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## Arene Ru(II)-Catalyzed Facile Synthesis of N-Acylhydrazones via ADC Strategy

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<p>Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.</p> <p>RSS49.cif          RSS46 6-membered.cif          Scheme 1. Transition-metal catalyzed Acceptorless Dehydrogenative Coupling (ADC) strategy.cdx          Scheme 2. Metal-mediated synthetic strategies for hydrazone synthesis via ADC.cdx          Scheme 3. Synthesis of arene-Ru(II) complexes 1 and 2..cdx          Scheme 4. Gram scale synthesis of (E)-N'-(4-methoxybenzylidene)benzohydrazide.cdx          Scheme 5. Control experiments.cdx          Scheme 6. Plausible mechanism.cdx</p>	

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## Arene Ru(II)- Catalyzed Facile Synthesis of *N*-Acylhydrazones via ADC Strategy

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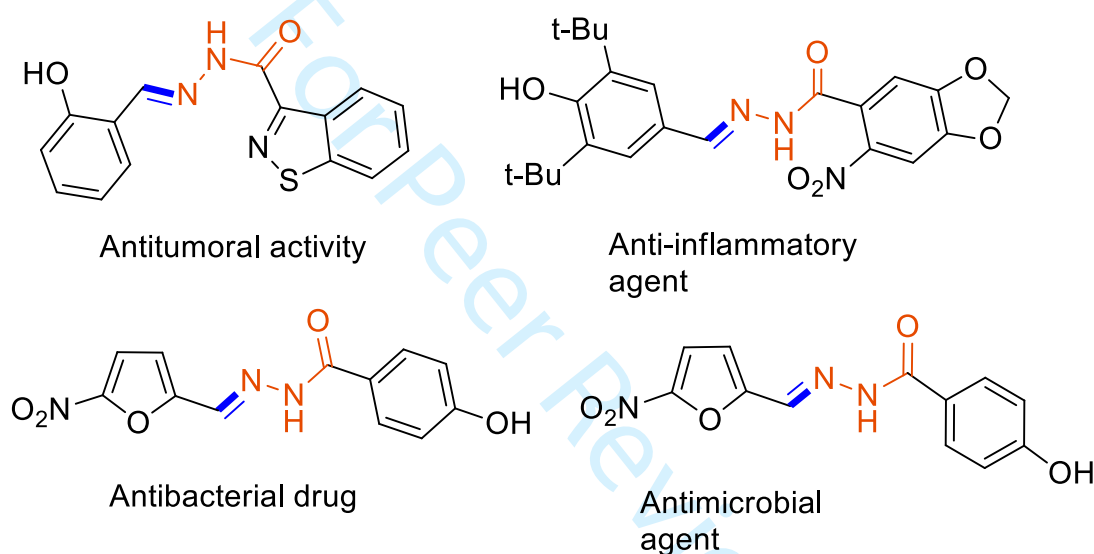
Laboratoire de Chimie Inorganique et Catalyse, Institut de Chimie, Université de Strasbourg, UMR 7177, CNRS, France. *Supporting Information Placeholder*

**Keywords:** benzohydrazides, ruthenium(II) complexes, acceptorless dehydrogenative coupling, alcohols, *N*-acylhydrazones

**ABSTRACT:** A facile catalytic one-pot synthesis of *N*-acylhydrazones (NAH) via acceptorless dehydrogenative coupling (ADC) of readily available alcohols and benzohydrazides ( $R_2CONHNH_2$ ) using arene ruthenium(II) complexes has been described. The coupling of alcohols with various benzohydrazides using ruthenium catalysts provide a wide range of *N*-acylhydrazones in good to excellent yields (63% - 93%; 32 examples). The present protocol offers high selectivity of hydrazones without any alkylated products and tolerates a range of functional groups. Control experiments indicate that the mechanism proceeds via acceptorless dehydrogenation of alcohols and hydrogen and water are the sole by-products. The gram scale synthesis illustrates the usefulness of the present strategy.

