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Graphical Abstract

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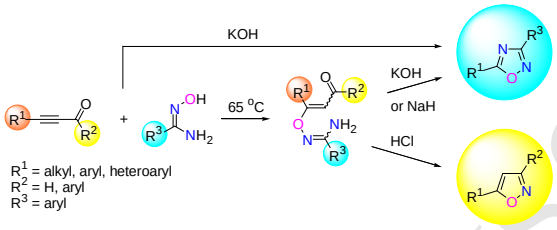

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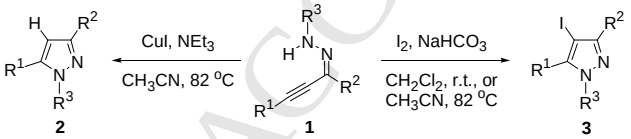
ABSTRACT

A novel synthesis of 1,2,4-oxadiazoles and isoxazoles is described by utilizing the reactions between amidoximes and α,β-alkynic aldehydes and/or ketones. Conjugate addition products, obtained from amidoximes and α,β-alkynic aldehydes and/or ketones, afford 1,2,4-oxadiazoles and isoxazoles when treated with bases and acids, respectively. 1,2,4-Oxadiazoles can also be synthesized directly from amidoximes and α,β-alkynic aldehydes in a one-pot manner under basic conditions. The reactions are general for a variety of starting compounds and tolerate the presence of aryl, heteroaryl and alkyl groups.

1. Introduction

Recently, α,β-alkynic aldehydes and ketones have emerged as valuable substrates in organic synthesis since they have two electrophilic centers and, when treated with binucleophiles, they can undergo cyclocondensation to afford a variety of important heterocycles, including pyrazoles,[1] isoxazoles,[2] pyridines,[3] pyrimidines,[4] thiophenes,[5] pyridopyrimidinones[6] and quinolines.[7] In this regard, we have recently reported the synthesis of α,β-alkynic hydrazones **1** and their regioselective conversion into pyrazole derivatives **2** and **3** (Scheme 1).[8] When treated with copper(I) iodide or molecular iodine, α,β-alkynic hydrazones **1** undergo electrophilic cyclization to afford pyrazoles **2** and 4-iodopyrazoles **3**, respectively, in good to excellent yields.



2 **1** **3**

Scheme 1. Synthesis of pyrazoles and 4-iodopyrazoles via electrophilic cyclization.

Amidoximes are known as popular binucleophilic reagents and have been extensively used in organic synthesis,[9] especially in the preparation of 1,2,4-oxadiazoles,[10] and pyrimidinones and/or their tautomer pyrimidines.[11] We reasoned that the reaction of amidoximes with α,β-alkynic aldehydes and ketones could lead to the formation of important heterocycles. Surprisingly, a search of the literature revealed very few reports concerning such reactions which are displayed in Scheme 2. Naidu and Sorenson showed that the treatment of the in situ generated alkylamidoxime **4** with a propargyl ketone provided 1,2,4-oxadiazoline **5**.[12] A group of researchers employed the reactions between properly substituted amidoximes **6** and propargyl ketones to synthesize medicinally important pyrimidine derivatives **7**.[13] In the first step of this synthesis, amidoximes **6** are converted to the corresponding amidinium salts, which then react with propargyl ketones to afford pyrimidines **7**. It is noteworthy to mention that the reaction of amidoximes **6** with acetylenic diesters, followed by the thermal rearrangement of the resulting Michael adducts, affords pyrimidinones **8** and/or their tautomers pyrimidines **9**.[11] To the best of our knowledge, the reaction of amidoximes with α,β-alkynic aldehydes is not known.

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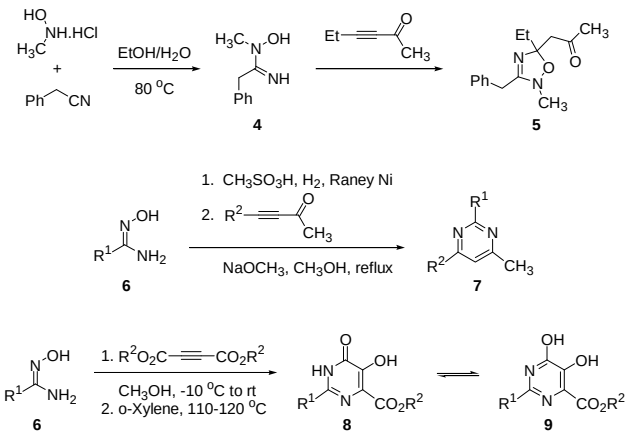
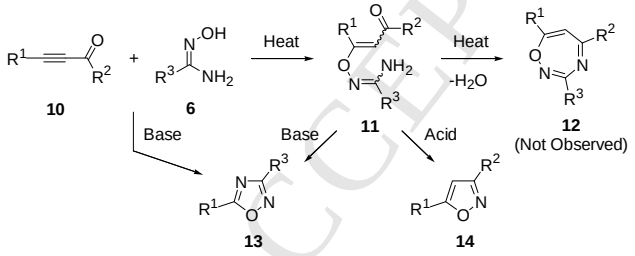


Scheme 2. Reaction of amidoximes with α,β-alkynic ketones and esters.

We anticipated that the reaction of amidoximes with α,β-alkynic aldehydes and ketones could lead to the formation of 1,2,4-oxadiazepine derivatives **12** via cyclocondensation of the intermediate conjugate addition products **11** (Scheme 3). In fact, compared to other heterocyclic compounds, oxadiazepines are less known and less explored,[14] although they have great potential for both pharmaceutical[15] and agricultural[16] benefits. To the best of our knowledge, 1,2,4-oxadiazepines are not known although the examples of their bridged, benzo, hydro and/or oxadiazepinone derivatives are known.[17] Unfortunately, the reaction of amidoximes **6** with α,β-alkynic aldehydes **10** did not produce the expected 1,2,4-oxadiazepines **12** and, from these reactions, conjugate addition products **11** were isolated (Scheme 3). Even at high temperatures, thermolysis of the conjugate addition products **11** did not yield 1,2,4-oxadiazepines **12**, and starting compounds were recovered with some decomposition. Interestingly, during these studies, we found that under basic and acidic conditions, conjugate addition products **11** afford 1,2,4-oxadiazoles **13** and isoxazoles **14** in good to high yields, respectively,[18] which are unprecedented reactions. We have also displayed that 1,2,4-oxadiazoles **13** can be synthesized directly from amidoximes **6** and propargyl aldehydes **10** in a one-pot manner under basic conditions (Scheme 3).

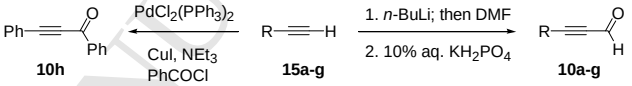


Scheme 3. Synthetic strategy for 1,2,4-oxadiazepines, 1,2,4-oxadiazoles and/or isoxazoles.

In fact, 1,2,4-oxadiazoles and isoxazoles have been intensely studied in recent decades as important classes of heterocycles, and still receive great attention due to their growing significance in both bioactive compounds and materials.[19,20] 1,2,4-Oxadiazoles and isoxazoles have been reported to exhibit a wide range of biological properties, such as analgesic,[21] anti-asthmatic,[22] anti-diabetic,[23] anthelmintic,[24] diuretic,[25] anti-inflammatory,[26] antiparasitic,[27] anti-HIV,[28] and/or antitumor[29] activities. Briefly, 1,2,4-oxadiazoles and isoxazoles are prominent targets for synthetic chemists primarily because of their diverse and potent biological properties. Over the years, numerous methods have been developed for the synthesis of these compounds,[30,31] and new variants continue to appear since they have a noteworthy impact as intermediates in the synthesis of various drugs and natural products. As part of a program to synthesize pharmaceutically important heterocycles,[1i,8,32] we have investigated the reaction of amidoximes with α,β-alkynic aldehydes and ketones, which afforded 1,2,4-oxadiazoles and isoxazoles depending upon the reaction conditions (Scheme 3). We herein report the full details of this study.

2. Results and Discussion

The required α,β-acetylenic aldehydes and ketones can be easily prepared according to known literature procedures, as depicted in Scheme 4. The lithiation of terminal alkynes **15a-g** with *n*-BuLi, followed by the formylation of the in situ generated lithium acetylides with DMF, affords α,β-acetylenic aldehydes **10a-g** in good to excellent yields.[8,33] It is noteworthy that a reverse quench into a phosphate buffer has proved to be the key for these high yielding formylation reactions. Diphenylpropynone (**10h**) can be prepared directly from phenylacetylene and benzoyl chloride by a palladium-catalyzed coupling reaction.[8,34]



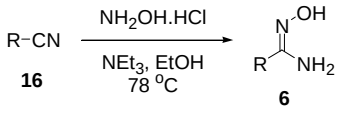
Scheme 4. Synthesis of α,β-alkynic aldehydes and ketones.

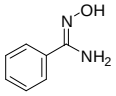
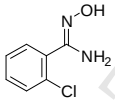
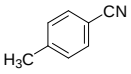
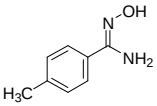
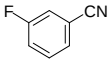
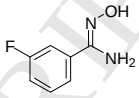
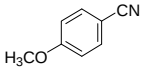
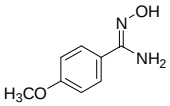
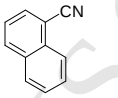
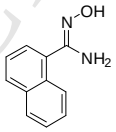
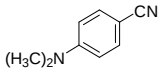
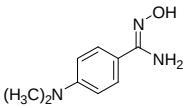
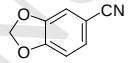
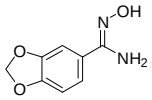
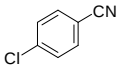
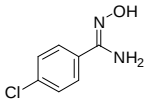
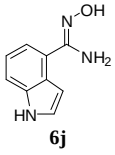
The necessary amidoximes **6** were readily synthesized according to a standard literature protocol in one-pot way as illustrated in Table 1. The reaction of nitriles **16** with hydroxylamine hydrochloride in the presence of triethylamine in refluxing ethanol provided the desired amidoximes **6**.[35] As seen in Table 1, a variety of amidoximes **6** were prepared from the corresponding nitriles **16** in moderate to good yields.

Subsequently, we investigated the reactions between amidoximes **6** and α,β-acetylenic aldehydes and ketones **10**. At moderate temperatures, these reactions exclusively produced conjugate addition products **11**. The results are given in Table 2. Best results were obtained in refluxing methanol. The progress of the reaction was monitored by TLC and it was seen that in most cases, the reaction went to completion in almost 2 h. Higher temperatures such as in dioxane at 100 °C did not increase the yields significantly. As seen in Table 2, a variety of conjugate addition products was synthesized in good to high yield. Due to the presence of double bonds, four possible stereoisomers can exist for the conjugate addition products **11** but these reactions afforded only one stereoisomer of **11** as indicated by the TLC analysis and NMR spectroscopy. However, the exact stereochemistry of these isomers could not be identified. As mentioned before, thermolysis of the conjugate addition products in refluxing dioxane or p-xylene did not provide 1,2,4-oxadiazepines **12**, which requires further investigation. These studies will be reported in due course.

The reactions of conjugate addition products **11** were investigated in the presence of bases and acids as well. First the reactions of conjugate addition products **11** were examined in the presence of bases, and for this purpose, KOH and NaH were employed (Table 3). Initially, conjugate addition product **11a** was treated with KOH in DCM at room temperature but no reaction occurred. However, the same reaction in refluxing dioxane afforded 3,5-diphenyl-1,2,4-oxadiazole (**13a**) (Table 3, Entry 1). Subsequently, the reaction of conjugate addition

Table 1. Synthesis of amidoximes.

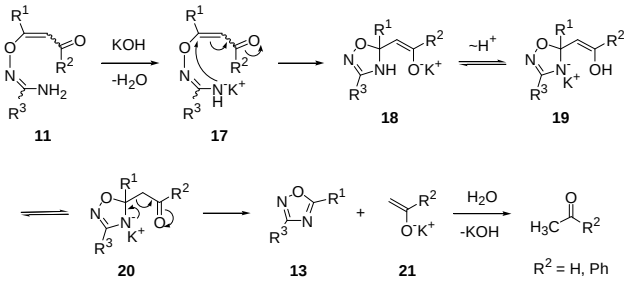


Entry	Nitrile	Amidoxime	% Yield[a]	Entry	Nitrile	Amidoxime	% Yield[a]
1	 **16a**	 **6a**	87	6	 **16f**	 **6f**	60
2	 **16b**	 **6b**	55	7	 **16g**	 **6g**	74
3	 **16c**	 **6c**	72	8	 **16h**	 **6h**	68
4	 **16d**	 **6d**	56	9	 **16i**	 **6i**	35
5	 **16e**	 **6e**	58	10	 **16j**	 **6j**	38

[a]Isolated yield.

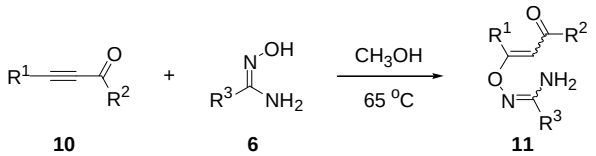
product **11a** was performed in the presence of NaH in acetonitrile at room temperature, which also afforded oxadiazole **13a** (Table 3, Entry 2). In summary, we discovered a novel oxadiazole-forming reaction from conjugate addition products **11**. As seen in Table 3, a variety of conjugate addition products **11** were employed and all yielded the expected oxadiazoles **13** in good to high yields (68-95%), except that isoxazole **13f** was obtained in a moderate yield (47%). Notably, NaH was more effective than KOH since NaH-mediated reactions went to completion at room temperature and mostly in shorter reaction times (Table 3, Entries 5-8, 15 and 16). However, the yields of oxadiazoles **13** obtained by both bases were found to be comparable. The reaction is surprisingly general for a diversity of conjugate addition products **11** without regard to the type of base and tolerates the presence of aryl, heteroaryl and alkyl groups. Interestingly, these reactions also furnish acetaldehyde (Table 3, Entries 1-14) or acetophenone (Table 3, Entries 15 and 16), depending upon the identity of R^2 group, along with oxadiazoles **13**. The isolation of acetaldehyde was not attempted due to its low boiling point (21 ^{o}C) but its occurrence was proved indirectly. We thought that if a conjugate addition product containing a ketone functionality such as **11l** is employed, the reaction would produce the isolable acetophenone instead of acetaldehyde. As anticipated, the reactions of conjugate addition product **11l** gave oxadiazole **13a** and acetophenone (Table 3, Entries 15 and 16). The formation of the latter implicitly proves the formation of acetaldehyde in those reactions. Obviously, the formation of such side products in these reactions presents imlications for the clarification of the reaction mechanism as it will be discussed below.

The mechanism proposed for the formation of 1,2,4-oxadiazoles **13** is shown in Scheme 5. First, hydrogen abstraction from the primary amine produces alkoxide **17**. Then intramolecular conjugate addition takes place to give five-membered compound **18**. Subsequently, hydrogen exchange yields compound **19**, which furnishes compound **20** upon keto-enol tautomerization. Finally, compound **20** undergoes rearrangement to afford 1,2,4-oxadiazole **13** and enolate **21**, the hydrolysis of the latter gives acetaldehyde or acetophenone depending upon the identity of R^2 group (Scheme 5).

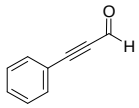
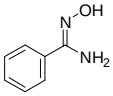
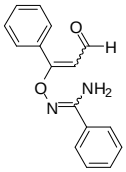
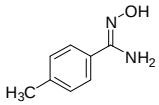
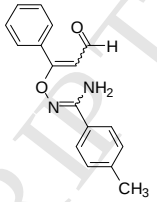
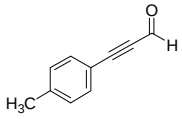
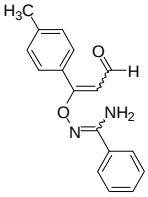
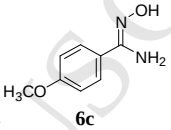
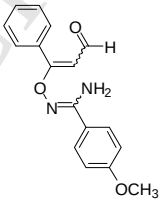
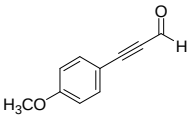
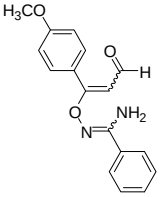
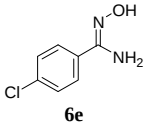
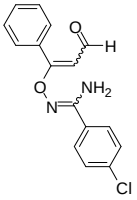
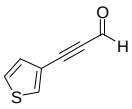
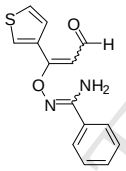
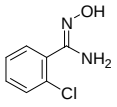
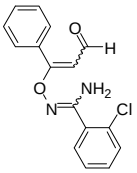
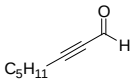
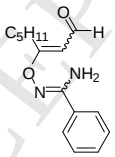
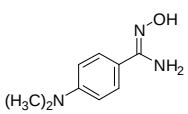
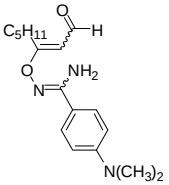
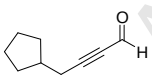
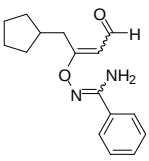
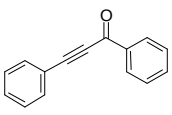
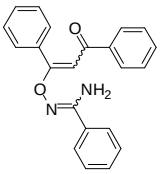


Scheme 5. Proposed mechanism for the formation of 1,2,4-oxadiazoles.

Table 2. Synthesis of conjugate addition products.



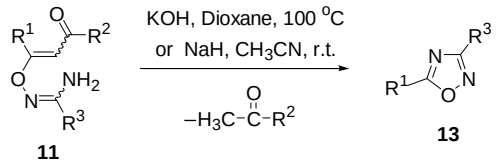
10 **6** **11**

Entry	Alkynal or Alkynone	Amidoxime	Conjugate Addition Product	%Yield[a]	Entry	Alkynal or Alkynone	Amidoxime	Conjugate Addition Product	%Yield[a]
1	 **10a**	 **6a**	 **11a**	84	7	**10a**	 **6b**	 **11g**	53
2	 **10b**	**6a**	 **11b**	78	8	**10a**	 **6c**	 **11h**	84
3	 **10c**	**6a**	 **11c**	69	9	**10a**	 **6e**	 **11i**	70
4	 **10d**	**6a**	 **11d**	89	10	**10a**	 **6f**	 **11j**	60
5	 **10e**	**6a**	 **11e**	82	11	**10e**	 **6d**	 **11k**	50
6	 **10f**	**6a**	 **11f**	92	12	 **10h**	**6a**	 **11l**	63

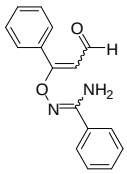
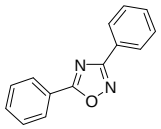
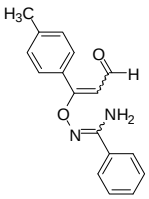
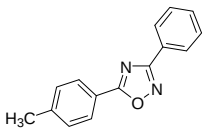
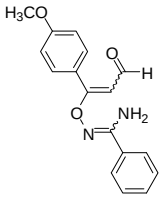
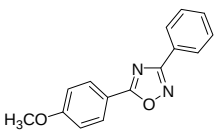
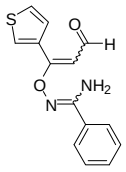
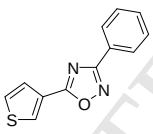
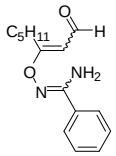
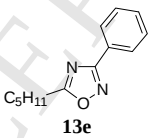
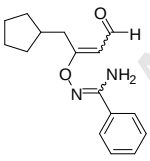
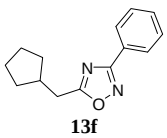
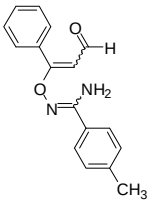
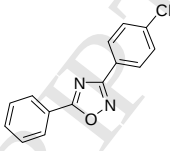
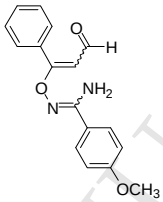
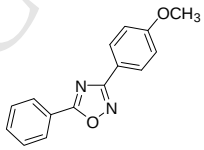
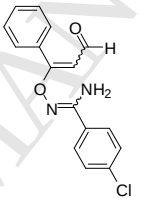
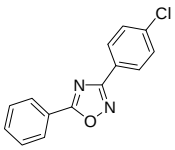
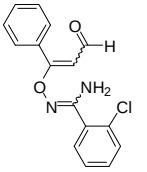
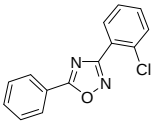
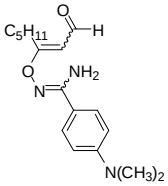
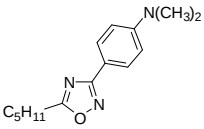
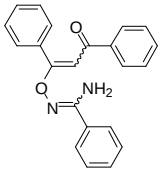
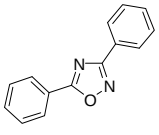
[a]Isolated yield.

Next we investigated the feasibility of one-pot synthesis of 1,2,4-oxadiazoles **13** directly from amidoximes **6** and propargyl aldehydes **10**. The results from a systematic study are given in Table 4. Initially, the reaction between propargyl aldehyde **10a** and amidoxime **6a** was tried with both KOH and NaH under previous conditions (Table 4, Entry 1). These reactions went to completion in a very short time such as 0.5 and 1 h and afforded oxadiazole **13a** in 61 and 53% yields, respectively. Since the reaction with KOH produced oxadiazole **13a** in a relatively higher yield as compared to that with NaH, one-pot synthesis of

Table 3. Synthesis of 1,2,4-oxadiazoles in the presence of KOH or NaH.



11 **13**

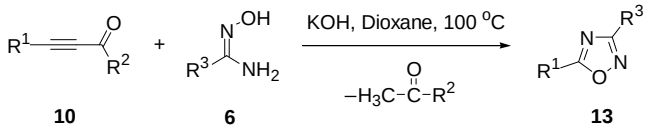
Entry	Conjugate Addition Product	Base	Time (h)	1,2,4-Oxadiazole	%Yield[a]
1	 **11a**	KOH	1	 **13a**	84
2		NaH	1		85
3	 **11b**	KOH	2	 **13b**	80
4	 **11c**	KOH	2	 **13c**	95
5	 **11d**	KOH	10	 **13d**	68
6		NaH	0.5		83
7	 **11e**	KOH	5	 **13e**	81
8		NaH	0.5		84
9	 **11f**	KOH	8	 **13f**	47
10	 **11g**	KOH	3	 **13g**	93
11	 **11h**	NaH	0.5	 **13h**	85
12	 **11i**	KOH	1	 **13i**	91
13	 **11j**	NaH	0.5	 **13j**	93
14	 **11k**	NaH	17	 **13k**	70
15[b]	 **11l**	KOH	5	 **13a**	87
16[c]		NaH	0.5		85

[a]Isolated yield.

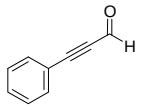
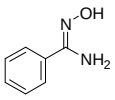
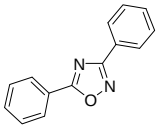
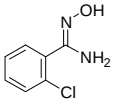
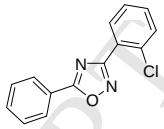
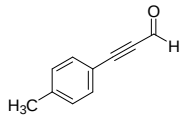
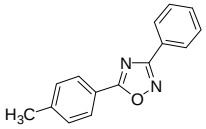
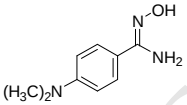
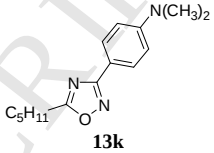
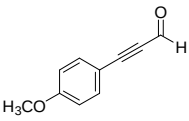
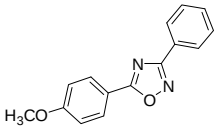
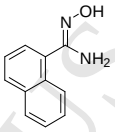
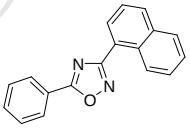
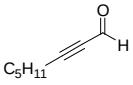
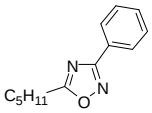
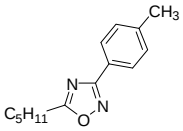
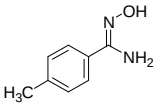
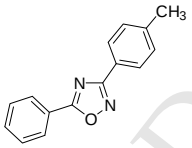
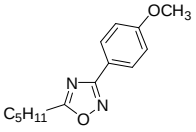
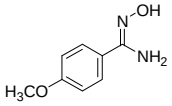
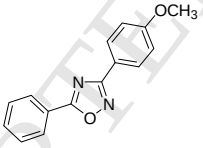
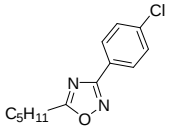
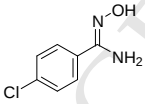
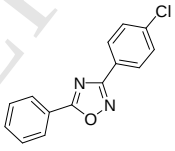
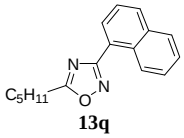
[b]Acetophenone was also isolated from this reaction in 63% yield.

[c]Acetophenone was also isolated from this reaction in 72% yield

Table 4. One-pot synthesis of 1,2,4-oxadiazoles in the presence of KOH.



10 **6** **13**

Entry	Alkynal or Alkynone	Amidoxime	Time (h)	Conjugate Addition Product	%Yield[a]	Entry	Alkynal or Alkynone	Amidoxime	Time (h)	Conjugate Addition Product	%Yield[a]
1[b]	 **10a**	 **6a**	0.5	 **13a**	61	8	**10a**	 **6f**	0.5	 **13j**	49
2	 **10b**	**6a**	1	 **13b**	55	9	**10e**	 **6d**	1	 **13k**	79
3	 **10c**	**6a**	0.5	 **13c**	76	10	**10a**	 **6h**	1	 **13m**	48
4	 **10e**	**6a**	1	 **13e**	72	11	**10e**	**6b**	1	 **13n**	80
5	**10a**	 **6b**	0.5	 **13g**	59	12	**10e**	**6c**	1	 **13o**	67
6	**10a**	 **6c**	0.5	 **13h**	60	13	**10e**	**6e**	1	 **13p**	76
7	**10a**	 **6e**	1	 **13i**	42	14	**10e**	**6h**	1	 **13q**	52

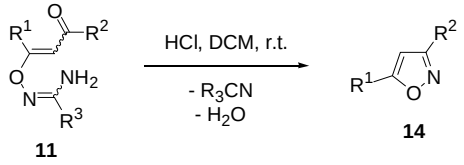
[a]Isolated yield.

[b]When the same reaction was carried out in the presence NaH in acetonitrile at room temperature, it went to completion in 1 h and produced oxadiazole **13a** in 53% yield.

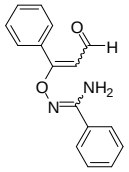
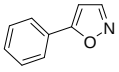
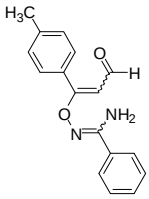
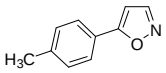
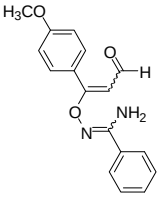
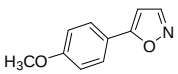
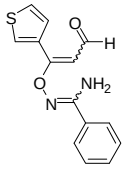
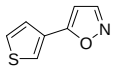
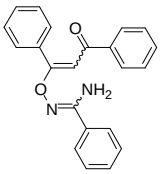
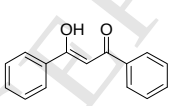
1,2,4-oxadiazoles **13** was conducted with KOH in refluxing dioxane (Table 4). As seen in Table 4, a variety of 1,2,4-oxadiazole derivatives **13** were synthesized by one-pot reaction. As expected, the reactions between propargyl aldehydes **10** and amidoximes **6** yielded in situ corresponding conjugate addition products **11**, which smoothly underwent to cyclization to form 3,5-disubstituted-1,2,4-oxadiazoles **13**. The yields of 3,5-diaryl-substituted 1,2,4-oxadiazoles ranged from 42 to 76% (Table 4, Entries 1-8 and 10). A one-pot procedure was also employed for the synthesis of 5-alkyl-3-aryl-1,2,4-oxadiazole derivatives (Table 4, Entries 9 and 11-14), which afforded corresponding oxadiazoles in 52 to 80% yields. Although one-pot syntheses gave slightly lower yields of oxadiazoles compared to their two-step syntheses, they saved time and chemicals since they required less purification.

