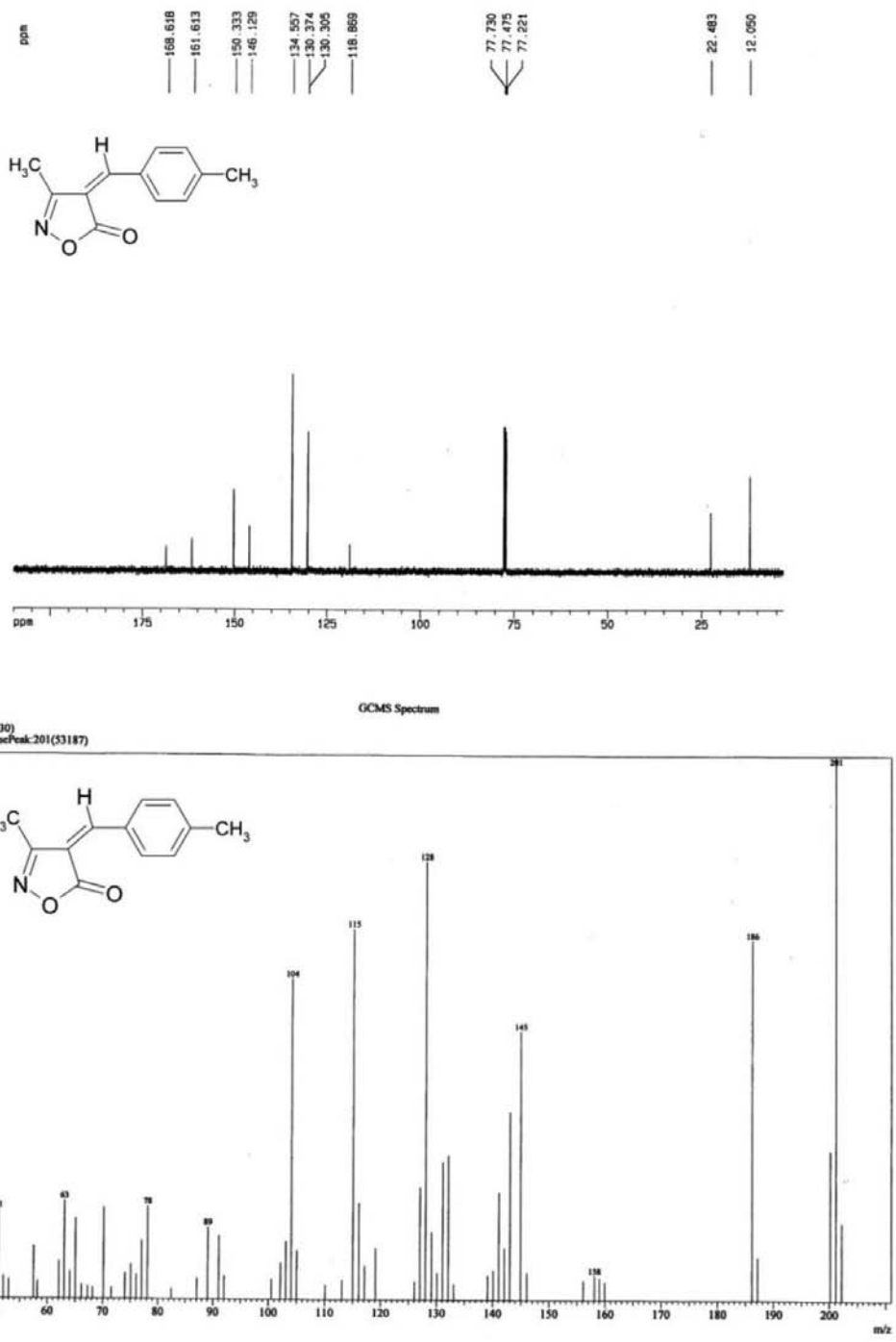



**Figure S8**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3d**.

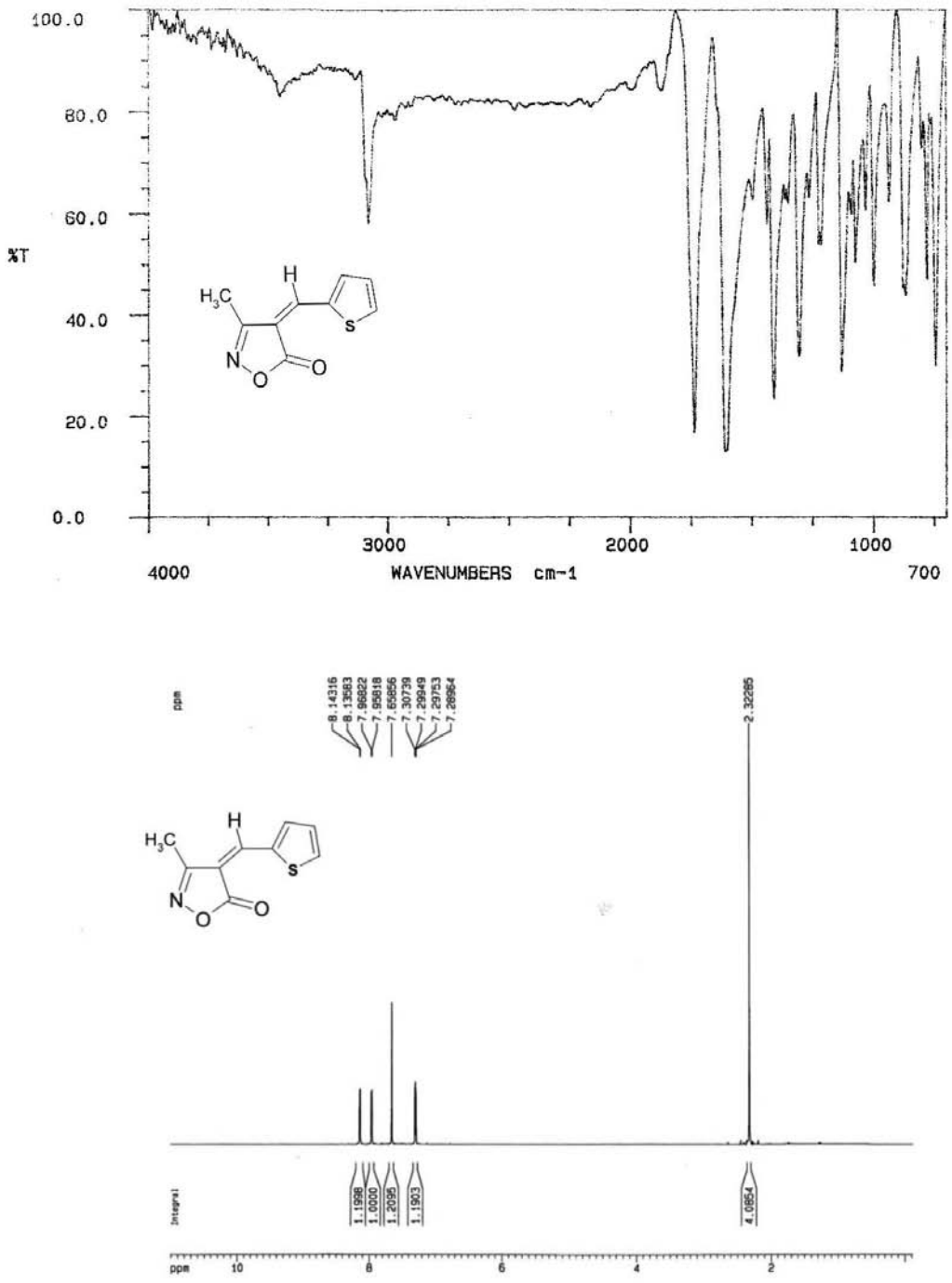