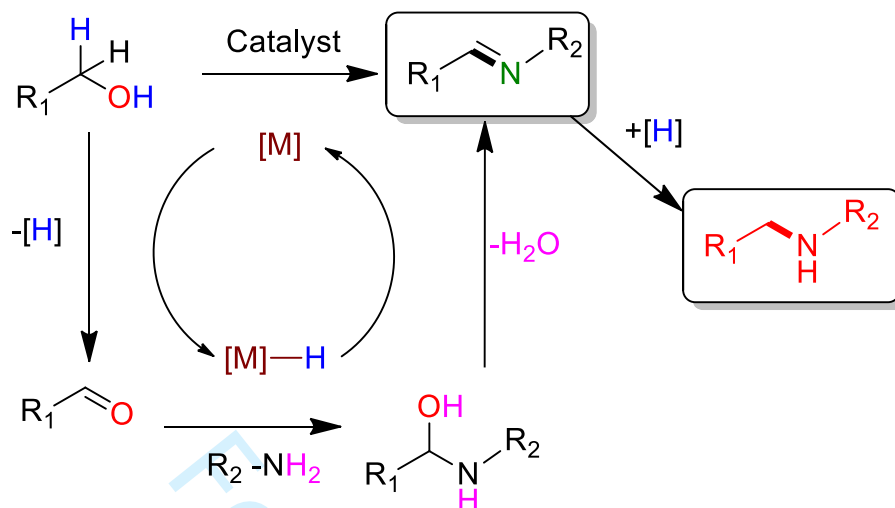
## INTRODUCTION

N-Acylhydrazones (NAHs) are influential class of compounds that demonstrate versatile reactivity and exhibit extensive applications in organic<sup>1</sup> and medicinal chemistry.<sup>2</sup> Because of their distinct structural and stereochemical reactivity, they act as electrophiles for the synthesis of valuable sort of nitrogen-containing compounds.<sup>3</sup> NAH scaffolds reveal significant biological activities, including antiviral<sup>4</sup> (influenza virus HSV-1<sup>5</sup>), antimicrobial,<sup>6</sup> antitubercular,<sup>7</sup> analgesic, anti-inflammatory,<sup>8</sup> antiproliferative,<sup>9</sup> anticonvulsant,<sup>10</sup> and antitrypanosomal<sup>11</sup> activities (**Figure 1**). Owing to these comprehensive biological applications, N-acylhydrazones are considered as ubiquitous structure which resulted in the development of new NAH based drugs.



**Figure 1.** Biologically active *N*-acylhydrazones

Traditionally, synthesis of *N*-acylhydrazones involves the condensation of carbonyl compounds and acylhydrazides.<sup>12</sup> Initially, alcohols are oxidized to the carbonyl compounds using toxic inorganic chemicals and further reaction with acylhydrazides yields the corresponding *N*-acylhydrazones. This conventional method for the synthesis of *N*-acylhydrazones, involves multistep process which produces waste and needs reaction workups, isolation and purification of the products. Metal-mediated direct synthesis of target molecules is a valuable approach in organic synthesis. Recently, Rassadin and co-workers reported gold(I) catalyzed hydrohydrazidation of terminal alkynes with acylhydrazides for the generation of keto-*N*-acylhydrazones, but the catalytic reaction requires high catalyst loading (6 mol%) and expensive alkynes. Unfortunately, the reaction is substrate specific which is limited to the synthesis of methylketone-*N*-acylhydrazones.<sup>13</sup>

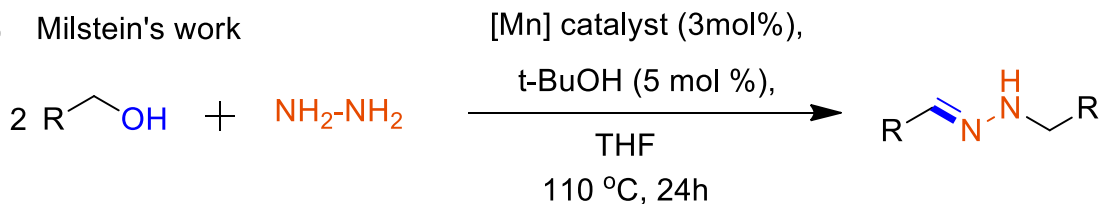
**Scheme 1.** Transition-metal catalyzed Acceptorless Dehydrogenative Coupling (ADC) strategy