The reactions of conjugate addition products **11** were also investigated in the presence of acid, such as hydrochloric acid. The results are shown in Table 5. Initially, the reaction of conjugate addition product **11a** was examined. Surprisingly, when conjugate addition product **11a** was treated with 2-3 drops

Table 5. Synthesis of isoxazoles in the presence of HCl.



11 **14**

Entry	Conjugate Addition Product	Time (h)	Isoxazole	%Yield[a]
1[b]	 **11a**	1	 **14a**	96
2	 **11b**	1	 **14b**	91
3	 **11c**	1	 **14c**	78
4	 **11d**	1	 **14d**	87
5[c]	 **11l**	1	 **22**	96

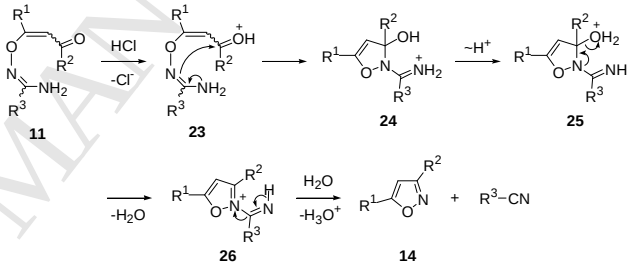
[a]Isolated yield.

[b]HPLC analysis of the crude reaction mixture proved the formation of benzonitrile as well in this reaction.

[c]Instead of benzonitrile, the salt of benzamidoxime (**6a**) was probably formed in this reaction but its isolation was not attempted.

of HCl in DCM at room temperature for approximately 30 minutes, the reaction led to formation of isoxazole **14a** in 96% yield (Table 5, Entry 1). A similar trend was observed in the reactions of other conjugate addition products **11b-d**, all of which, upon treatment with HCl, afforded the corresponding isoxazoles **14b-d** (Table 5, Entry 2-4). It is noteworthy that the formation of isoxazoles **14** from conjugated addition products **11** is unprecedented. These reactions yielded isoxazole derivatives **14** in good to high yields (78-96%). Interestingly, these reactions afforded nitrile derivatives (R_3CN) as well, along with isoxazoles **14**, but their isolation was not attempted. However, the formation of nitriles in these reactions was proved by the HPLC analysis of the crude reaction mixture in one case (Table 5, Entry 1), which confirmed the presence of benzonitrile in the reaction mixture. Clearly, the formation of benzonitrile in these reactions is important from a mechanistic point of view and it will be discussed later. Surprisingly, when treated with HCl, conjugate addition product **11l**, which bears a ketone functionality, underwent hydrolysis and afforded 3-hydroxy-1,3-diphenyl-2-propen-1-one (**22**), the enol form of 1,3-diphenylpropane-1,3-dione, in 96% yield (Table 5, Entry 5). Instead of benzonitrile, benzamidoxime (**11a**) probably resulted from this reaction but, in the acidic conditions, it might be converted to a salt that escaped isolation during column chromatography. No further effort was spent to isolate this salt.

The mechanism proposed for the formation of isoxazoles **14** is given in Scheme 6. The carbonyl moiety of **11** is first protonated to give compound **23**. Subsequently, intramolecular nucleophilic attack of the secondary nitrogen at the protonated carbonyl group produces compound **24**, in which proton transfer from the iminium to the hydroxyl group affords compound **25**. Water elimination then yields compound **26**. Finally, nitrile elimination from **26** gives isoxazole **14** (Scheme 6).



Scheme 6. Proposed mechanism for the formation of isoxazoles.

3. Conclusion

In summary, we have reported two new methods for the synthesis of 1,2,4-oxadiazoles and isoxazoles by employing the reactions between amidoximes and α,β-alkynic aldehydes and/or ketones. The reactions of amidoximes with α,β-alkynic aldehydes and ketones in refluxing methanol exclusively yielded conjugate addition products. When treated with KOH in dioxane at 100 °C or NaH in acetonitrile at room temperature, conjugate addition products afforded a wide range of 1,2,4-oxadiazoles in good to high yields, along with acetaldehyde or acetophenone as side product. One-pot synthesis of 1,2,4-oxadiazoles was also achieved by the KOH-mediated reaction of amidoximes with α,β-alkynic aldehydes in refluxing dioxane. On the other hand, when treated with a few drops of HCl in DCM at room temperature, conjugate addition products furnished isoxazoles in good to high yields, accompanied with benzonitrile as side product. In conclusion, the chemistry developed here is very versatile and accommodates various functional groups. Also, the synthesized heterocycles are of potential utility as new pharmacophores and scaffolds for drug discovery. In addition, they offer scope for further mechanistic and synthetic investigations of 1,2,4-oxadiazoles and isoxazoles in organic and medicinal chemistry.

4. Experimental section

4.1. General information

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (*J*) are reported in Hertz (Hz), and spin multiplicities are presented by the following symbols: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parentheses as C, CH, CH_2 and CH_3. Infrared spectra (IR) were recorded by using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are indicated relative to most intense band, and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). Mass spectra (MS) were obtained by using Electrospray Ionization (ESI) with Micro-Tof; *m/z* values are reported (For each measurement, the mass scale was recalibrated with sodium formiate clusters, and samples were dissolved and measured in MeOH). High resolution mass spectra (HRMS) were also obtained by using Electrospray Ionization (ESI) with Micro-Tof. Melting points were determined on a capillary melting point apparatus and they were uncorrected. Flash chromatography was performed using thick-walled glass columns and "flash grade" silica (230-400 mesh). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica gel plates and visualization was effected with short wavelength UV lamp (254 nm). The relative proportions of solvents in chromatography solvent mixtures refer to the volume:volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in reactions distilled for purity. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in oven prior to use. α,β-Alkynic aldehydes and ketones **10a-h** were synthesized according to standard literature procedures.[8,33,34] Nitrile compounds **16a-j** were commercially available.

4.2. General Procedure for the synthesis of amidoximes (6) (Table 1)

To a stirred solution of the corresponding nitrile **16** (5.00 mmol) and NEt_3 (9.00 mmol) in absolute EtOH (25 mL) was slowly added hydroxylamine hydrochloride (7.50 mmol) and the resulting solution was heated under reflux until the nitrile was consumed (The progress of the reaction was monitored by routine TLC for the disappearance of nitrile). After the solvent was removed on a rotary evaporator to nearly dryness, ethyl acetate (50 mL) and water (50 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:2) as the eluent to afford the corresponding amidoxime **6**.

*4.2.1. N'-Hydroxybenzimidamide (**6a**) (Table 1, Entry 1).* Benzonitrile (**16a**) (500 mg, 4.85 mmol), hydroxylamine hydrochloride (502 mg, 7.27 mmol) and NEt_3 (882 mg, 8.73 mmol) were employed to afford 574 mg (87%) of the indicated product as a white solid: mp 72-75 ^{o}C (lit[36c] 72.1-73.2 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.4 Hz, 2H), 7.48-7.36 (m, 3H), 4.94 (br s, 2H), (OH peak was not observed due to H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5 (C), 130.3 (C), 127.9 (CH), 126.6 (CH), 123.8 (CH). The spectral data were in agreement with those reported previously for this compound.[36]

*4.2.2. N'-Hydroxy-4-methylbenzimidamide (**6b**) (Table 1, Entry 2).* 4-Methylbenzonitrile (**16b**) (250 mg, 2.13 mmol), hydroxylamine hydrochloride (221 mg, 3.20 mmol) and NEt_3 (387 mg, 3.84 mmol) were employed to afford 176 mg (55%) of the indicated product as a white solid: mp 145-147 ^{o}C (lit[36b] 146 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7. 54 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.97 (br s, 2H), 2.39 (s, 3H) (OH peak was not observed due to H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7 (C), 140.2 (C), 129.5 (C), 129.3 (CH), 125.7 (CH), 21.3 (CH_3). The spectral data were in agreement with those reported previously for this compound.[36b]

*4.2.3. N'-Hydroxy-4-methoxybenzimidamide (**6c**) (Table 1, Entry 3).* 4-Methoxybenzonitrile (**16c**) (250 mg, 1.88 mmol), hydroxylamine hydrochloride (195 mg, 2.81 mmol) and NEt_3 (342 mg, 3.38 mmol) were employed to afford 225 mg (72%) of the indicated product as a white solid: mp 120-121 ^{o}C (lit[36b] 119-120 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.87 (br s, 2H), 3.85 (s, 3H) (OH peak was not observed due to H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0 (C), 152.6 (C), 127.2 (CH), 124.9 (C), 114.0 (CH), 55.4 (CH_3). The spectral data were in agreement with those reported previously for this compound.[36b]

*4.2.4. 4-(Dimethylamino)-N'-hydroxybenzimidamide (**6d**) (Table 1, Entry 4).* 4-(Dimethylamino)benzonitrile (**16d**) (250 mg, 1.71 mmol), hydroxylamine hydrochloride (177 mg, 2.56 mmol) and NEt_3 (311 mg, 3.10 mmol) were employed to afford 172 mg (56%) of the indicated product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 4.97 (br s, 2H), 2.99 (s, 6H) (OH peak was not observed due to H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7 (C), 150.7 (C), 125.9 (CH), 118.0 (C), 110.8 (CH), 39.1 (CH_3). The spectral data were in agreement with those reported previously for this compound.[37]

*4.2.5. 4-Chloro-N'-hydroxybenzimidamide (**6e**) (Table 1, Entry 5).* 4-Chlorobenzonitrile (**16e**) (400 mg, 2.91 mmol), hydroxylamine hydrochloride (302 mg, 4.37 mmol) and NEt_3 (529 mg, 5.24 mmol) were employed to afford 287 mg (58%) of the indicated product as a white solid: mp 132-134 ^{o}C (lit[36b] 133 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 4.88 (br s, 2H) (OH peak was not observed due to H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8 (C), 136.1 (C), 130.9 (C), 128.9 (CH), 127.2 (CH). The spectral data were in agreement with those reported previously for this compound.[36b]

*4.2.6. 2-Chloro-N'-hydroxybenzimidamide (**6f**) (Table 1, Entry 6).* 2-Chlorobenzonitrile (**16f**) (400 mg, 2.91 mmol), hydroxylamine hydrochloride (302 mg, 4.37 mmol) and NEt_3 (529 mg, 5.24 mmol) were employed to afford 296 mg (60%) of the indicated product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.4 Hz, 1H), 7.47-7.39 (m, 3H), 5.06 (br s, 2H) (OH peak was not observed due to H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7 (C), 133.7 (C), 132.6 (C), 131.0 (CH), 130.7 (CH), 130.2 (CH), 127.0 (CH). The spectral data were in agreement with those reported previously for this compound.[38]

*4.2.7. 3-Fluoro-N'-hydroxybenzimidamide (**6g**) (Table 1, Entry 7).* 3-Fluorobenzonitrile (**16g**) (400 mg, 3.30 mmol), hydroxylamine hydrochloride (342 mg, 4.96 mmol) and NEt_3 (600 mg, 5.94 mmol) was employed to afford 376 mg (74%) of the indicated product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.35 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 1H), 4.95 (br s, 2H) (OH peak was not observed due to H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8 (d, *J* = 245 Hz, C), 151.7 (C), 134.5

(d, *J* = 8 Hz, C), 130.3 (d, *J* = 8 Hz, CH), 121.5 (d, *J* = 2.5 Hz, CH), 116.9 (d, *J* = 21 Hz, CH), 113.2 (d, *J* = 23 Hz, CH). The spectral data were in agreement with those reported previously for this compound.[39]

*4.2.8. N'-Hydroxy-1-naphthimidamide (**6h**) (Table 1, Entry 8).* 1-Naphthonitrile (**16h**) (400 mg, 2.61 mmol), hydroxylamine hydrochloride (271 mg, 3.92 mmol) and NEt_3 (475 mg, 4.70 mmol) was employed to afford 330 mg (68%) of the indicated product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.2 Hz, 2H), 7.95-7.85 (m, 2H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.54-7.44 (m, 2H), 5.06 (br s, 2H) (OH peak was not observed due to H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7 (C), 133.7 (C), 131.2 (C), 130.1 (CH), 128.4 (C), 128.3 (CH), 126.9 (CH), 126.8 (CH), 126.2 (CH), 125.4 (CH), 125.1 (CH). The spectral data were in agreement with those reported previously for this compound.[40]

*4.2.9. N'-Hydroxybenzo[d][1,3]dioxole-5-carboximidamide (**6i**) (Table 1, Entry 9).* Benzo[d][1,3]dioxole-5-carbonitrile (**16i**) (400 mg, 2.72 mmol), hydroxylamine hydrochloride (282 mg, 4.08 mmol) and NEt_3 (495 mg, 4.90 mmol) were employed to afford 172 mg (35%) of the indicated product as a yellow solid**.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.50 (s, 1H), 7.25-7.15 (m, 2H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.03 (s, 2H), 5.71 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.5 (C), 147.8 (C), 147.1 (C), 127.4 (C), 119.3 (CH), 107.8 (CH), 105.7 (CH), 101.1 (CH_2). The spectral data were in agreement with those reported previously for this compound.[41]

*4.2.10. N'-Hydroxy-1H-indole-4-carboximidamide (**6j**) (Table 1, Entry 10).* 1*H*-Indole-4-carbonitrile (**16j**) (400 mg, 2.81 mmol), hydroxylamine hydrochloride (292 mg, 4.23 mmol) and NEt_3 (513 mg, 5.07 mmol) were employed to afford 188 mg (38%) of the indicated product as a yellowish solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.1 (s, 1H), 9.54 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.84 (s, 1H), 5.67 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.9 (C), 136.7 (C), 125.8 (CH), 125.6 (C), 125.4 (C), 120.8 (CH), 117.7 (CH), 112.7 (CH), 103.0 (CH). The spectral data were in agreement with those reported previously for this compound.[42]

4.3. General Procedure for the synthesis of conjugate addition products (11) (Table 2).

To a stirred solution of the corresponding propargyl aldehyde or ketone **10** (1.00 mmol) in absolute MeOH (20 mL) was added the proper amidoxime **6** (1.00 mmol) and the resulting mixture was heated under reflux for 2 h. After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (50 mL) and water (50 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent to afford the corresponding conjugate addition product **11**.

*4.3.1. N'-((3-Oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11a**) (Table 2, Entry 1).* 3-Phenyl-2-propynal (phenylpropiolaldehyde) (**10a**) (130 mg, 1.00 mmol) and *N'*-hydroxybenzimidamide (**6a**) (136 mg, 1.00 mmol) were employed to afford 224 mg (84%) of the indicated product as a yellow solid: mp 123-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 2H), 7.60-7.51 (m, 3H), 7.50-7.40 (m, 5H), 6.51 (d, *J* = 8.5 Hz, 1H), 5.34 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0 (CH), 175.9 (C), 156.1 (C), 132.0 (C), 131.1 (CH), 130.9 (CH), 130.8 (C), 130.0 (CH), 128.8 (CH), 128.5 (CH), 126.5 (CH), 107.8 (CH); IR (neat): 3477, 3363, 3195, 3058, 2858, 1627, 1604, 1585, 1558, 1398, 1340, 1205, 1157, 1114, 1080, 1026, 900, 844, 763 cm^{-1}; MS (ESI, *m/z*): 289.10 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{14}N_2O_2Na$: 289.0953 $[M+Na]^+$, found: 289.0947.

*4.3.2. N'-((3-Oxo-1-(p-tolyl)prop-1-en-1-yl)oxy)benzimidamide (**11b**) (Table 2, Entry 2).* 3-*p*-Tolylpropiolaldehyde (**10b**) (140 mg, 0.97 mmol) and *N'*-hydroxybenzimidamide (**6a**) (132 mg, 0.97 mmol) were employed to afford 212 mg (78%) of the indicated product as a yellow solid: mp 134-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.54-7.42 (m, 5H), 7.30 (d, *J* = 7.8 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.20 (br s, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0 (CH), 175.8 (C), 155.8 (C), 141.4 (C), 131.1 (CH), 130.9 (C), 130.0 (CH), 129.2 (CH), 128.8 (CH), 126.4 (CH), 107.7 (CH), 21.5 (CH_3); IR (neat): 3490, 3338, 3182, 2837, 1633, 1585, 1558, 1506, 1394, 1338, 1209, 1157, 1110, 1020, 896, 837, 779, 742 cm^{-1}; MS (ESI, *m/z*): 303.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_2Na$: 303.1109 $[M+Na]^+$, found: 303.1104.

*4.3.3. N'-((1-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)oxy)benzimidamide (**11c**) (Table 2, Entry 3).* 3-(4-Methoxyphenyl)propiolaldehyde (**10c**) (160 mg, 1.00 mmol) and *N'*-hydroxybenzimidamide (**6a**) (136 mg, 1.00 mmol) were employed to afford 205 mg (69%) of the indicated product as a brownish yellow solid: mp 119-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.52-7.44 (m, 3H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.47 (d, *J* = 8.2 Hz, 1H), 5.14 (br s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0 (CH), 174.5 (C), 161.0 (C), 155.0 (C), 132.1 (C), 130.9 (CH), 130.2 (CH), 128.4 (CH), 127.9 (CH), 123.0 (C), 113.5 (CH), 107.0 (CH), 54.5 (CH_3); IR (neat): 3446, 3330, 3284, 3197, 2856, 1652, 1587, 1560, 1506, 1394, 1346, 1299, 1249, 1174, 1110, 1026, 898, 846, 777 cm^{-1}; MS (ESI, *m/z*): 319.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_3Na$: 319.1059 $[M+Na]^+$, found: 319.1053.

*4.3.4. N'-((3-Oxo-1-(thiophen-3-yl)prop-1-en-1-yl)oxy)benzimidamide (**11d**) (Table 2, Entry 4).* 3-(Thiophen-3-yl)propiolaldehyde (**10d**) (130 mg, 0.95 mmol) and *N'*-hydroxybenzimidamide (**6a**) (130 mg, 0.95 mmol) were employed to afford 233 mg (89%) of the indicated product as a light yellow solid: mp 134-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (d, *J* = 8.4 Hz, 1H), 7.76-6.80 (m, 3H), 7.56-7.42 (m, 4H), 7.34 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 5.18 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4 (CH), 170.2 (C), 155.8 (C), 132.8 (C), 131.2 (CH), 130.9 (C), 129.3 (CH), 128.9 (CH), 128.2 (CH), 126.45 (CH), 126.4 (CH), 108.3 (CH); IR (neat): 3469, 3292, 3157, 2866, 1627, 1600, 1579, 1560, 1521, 1419, 1390, 1357, 1313, 1191, 1157, 1101, 1072, 1028, 877, 846, 798, 779 cm^{-1}; MS (ESI, *m/z*): 295.05 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{12}N_2O_2SNa$: 295.0517 $[M+Na]^+$, found: 295.0512.

*4.3.5. N'-((1-Oxooct-2-en-3-yl)oxy)benzimidamide (**11e**) (Table 2, Entry 5).* Oct-2-ynal (**10e**) (120 mg, 0.97 mmol) and *N'*-hydroxybenzimidamide (**6a**) (132 mg, 0.97 mmol) were employed to afford 207 mg (82%) of the indicated product as a yellow solid: mp 72-74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (d, *J* = 8.4 Hz, 1H), 7.55-7.40 (m, 2H), 7.30-7.10 (m, 3H), 6.26 (d, *J* = 8.2 Hz, 1H), 5.32 (br s, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 1.80-1.66 (m, 2H), 1.46-1.26 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5 (CH), 178.6 (C), 155.6 (C), 131.0 (CH), 128.7 (CH), 126.4 (CH), 126.3 (C), 106.1 (CH), 31.4 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 22.3 (CH_2), 13.9 (CH_3); IR (neat): 3485, 3309, 3165, 2947, 2927, 2860, 1633, 1604, 1585,

1566, 1456, 1398, 1328, 1217, 1161, 1085, 974, 920, 894, 844, 775 cm^{-1}; MS (ESI, *m/z*): 283.14 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{20}N_2O_2Na$: 283.1422 $[M+Na]^+$, found: 283.1417.

*4.3.6. N'-((1-Cyclopentyl-4-oxobut-2-en-2-yl)oxy)benzimidamide (**11f**) (Table 2, Entry 6).* 4-Cyclopentylbut-2-ynal (**10f**) (130 mg, 0.95 mmol) and *N'*-hydroxybenzimidamide (**6a**) (130 mg, 0.95 mmol) were employed to afford 239 mg (92%) of the indicated product as a white solid: mp 78-81 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.81 (d, *J* = 8.4 Hz, 1H), 7.75-7.62 (m, 2H), 7.50-7.35 (m, 3H), 6.30 (d, *J* = 8.4 Hz, 1H), 5.29 (br s, 2H), 2.70 (d, *J* = 7.4 Hz, 2H), 2.25-2.15 (m, 1H), 1.87-1.80 (m, 2H), 1.75-1.55 (m, 4H), 1.40-1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7 (CH), 178.3 (C), 155.7 (C), 130.9 (CH), 128.7 (CH), 126.4 (CH), 106.5 (CH), 39.5 (CH), 35.3 (CH_2), 32.5 (CH_2), 24.7 (CH_2); IR (neat): 3433, 3328, 2954, 2854, 1627, 1568, 1444, 1402, 1340, 1174, 1112, 902, 844, 773 cm^{-1}; MS (ESI, *m/z*): 295.14 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{20}N_2O_2Na$: 295.1422 $[M+Na]^+$, found: 295.1417.

*4.3.7. 4-Methyl-N'-((3-oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11g**) (Table 2, Entry 7).* 3-Phenyl-2-propynal (**10a**) (130 mg, 1.00 mmol) and *N'*-hydroxy-4-methylbenzimidamide (**6b**) (150 mg, 1.00 mmol) were employed to afford 149 mg (53%) of the indicated product as an orange solid: mp 127-130 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.51 (d, *J* = 8.5 Hz, 1H), 7.66-7.58 (m, 4H), 7.56-7.48 (m, 3H), 7.27 (d, *J* = 7.3 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.16 (br s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9 (CH), 175.7 (C), 155.9 (C), 141.5 (C), 132.1 (C), 130.9 (CH), 130.0 (CH), 129.5 (CH), 128.5 (CH), 127.9 (C), 126.3 (CH), 107.9 (CH), 21.4 (CH_3); IR (neat): 3490, 3315, 3180, 2864, 1627, 1581, 1556, 1400, 1342, 1207, 1163, 1112, 1080, 891, 850, 821, 786, 758 cm^{-1}; MS (ESI, *m/z*): 303.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_2Na$: 303.1109 $[M+Na]^+$, found: 303.1104.

*4.3.8. 4-Methoxy-N'-((3-oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11h**) (Table 2, Entry 8).* 3-Phenyl-2-propynal (**10a**) (130 mg, 1.00 mmol) and *N'*-hydroxy-4-methoxybenzimidamide (**6c**) (166 mg, 1.00 mmol) were employed to afford 249 mg (84%) of the indicated product as a yellow solid: mp 133-135 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.49 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.65-7.57 (m, 2H), 7.55-7.45 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 8.5 Hz, 1H), 5.10 (br s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0 (CH), 175.9 (C), 161.9 (C), 155.9 (C), 132.1 (C), 130.9 (CH), 130.2 (CH), 128.4 (CH), 127.9 (CH), 123.0 (C), 114.2 (CH), 107.7 (CH), 55.4 (CH_3); IR (neat): 3477, 3336, 3195, 2829, 1633, 1600, 1583, 1560, 1519, 1446, 1409, 1392, 1338, 1305, 1251, 1155, 1110, 1072, 1022, 891, 829, 786, 758 cm^{-1}; MS (ESI, *m/z*): 319.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_3Na$: 319.1059 $[M+Na]^+$, found: 319.1053.

*4.3.9. 4-Chloro-N'-((3-oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11i**) (Table 2, Entry 9).* 3-Phenyl-2-propynal (**10a**) (130 mg, 1.00 mmol) and 4-chloro-*N'*-hydroxybenzimidamide (**6e**) (170 mg, 1.00 mmol) were employed to afford 210 mg (70%) of the indicated product as a yellow solid: mp 167-170 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.48 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.62-7.54 (m, 2H), 7.54-7.48 (m, 3H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 8.4 Hz, 1H), 5.20 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9 (CH), 175.6 (C), 154.9 (C), 137.3 (C), 131.9 (C), 130.9 (CH), 130.0 (CH), 129.3 (C), 129.1 (CH), 128.5 (CH), 127.7 (CH), 107.9 (CH); IR (neat): 3485, 3311, 3182, 2860, 1629, 1581, 1554, 1490, 1396, 1342, 1205, 1155, 1114, 1087, 1014, 894, 833, 771 cm^{-1}; MS (ESI, *m/z*): 323.06 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{13}ClN_2O_2Na$: 323.0563 $[M+Na]^+$, found: 323.0558.

*4.3.10. 2-Chloro-N'-(3-oxo-1-phenylprop-1-enyloxy)benzimidamide (**11j**) (Table 2, Entry 10).* 3-Phenyl-2-propynal (**10a**) (130 mg, 1.00 mmol) and 2-chloro-*N'*-hydroxybenzimidamide (**6f**) (170 mg, 1.00 mmol) were employed to afford 180 mg (60%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 9.40 (d, *J* = 8.4 Hz, 1H), 7.62-7.32 (m, 9H), 6.40 (d, *J* = 8.4 Hz, 1H), 5.35 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9 (CH), 175.5 (C), 155.4 (C), 131.9 (CH), 131.7 (CH), 131.2 (CH), 130.9 (CH), 130.4 (C), 130.1 (CH), 129.0 (C), 128.5 (CH), 127.1 (CH), 125.9 (C), 107.9 (CH); MS (ESI, *m/z*): 323.06 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{13}ClN_2O_2Na$: 323.0563 $[M+Na]^+$, found: 323.0559.

*4.3.11. 4-(Dimethylamino)-N'-(1-oxooct-2-en-3-yloxy)benzimidamide (**11k**) (Table 2, Entry 11).* Oct-2-ynal (**10e**) (120 mg, 0.97 mmol) and 4-(dimethylamino)-*N'*-hydroxybenzimidamide (**6d**) (174 mg, 0.97 mmol) were employed to afford 147 mg (50%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 9.85 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.2 Hz, 2H), 6.29 (d, *J* = 8.3 Hz, 1H), 5.03 (br s, 2H), 3.00 (s, 6H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.80-1.65 (m, 2H), 1.50-1.30 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4 (CH), 178.6 (C), 155.7 (C), 152.2 (C), 127.3 (CH), 117.6 (C), 111.6 (CH), 106.1 (CH), 40.2 (CH_3), 31.4 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3); IR (neat): 3429, 3317, 3222, 2964, 2965, 2840, 2765, 1631, 1579, 1542, 1396, 1332, 1218, 1170, 1087, 923, 858, 819, 734 cm^{-1}; MS (ESI, *m/z*): 326.18 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{25}N_3O_2Na$: 326.1844 $[M+Na]^+$, found: 326.1837.

*4.3.12. N'-((3-Oxo-1,3-diphenylprop-1-en-1-yl)oxy)benzimidamide (**11l**) (Table 2, Entry 12).* 1,3-Diphenylpropynone (1,3-diphenylprop-2-yn-1-one) (**10h**) (200 mg, 0.97 mmol) and *N'*-hydroxybenzimidamide (**6a**) (132 mg, 0.97 mmol) were employed to afford 209 mg (63%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.8 Hz, 2H), 7.79 (d, *J* = 7.4 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.56-7.44 (m, 6H), 7.44-7.38 (m, 4H), 5.17 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 169.1, 155.5, 139.9, 134.2, 131.8, 131.0, 129.9, 129.4, 128.8, 128.7, 128.3, 128.2, 128.0, 126.5, 100.4; MS (ESI, *m/z*): 365.13 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{22}H_{18}N_2O_2Na$: 365.1266 $[M+Na]^+$, found: 365.1260.

4.4. General Procedure for the synthesis of 1,2,4-oxadiazoles (13) in the presence of KOH or NaH (Table 3).

If KOH was employed, KOH (0.25 mmol) was added to a stirred solution of the corresponding conjugate addition product **11** (0.25 mmol) in dioxane (10 mL) under argon. After the resulting mixture was heated under reflux for the appropriate time, the mixture was allowed to cool to room temperature. If NaH was employed, 1.05 equiv. of NaH (60% suspension in mineral oil) was added to a stirred solution of the corresponding conjugate addition product **11** (0.25 mmol) in acetonitrile (10 mL) under argon, and the resulting mixture was stirred at room temperature for the appropriate time. In both cases, after the reaction was over, the obtained mixture was filtered to remove undissolved base and the filtrate was washed with diethyl ether (2 x 25 mL). The combined organic layers were then removed on a rotary evaporator to give the crude product, which was purified by flash column chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluent to afford the corresponding 1,2,4-oxadiazole **13**.