**Figure S9**. IR spectrum and $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3e**.

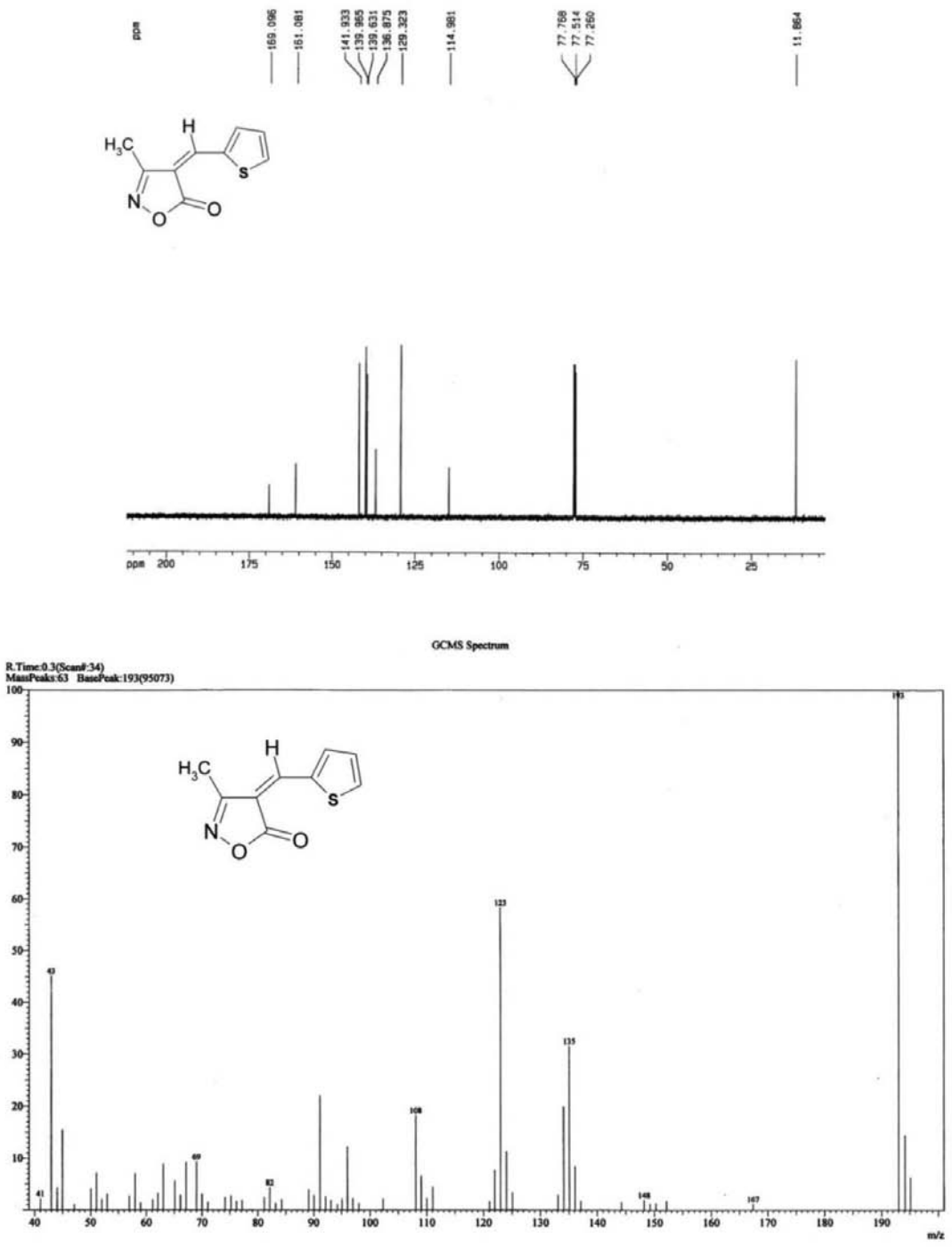
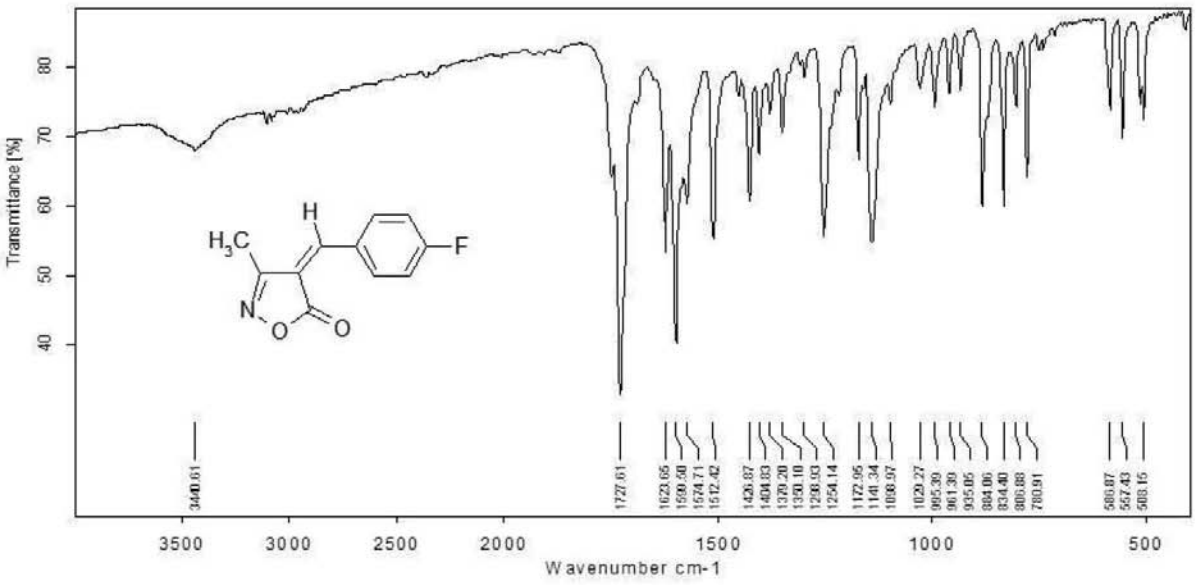