The direct synthesis of substituted hydrazones from acceptorless dehydrogenative coupling (ADC) of alcohols has been received much attention recently (**Scheme 1**). This protocol is apparently attractive because of alcohols are abundant, inexpensive, commercially available, easy to store and have a low toxicity. Milstein and co-workers elegantly reported manganese pincer catalyst (3 mol %) for the synthesis of *N*-substituted hydrazones from alcohols and hydrazine hydrate via acceptorless dehydrogenative coupling using 5 mol % of *t*-BuOK (Scheme 2a).<sup>14</sup> Li, et al., demonstrated acceptorless dehydrogenative coupling of primary alcohols and arylhydrazine for the synthesis of arylhydrazones using 0.5 mol % of commercially available iridium catalyst in the presence of KOH at 130°C (Scheme 2b).<sup>15</sup> Despite the reports on substituted hydrazones, metal mediated synthesis of *N*-acylhydrazones from alcohols remains unexplored. In light of this, we have attempted to synthesize *N*-acylhydrazones by acceptorless dehydrogenative coupling of alcohols and benzohydrazides using ruthenium(II) arene catalysts. The reaction proceeded smoothly to yield the respective *N*-acylhydrazone products with complete selectivity and hydrogen and water are the only by-products. To the best of our knowledge, there is no report available on the metal mediated synthesis of *N*-acylhydrazones from alcohols and benzohydrazides. In continuation of our quest to develop new catalysts for the C-N bond forming reactions,<sup>16</sup> herein we report the direct synthesis of *N*-acylhydrazones using 0.5 mol% catalyst loading.

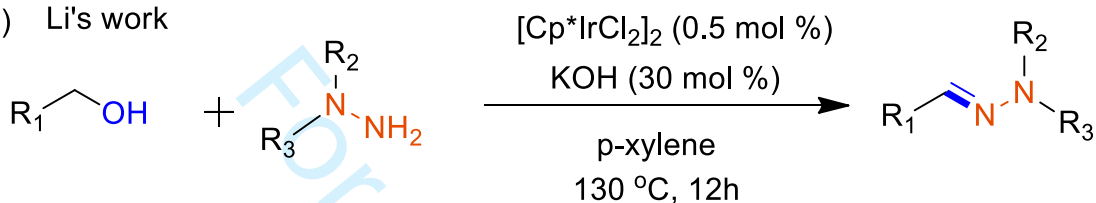
**Scheme 2.** Metal-mediated synthetic strategies for hydrazone synthesis via ADC