*4.4.1. 3,5-Diphenyl-1,2,4-oxadiazole (**13a**) (Table 3, Entry 1).* *N'*-((3-Oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11a**) (60 mg, 0.23 mmol) and KOH (13 mg, 0.23 mmol) were employed to afford 43 mg (84%) of the indicated product as a

white solid: mp 107-108 °C (lit[43] 107-108 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-8.16 (m, 4H), 7.65-7.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7 (C), 168.9 (C), 132.7 (CH), 131.2 (CH), 129.1 (CH), 128.8 (CH), 128.2 (CH), 1278.6 (CH), 127.1 (C), 124.4 (C). The spectral data were in agreement with those reported previously for this compound.[43]

*4.4.2. 3,5-Diphenyl-1,2,4-oxadiazole **(13a)** (Table 3, Entry 2).* *N'*-((3-Oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11a**) (65 mg, 0.24 mmol) and NaH (11 mg, 0.25 mmol) were employed to afford 46 mg (85%) of the indicated product.

*4.4.3. 3-Phenyl-5-(p-tolyl)-1,2,4-oxadiazole **(13b)** (Table 3, Entry 3).* *N'*-((3-Oxo-1-(*p*-tolyl)prop-1-en-1-yl)oxy)benzimidamide (**11b**) (70 mg, 0.25 mmol) and KOH (14 mg, 0.25 mmol) were employed to afford 47 mg (80%) of the indicated product as a white solid: mp 116-118 °C (lit[44] 117-118 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.02 (m, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.42-7.36 (m, 3H), 7.22 (d, J = 8.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9 (C), 168.9 (C), 143.4 (C), 131.1 (CH), 129.8 (CH), 128.8 (CH), 128.1 (CH), 127.5 (CH), 127.2 (C), 121.7 (C), 21.7 (CH_3). The spectral data were in agreement with those reported previously for this compound.[44]

*4.4.4. 5-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazole **(13c)** (Table 3, Entry 4).* *N'*-((1-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)oxy)benzimidamide (**11c**) (70 mg, 0.24 mmol) and KOH (13 mg, 0.24 mmol) were employed to afford 58 mg (95%) of the indicated product as a white solid: mp 97-98 °C (lit[44] 97-98 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.15 (m, 4H), 7.55-7.50 (m, 3H), 7.02 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6 (C), 168.8 (C), 163.2 (C), 131.0 (CH), 130.1 (CH), 128.8 (CH), 127.5 (CH), 127.2 (C), 116.9 (C), 114.5 (CH), 55.5 (CH_3). The spectral data were in agreement with those reported previously for this compound.[44]

*4.4.5. 3-Phenyl-5-(thiophen-3-yl)-1,2,4-oxadiazole **(13d)** (Table 3, Entry 5).* *N'*-((3-Oxo-1-(thiophen-3-yl)prop-1-en-1-yl)oxy)benzimidamide (**11d**) (65 mg, 0.24 mmol) and KOH (13 mg, 0.24 mmol) were employed to afford 37 mg (68%) of the indicated product as a white solid: mp 109-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 2.8 Hz, 1H), 8.22-8.15 (m, 2H), 7.76 (d, J = 4.9 Hz, 1H), 7.55-7.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (C), 168.8 (C), 131.2 (CH), 130.1 (CH), 128.8 (CH), 127.5 (CH), 127.4 (CH), 127.0 (C), 126.7 (CH), 126.0 (C); IR (neat): 3015, 2921, 1596, 1527, 1444, 1352, 1253, 1211, 1126, 1068, 918, 858,736, 713, 688 cm^{-1}; MS (ESI, *m/z*): 251.03 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{12}H_8N_2OSNa$: 251.0255 $[M+Na]^+$, found: 251.0250. The spectral data were in agreement with those reported previously for this compound.[45]

*4.4.6. 3-Phenyl-5-(thiophen-3-yl)-1,2,4-oxadiazole **(13d)** (Table 3, Entry 6).* *N'*-((3-Oxo-1-(thiophen-3-yl)prop-1-en-1-yl)oxy)benzimidamide (**11d)** (60 mg, 0.22 mmol) and NaH (9 mg, 0.23 mmol) were employed to afford 42 mg (83%) of the indicated product.

*4.4.7. 5-Pentyl-3-phenyl-1,2,4-oxadiazole **(13e)** (Table 3, Entry 7).* *N'*-((1-Oxooct-2-en-3-yl)oxy)benzimidamide (**11e**) (65 mg, 0.25 mmol) and KOH (14 mg, 0.25 mmol) were employed to afford 44 mg (81%) of the indicated product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.04 (m, 2H), 7.53-7.43 (m, 3H), 2.94 (t, J = 7.6 Hz, 2H), 1.98-1.78 (m, 2H), 1.56-1.29 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0 (C), 168.3 (C), 130.9 (CH), 128.8 (CH), 127.4 (CH), 127.1 (C), 31.2 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 22.2 (CH_2), 13.8 (CH_3). The spectral data were in agreement with those reported previously for this compound.[46]

*4.4.8. 5-Pentyl-3-phenyl-1,2,4-oxadiazole **(13e)** (Table 3, Entry 8).* *N'*-((1-Oxooct-2-en-3-yl)oxy)benzimidamide (**11e**) (65 mg, 0.25 mmol) and NaH (12 mg, 0.26 mmol) were employed to afford 45 mg (84%) of the indicated product.

*4.4.9. 5-(Cyclopentylmethyl)-3-phenyl-1,2,4-oxadiazole **(13f)** (Table 3, Entry 9).* *N'*-((1-Cyclopentyl-4-oxobut-2-en-2-yl)oxy)benzimidamide (**11f**) (65 mg, 0.24 mmol) and KOH (13 mg, 0.24 mmol) were employed to afford 26 mg (47%) of the indicated product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.08 (m, 2H), 7.53-7.45 (m, 3H), 2.95 (d, J = 7.4 Hz, 2H), 2.50-2.40 (m, 1H), 1.98-1.82 (m, 2H), 1.80-1.60 (m, 4H), 1.40-1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2 (C), 167.7 (C), 130.5 (CH), 128.3 (CH), 126.9 (CH), 126.6 (C), 37.5 (CH), 31.9 (CH_2), 24.5 (CH_2); MS (ESI, *m/z*): 251.12 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{16}N_2ONa$: 251.1160 $[M+Na]^+$, found: 251.1155.

*4.4.10. 5-Phenyl-3-(p-tolyl)-1,2,4-oxadiazole **(13g)** (Table 3, Entry 10).* 4-Methyl-*N'*-((3-oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11g**) (70 mg, 0.25 mmol) and KOH (14 mg, 0.25 mmol) were employed to afford 55 mg (93%) of the indicated product as a white solid: mp 101-103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 7.1 Hz, 2H), 8.08 (d, J = 8.1 Hz, 2H), 7.65-7.55 (m, 3H), 7.32 (d, J = 7.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6 (C), 168.0 (C), 140.5 (C), 131.7 (CH), 129.6 (CH), 129.0 (CH), 128.2 (CH), 127.5 (CH), 124.4 (C), 124.2 (C), 20.6 (CH_3). The spectral data were in agreement with those reported previously for this compound.[47]

*4.4.11. 3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole **(13h)** (Table 3, Entry 11).* 4-Methoxy-*N'*-((3-Oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11h**) (70 mg, 0.24 mmol) and NaH (10 mg, 0.25 mmol) were employed to afford 52 mg (85%) of the indicated product as a white solid: mp 100-101 °C (lit[44] 96-98 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 6.9 Hz, 2H), 8.12 (d, J = 8.8 Hz, 2H), 7.62-7.50 (m, 3H), 7.01 (d, J = 8.6 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4 (C), 168.7 (C), 161.9 (C), 132.6 (CH), 129.1 (CH), 129.0 (CH), 128.1 (CH), 124.5 (C), 119.5 (C), 114.3 (CH), 55.4 (CH_3). The spectral data were in agreement with those reported previously for this compound.[44,48]

*4.4.12. 3-(4-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole **(13i)** (Table 3, Entry 12).* 4-Chloro-*N'*-((3-oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11i**) (75 mg, 0.25 mmol) and KOH (14 mg, 0.25 mmol) were employed to afford 58 mg (91%) of the indicated product as a white solid: mp 109-112 °C (lit[44] 108-110 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 7.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 7.54-7.42 (m, 3H), 7.37 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9 (C), 168.2 (C), 137.3 (C), 132.8 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.2 (CH), 125.5 (C), 124.2 (C). The spectral data were in agreement with those reported previously for this compound.[44]

*4.4.13. 3-(2-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole **(13j)** (Table 3, Entry 13).* 2-Chloro-*N'*-(3-oxo-1-phenylprop-1-enyloxy)benzimidamide (**11j**) (75 mg, 0.25 mmol) and NaH (11 mg, 0.26 mmol) were employed to afford 60 mg (93%) of the indicated product as a white solid: mp 86-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$)*:* δ 8.22 (d, J = 7.9 Hz, 2H), 8.03 (dd, J = 7.2, 1.7 Hz, 1H), 7.65-7.54 (m, 4H), 7.50-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3 (C), 167.8 (C), 133.6 (C), 132.9 (CH), 131.9 (CH), 131.6 (CH), 130.9 (CH), 129.1 (CH), 128.2 (CH), 126.9 (CH), 126.3 (C), 124.1 (C). The spectral data were in agreement with those reported previously for this compound.[49]

*4.4.14. N,N-Dimethyl-4-(5-pentyl-1,2,4-oxadiazol-3-yl)aniline **(13k)** (Table 3, Entry 14).* 4-(Dimethylamino)-*N'*-(1-oxooct-2-en-

3-yloxy)benzimidamide (**11k**) (70 mg, 0.23 mmol) and NaH (10 mg, 0.24 mmol) were employed to afford 42 mg (70%) of the indicated product as a white solid: mp 49-51 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 3.02 (s, 6H), 2.90 (t, J = 7.6 Hz, 2H), 1.85-1.75 (m, 2H), 1.40-1.20 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3 (C), 168.3 (C), 152.0 (C), 128.6 (CH), 111.8 (CH), 40.2 (CH_3), 31.2 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 22.2 (CH_2), 13.8 (CH_3); MS (ESI, m/z): 282.16 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{21}N_3NaO$: 282.1582 $[M+Na]^+$, found: 282.1577.

*4.4.15. 3,5-Diphenyl-1,2,4-oxadiazole (**13a**) (Table 3, Entry 15).* *N*′-((3-Oxo-1,3-diphenylprop-1-en-1-yl)oxy)benzimidamide (**11l**) (100 mg, 0.29 mmol) and KOH (16 mg, 0.29 mmol) were employed to afford 56 mg (87%) of the indicated product.

*4.4.16. 3,5-Diphenyl-1,2,4-oxadiazole (**13a**) (Table 3, Entry 16).* *N*′-((3-Oxo-1,3-diphenylprop-1-en-1-yl)oxy)benzimidamide (**11l**) (100 mg, 0.29 mmol) and NaH (7 mg, 0.30 mmol) were employed to afford 55 mg (85%) of the indicated product.

4.5. General Procedure for the one-pot synthesis of 1,2,4-oxadiazoles (13) in the presence of KOH (Table 4).

To a stirred solution of the corresponding propargyl aldehyde **10** (0.50 mmol) in dioxane (15 mL) under argon was added the relevant amidoxime **6** (0.65 mmol) and KOH (0.50 mmol) and the resulting mixture was heated under reflux for the appropriate time. After the reaction was over, the mixture was allowed to cool to room temperature and filtrated to remove undissolved KOH. Organic solvent was then removed on a rotary evaporator to give the crude product, which was purified by flash column chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluent to afford the corresponding 1,2,4-oxadiazole **13**.

*4.5.1. 3,5-Diphenyl-1,2,4-oxadiazole (**13a**) (Table 4, Entry 1).* 3-Phenyl-2-propynal (**10a**) (65 mg, 0.5 mmol), *N*′-hydroxybenzimidamide (**6a**) (89 mg, 0.65 mmol) and KOH (28 mg, 0.50 mmol) were employed to afford 68 mg (61%) of the indicated product.

*4.5.2. 3-Phenyl-5-(p-tolyl)-1,2,4-oxadiazole (**13b**) (Table 4, Entry 2).* 3-*p*-Tolylpropiolaldehyde (**10b**) (70 mg, 0.48 mmol), *N*′-hydroxybenzimidamide (**6a**) (86 mg, 0.63 mmol) and KOH (27 mg, 0.48 mmol) were employed to afford 62 mg (55%) of the indicated product.

*4.5.3. 5-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazole (**13c**) (Table 4, Entry 3).* 3-(4-Methoxyphenyl)propiolaldehyde (**10c**) (80 mg, 0.50 mmol), *N*′-hydroxybenzimidamide (**6a**) (89 mg, 0.65 mmol) and KOH (28 mg, 0.50 mmol) were employed to afford 96 mg (76%) of the indicated product.

*4.5.4. 5-Pentyl-3-phenyl-1,2,4-oxadiazole (**13e**) (Table 4, Entry 4).* Oct-2-ynal (**10e**) (60 mg, 0.48 mmol), *N*′-hydroxybenzimidamide (**6a**) (86 mg, 0.63 mmol) and KOH (27 mg, 0.48 mmol) were employed to afford 75 mg (72%) of the indicated product.

*4.5.5. 5-Phenyl-3-(p-tolyl)-1,2,4-oxadiazole (**13g**) (Table 4, Entry 5).* 3-Phenyl-2-propynal (**10a**) (65 mg, 0.50 mmol), *N*′-hydroxy-4-methylbenzimidamide (**6b**) (98 mg, 0.65 mmol) and KOH (28 mg, 0.50 mmol) were employed to afford 70 mg (59%) of the indicated product.

*4.5.6. 3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (**13h**) (Table 4, Entry 6).* 3-Phenyl-2-propynal (**10a**) (65 mg, 0.50 mmol), *N*′-hydroxy-4-methoxybenzimidamide (**6c**) (108 mg, 0.65 mmol) and KOH (28 mg, 0.50 mmol) were employed to afford 76 mg (60%) of the indicated product.

*4.5.7. 3-(4-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole (**13i**) (Table 4, Entry 7).* 3-Phenyl-2-propynal (**10a**) (65 mg, 0.50 mmol), 4-chloro-*N*′-hydroxybenzimidamide (**6e**) (110 mg, 0.65 mmol) and KOH (28 mg, 0.50 mmol) were employed to afford 54 mg (42%) of the indicated product.

*4.5.8. 3-(2-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole (**13j**) (Table 4, Entry 8).* 3-Phenyl-2-propynal (**10a**) (60 mg, 0.46 mmol), 2-chloro-*N*′-hydroxybenzimidamide (**6f**) (102 mg, 0.60 mmol) and KOH (26 mg, 0.46 mmol) were employed to afford 58 mg (49%) of the indicated product.

*4.5.9. N,N-Dimethyl-4-(5-pentyl-1,2,4-oxadiazol-3-yl)aniline (**13k**) (Table 4, Entry 9).* Oct-2-ynal (**10e**) (60 mg, 0.48 mmol), 4-(dimethylamino)-*N*′-hydroxybenzimidamide (**6d**) (113 mg, 0.63 mmol) and KOH (27 mg, 0.48 mmol) were employed to afford 98 mg (79%) of the indicated product.

*4.5.10. 3-(Naphthalen-1-yl)-5-phenyl-1,2,4-oxadiazole (**13m**) (Table 4, Entry 10).* 3-Phenyl-2-propynal (**10a**) (65 mg, 0.50 mmol), *N*′-hydroxy-1-naphthimidamide (**6h**) (121 mg, 0.65 mmol) and KOH (28 mg, 0.50 mmol) were employed to afford 65 mg (48%) of the indicated product as a yellow solid: mp 87-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 7.1 Hz, 1H), 8.30 (d, J = 7.5 Hz, 2H), 8.03 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.1 Hz, 1H), 7.65-7.55 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3 (C), 170.8 (C), 135.4 (C), 134.7 (CH), 133.3 (CH), 132.2 (C), 130,9 (CH), 130.6 (CH), 130.1 (CH), 129.7 (CH), 129.0 (CH), 127.85 (CH), 127.8 (CH), 126.6 (CH), 125.7 (C), 125.5 (C); MS (ESI, m/z): 295.08 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{18}H_{12}N_2NaO$: 295.0847 $[M+Na]^+$, found: 295.0842.

*4.5.11. 5-Pentyl-3-(p-tolyl)-1,2,4-oxadiazole (**13n**) (Table 4, Entry 11).* Oct-2-ynal (**10e**) (50 mg, 0.40 mmol), *N*′-hydroxy-4-methylbenzimidamide (**6b**) (78 mg, 0.52 mmol) and KOH (23 mg, 0.40 mmol) were employed to afford 74 mg (80%) of the indicated product as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 2.30 (s, 3H), 1.82-1.75 (m, 2H), 1.40-1.20 (m, 4H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9 (C), 168.2 (C), 141.3 (C), 129.5 (CH), 127.3 (CH), 124.2 (C), 31.2 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 22.2 (CH_3), 21.5 (CH_2), 13.8 (CH_3); IR (neat): 2956, 2929, 1589, 1568, 1411, 1363, 1180, 116, 902, 829, 740 cm^{-1}; MS (ESI, m/z): 253.13 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO$: 253.1317 $[M+Na]^+$, found: 253.1311.

*4.5.12. 3-(4-Methoxyphenyl)-5-pentyl-1,2,4-oxadiazole (**13o**) (Table 4, Entry 12).* Oct-2-ynal (**10e**) (50 mg, 0.40 mmol), *N*′-hydroxy-4-methoxybenzimidamide (**6c**) (86 mg, 0.52 mmol) and KOH (23 mg, 0.40 mmol) were employed to afford 66 mg (67%) of the indicated product as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H), 2.91 (td, J = 7.5, 2.9 Hz, 2H), 1.95-1.80 (m, 2H), 1.45-1.30 (m, 4H), 1.00-0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7 (C), 167.9 (C), 161.8 (C), 128.9 (CH), 119.5 (C), 114.2 (CH), 55.3 (CH_3), 31.2 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 22.2 (CH_2), 13.8 (CH_3); IR (neat): 2956, 2933, 1614, 1591, 1569, 1483, 1423, 1363, 1301, 1251, 1172, 1107, 1029, 900, 839, 752 cm^{-1}; MS (ESI, m/z): 269.13 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO_2$: 269.1266 $[M+Na]^+$, found: 269.1260.

*4.5.13. 3-(4-Chlorophenyl)-5-pentyl-1,2,4-oxadiazole (**13p**) (Table 4, Entry 13).* Oct-2-ynal (**10e**) (50 mg, 0.40 mmol), 4-chloro-*N*′-hydroxybenzimidamide (**6e**) (89 mg, 0.52 mmol) and

KOH (23 mg, 0.40 mmol) were employed to afford 76 mg (76%) of the indicated product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 2.95-2.85 (m, 2H), 1.92-1.78 (m, 2H), 1.49-1.29 (m, 4H), 0.95-0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.2 (C), 167.4 (C), 137.1 (C), 129.1 (CH), 128.7 (CH), 125.6 (C), 31.1 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 22.2 (CH_2), 13.8 (CH_3); IR (neat): 2954, 2927, 1591, 1562, 1465, 1407, 1365, 1085, 1008, 904, 839, 785, 744 cm^{-1}; MS (ESI, m/z): 273.08 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{13}H_{15}N_2ClNaO$: 273.0771 $[M+Na]^+$, found: 273.0767.

4.5.14. 3-(Naphthalen-1-yl)-5-pentyl-1,2,4-oxadiazole ***(13q)*** *(Table 4, Entry 14).* Oct-2-ynal (**10e**) (60 mg, 0.48 mmol), *N'*-hydroxy-1-naphthimidamide (**6h**) (116 mg, 0.62 mmol) and KOH (27 mg, 0.48 mmol) were employed to afford 67 mg (52%) of the indicated product as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$)*:* δ 9.01 (d, J = 9.0 Hz, 1H), 8.30 (d, J = 7.25 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.1 Hz, 1H), 7.65-7.55 (m, 2H), 3.01 (t, J = 7.9 Hz, 2H), 1.95 (quintet, 2H), 1.55-1.40 (m, 4H), 0.97 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1 (C), 168.7 (C), 134.0 (C), 131.7 (CH), 130.7 (C), 129.3 (CH), 128.6 (CH), 127.5 (CH), 126.4 (CH), 126.3 (CH), 125.0 (CH), 124.1 (C), 31.3 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 22.2 (CH_2), 13.9 (CH_3); IR (neat): 2954, 2929, 1579, 1514, 1456, 1352, 1307, 1261, 1145, 1020, 900, 806, 775 cm^{-1}; MS (ESI, m/z): 289.13 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{18}N_2NaO$: 289.1317 $[M+Na]^+$, found: 289.1311.

4.6. General Procedure for the synthesis of isoxazoles (14) in the presence of HCl (Table 5).

To a stirred solution of the corresponding conjugate addition product **11** (0.25 mmol) in dichloromethane (10 mL) was added 2 or 3 drops of concentrated HCl and the resulting mixture was stirred at room temperature for approximately 1 h (The progress of the reaction was monitored by routine TLC for the disappearance of conjugate addition product). After the reaction was over, water (25 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluent to afford the corresponding isoxazole **14**.

4.6.1. 5-Phenylisoxazole ***(14a)*** *(Table 5, Entry 1). N'*-((3-Oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (**11a**) (60 mg, 0.23 mmol) was employed to afford 32 mg (96%) of the indicated product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 1.4 Hz, 1H), 7.85-7.75 (m, 2H), 7.55-7.40 (m, 3H), 6.51 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (C), 130.2 (CH), 128.7 (CH), 127.0 (C), 126.1 (CH), 98.7 (CH). The spectral data were in agreement with those reported previously for this compound.[50]

4.6.2. 5-(p-Tolyl)isoxazole ***(14b)*** *(Table 5, Entry 2). N'*-((3-Oxo-1-(p-tolyl)prop-1-en-1-yl)oxy)benzimidamide (**11b**) (70 mg, 0.25 mmol) was employed to afford 36 mg (91%) of the indicated product as a white solid: mp 61-62 ^{o}C (lit[51a] 60-61 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 1.1 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 6.36 (d, J =1.5 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (C), 150.8 (CH), 140.5 (C), 129.7 (CH), 125.8 (CH), 124.6 (C), 98.0 (CH), 21.4 (CH_3). The spectral data were in agreement with those reported previously for this compound.[51]

4.6.3. 5-(4-Methoxyphenyl)isoxazole ***(14c)*** *(Table 5, Entry 3). N'*-((1-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)oxy)benzimidamide (**11c**) (70 mg, 0.24 mmol) was employed to afford 33 mg (78%) of the indicated product as a white solid: mp 64-65 ^{o}C (lit[50] 61-63 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 6.39 (d, J = 1.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (C), 161.1 (C), 150.8 (CH), 127.5 (CH), 120.2 (C), 114.4 (CH), 97.2 (CH), 55.4 (CH_3). The spectral data were in agreement with those reported previously for this compound.[50]

4.6.4. 5-(Thiophen-3-yl)isoxazole ***(14d)*** *(Table 5, Entry 4). N'*-((3-Oxo-1-(thiophen-3-yl)prop-1-en-1-yl)oxy)benzimidamide (**11d**) (65 mg, 0.24 mmol) was employed to afford 32 mg (87%) of the indicated product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.78 (s, 1H), 7.45-7.35 (m, 2H), 6.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6 (C), 150.6 (CH), 128.7 (C), 127.0 (CH), 125.4 (CH), 124.3 (CH), 98.4 (CH); MS (ESI, m/z): 174.00 $[M+Na]^+$; HRMS (ESI): calcd. for C_7H_5NOSNa: 173.9990 $[M+Na]^+$, found: 173.9994.

4.6.5. 3-Hydroxy-1,3-diphenyl-2-propen-1-one ***(22)*** *(Table 5, Entry 5). N'*-((3-Oxo-1,3-diphenylprop-1-en-1-yl)oxy)benzimidamide (**11l**) (100 mg, 0.29 mmol) was employed to afford 63 mg (96%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.78 (br s, 1H), 7.96-7.85 (m, 4H), 7.65-7.47 (m, 6H), 6.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.9 (C), 135.8 (C), 132.6 (CH), 128.9 (CH), 127.1 (CH), 93.4 (CH). The spectral data were in agreement with those reported previously for this compound.[52]

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Supplementary Material

Copies of ^{1}H NMR and ^{13}C NMR spectra can be found online at http://www.sciencedirect.com. Supplementary data related to this article can be found at http://dx.doi.org/xxx.

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SUPPLEMENTARY MATERIAL

for

A Novel Synthesis of 1,2,4-Oxadiazoles and Isoxazoles

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Table of Contents

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Copies of ^{1}H and ^{13}C NMR spectra

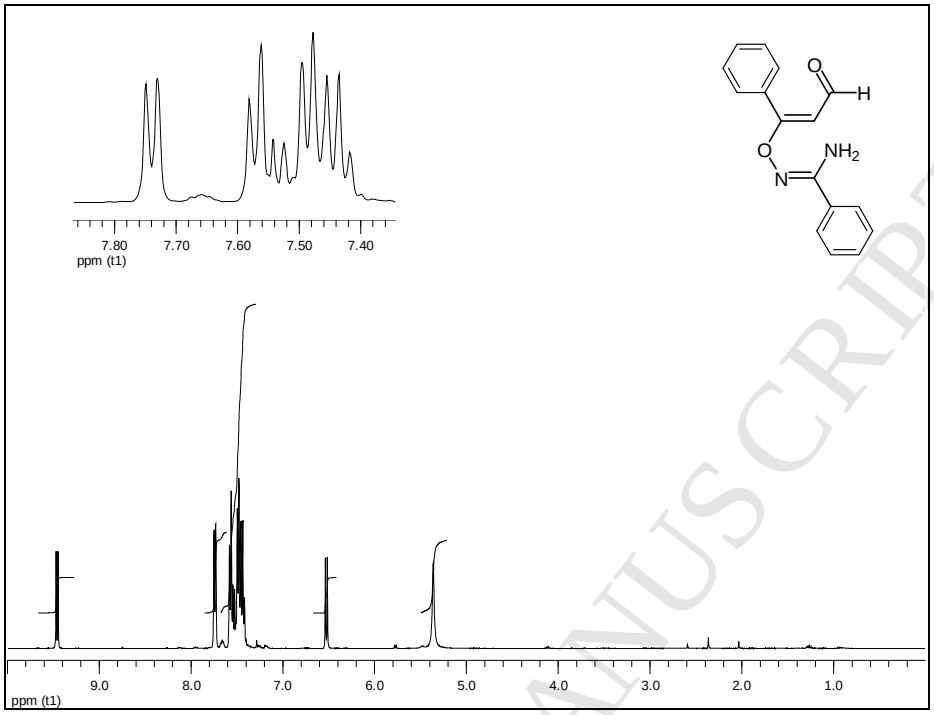


Figure S1. ^{1}H NMR spectrum of **11a**.

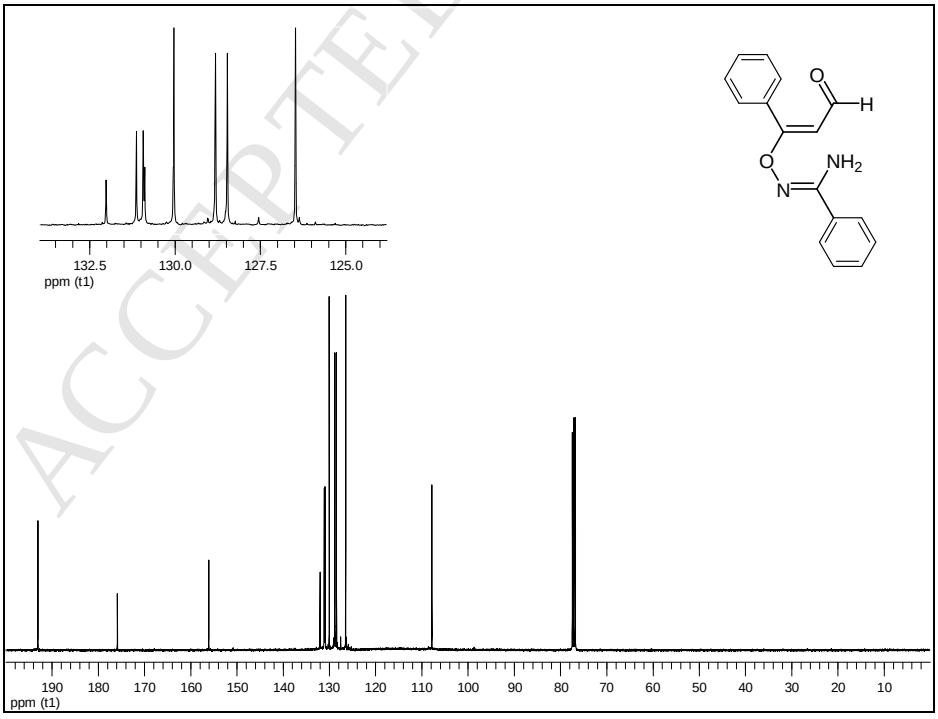


Figure S2. ^{13}C NMR spectrum of **11a**.