**Figure S10**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3e**.



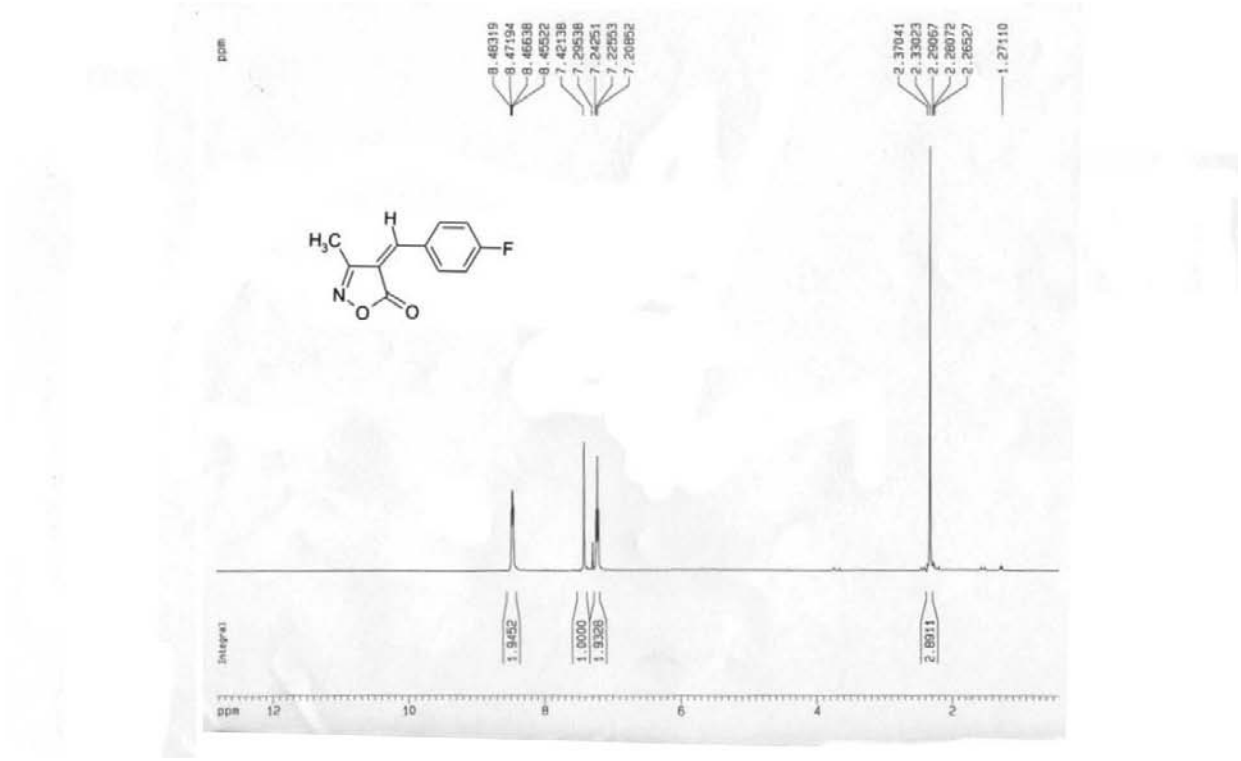




**Figure S11**. IR spectrum and $^1$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3f**.

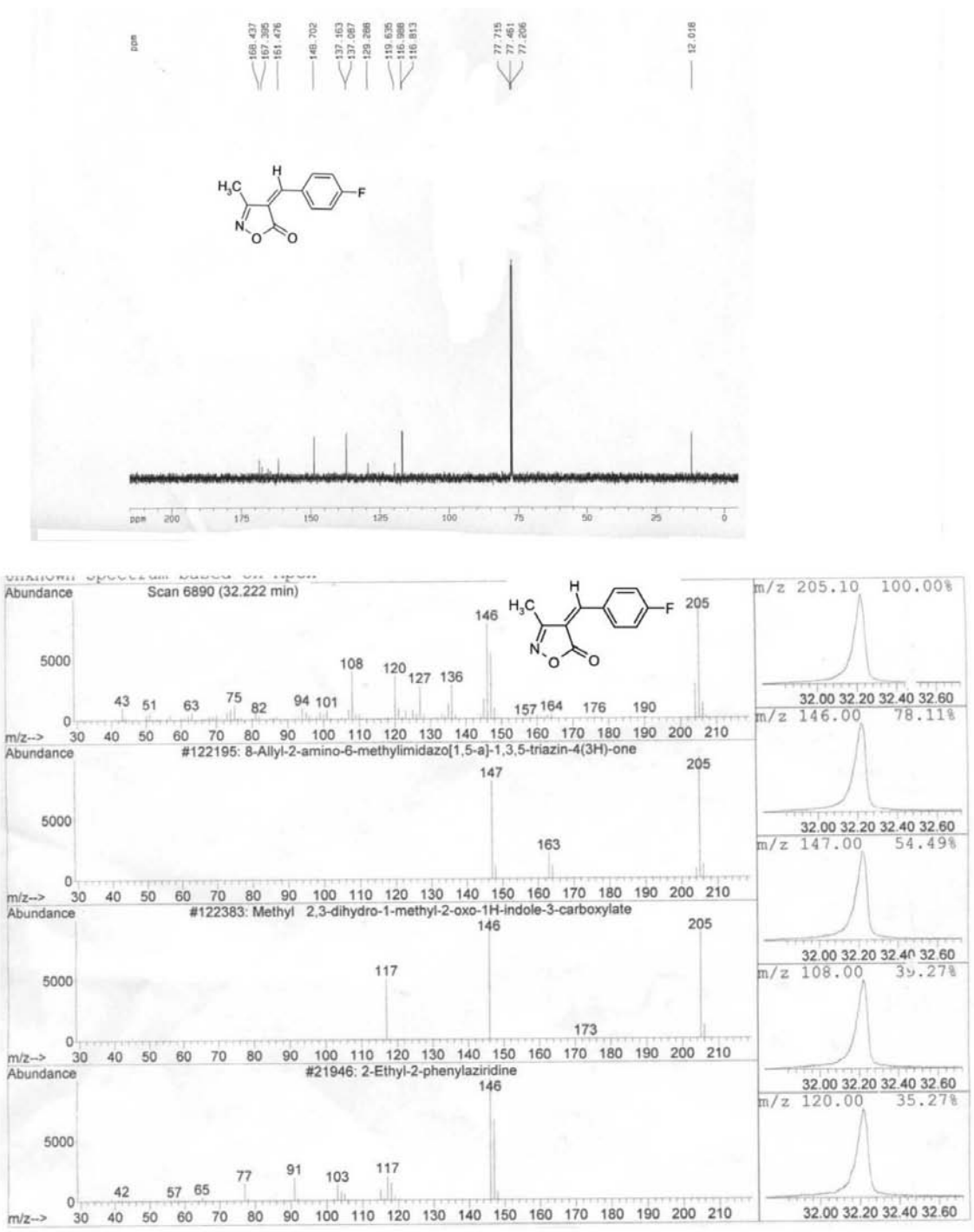
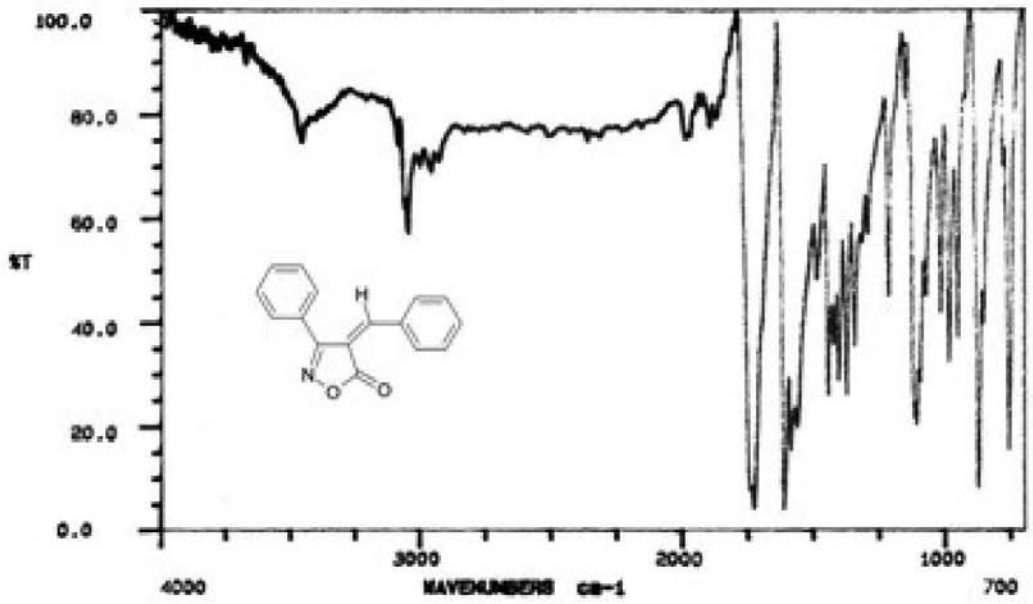