Previous work

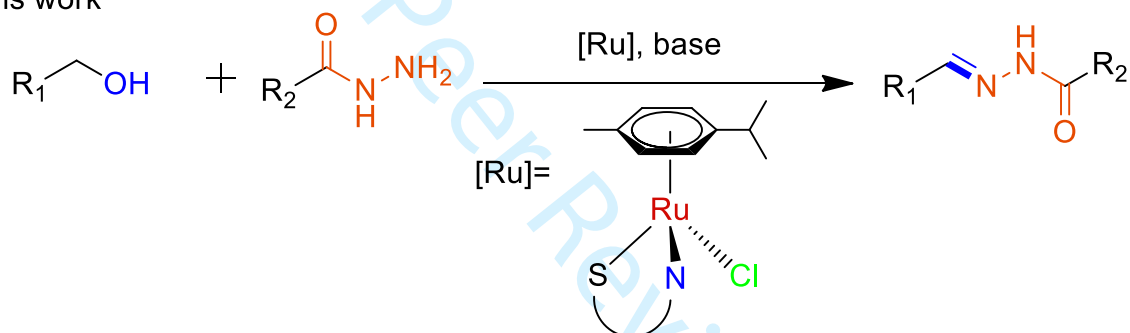
(a) Milstein's work



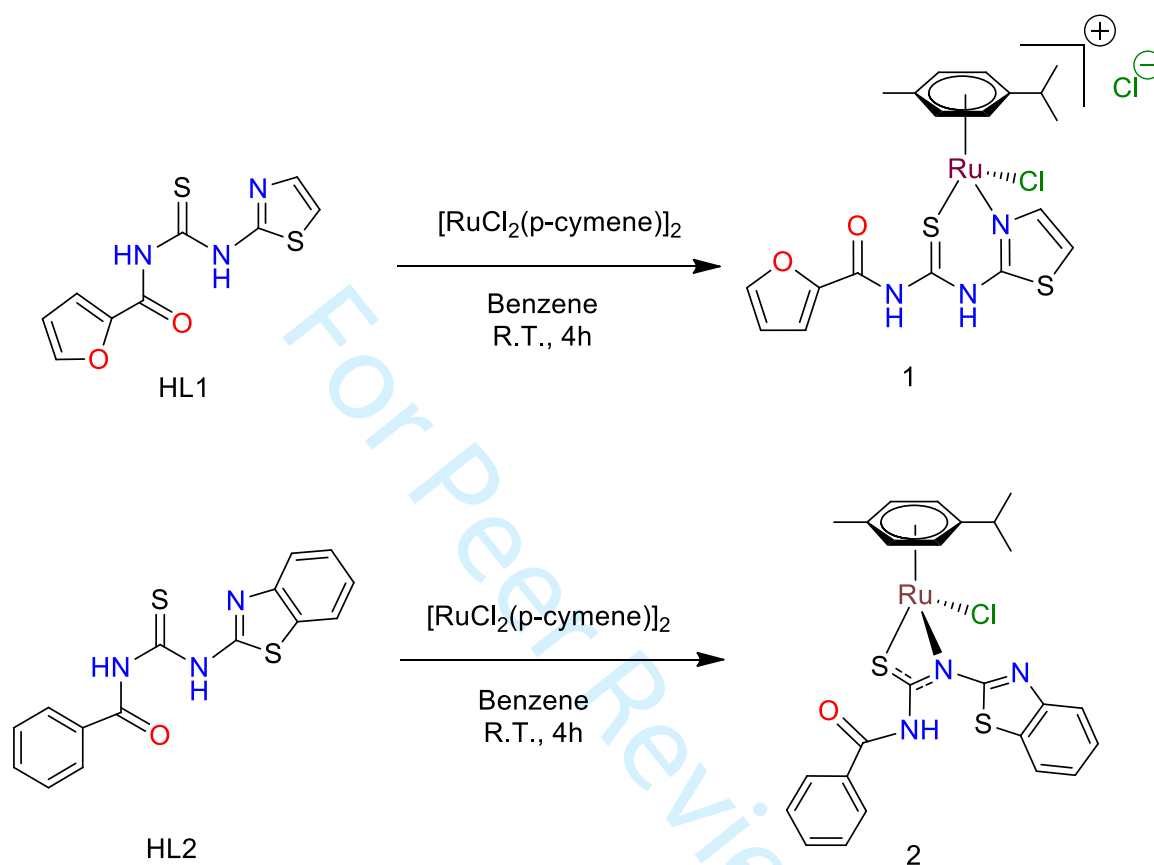
(b) Li's work



This work

**RESULTS AND DISCUSSION**

Treatment of Ru(II) arene precursor  $[\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})]_2$  with bidentate ligands 1-(furan-5-carbonyl)-3-(thiazol-2-yl)thiourea (HL1) and 1-(benzo[d]thiazol-2-yl)-3-benzoylthiourea (HL2) at room temperature resulted in two types of arene-Ru(II) complexes 1 and 2 in 85% and 79%, respectively (**Scheme 3**).

**Scheme 3.** Synthesis of arene-Ru(II) complexes **1** and **2**.

The FT-IR spectra of the complexes **1** and **2** were compared to that of the free ligands. In complex **1**, the bands corresponding to N-H and C=O groups of the ligands remain unaltered upon complexation, which confirms that they do not involve in coordination whereas in complex **2**, the disappearance of band corresponding to NH(thiocarbonyl) confirms that the nitrogen is coordinated to the ruthenium atom. On the other hand, the decrease in the C=S stretching frequency from  $1263$  to  $1217\text{ cm}^{-1}$  in complex **1**, suggests that the ligand is coordinated to ruthenium ion *via* neutral sulphur atom. Thus, the IR spectra of the complexes clearly indicated that ligand HL1 acts as a 4-electron (*N,S*)-chelator in contrast to ligand HL2 which turns out to be a 3-electron (*N,S*)-chelator.