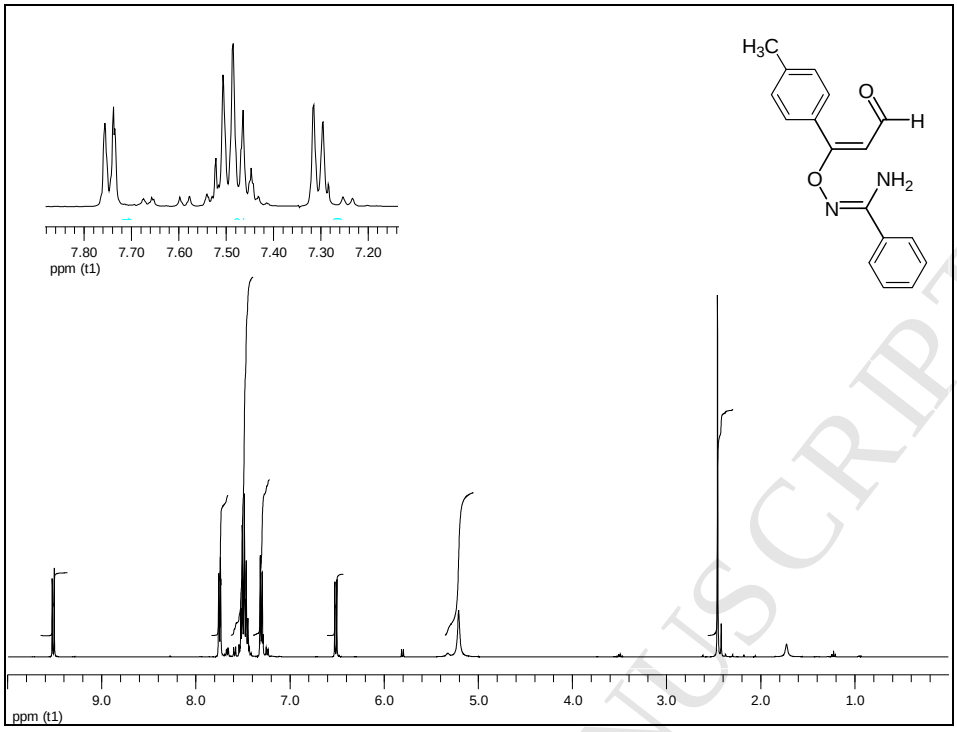


Figure S3. ^{1}H NMR spectrum of **11b**.

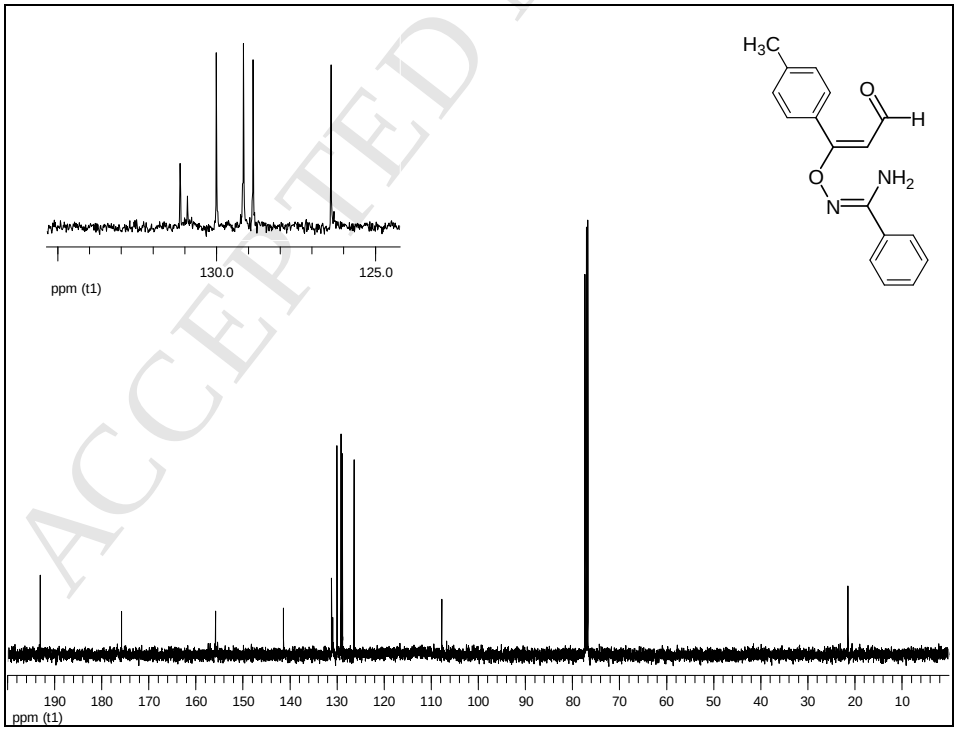


Figure S4. ^{13}C NMR spectrum of **11b**.

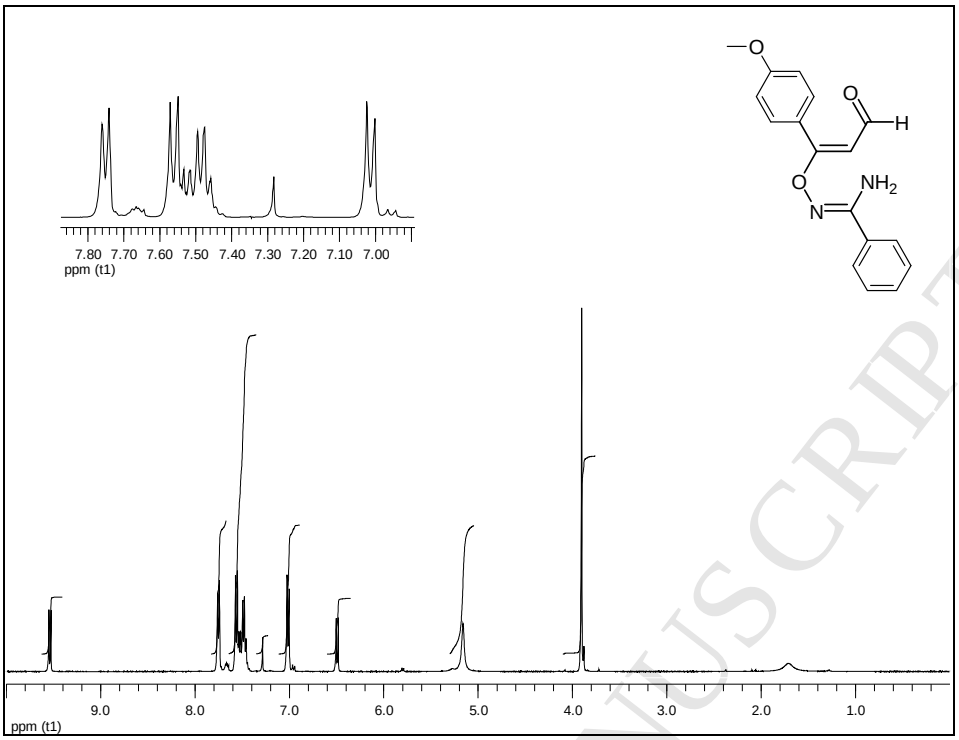


Figure S5. ^{1}H NMR spectrum of **11c**.

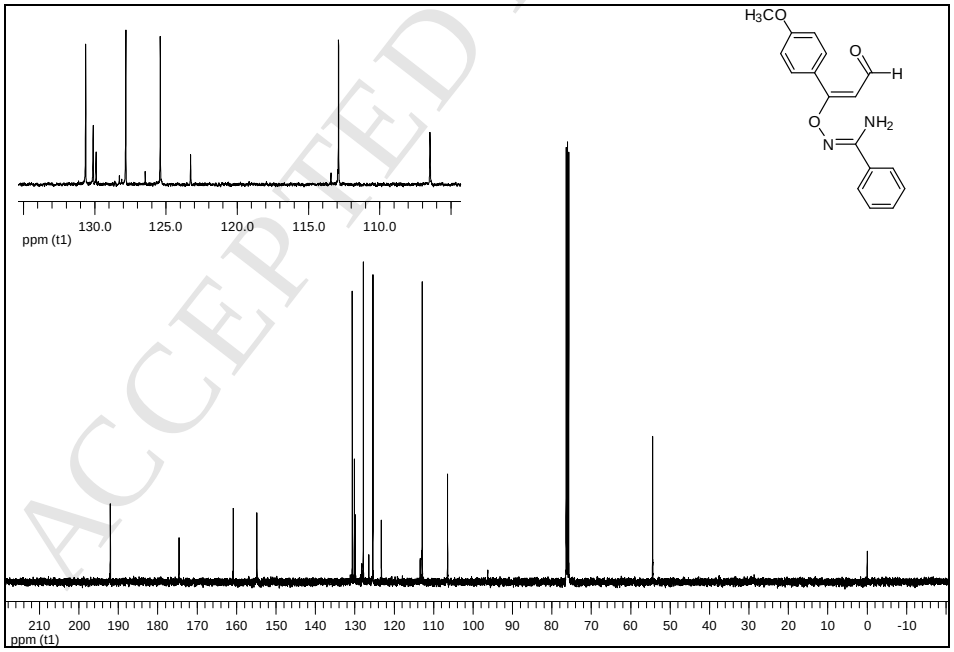
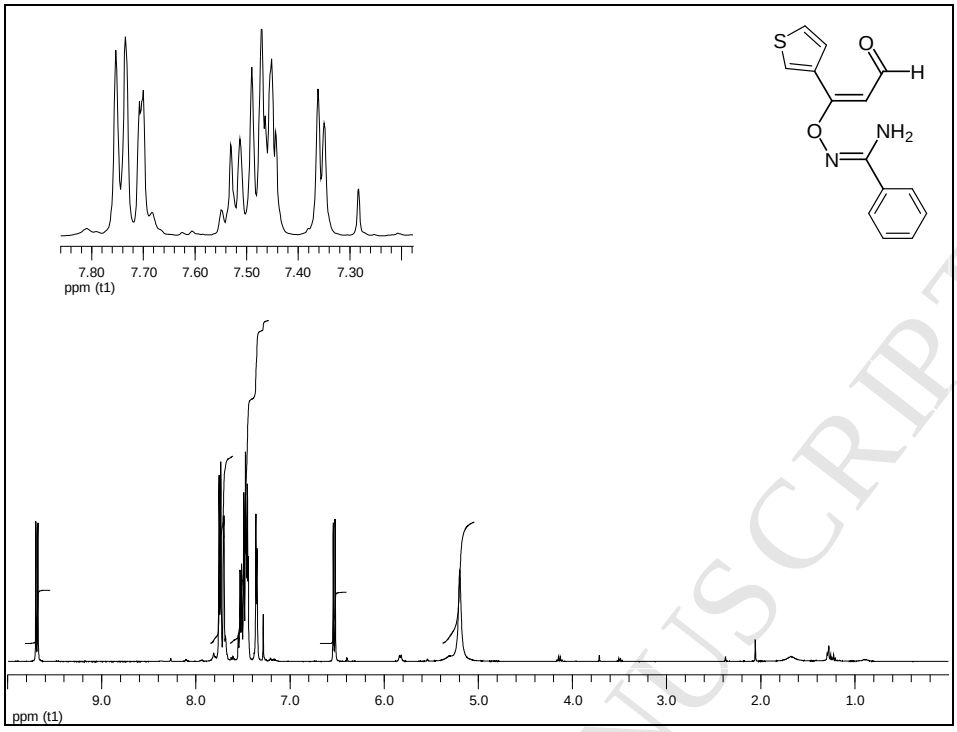


Figure S6. ^{13}C NMR spectrum of **11c**.



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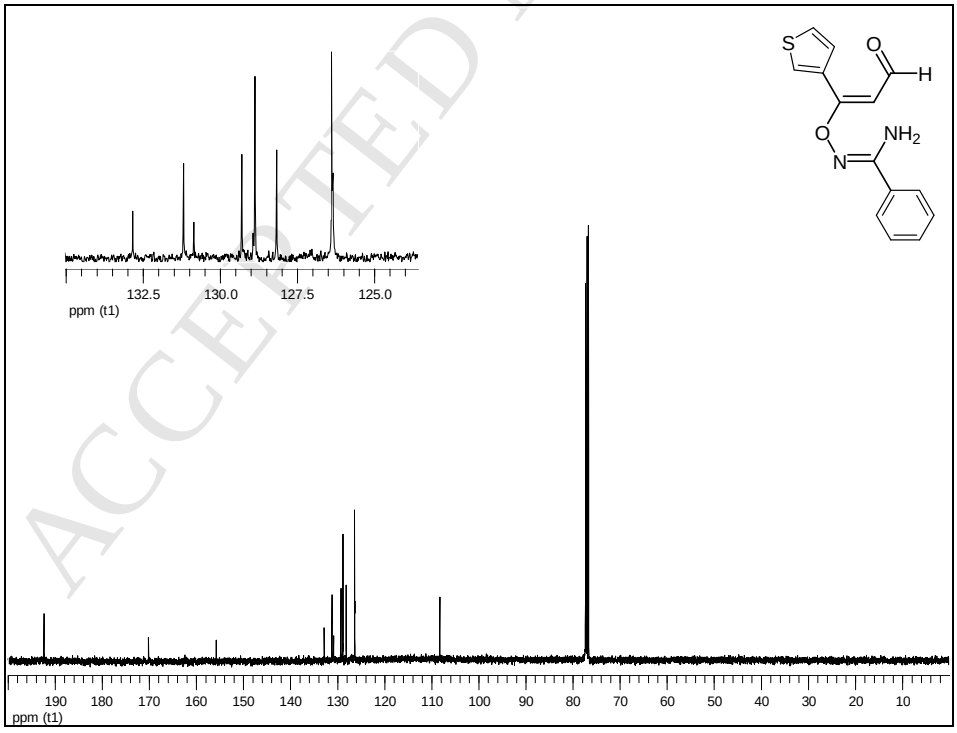
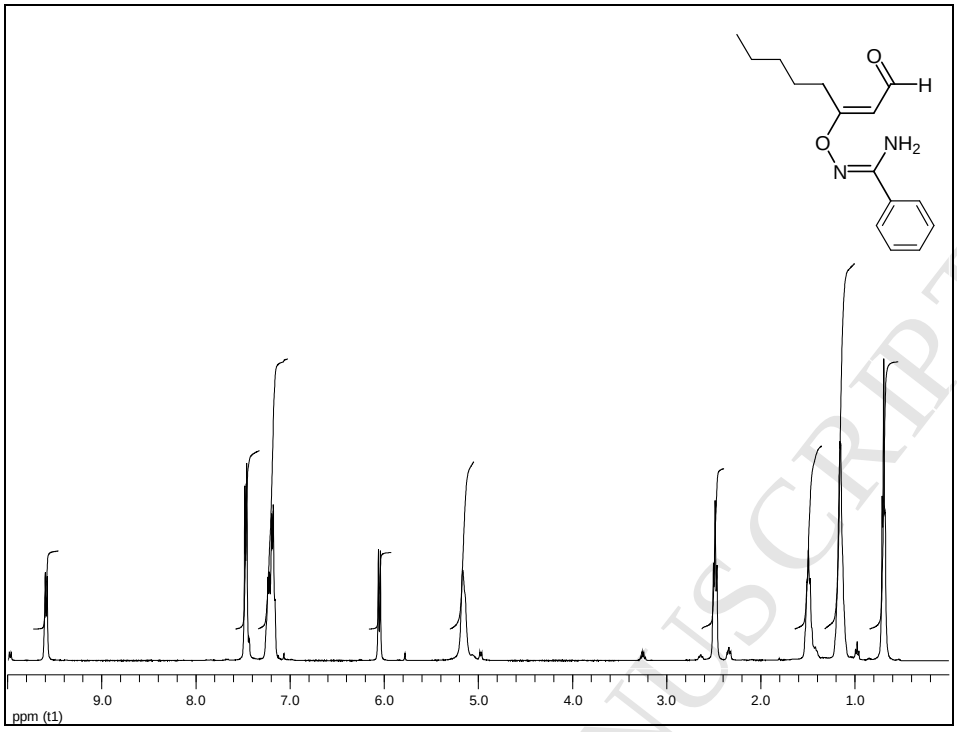


Figure S8. ^{13}C NMR spectrum of **11d**.



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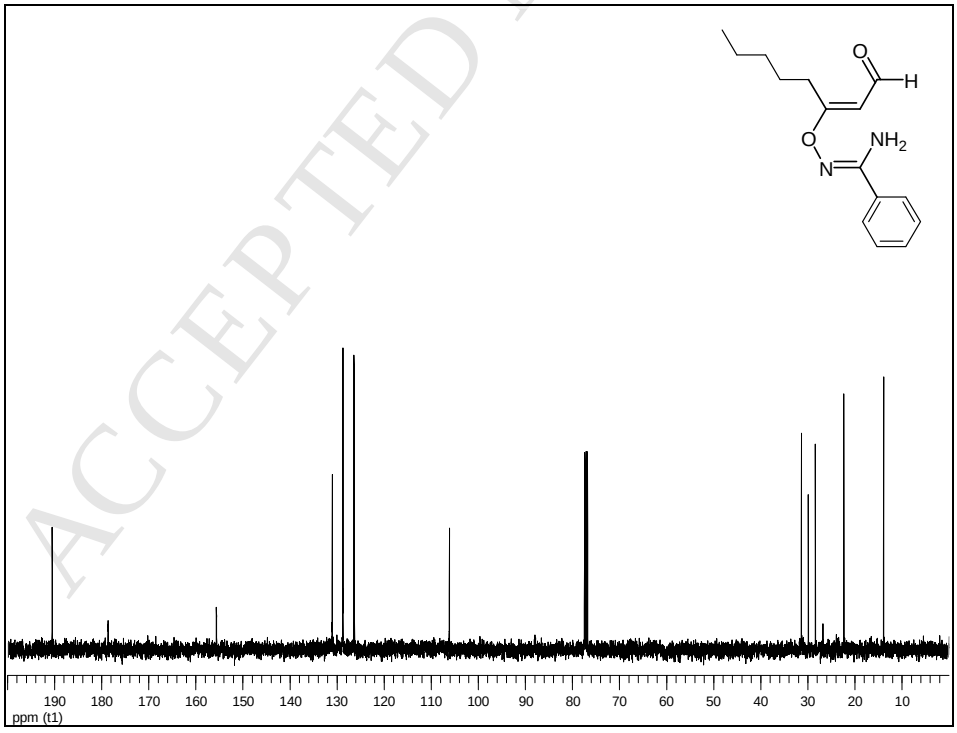

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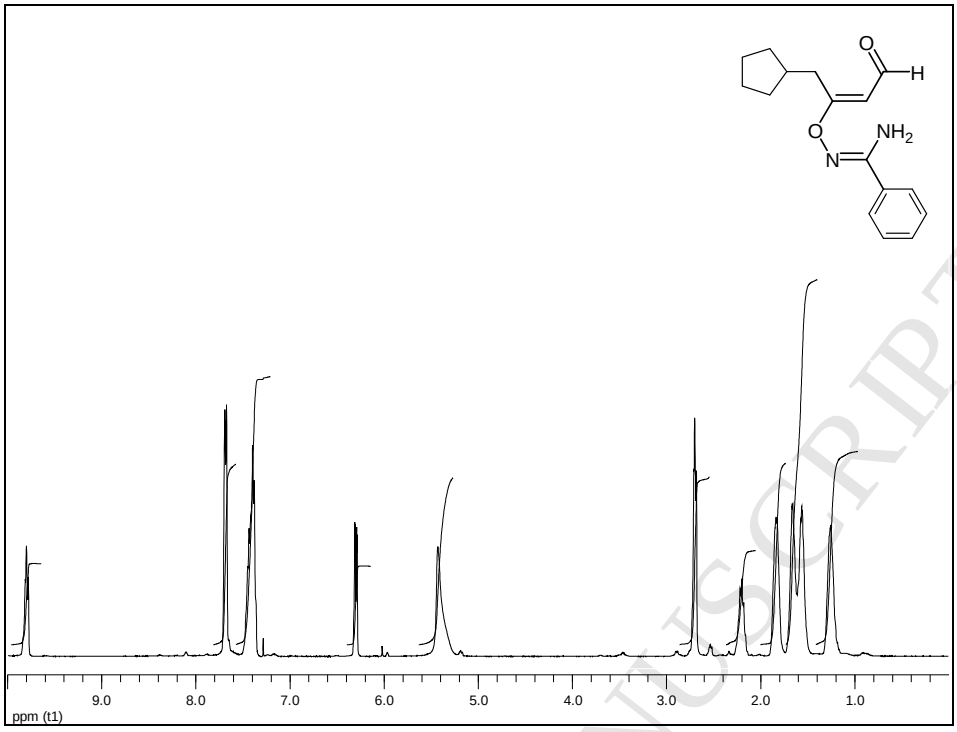

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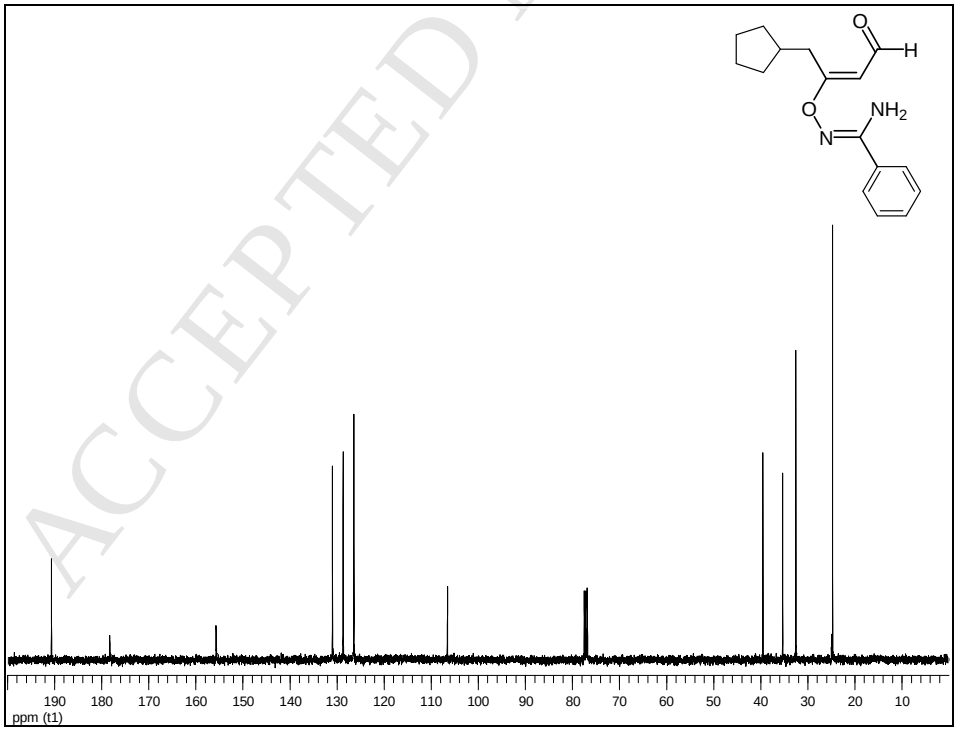

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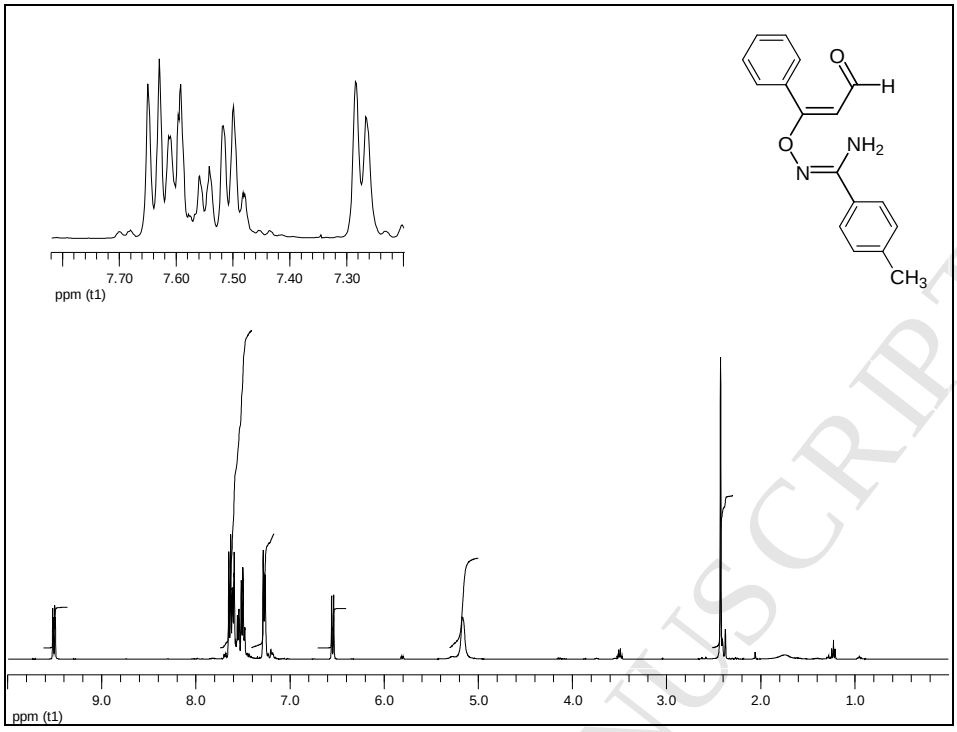

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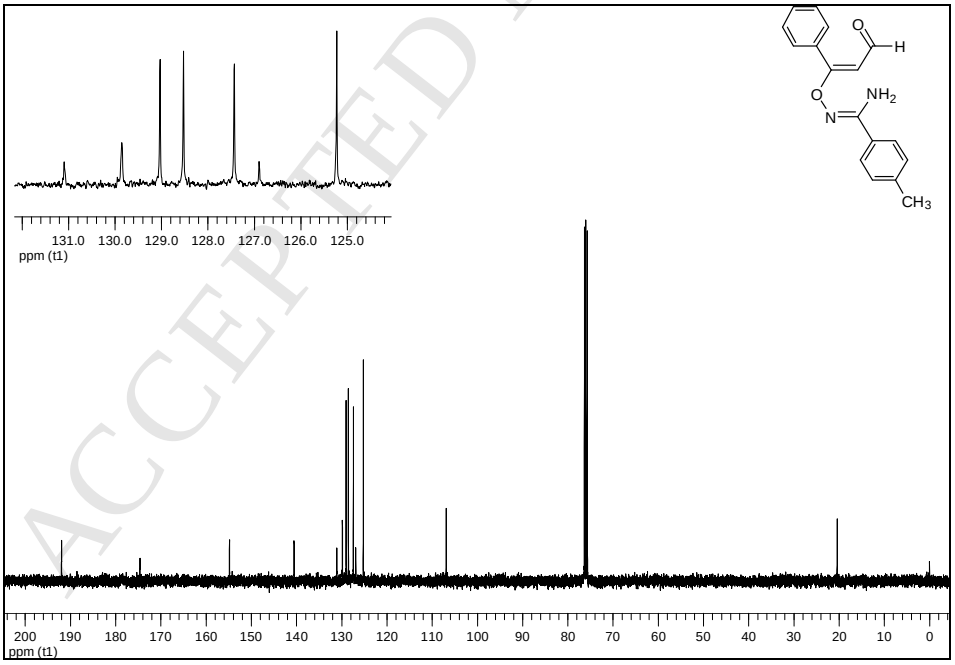