**Figure S12**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3f**.



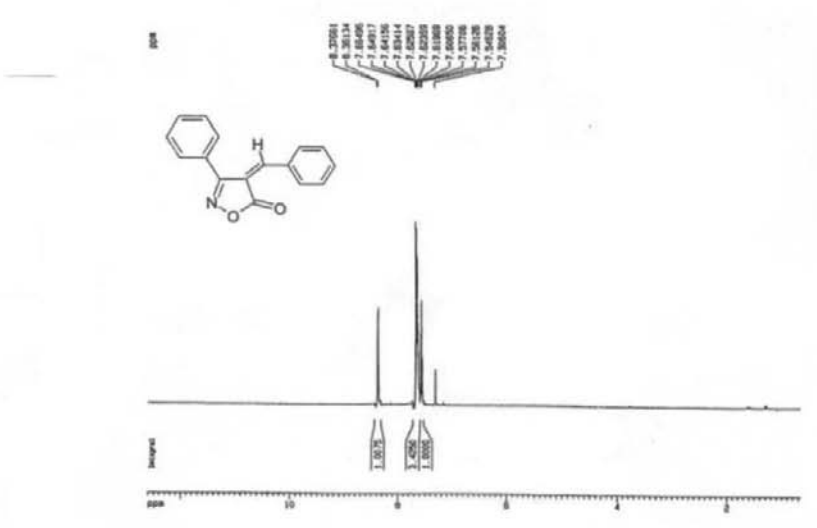




**Figure S13**. IR spectrum and $^{1}H$ NMR spectrum (500 MHz, $CDCl_3$) of compound **3g**.

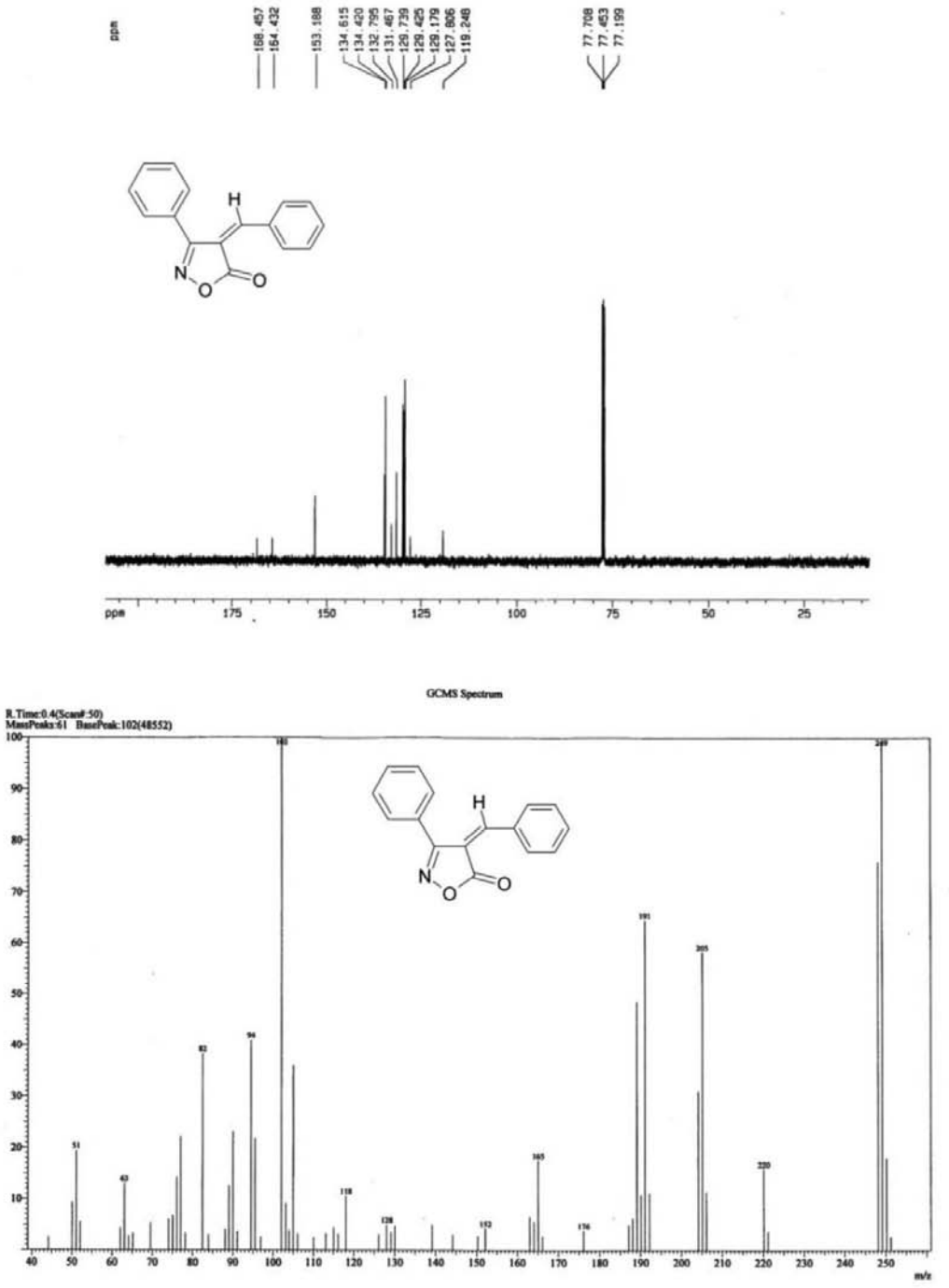
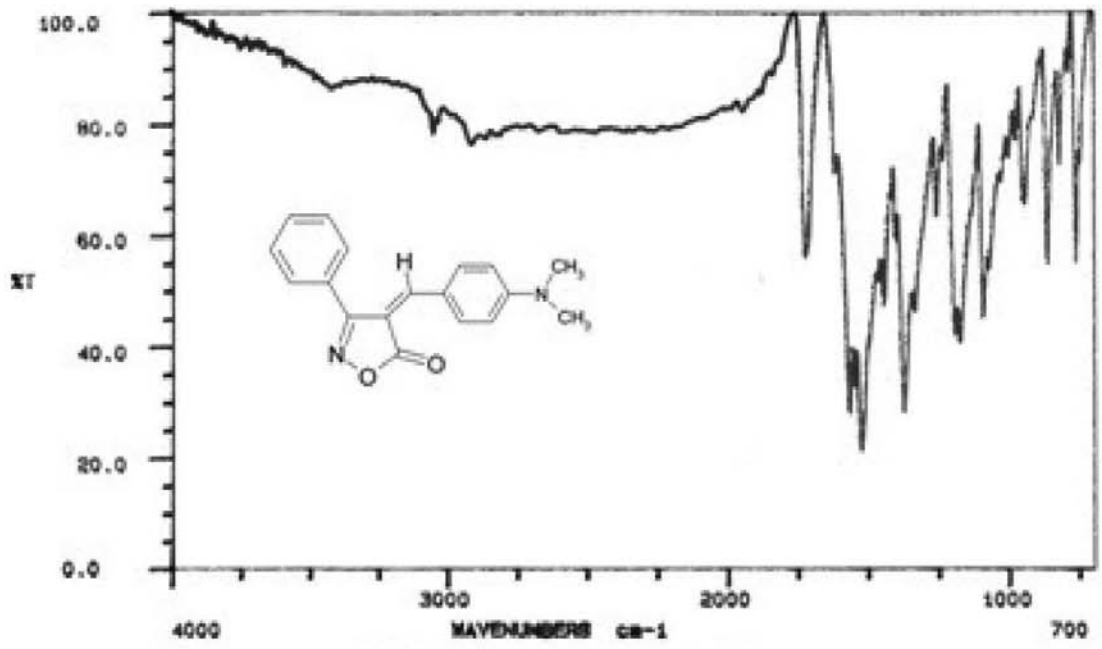