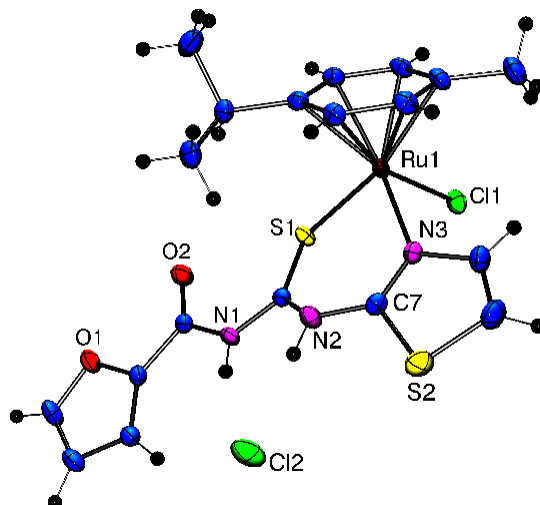
In the  $^1\text{H}$  NMR spectra of complexes **1** and **2**, the resonances due to the aromatic protons of the coordinated ligand (HL1) and (HL2) were observed in the region  $\delta = 7.87\text{-}6.64$  ppm and  $\delta =$

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3 8.15-7.36 ppm, respectively. The signals owing to *p*-cymene moiety of the complexes were found  
4 in the region of 5.82-5.47, 2.95-2.78, 2.17-2.08 and 1.33-1.18 ppm. The disappearance of signal  
5 due to thiocarbonyl attached NH in complex **2**, confirms the coordination of nitrogen atom in  
6 anionic form. Further, in the <sup>13</sup>C NMR spectra of complexes **1** and **2**, signals appeared in the region  
7 175.3–175.0 and 158.0–151.3 ppm attributed to the C=S and C=O carbons, respectively. The  
8 aromatic carbons of *p*-cymene moieties resonate in the expected range of 84.93–101.42 ppm.  
9 Further, the peaks corresponding to CH and CH<sub>3</sub> carbons of *p*-cymene moieties were observed in  
10 the region  $\delta = 30.79$ -29.94 ppm and  $\delta = 22.57$ -17.83 ppm, respectively.  
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17 The molecular structure of the complexes **1** and **2** were unambiguously confirmed with the  
18 aid of single crystal X-ray diffraction study. It is inferred from the XRD data that the complex **1**  
19 crystallizes as triclinic with the space group P-1 whereas complex **2** crystallizes as monoclinic  
20 with the space group P21/*c*. The molecular structure of complexes **1** and **2** exhibit a pseudo  
21 octahedral geometry with a “3-legged piano-stool” arrangement around the Ru(II) ion. In the  
22 cationic complex **1**, the seat was occupied by the *p*-cymene moiety and the legs by the thione  
23 sulphur (neutral form) and thiazole nitrogen of the ligand (HL1) and chlorine atom. In contrast, in  
24 the neutral complex **2**, the seat of piano-stool was occupied by the *p*-cymene moiety and the  
25 remaining sites by the nitrogen (anionic form) attached to thiocarbonyl, thione sulphur of the  
26 ligand (HL2) and a chloride ligand. The bond lengths of Ru(1)-Cl(1), Ru(1)-S(1) and Ru(1)-N(3)  
27 in complex **1** were found to be 2.411, 2.3585 and 2.0884 Å, respectively and in complex **2**, bond  
28 lengths of Ru(1)-Cl(1), Ru(1)-S(1) and Ru(1)-N(2) were found to be 2.3986, 2.3961 and 2.125 Å,  
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6 **Figure 2. ORTEP plots of complexes 1. Thermal ellipsoids are shown at the 50%**  
7 **probability level.**



26 **Figure 3. ORTEP plots of complexes 2. Thermal ellipsoids are shown at the 50% probability**  
27 **level.**