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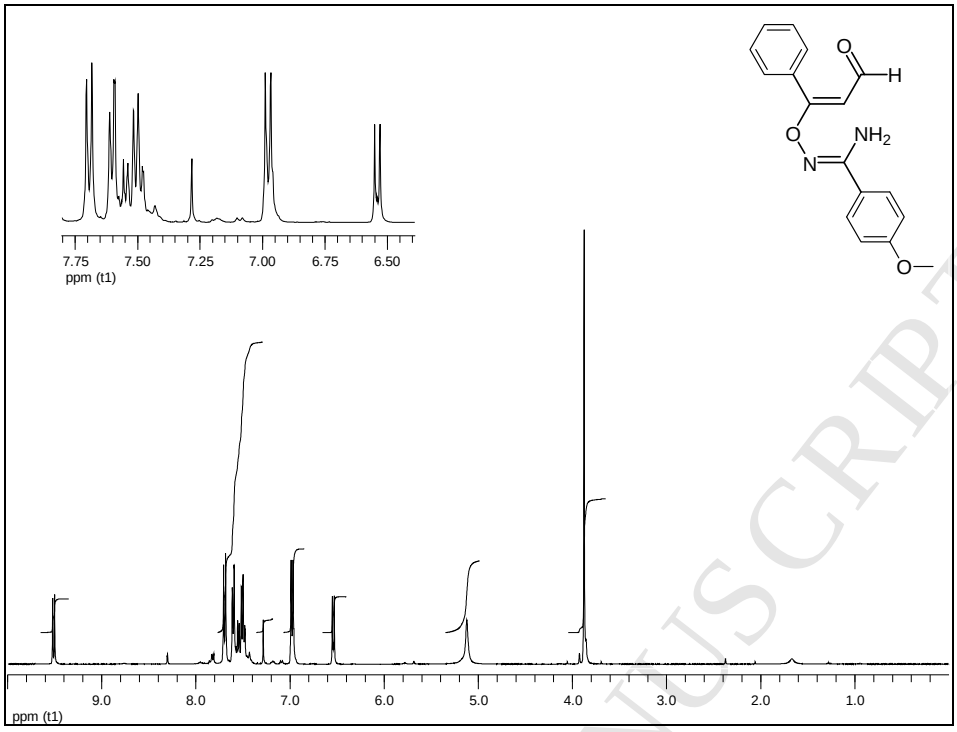

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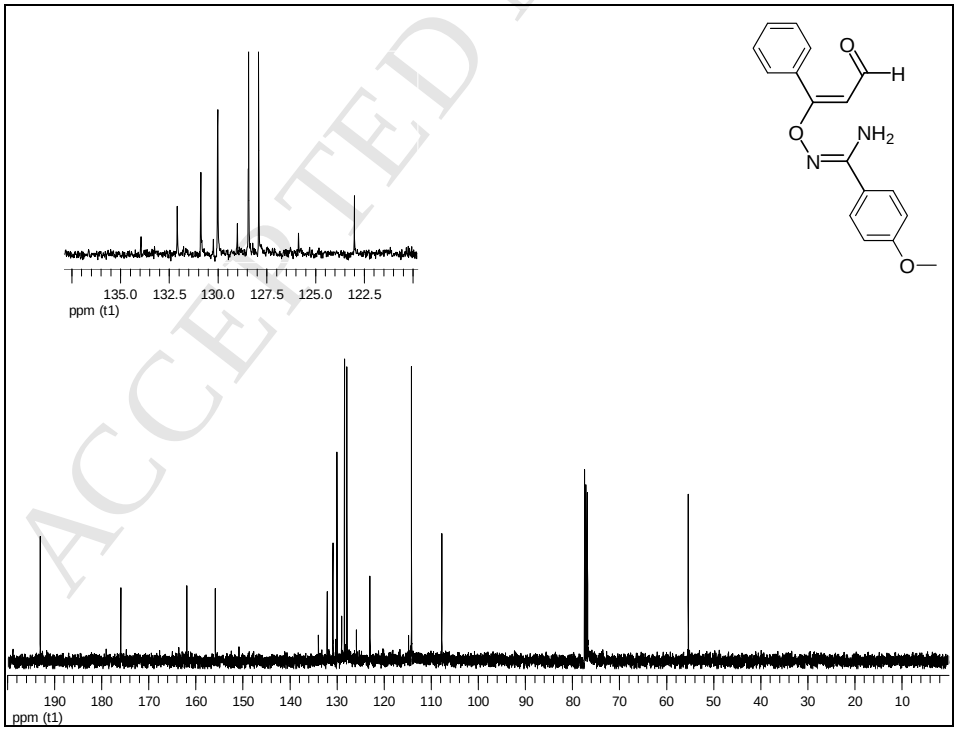

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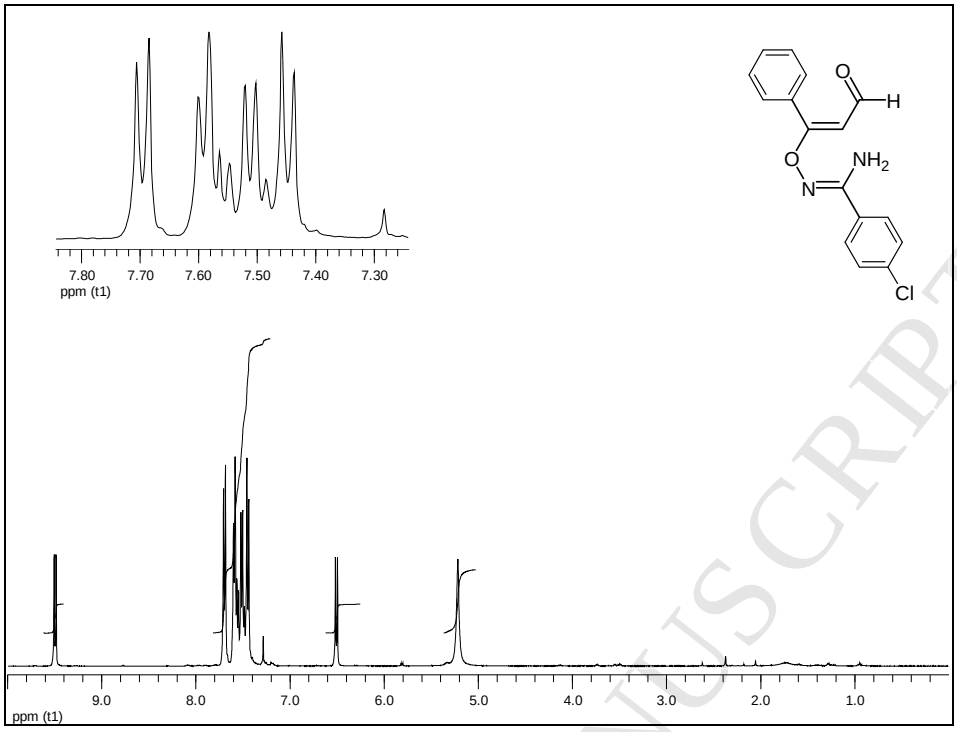

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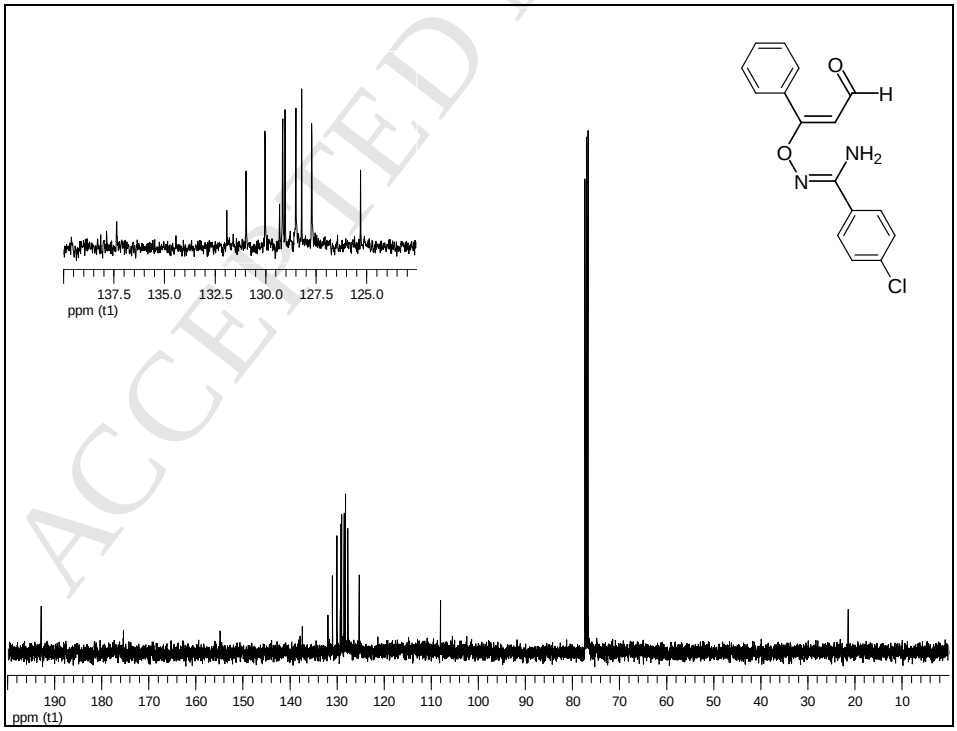

Figure S18. ^{13}C NMR spectrum of **11i**.

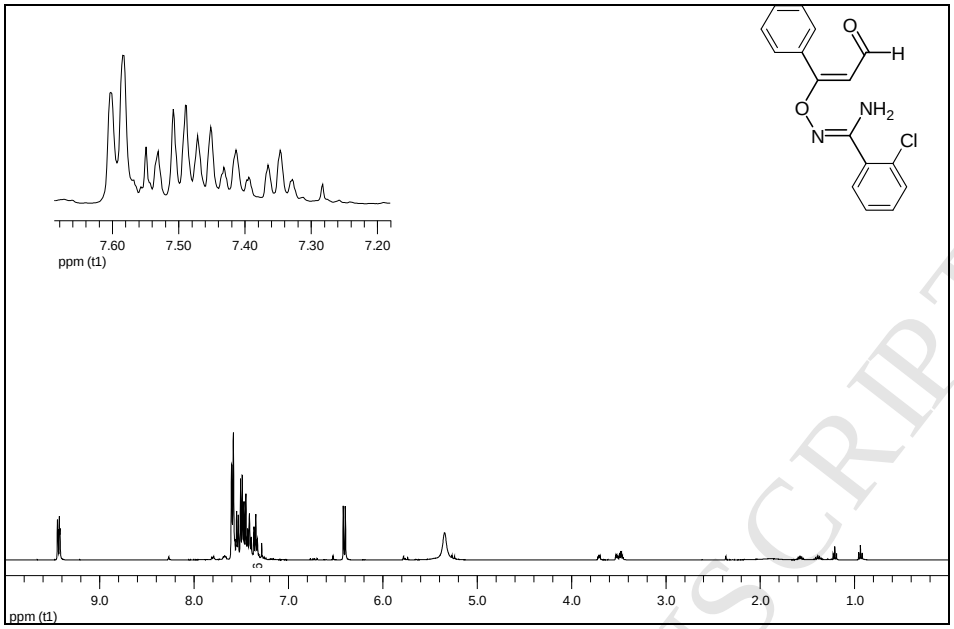

Figure S19. ^{1}H NMR spectrum of **11j**.

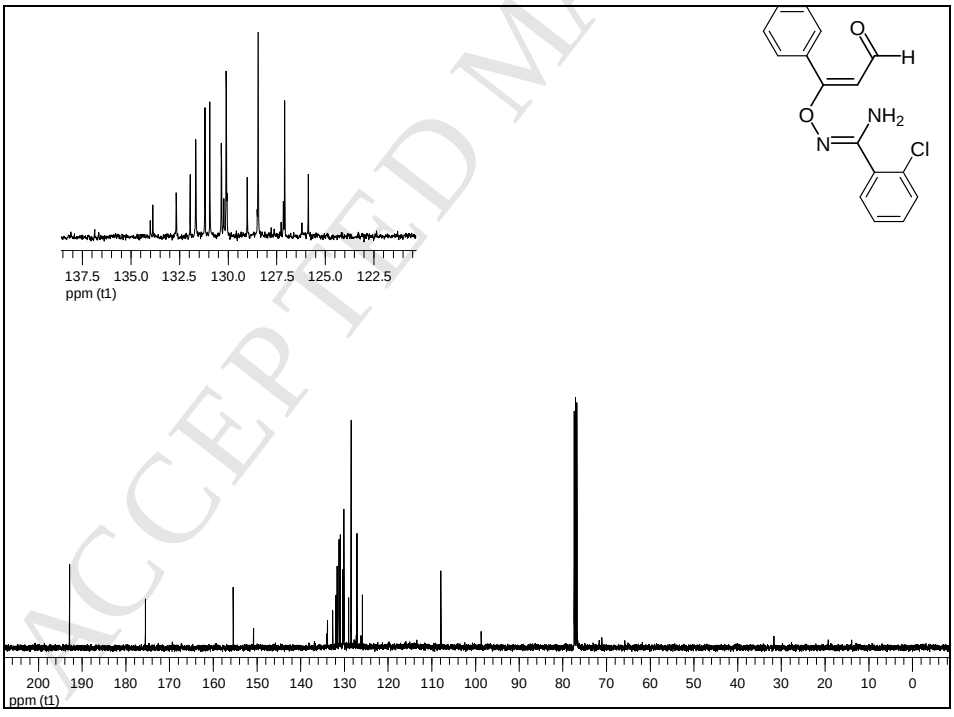

Figure S20. ^{13}C NMR spectrum of **11j**.

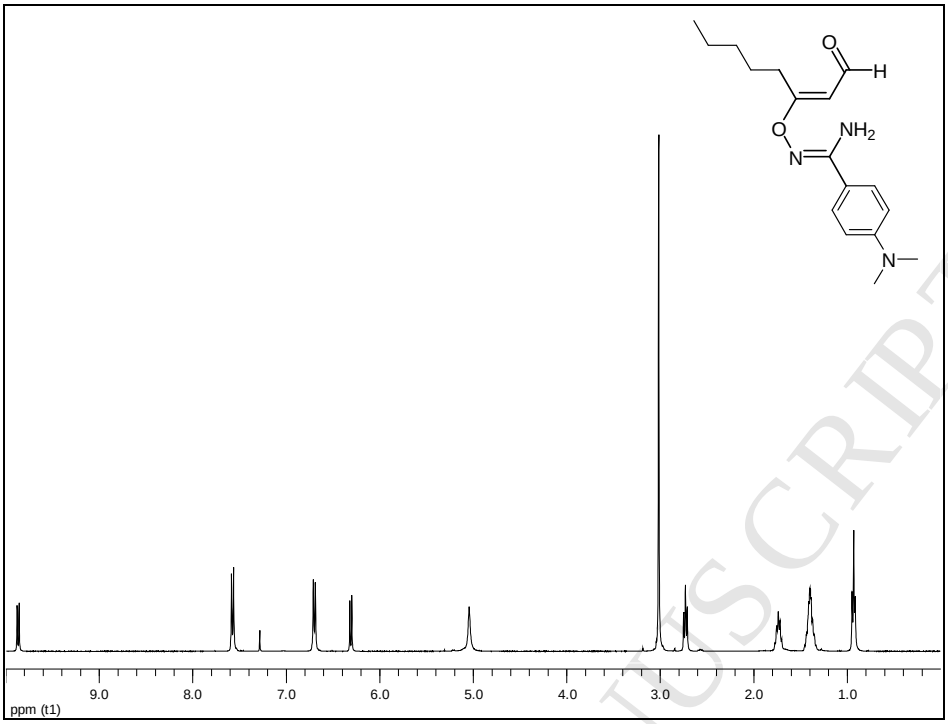

Figure S21. ^{1}H NMR spectrum of **11k**.

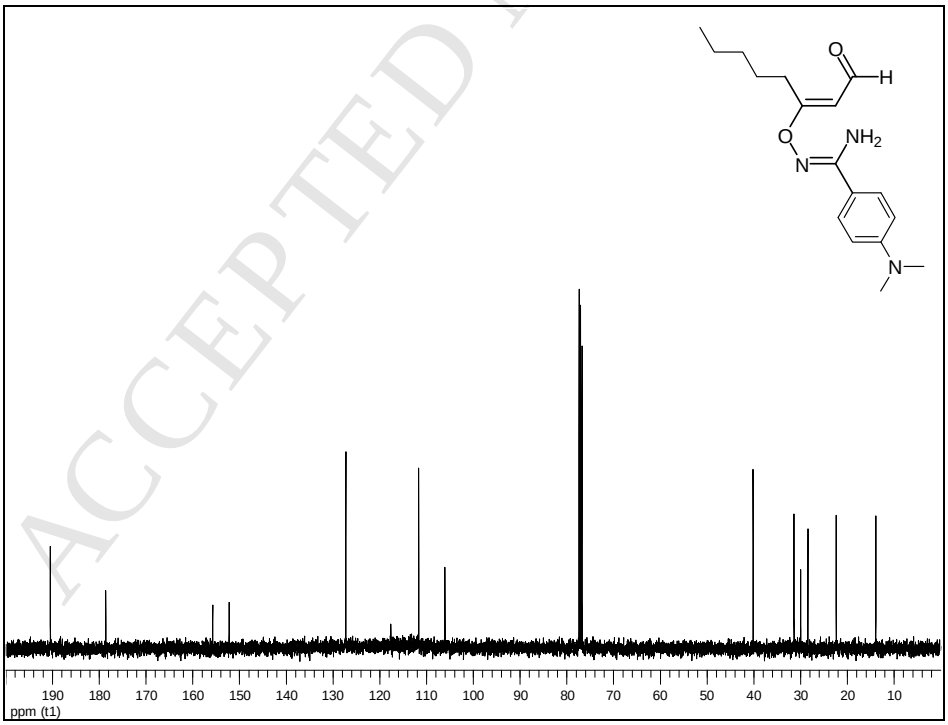

Figure S22. ^{13}C NMR spectrum of **11k**.

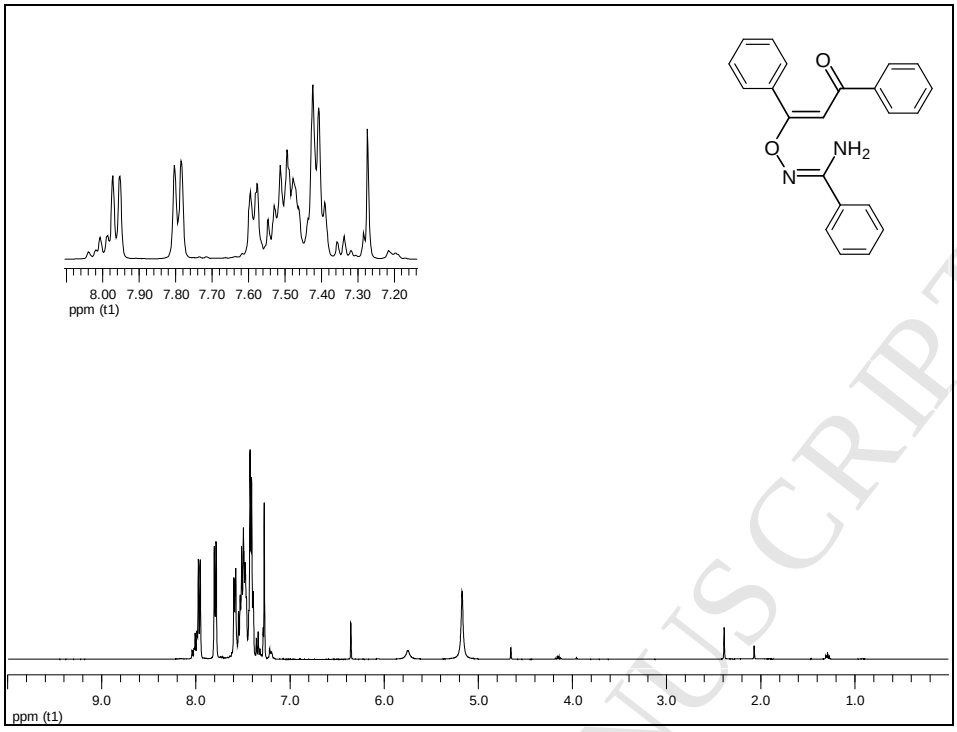

Figure S23. ^{1}H NMR spectrum of **11l**.

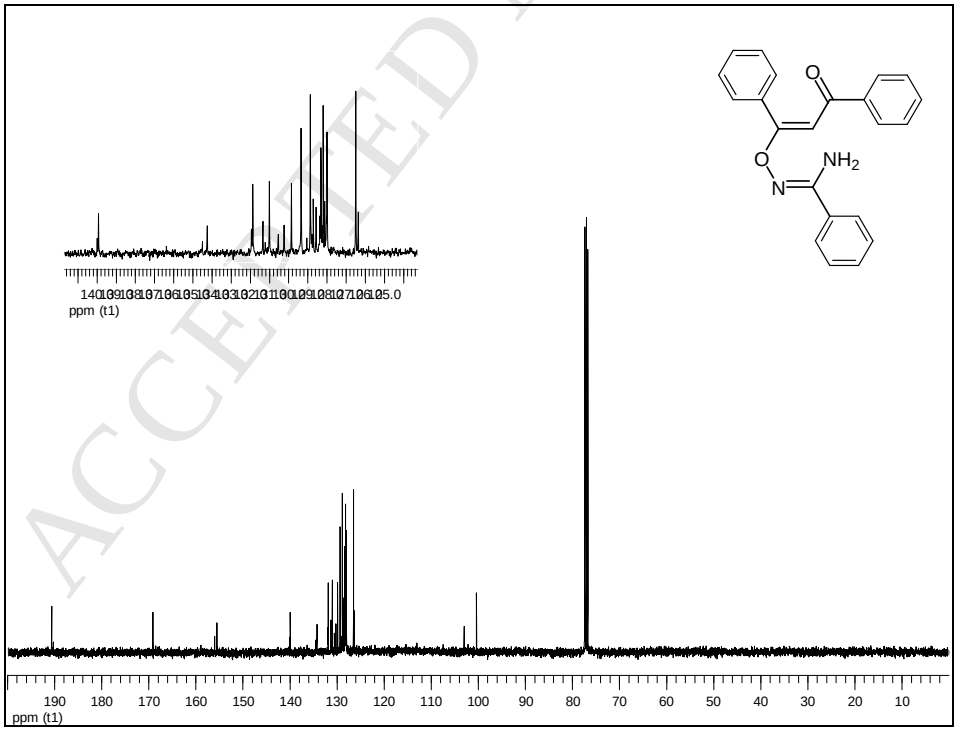

Figure S24. ^{13}C NMR spectrum of **11l**.

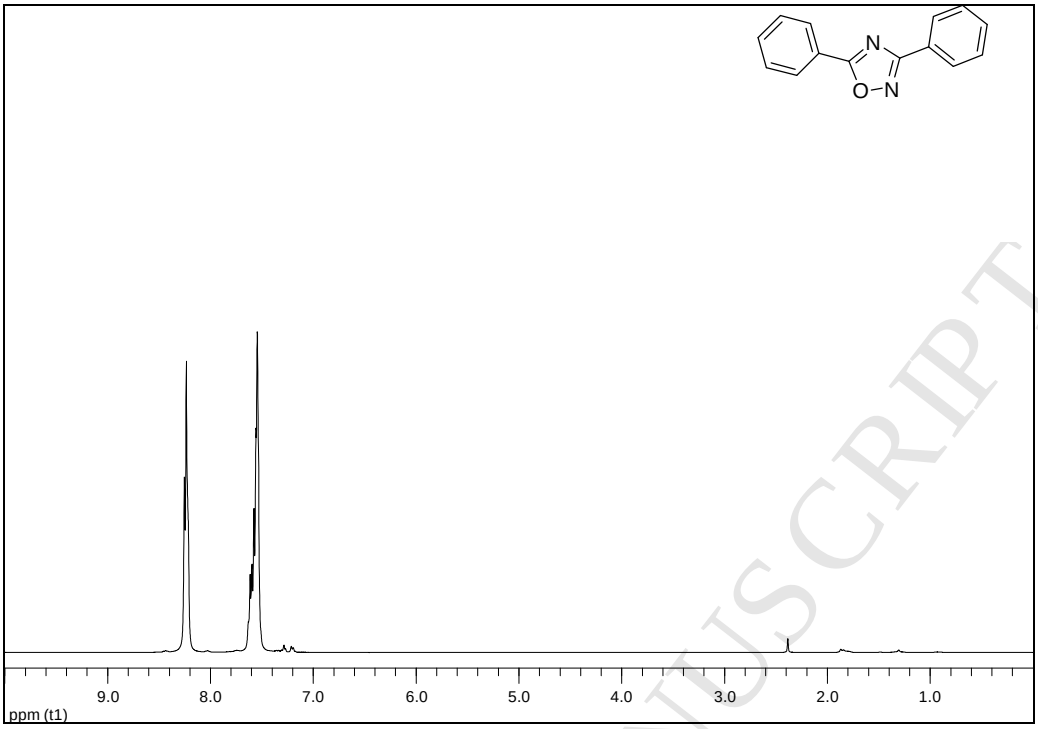

Figure S25. ^{1}H NMR spectrum of **13a**.

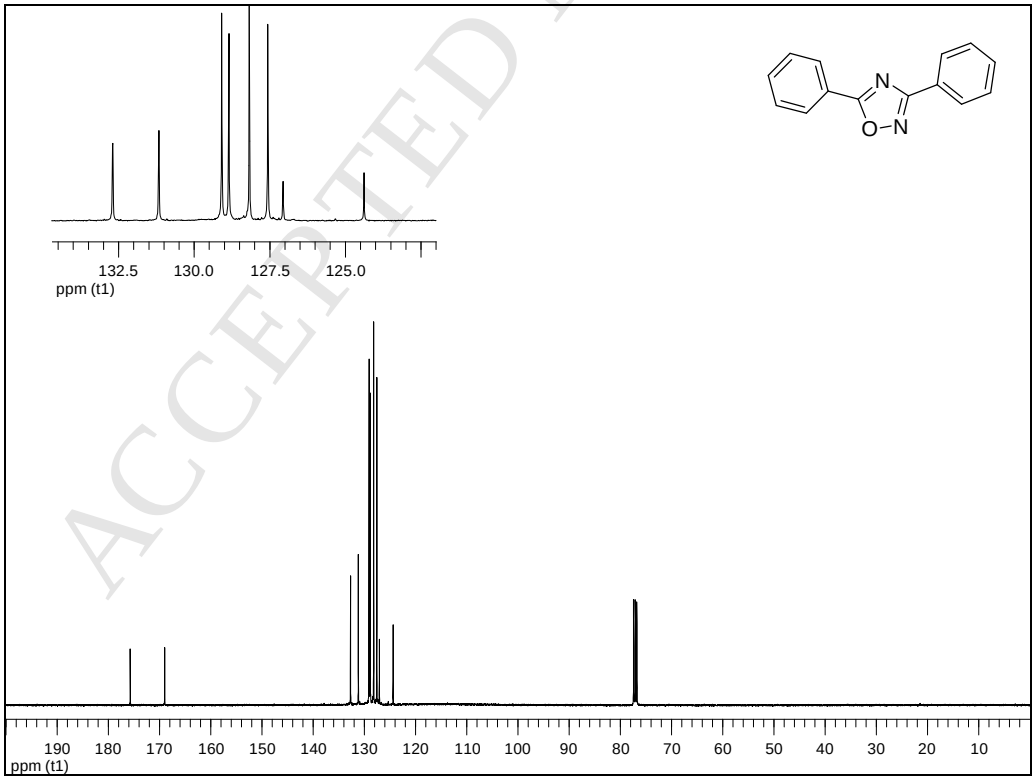

Figure S26. ^{13}C NMR spectrum of **13a**.