**Figure S14**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3g**.



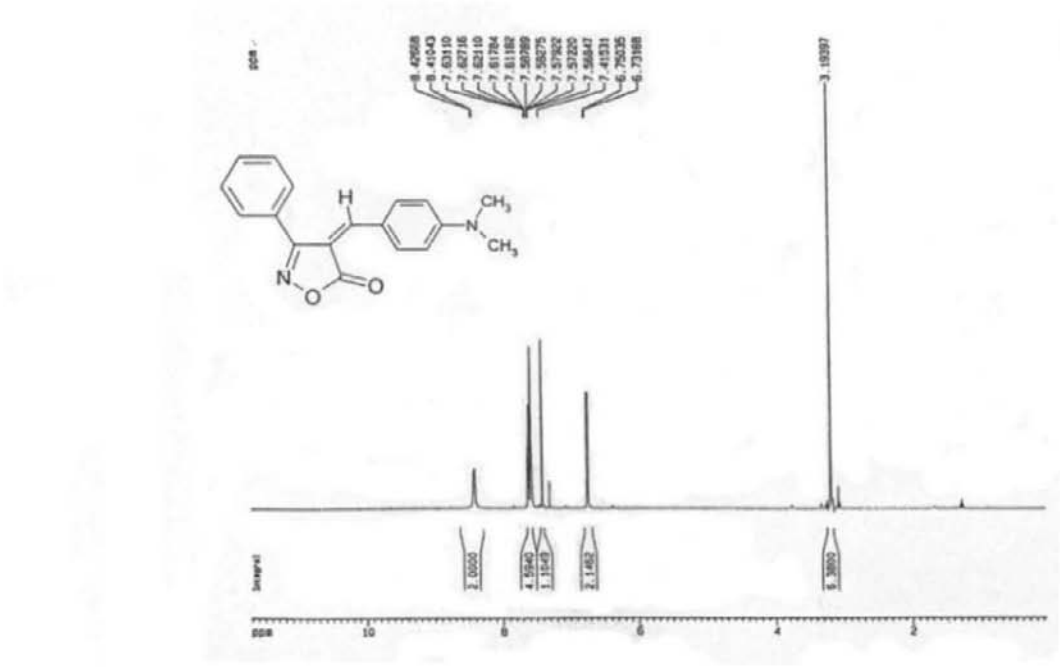



**Figure S15**. IR spectrum and $^1$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3h**.

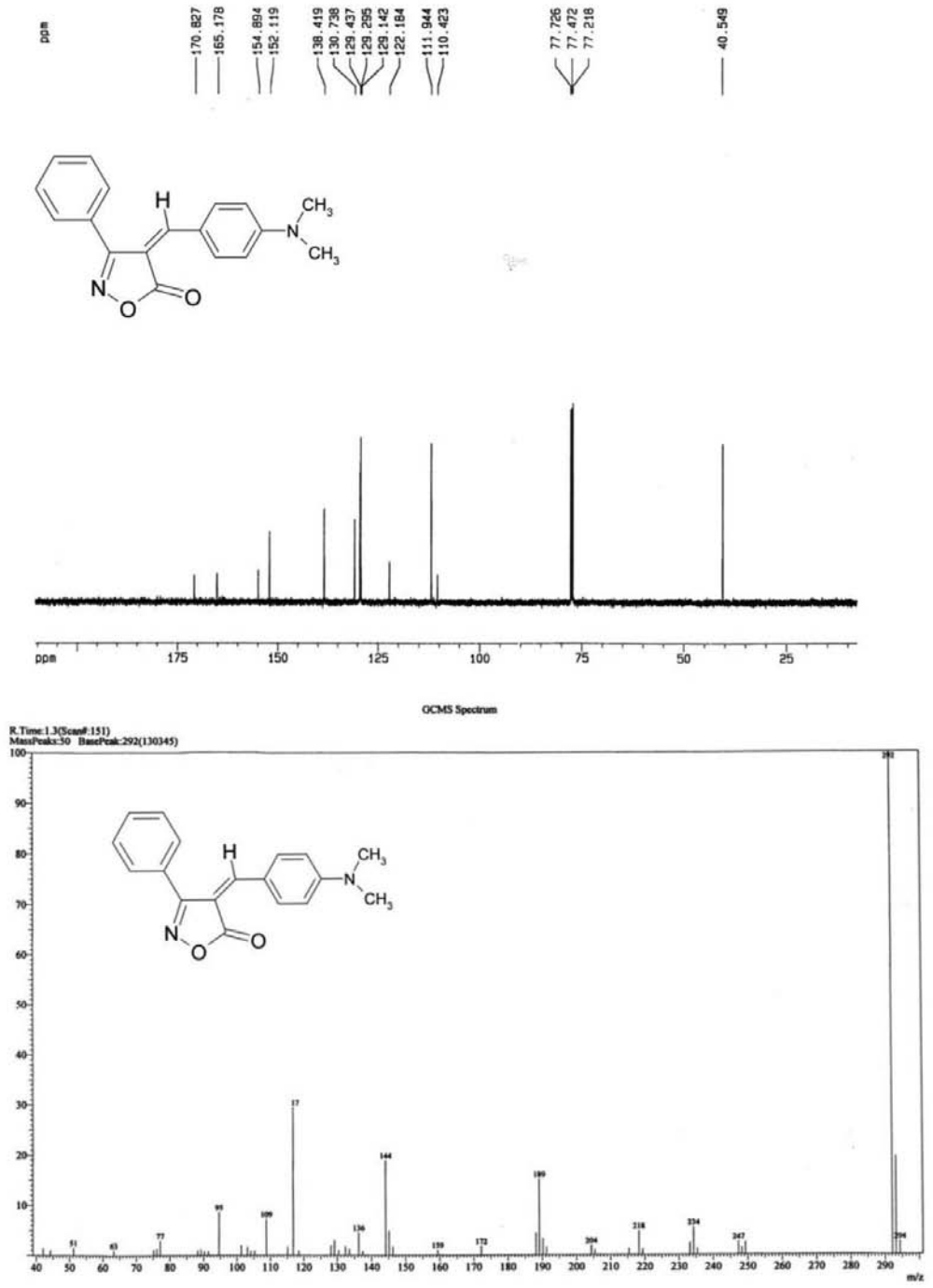
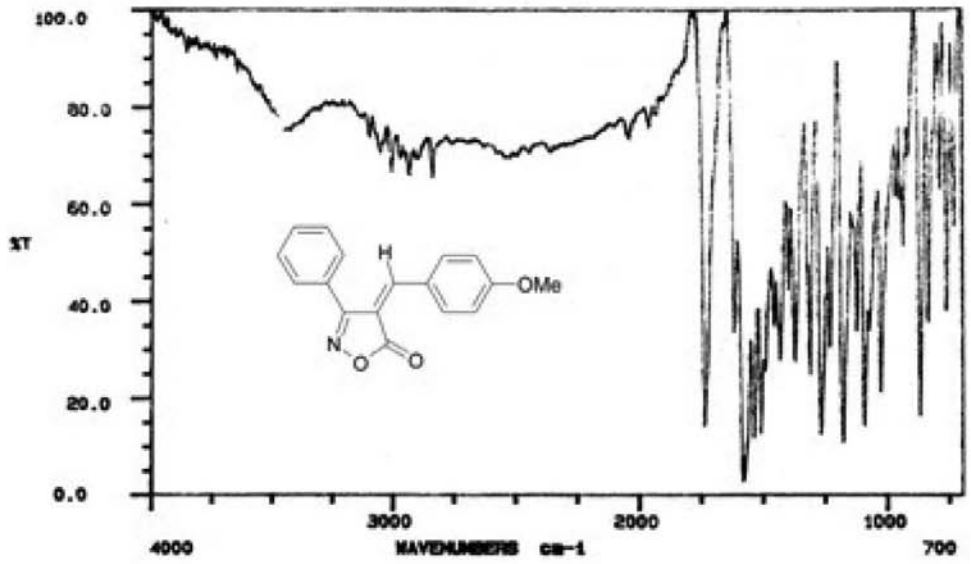