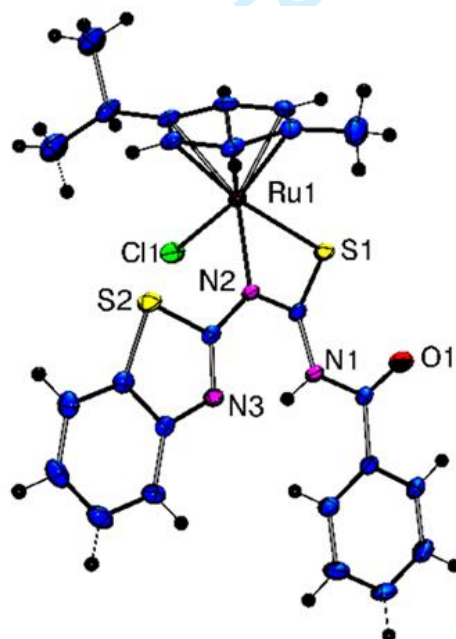
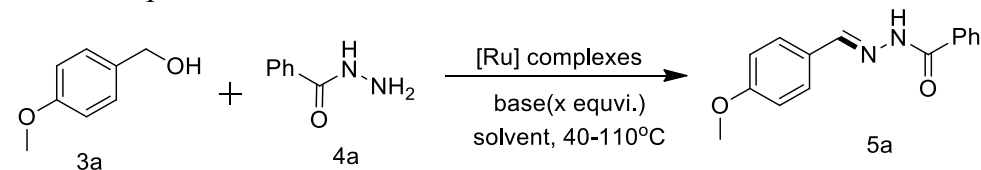


Table 1. Optimization of the reaction conditions<sup>a</sup>



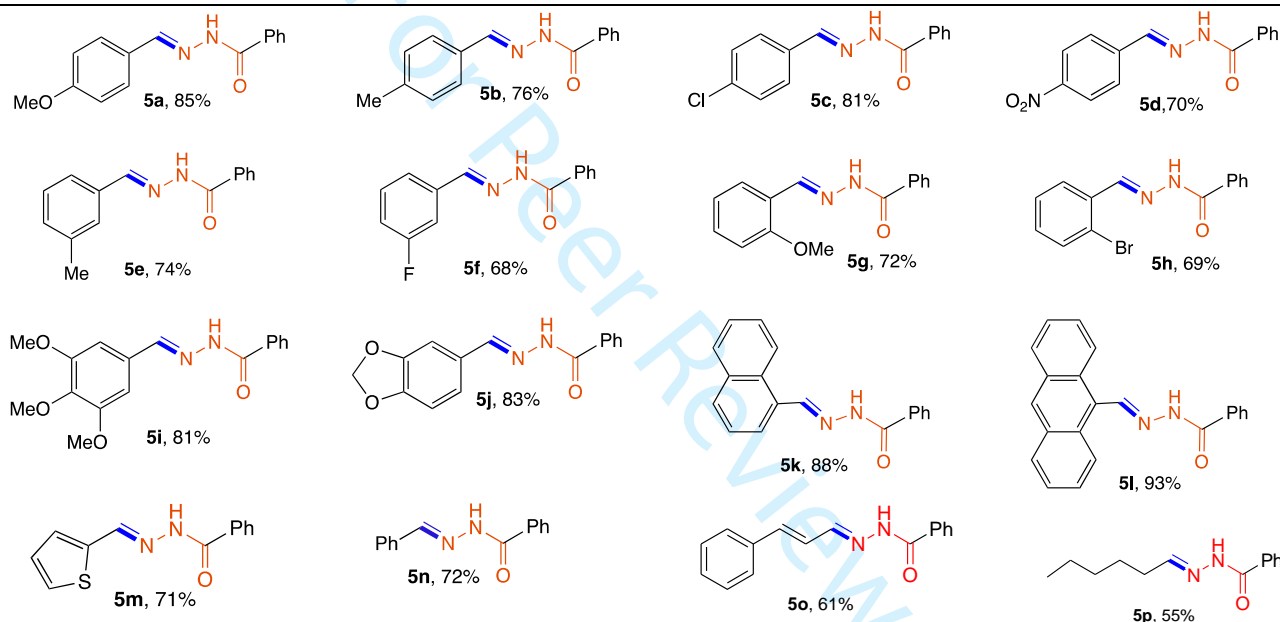
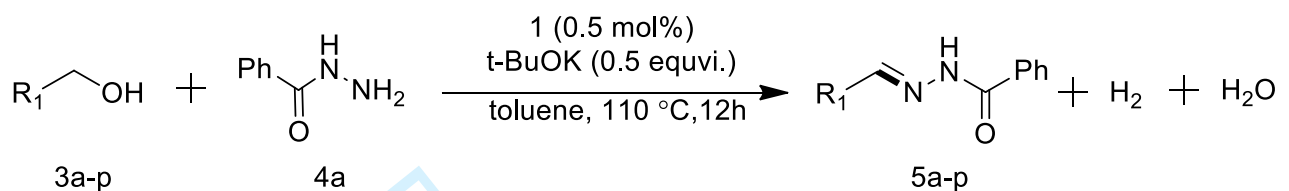
Complexes	Solvent	Base	T (°C)	Yield (%) <sup>b</sup>
1	THF	<i>t</i> -BuOK	66	48
2	CH <sub>2</sub> Cl <sub>2</sub>	<i>t</i> -BuOK	40	46
3	PhCH <sub>3</sub>	<i>t</i> -BuOK	80	65
4	<i>t</i> -BuOH	<i>t</i> -BuOK	83	<10
5	PhCH <sub>3</sub>	<i>t</i> -BuOK	110	85
6	PhCH <sub>3</sub>	KOH	110	79
7	PhCH <sub>3</sub>	LiOH.H <sub>2</sub> O	110	<15
8	PhCH <sub>3</sub>	<i>t</i> -BuOK	110	67
9 <sup>c</sup>	PhCH <sub>3</sub>		110	NR
10 <sup>d</sup>	PhCH <sub>3</sub>	<i>t</i> -BuOK	110	NR
11 <sup>e</sup>	PhCH <sub>3</sub>	<i>t</i> -BuOK	110	51