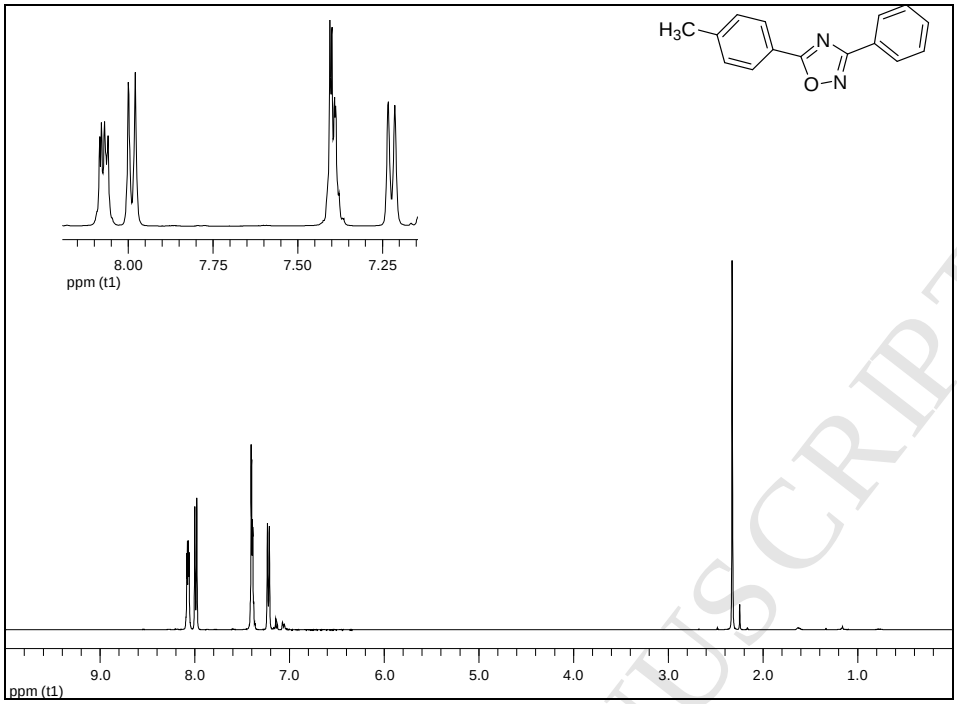

Figure S27. ^{1}H NMR spectrum of **13b**.

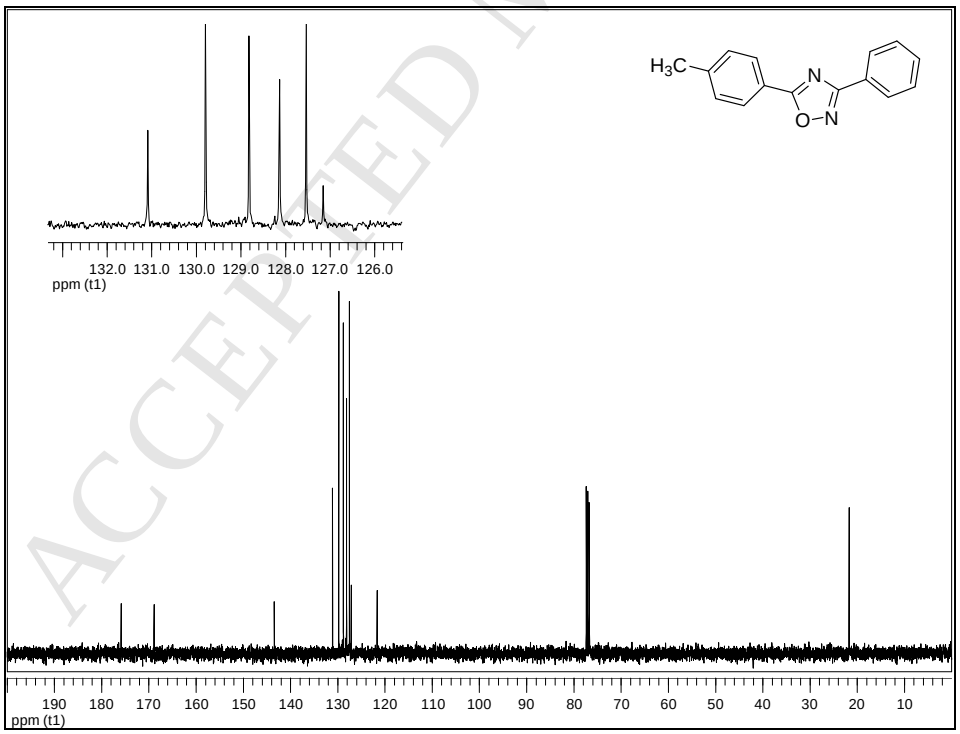

Figure S28. ^{13}C NMR spectrum of **13b**.

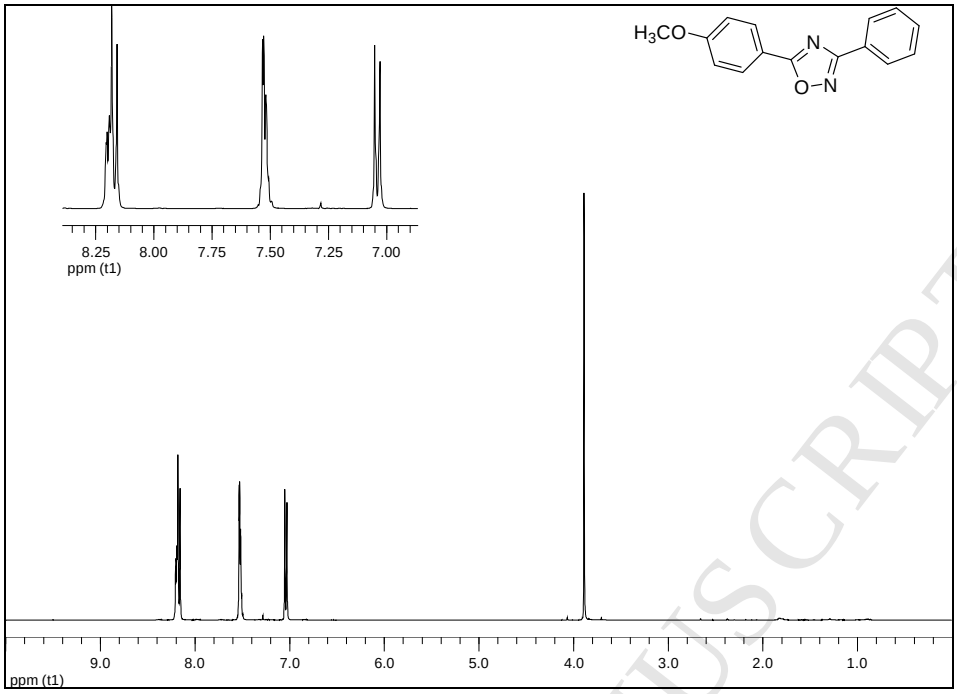

Figure S29. ^{1}H NMR spectrum of **13c**.

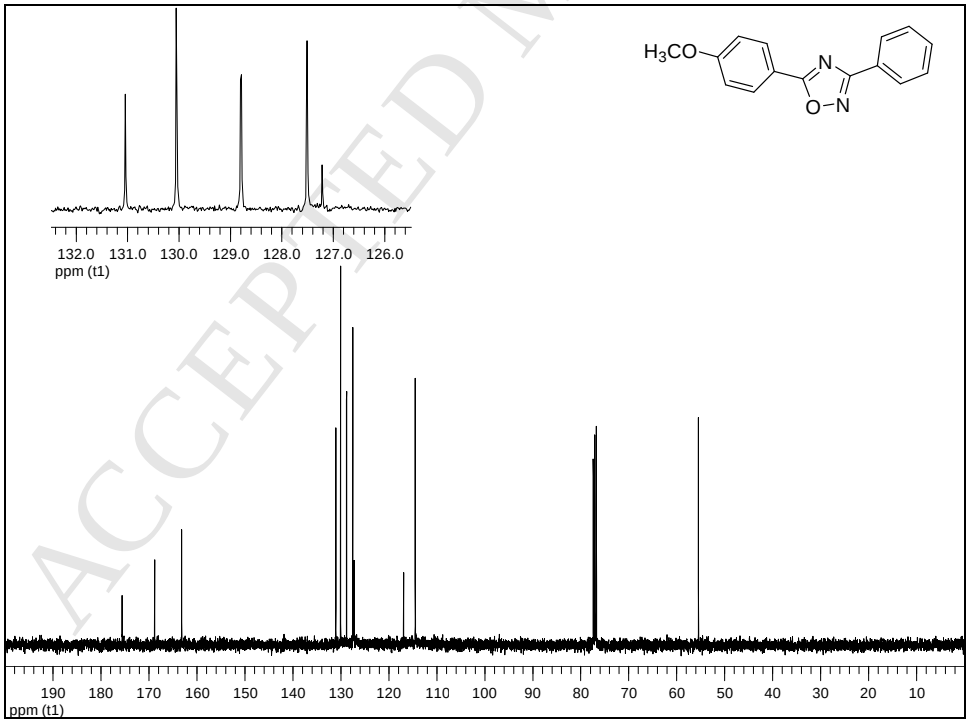

Figure S30. ^{13}C NMR spectrum of **13c**.

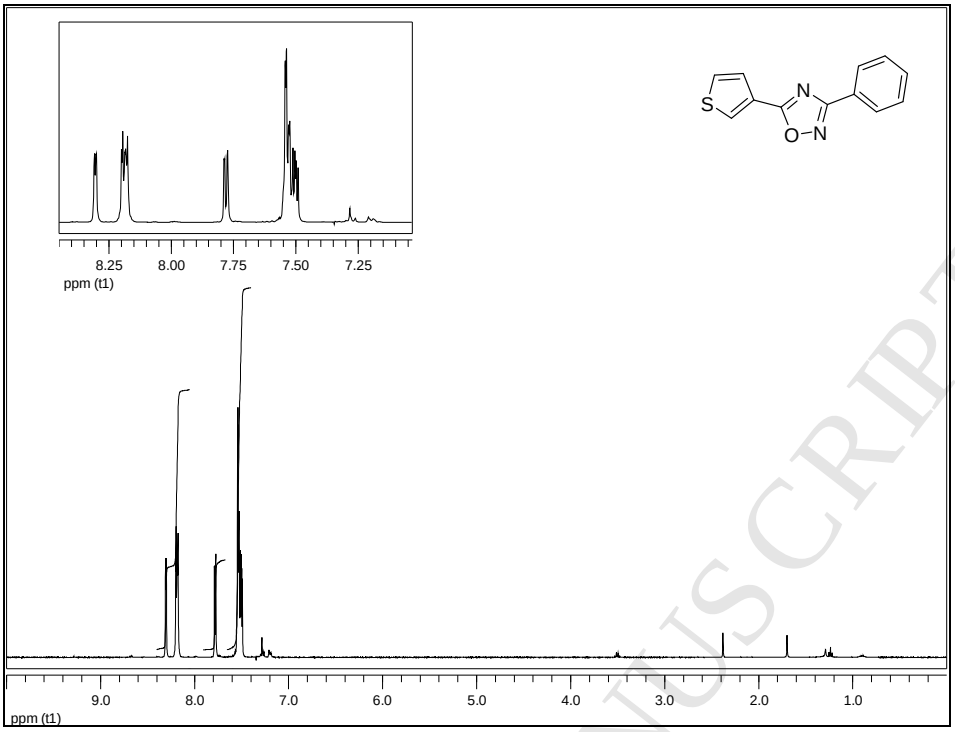

Figure S31. ^{1}H NMR spectrum of **13d**.

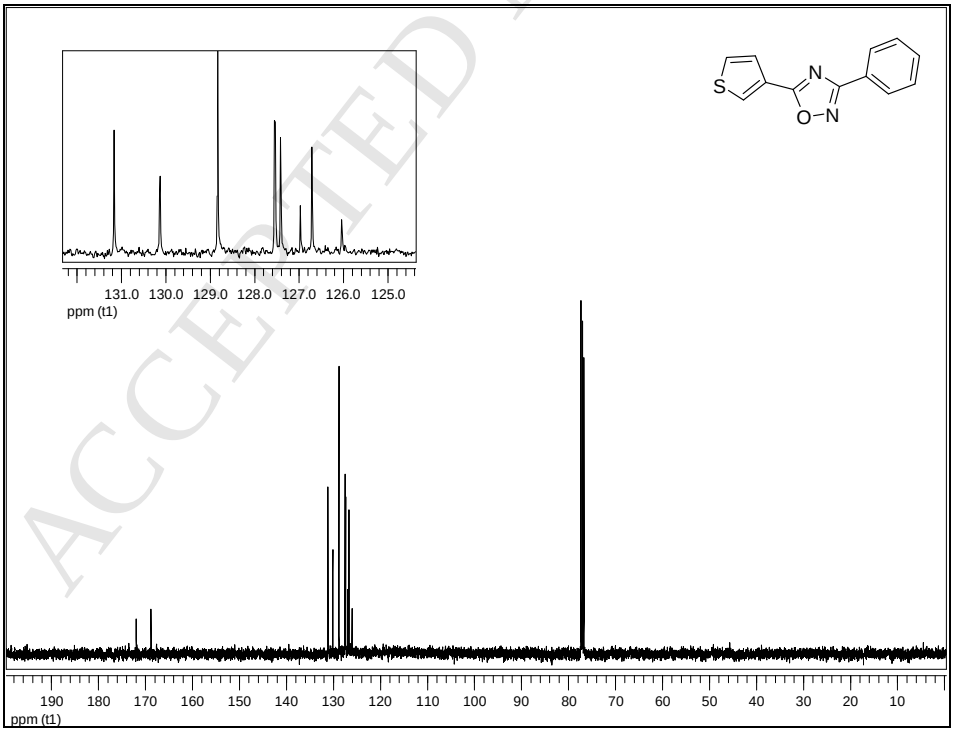

Figure S32. ^{13}C NMR spectrum of **13d**.

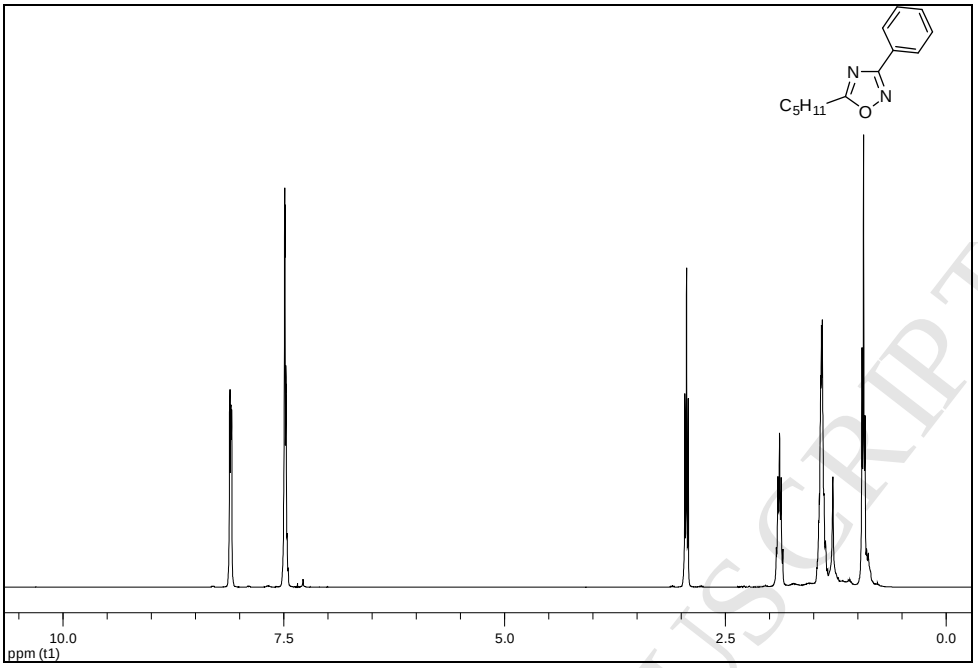

Figure S33. ^{1}H NMR spectrum of **13e**.

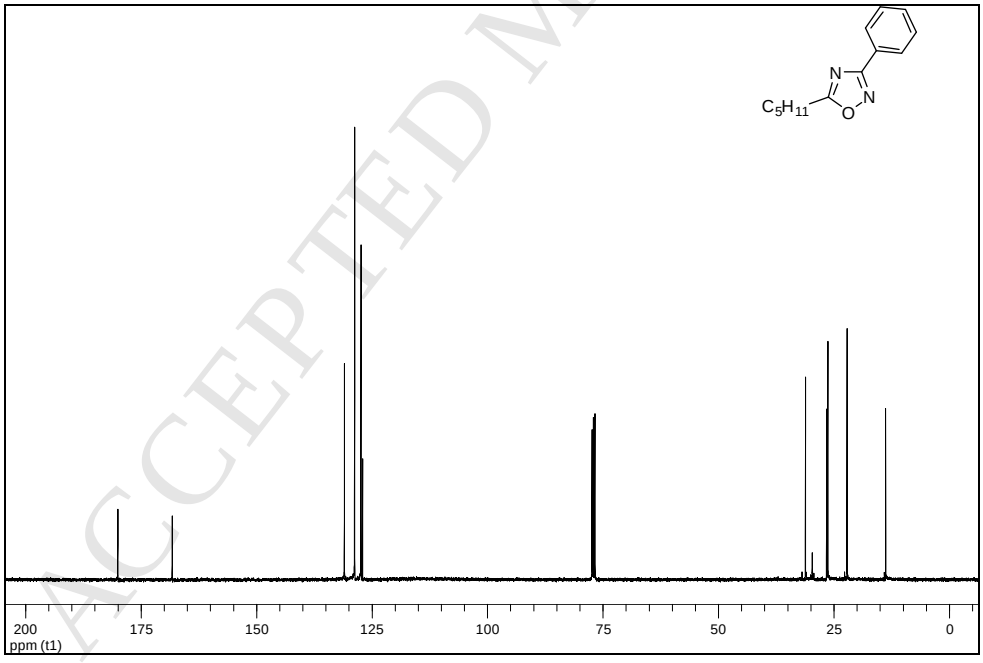

Figure S34. ^{13}C NMR spectrum of **13e**.

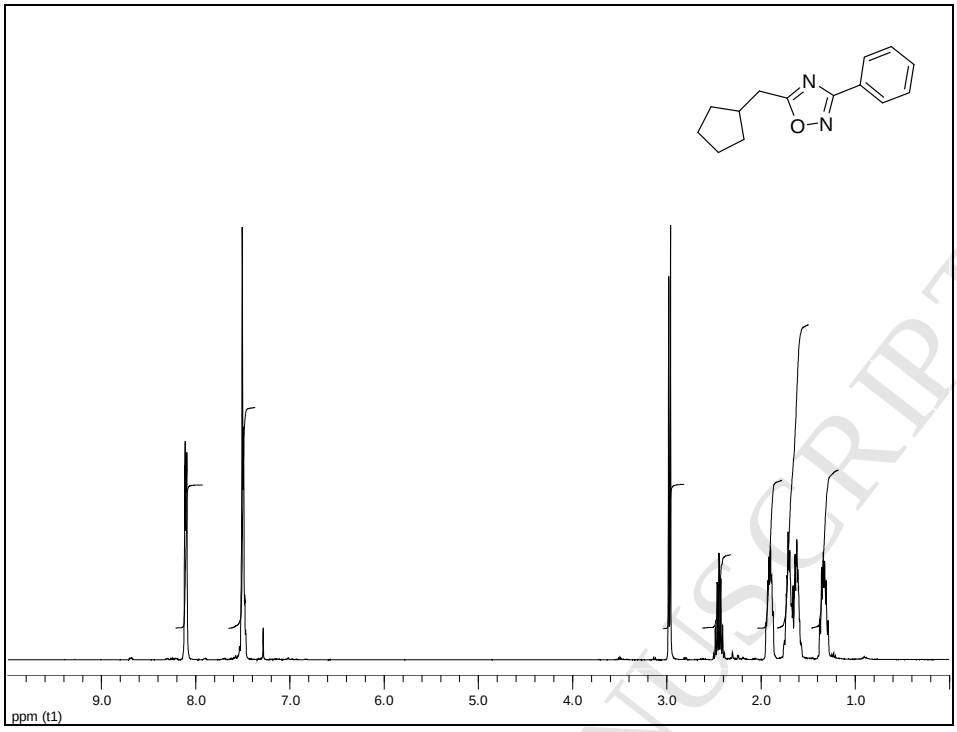

Figure S35. ^{1}H NMR spectrum of **13f**.

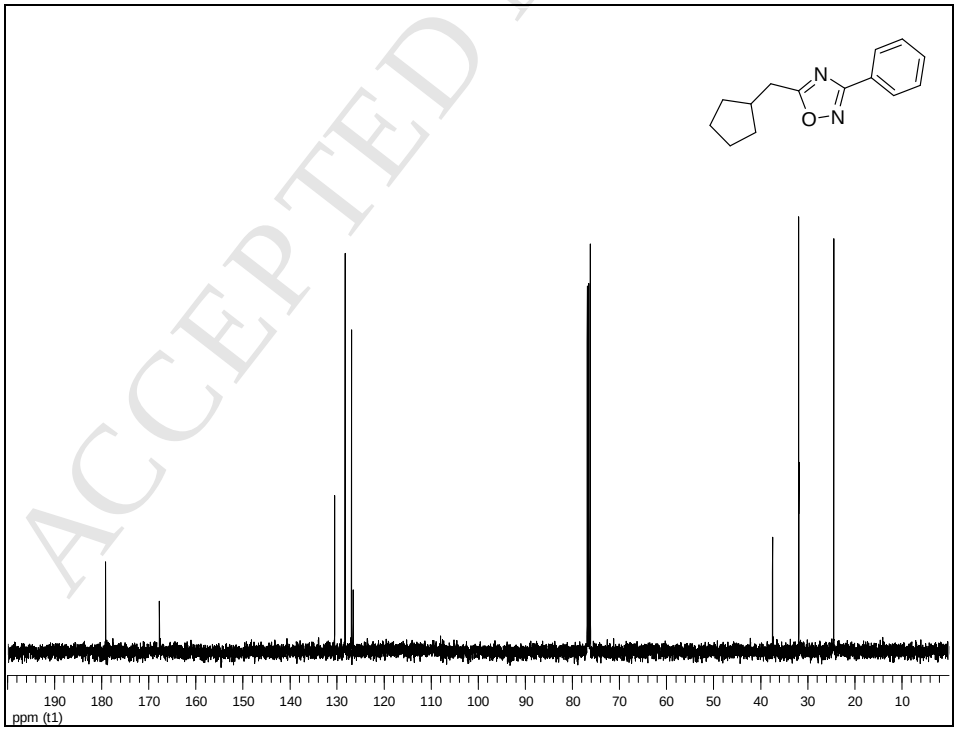

Figure S36. ^{13}C NMR spectrum of **13f**.

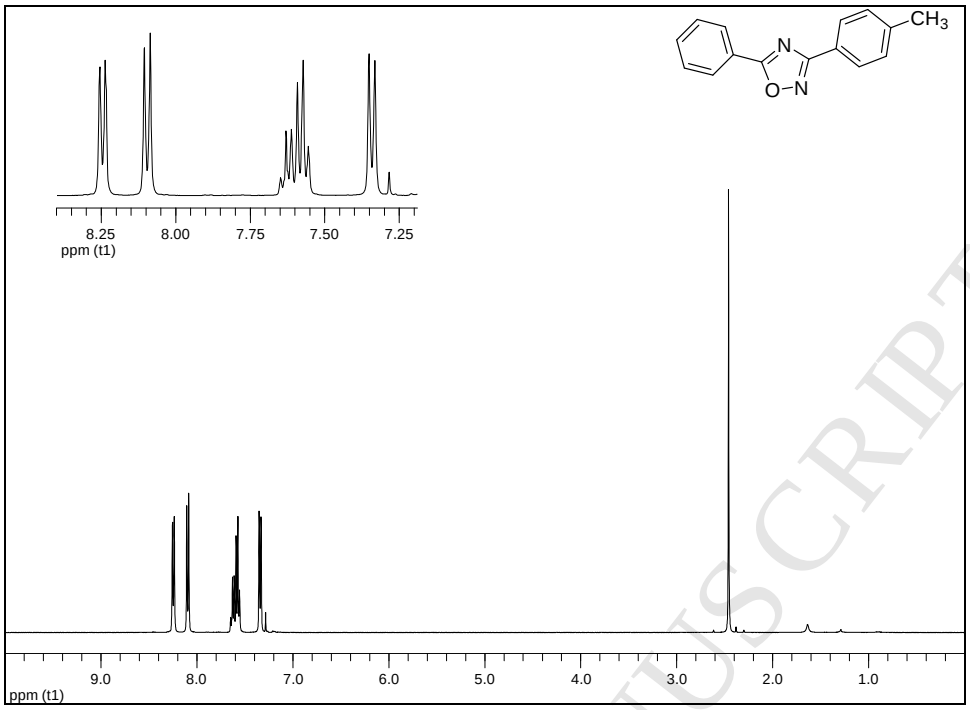

Figure S37. ^{1}H NMR spectrum of **13g**.

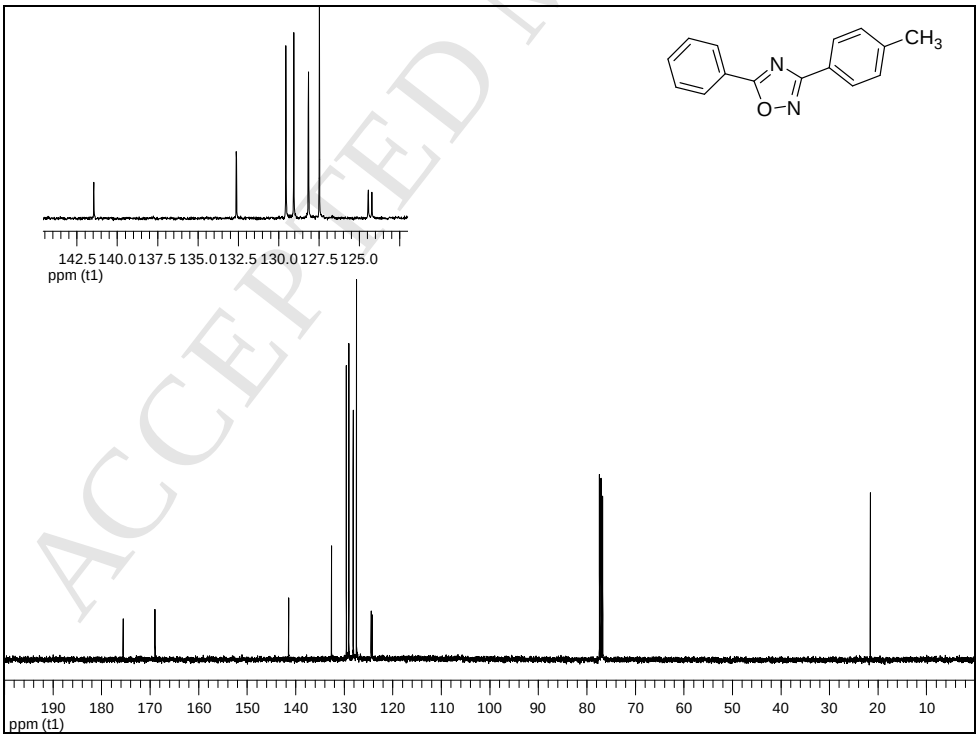

Figure S38. ^{13}C NMR spectrum of **13g**.

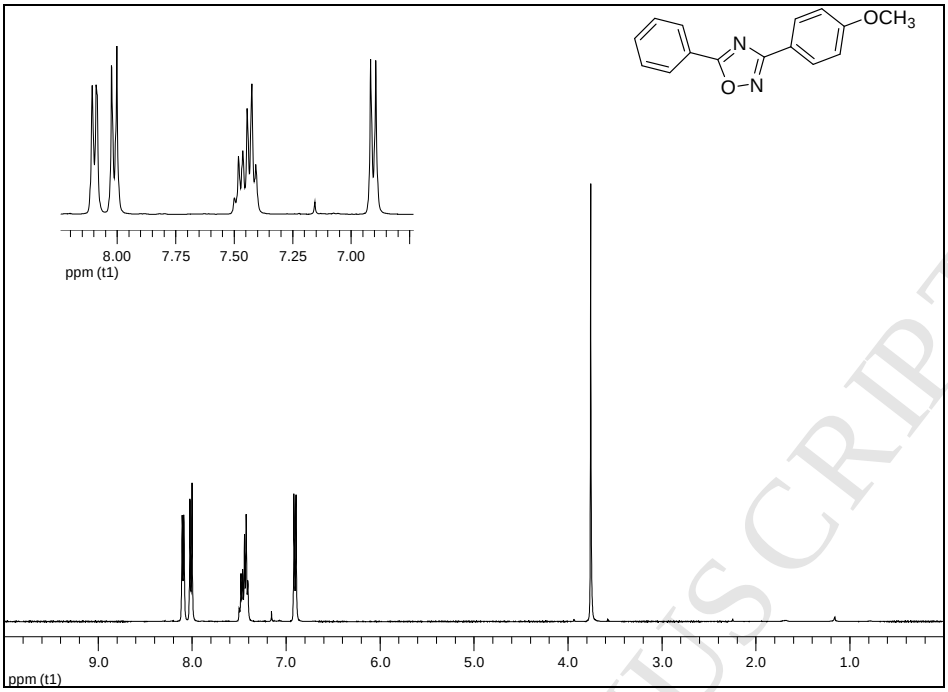

Figure S39. ^{1}H NMR spectrum of **13h**.