**Figure S16**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3h**.



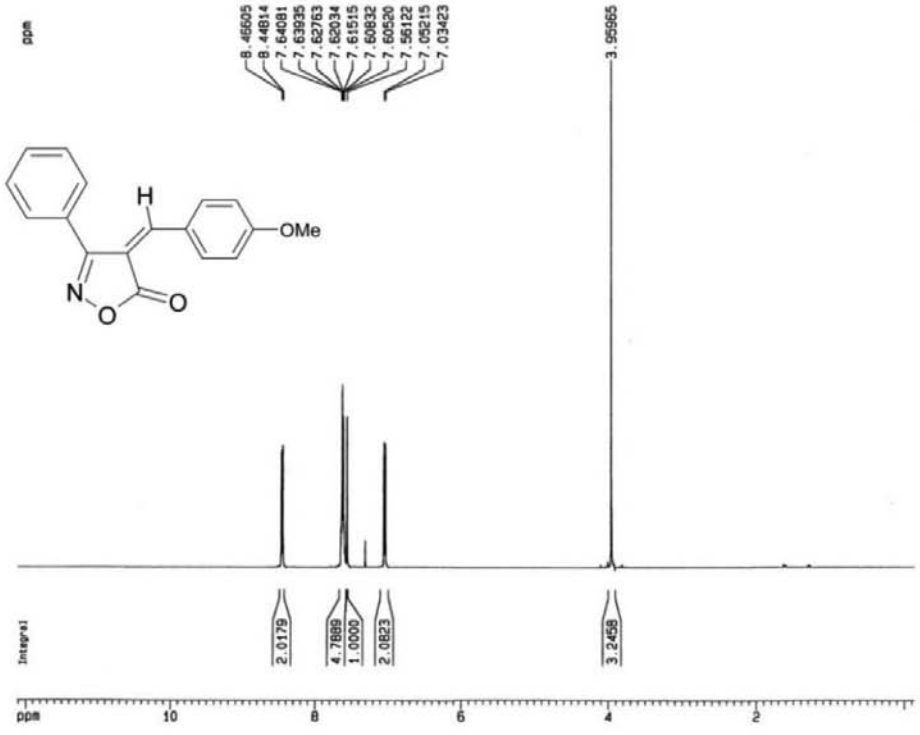




**Figure S17**. IR spectrum and $^1$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3i**.

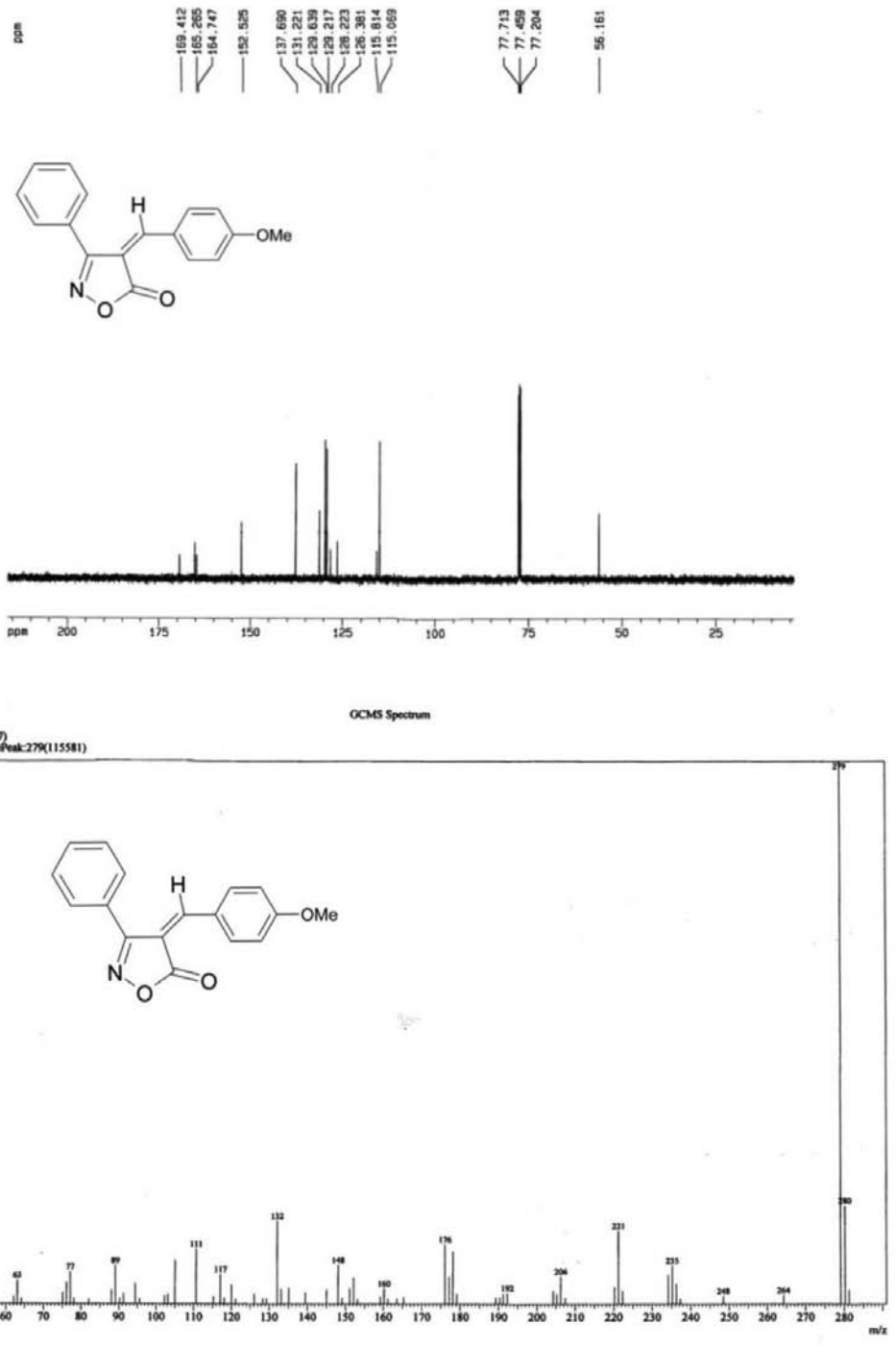