<sup>a</sup>Reaction conditions: Complex 1 (0.5 mol %), 4-methoxybenzyl alcohol 3a (1 mmol), benzohydrazide 4a (1 mmol), *t*-BuOK (0.5 mmol), solvent (3 mL) for 12 h; <sup>b</sup>yield of the isolated product; <sup>c</sup>in the absence of base; <sup>d</sup>in the absence of catalyst 1; <sup>e</sup>0.25 mol% of complex 1.

For optimization of the catalytic synthesis of *N*-acylhydrazones, an equimolar ratio of 4-methoxybenzyl alcohol (**3a**) and benzohydrazide (**4a**) were employed as model substrates in the presence of 0.5 mol% of complex **1**. We began the optimization using *t*-BuOK (0.5 mmol) as a base in THF medium at 66°C, after 12 hours, the corresponding product was isolated in 48% yield (**Table 1, entry 1**). A few common solvents such as THF, CH<sub>2</sub>Cl<sub>2</sub>, PhCH<sub>3</sub> and *t*-BuOH were employed and we found that the higher isolated yield was obtained in toluene at 80°C (**Table 1, entries 1-4**). Interestingly, repeated the run at the reflux temperature of toluene favored the formation of the desired product and **5a** was isolated in 85% yield (**Table 1, entry 5**). Among all the bases, *t*-BuOK was found to be the most suitable base (**Table 1, entry 5**). However, using KOH as the base under the same reaction conditions gave **5a** in 79% yield (**Table 1, entry 6**). The isolated yields of **5a** dropped off to <15% when LiOH.H<sub>2</sub>O was employed as the base (**Table 1, entry 7**). It is interesting to note that among complexes **1** and **2**, the cationic ruthenium complex **1**

gave the highest isolated yield (**Table 1, entries 5 and 8**). As expected, the reaction did not occur in the absence of base or catalyst (**Table 1, entries 9 and 10**). The decreasing of the catalyst loading resulted in a lower formation of **5a** (**Table 1, entry 11**).