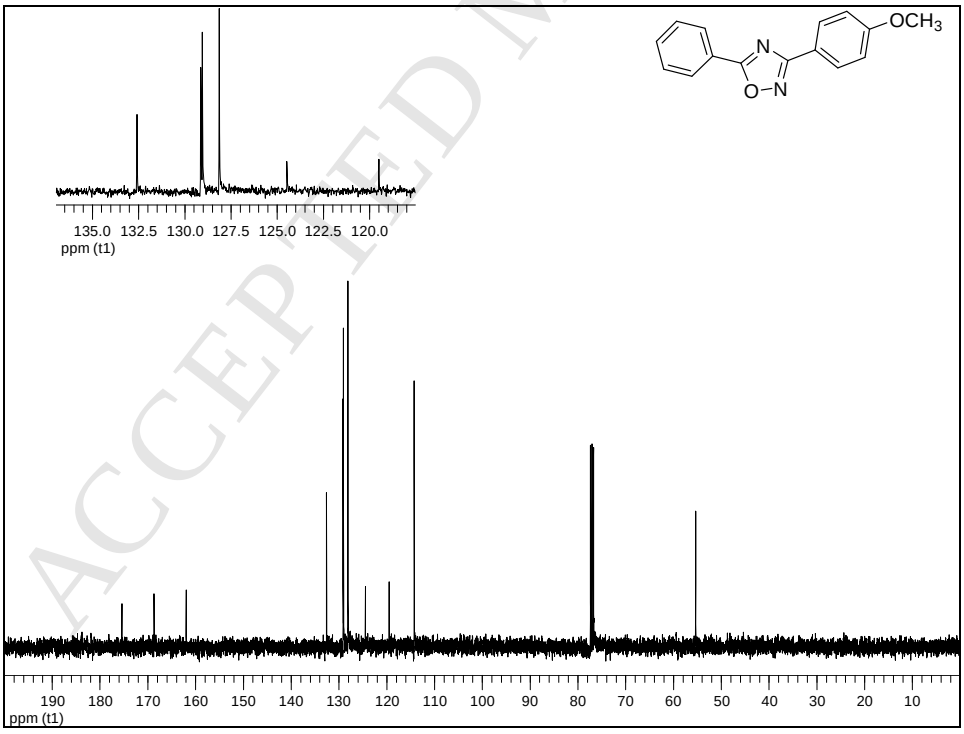

Figure S40. ^{13}C NMR spectrum of **13h**.

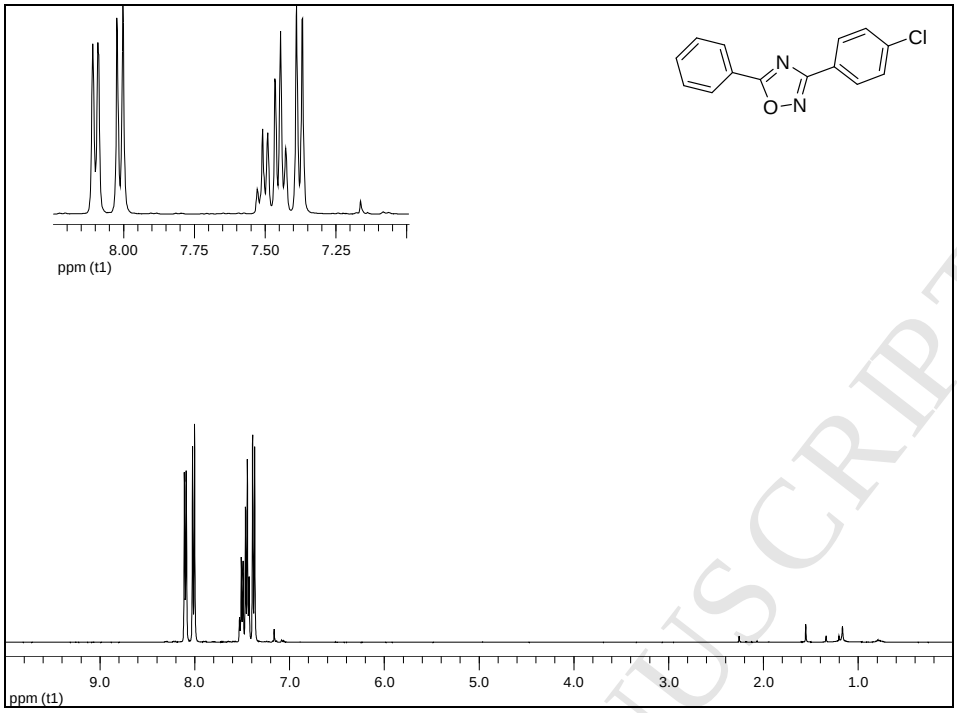

Figure S41. ^{1}H NMR spectrum of **13i**.

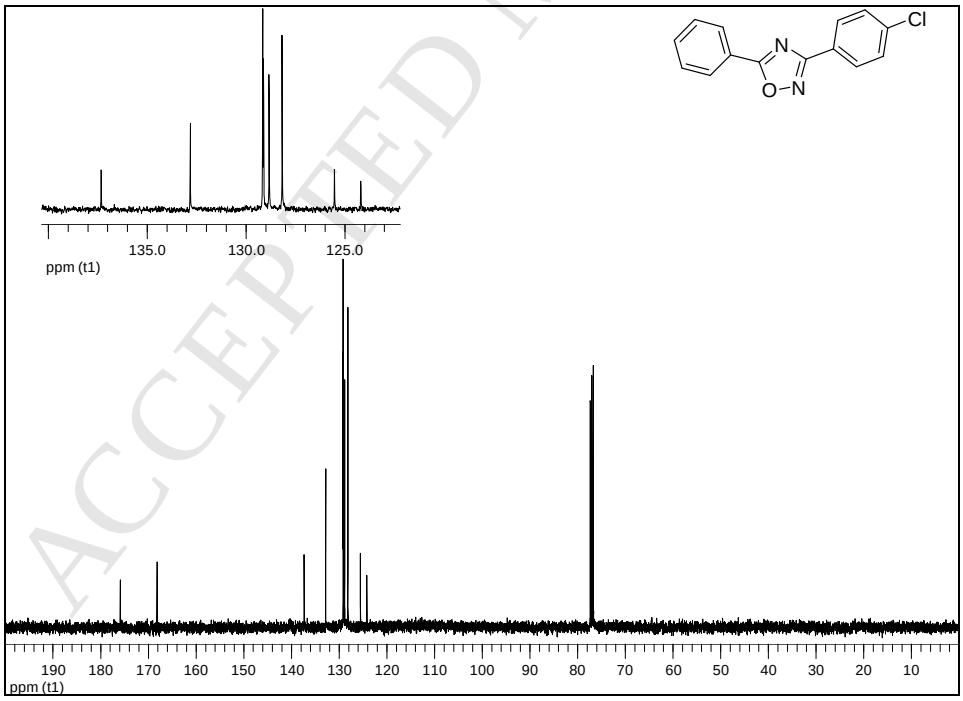

Figure S42. ^{13}C NMR spectrum of **13i**.

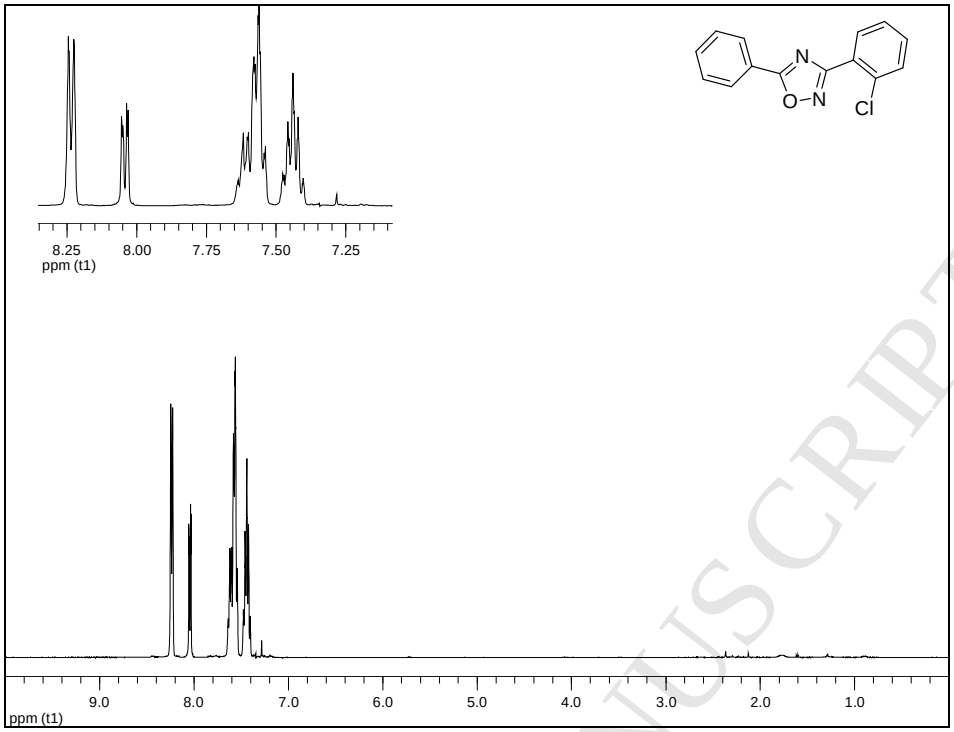

Figure S43. ^{1}H NMR spectrum of **13j**.

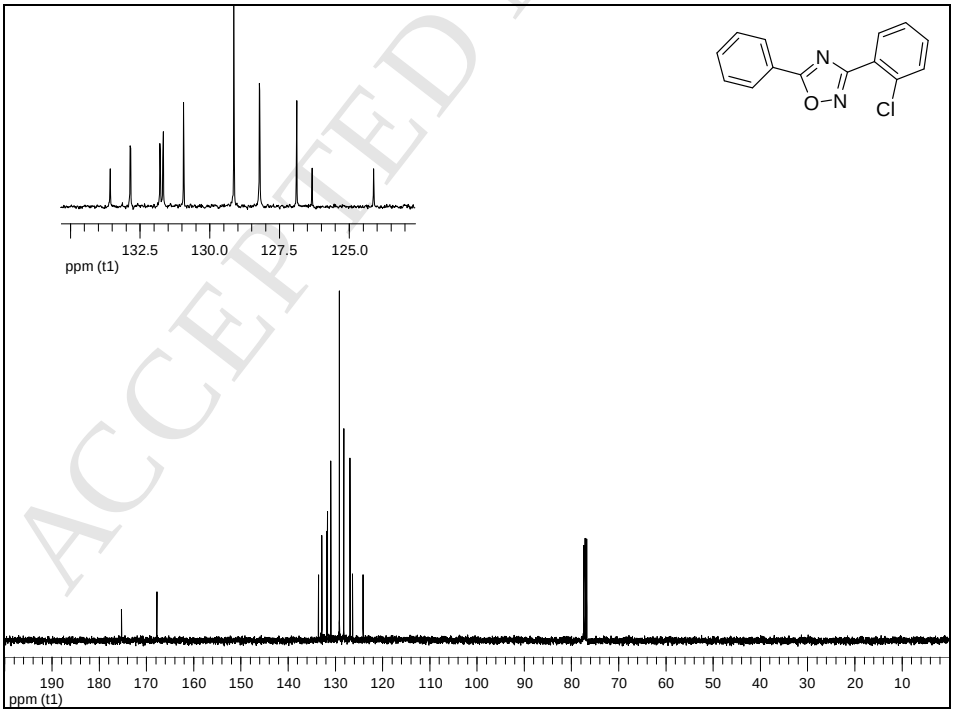

Figure S44. ^{13}C NMR spectrum of **13j**.

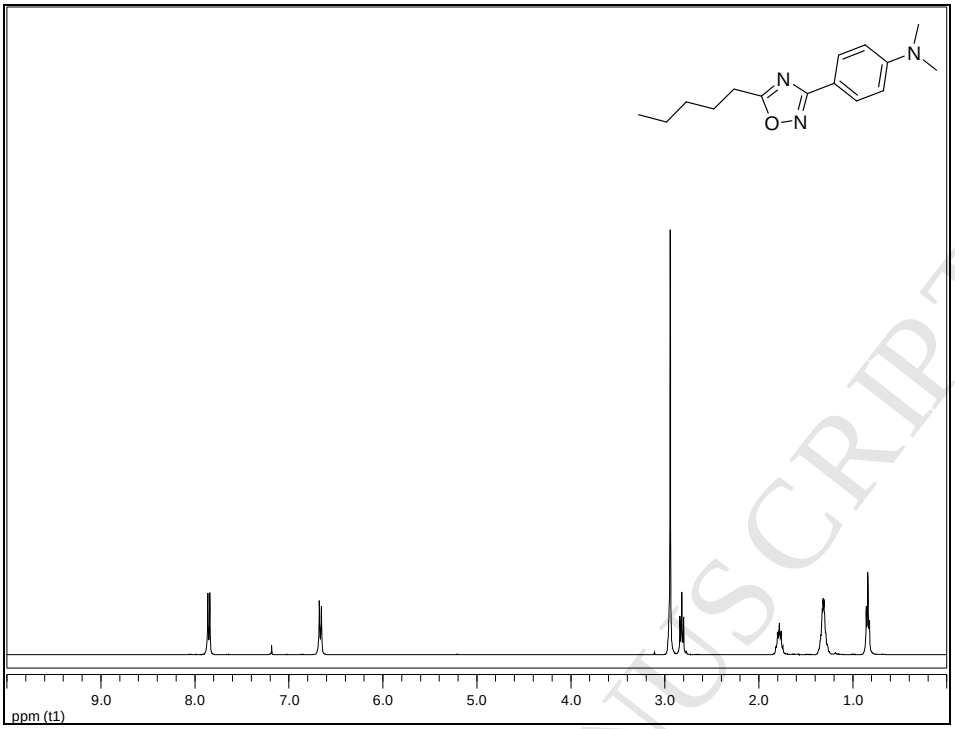

Figure S45. ^{1}H NMR spectrum of **13k**.

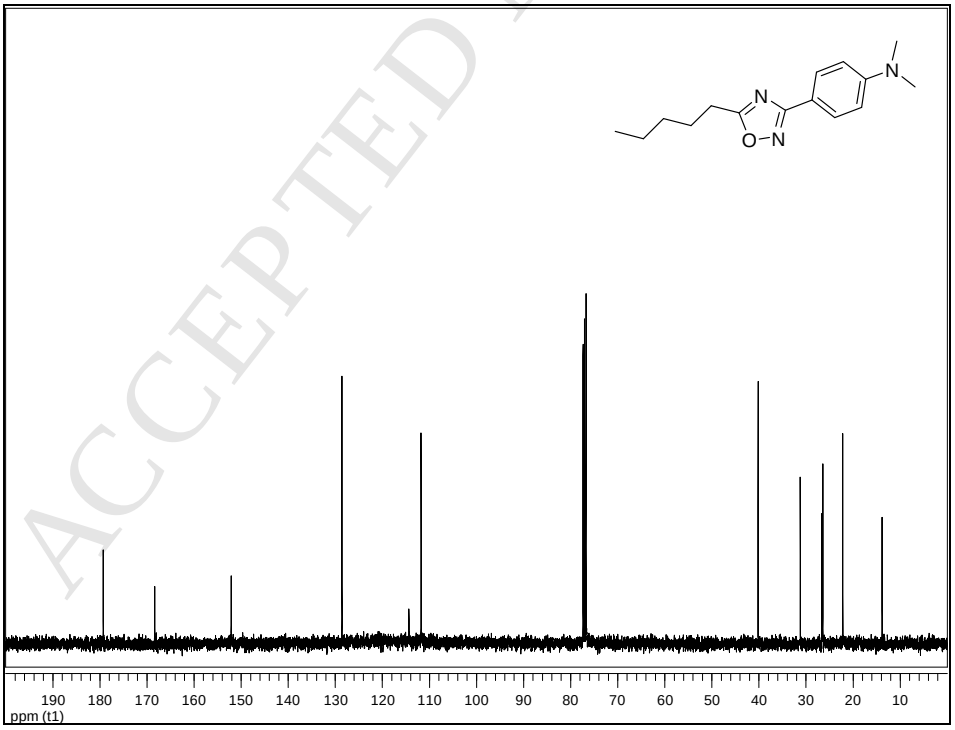

Figure S46. ^{13}C NMR spectrum of **13k**.

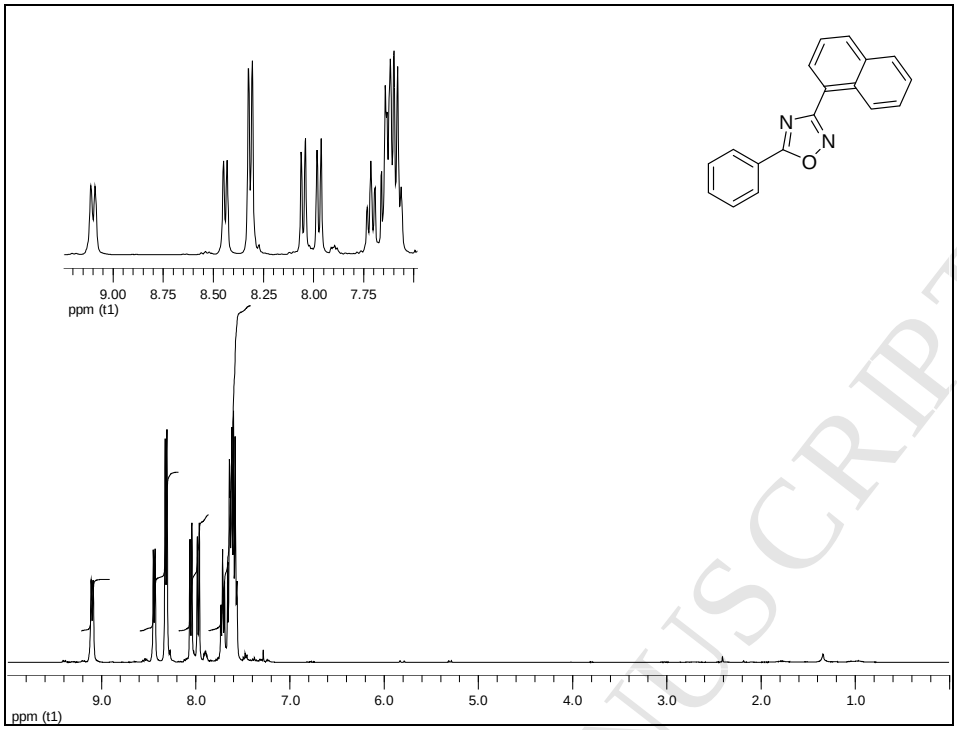

Figure S47. ^{1}H NMR spectrum of **13m**.

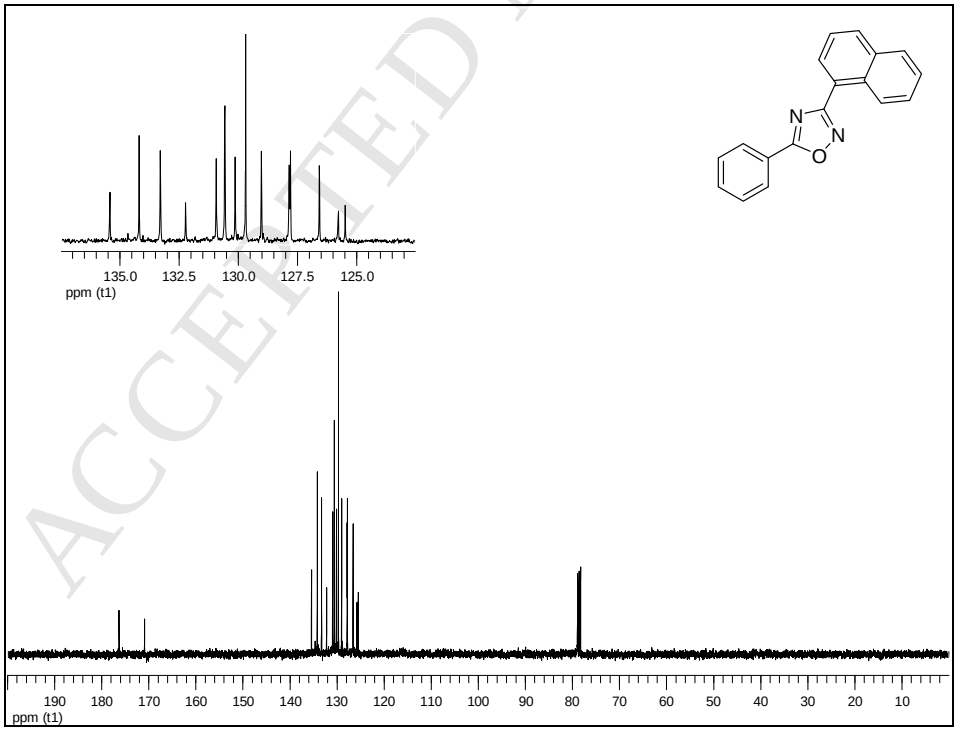

Figure S48. ^{13}C NMR spectrum of **13m**.

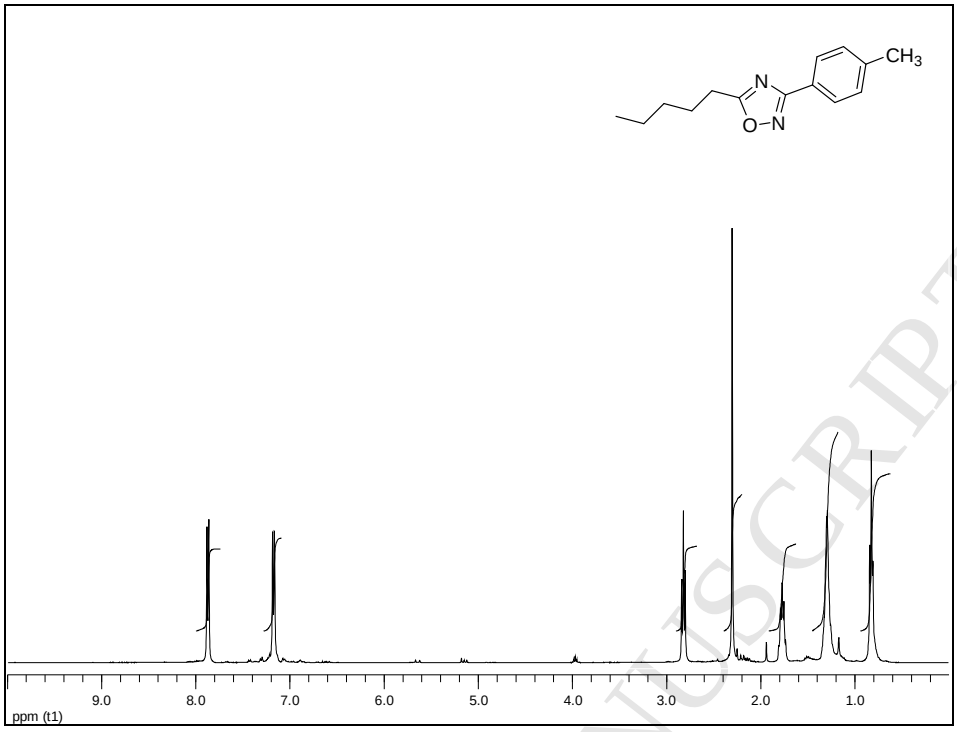

Figure S49. ^{1}H NMR spectrum of **13n**.

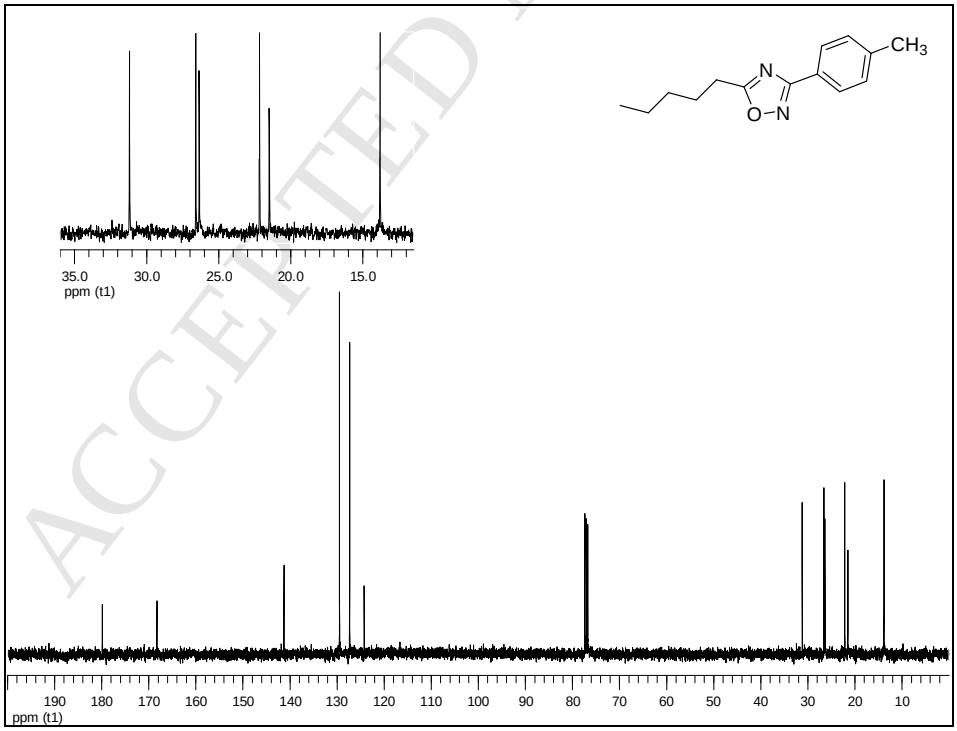

Figure S50. ^{13}C NMR spectrum of **13n**.

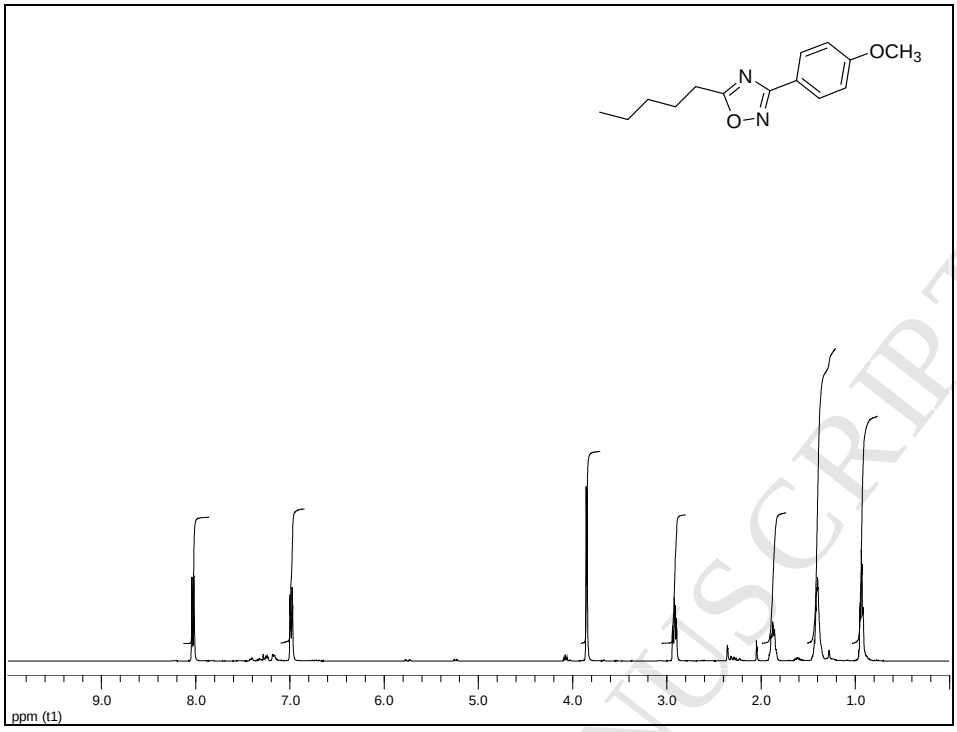

Figure S51. ^{1}H NMR spectrum of **13o**.