**Figure S18**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3i**.

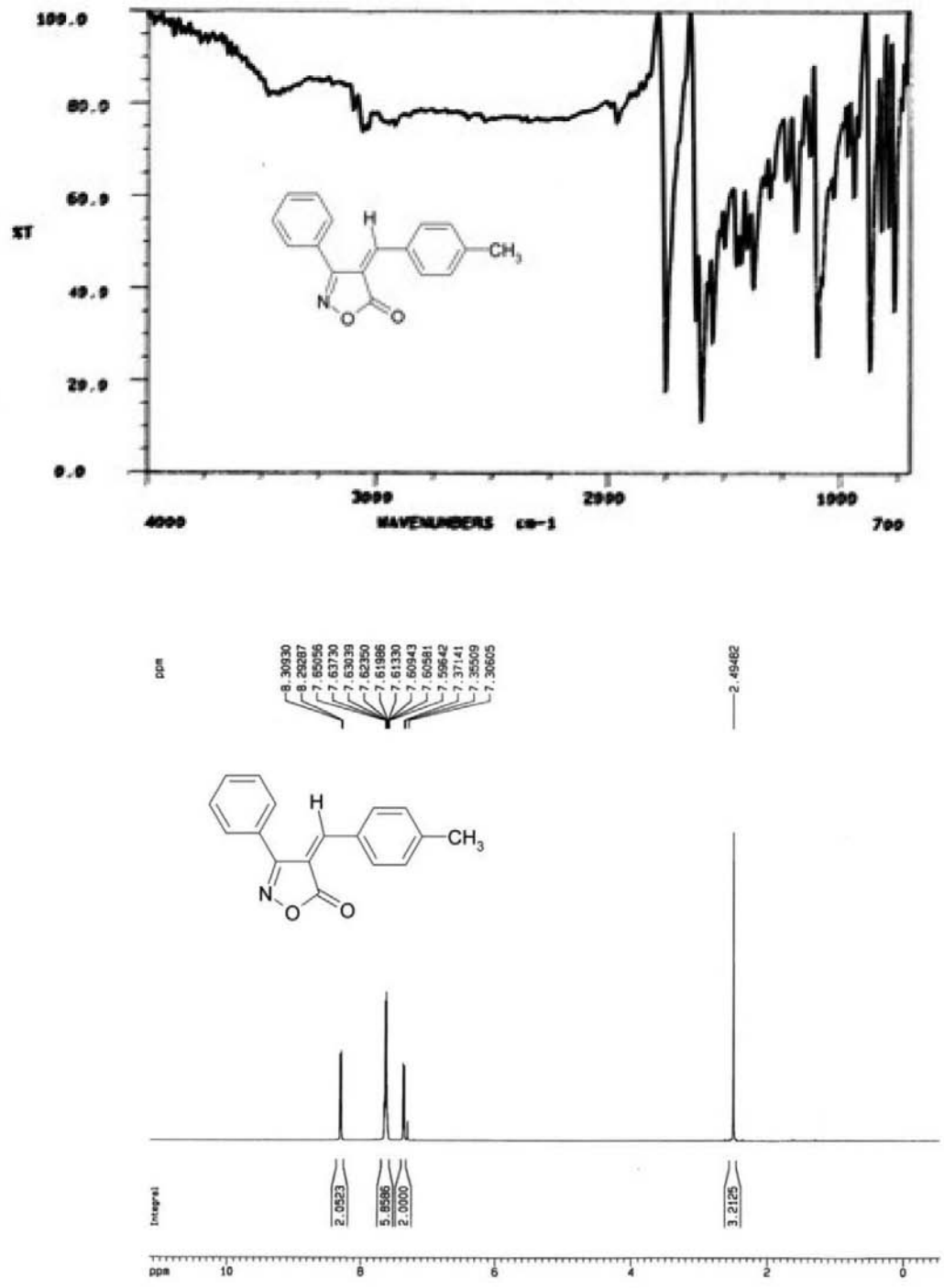



**Figure S19**. IR spectrum and $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3j**.

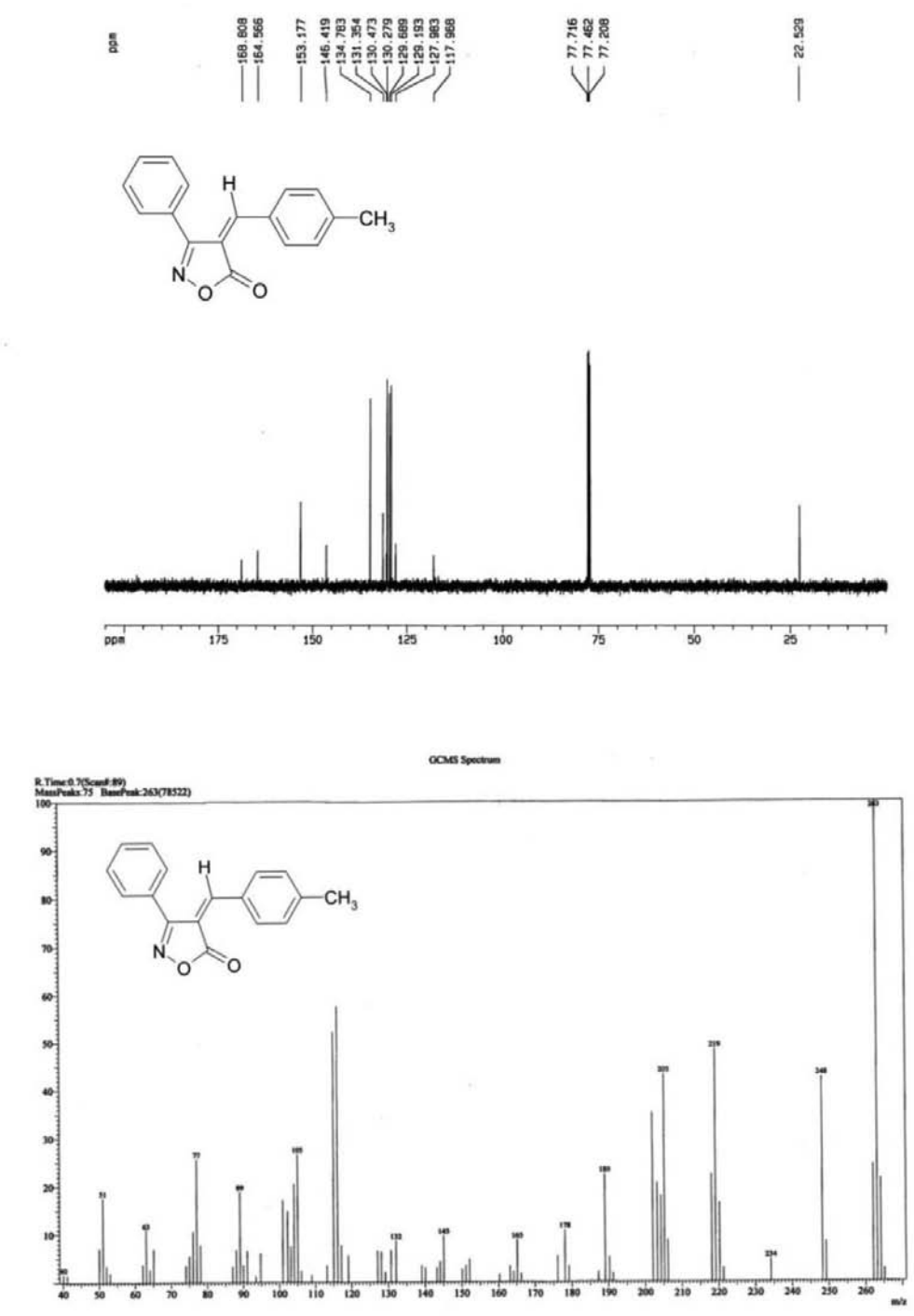



**Figure S20**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3j**.