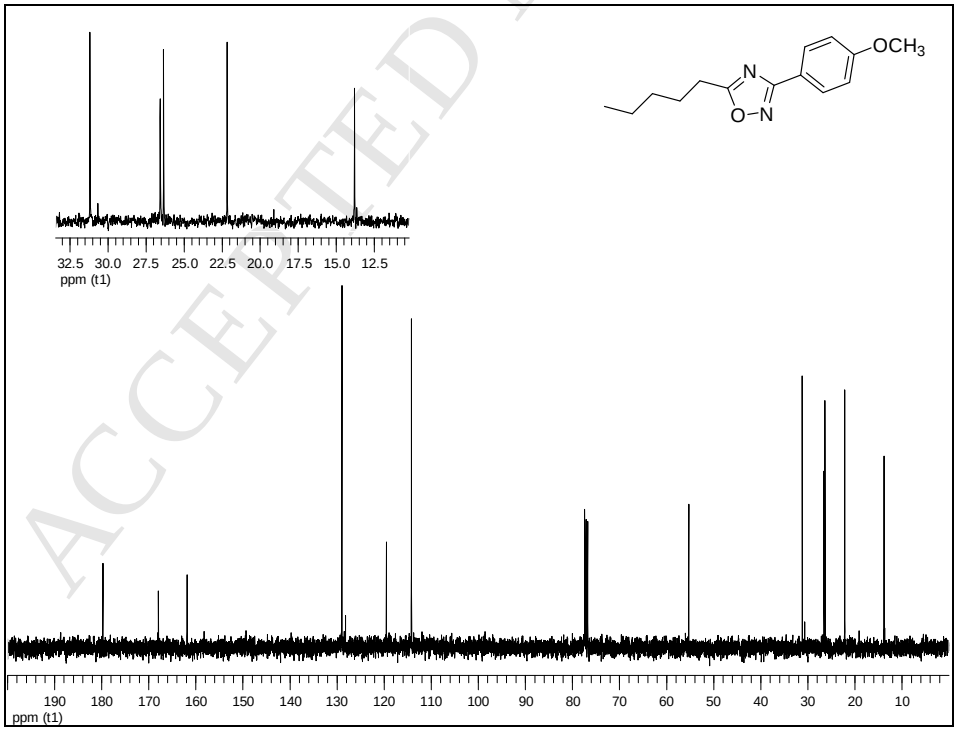

Figure S52. ^{13}C NMR spectrum of **13o**.

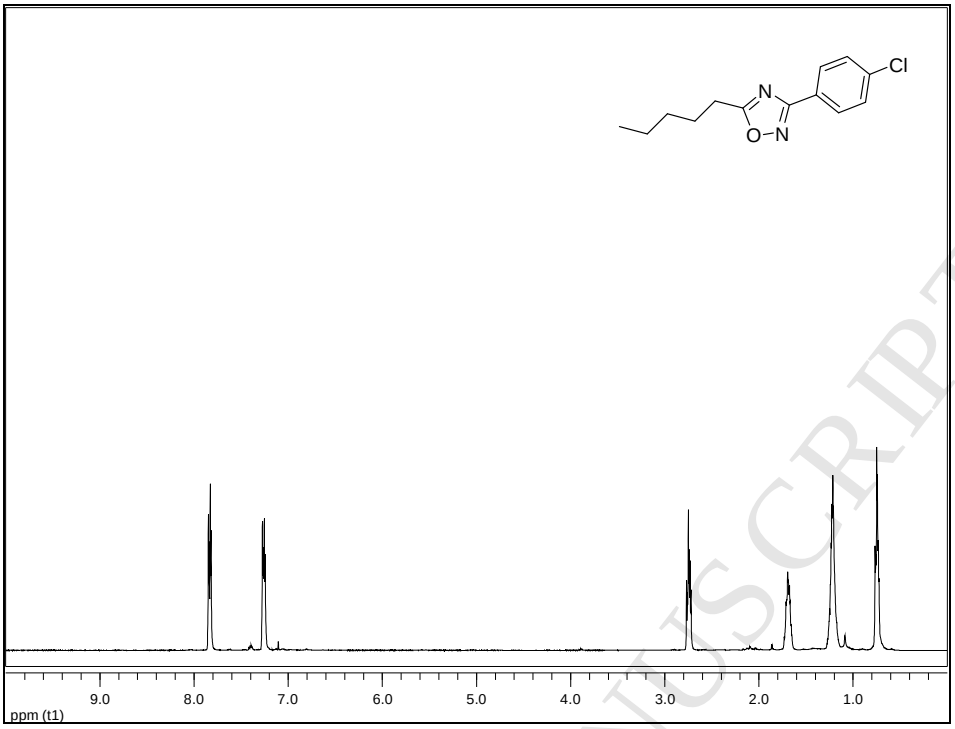

Figure S53. ^{1}H NMR spectrum of **13p**.

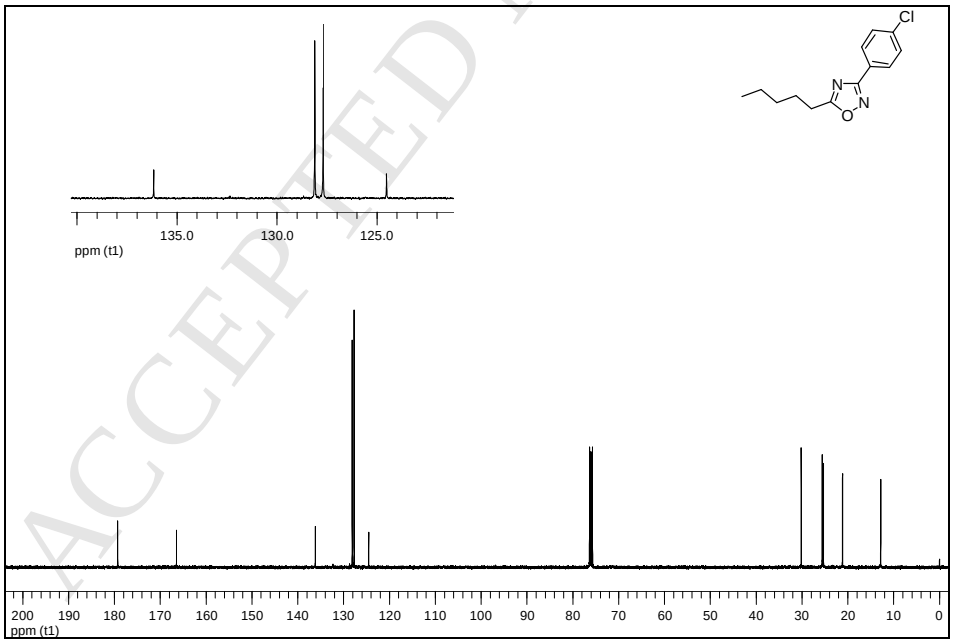

Figure S54. ^{13}C NMR spectrum of **13p**.

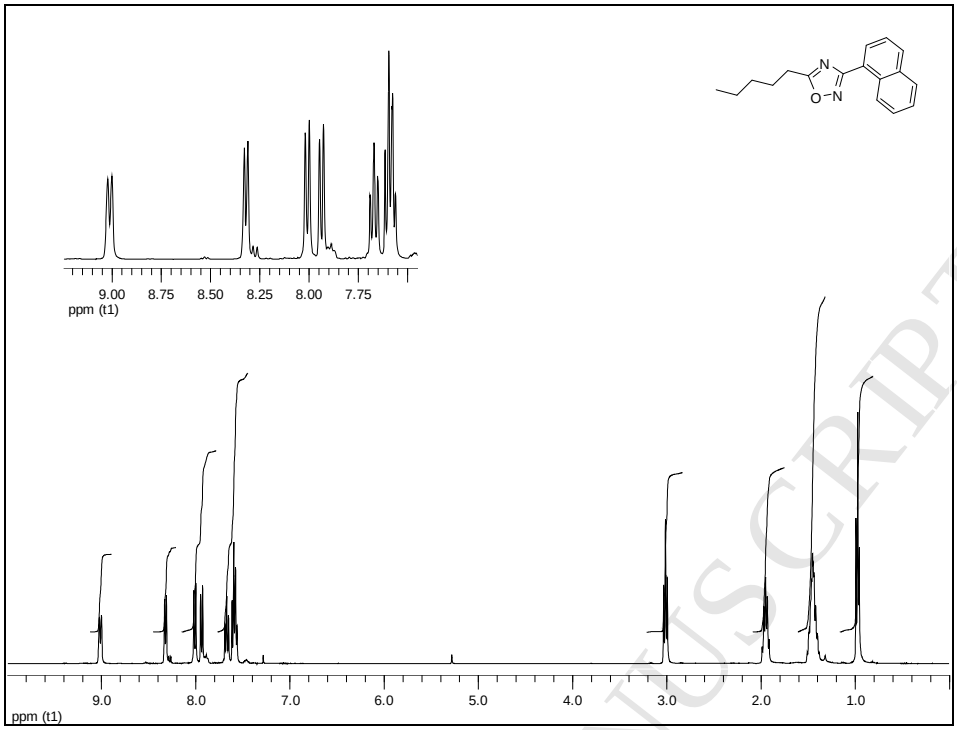

Figure S55. ^{1}H NMR spectrum of **13q**.

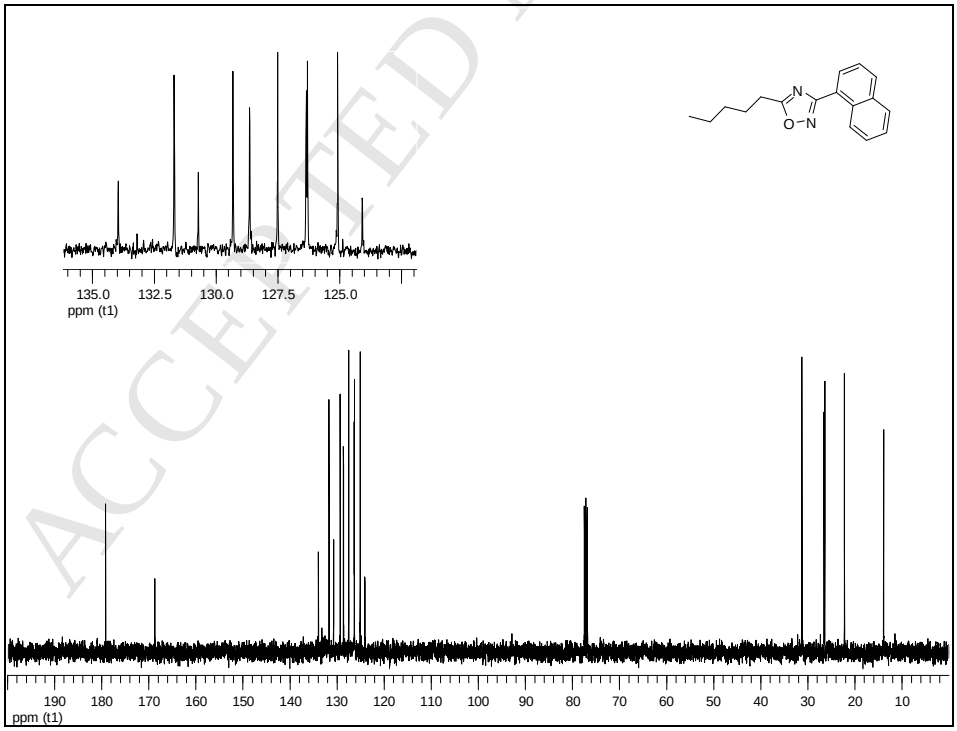

Figure S56. ^{13}C NMR spectrum of **13q**.

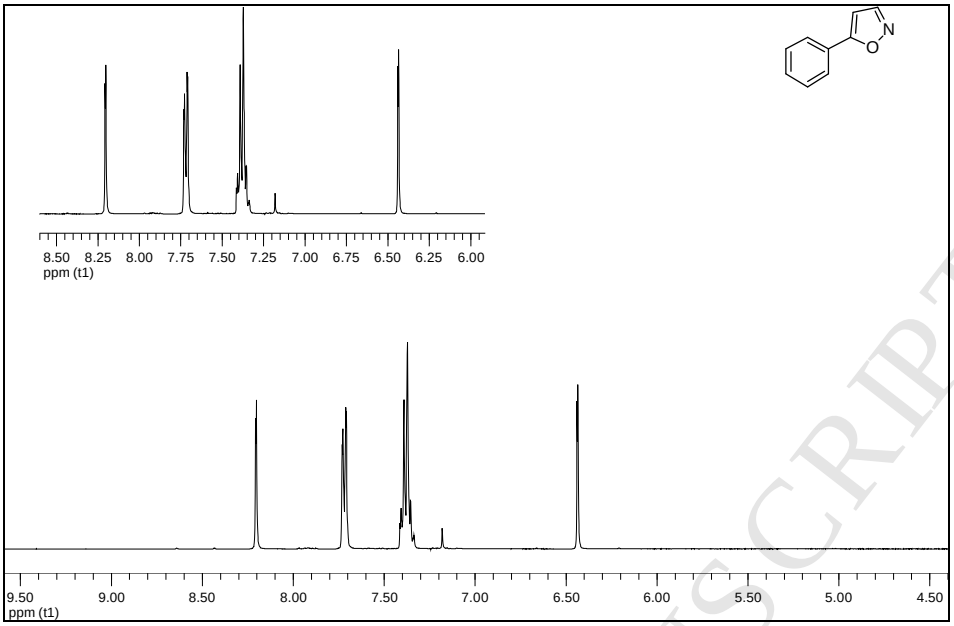

Figure S57. ^{1}H NMR spectrum of **14a**.

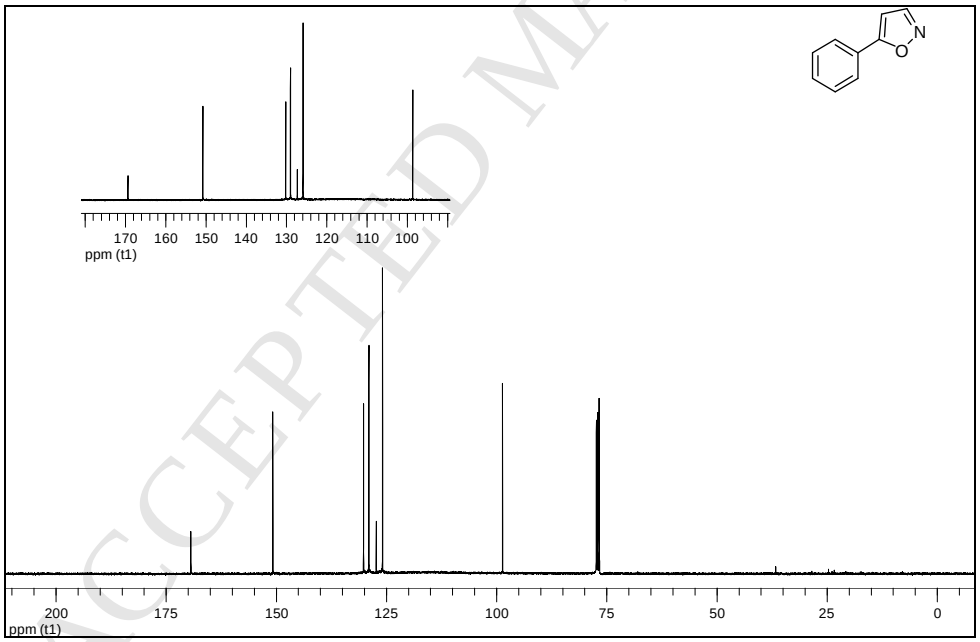

Figure S58. ^{13}C NMR spectrum of **14a**.

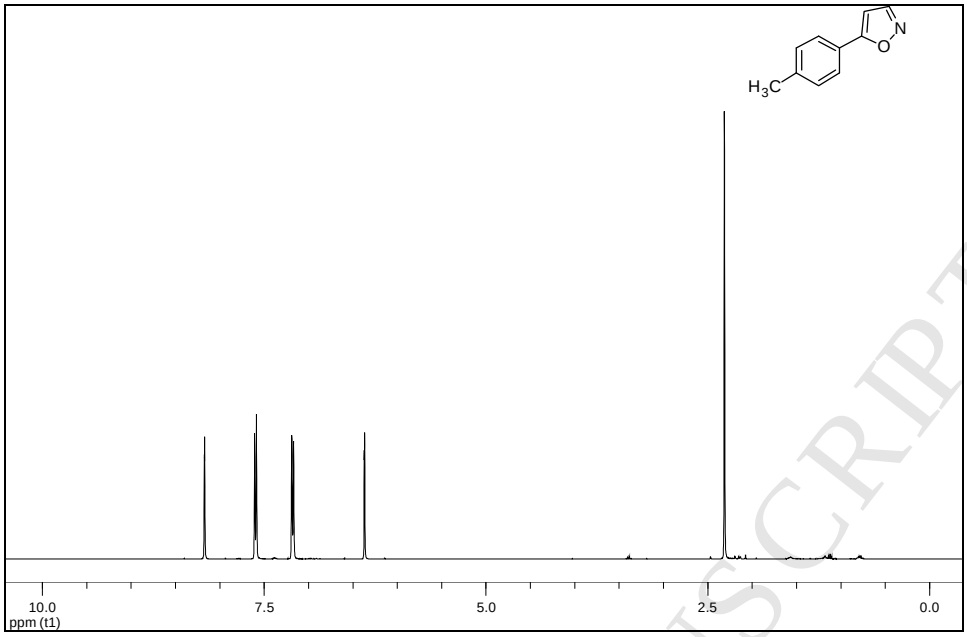

Figure S59. ^{1}H NMR spectrum of **14b**.

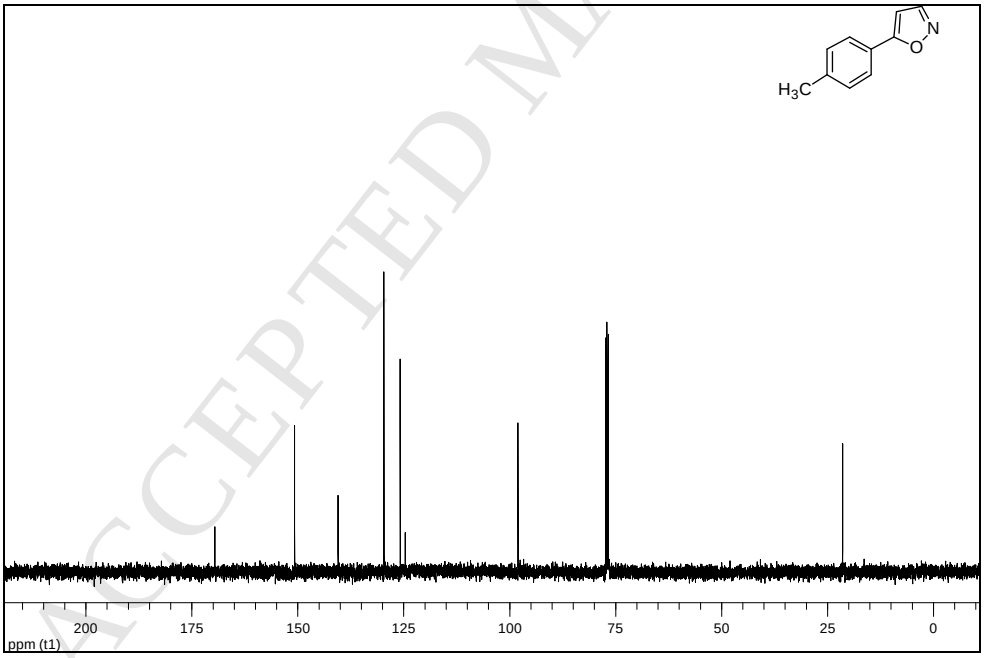

Figure S60. ^{13}C NMR spectrum of **14b**.

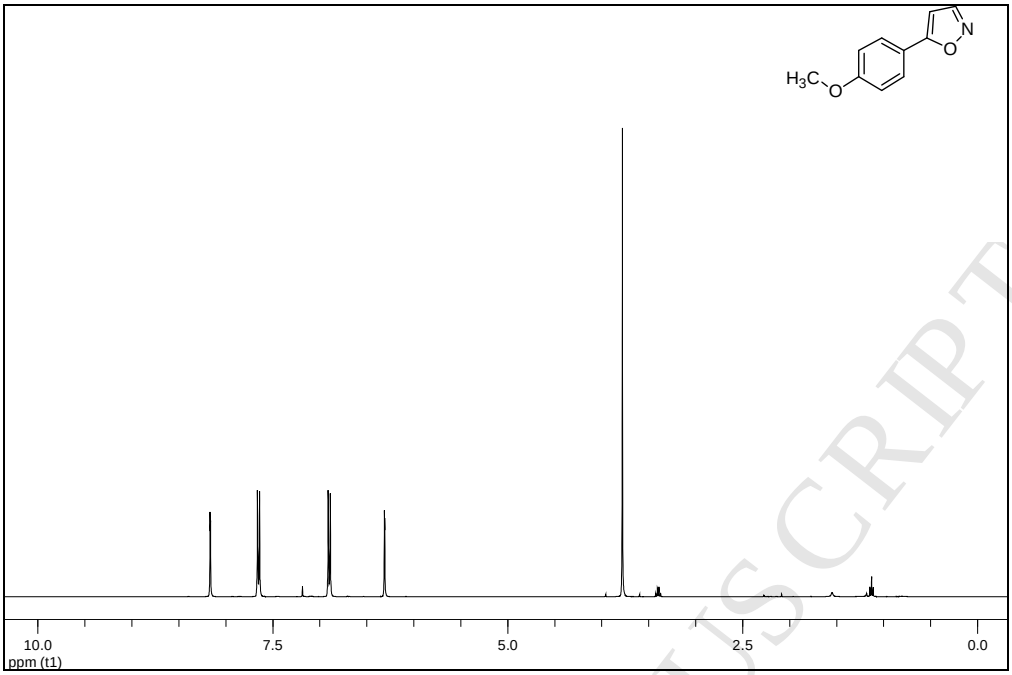

Figure S61. ^{1}H NMR spectrum of **14c**.

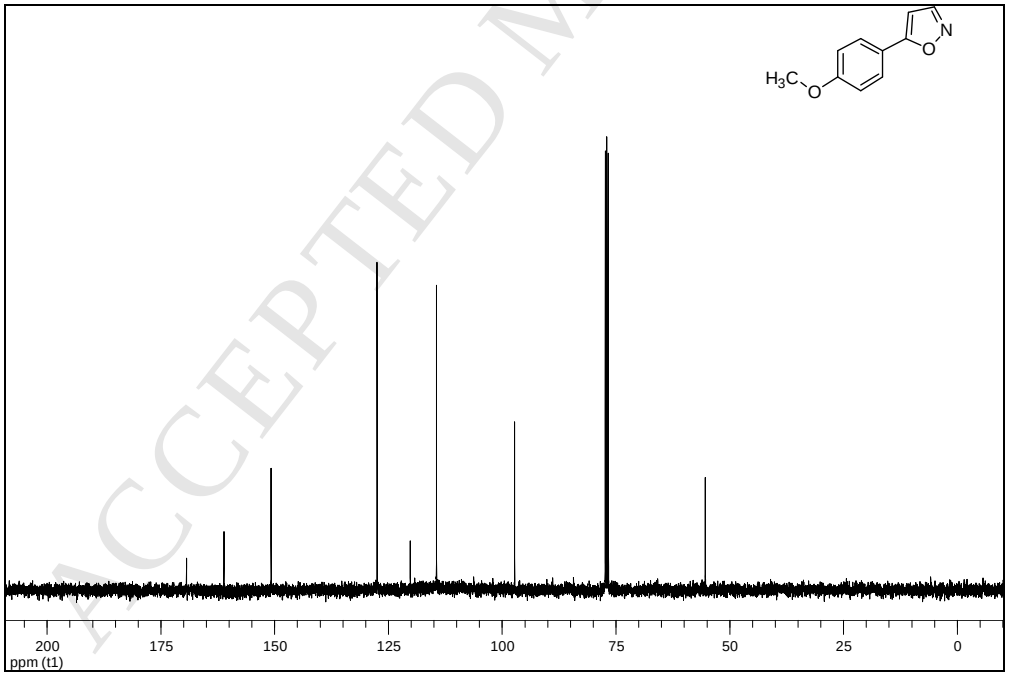

Figure S62. ^{13}C NMR spectrum of **14c**.

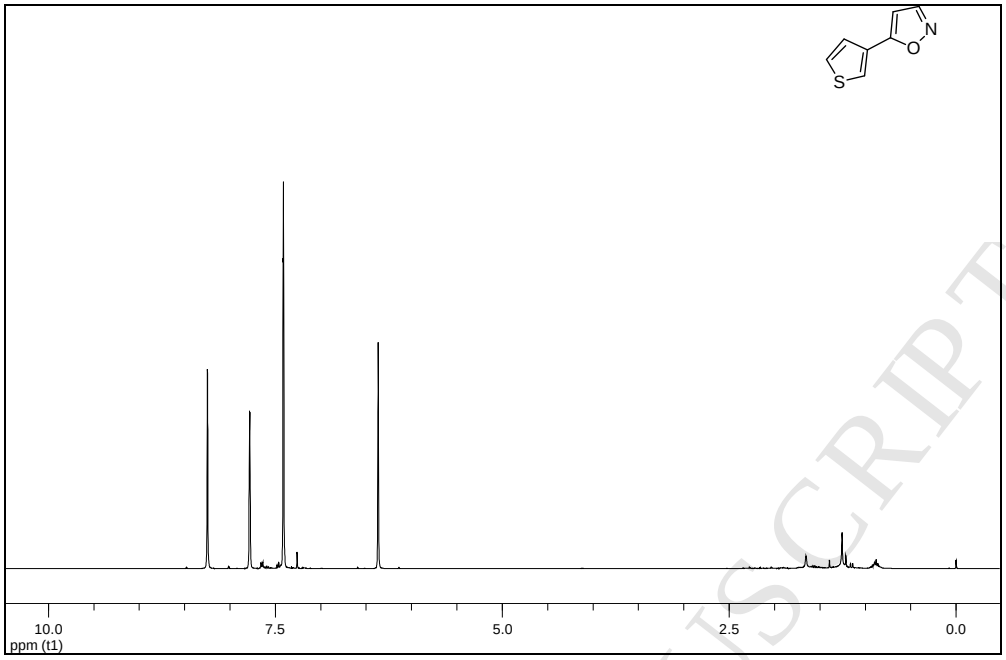

Figure S63. ^{1}H NMR spectrum of **14d**.

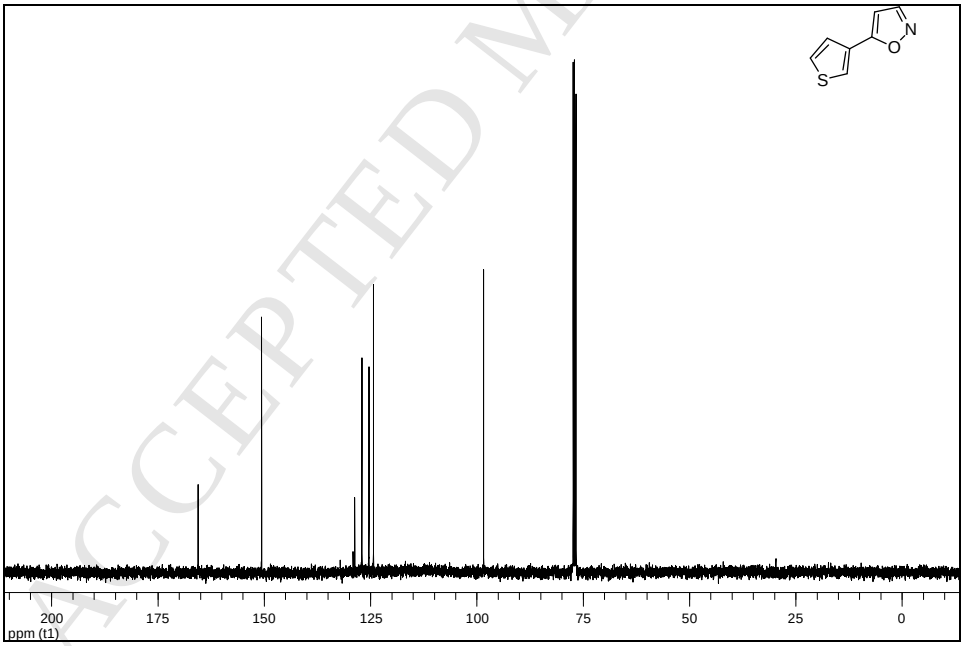

Figure S64. ^{13}C NMR spectrum of **14d**.