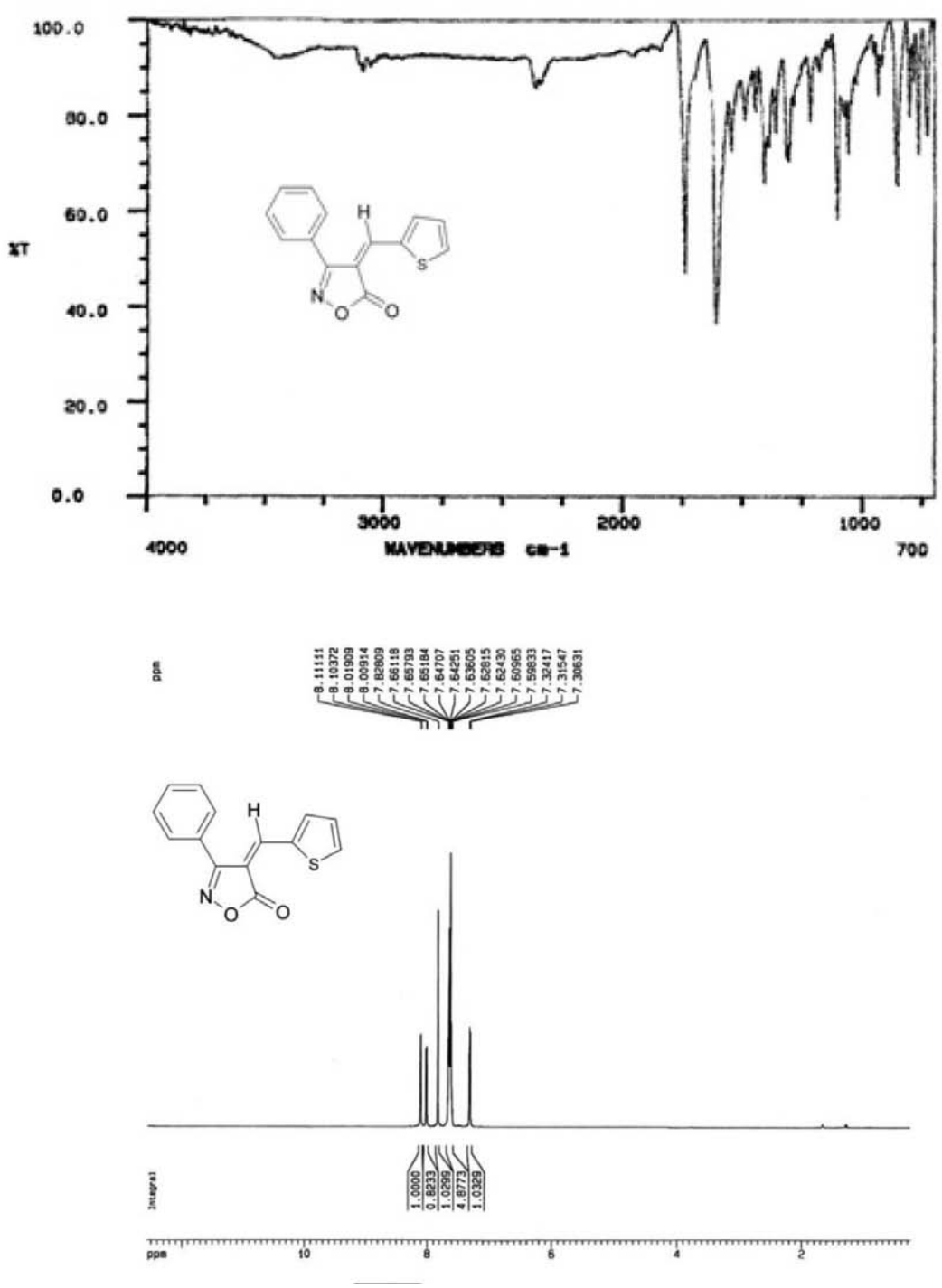



**Figure S21**. IR spectrum and $^1$H NMR spectrum (500 MHz, $CDCl_3$) of compound **3k**.

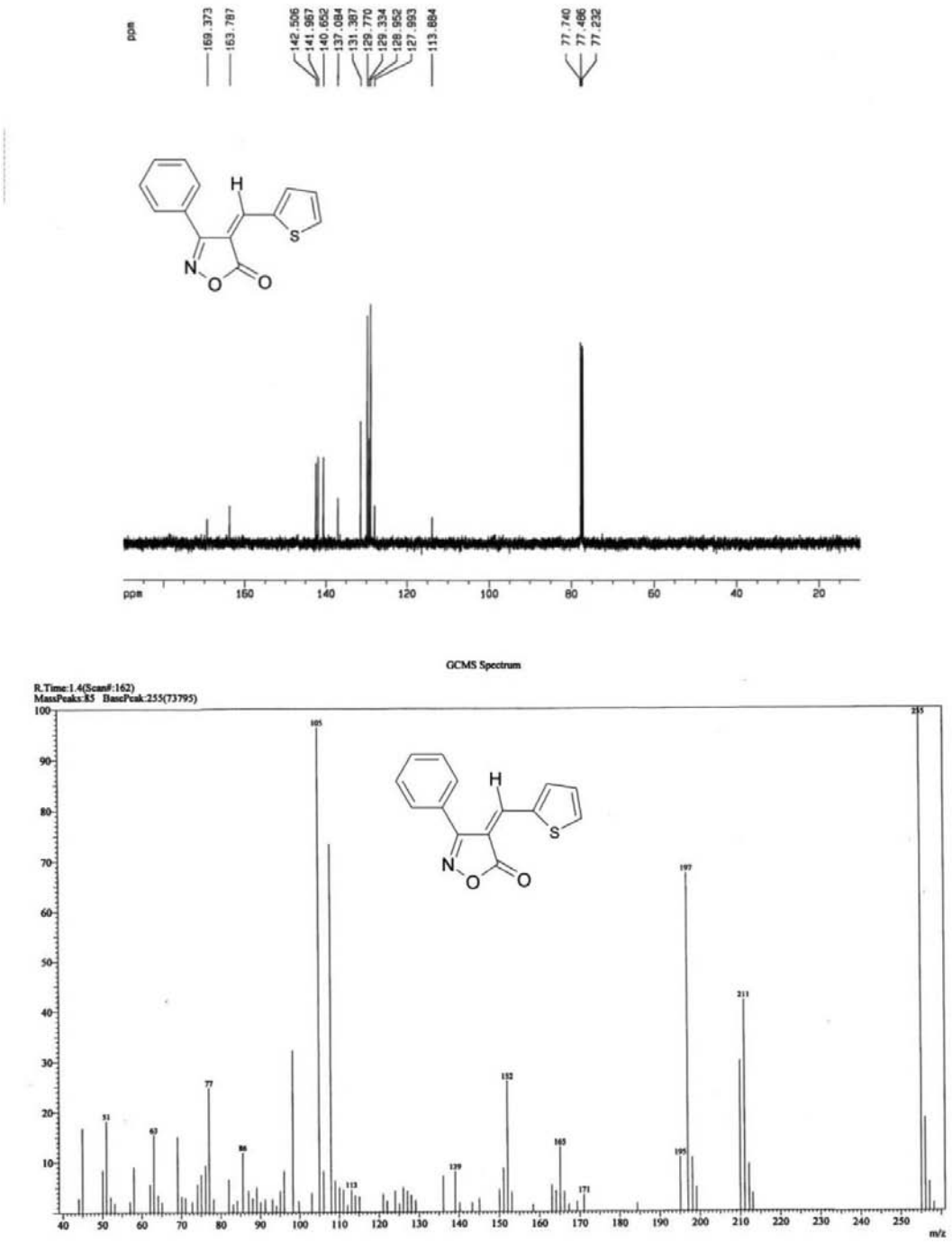



**Figure S22**. $^{13}C$ NMR spectrum (126 MHz, $CDCl_3$) and mass spectrum of compound **3k**.