**Table 2.** Scope of the ruthenium-catalyzed coupling of benzohydrazides with substituted aromatic alcohols.<sup>a</sup>



<sup>a</sup>Reaction conditions: Complex **1** (0.5 mol %), substituted benzyl alcohols **3a-p** (1 mmol), benzohydrazide **4a** (1 mmol), *t*-BuOK (0.5 mmol), and toluene (3 mL) were heated at 110 °C for 12 h; <sup>b</sup> Yield of the isolated product.

After optimizing the catalytic conditions, in order to explore the generality of the protocol various primary alcohols were tested. We can see that the introduction of substituents on the aromatic ring of the benzyl alcohol does not inhibit the coupling reaction (**Table 2**). The use of alcohols bearing electron-rich (4-MeO-C<sub>6</sub>H<sub>4</sub> (**3a**), 4-Me-C<sub>6</sub>H<sub>4</sub> (**3b**)) and electron-deficient (4-Cl-C<sub>6</sub>H<sub>4</sub> (**3c**), 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> (**3d**)) substituents only slightly affects the amounts of *N*-acylhydrazones **5a-5d** formed (SI, Figures 5-12) Conversely, the presence of a fluorine atom at the *meta*-position (**3f**) affects the formation of the corresponding *N*-acylhydrazone **5f** (SI, Figures 13-14) the product

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3 is isolated in 68% yield, while the 3-methylbenzyl alcohol (3e) gave a 74% yield of product **5e**(SI,  
4 Figures 14-15). Surprisingly, good isolated yields were observed when benzyl alcohols bearing  
5 sterically hindered substituents at *ortho*-position (2-MeO-C<sub>6</sub>H<sub>4</sub> (**5g**), 2-Br-C<sub>6</sub>H<sub>4</sub> (**5h**)) (SI, Figures  
6 16-20) were employed. Similarly, 81% of the corresponding N-acylhydrazone **5i** (SI, Figures 21-  
7 22) was obtained using 3,4,5-trimethoxybenzyl alcohol (3i). Using piperonyl alcohol (3j), led to  
8 the formation the corresponding product **5j** (SI, Figures 23-24) in 83% yield. We can note that 1-  
9 naphthalenemethanol (3k) and 9-anthracenemethanol (3l) were also found to be reactive substrates  
10 as they gave 88% and 93% of the products **5k** and **5l**, (SI, Figures 25-28) respectively. The reaction  
11 of a heteroaromatic alcohol such as 2-thiophenemethanol (3m) gave 71% of the corresponding *N*-  
12 acylhydrazone **5m** (SI, Figures 29-30). Further, the present protocol works well with cinnamyl  
13 alcohol and *n*-hexanol to render the hydrazone products **5o** and **5p** (SI, Figures 31-36) in good to  
14 moderate yields respectively.  
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17 The substrate scope was further extended to the substituent of benzohydrazide (4b-f) (**Table 3**).  
18 The reaction of 4-methoxybenzohydrazide (4b) with benzyl alcohol (3n) delivered the  
19 corresponding *N*-acylhydrazone **6a** (SI, Figures 37-38) in 87% yield. Similarly, the reactions of 4-  
20 methoxybenzohydrazide (4b) with both electron poor (-Cl (3c) and -NO<sub>2</sub> (3d)) or electron rich (-  
21 MeO (3a)) arylmethyl alcohols led to the formation of the desired products **6b-6d** (SI, Figures 39-  
22 44) with yield up to 78%. Further, the benzohydrazide reaction with 4-chlorobenzyl alcohol to give  
23 **6e** in 74% isolated yield (SI, Figures 45-46). Expectedly, 4-chlorobenzohydrazide (4c) reacted  
24 with chloro- and methyl- substituted aryl alcohols and the corresponding products were isolated in  
25 64% (**6f**) and 73% (**6g**) (SI, Figures 47-50) yields, respectively. Furthermore, the reaction of 2-  
26 thiophenemethanol (3m) with 4- chlorobenzohydrazide (4c) led to compound **6h** (SI, Figures 51-  
27 52) in 72% yield. It is gratifying to note that the benzohydrazide bearing weakly deactivating -Br  
28 group (4d) provided of N-acylhydrazones (**6i-6l**) (SI, Figures 53-60) with good yields (55-78%).  
29 Interestingly, furan-2-carbohydrazide (4e) and 2-thiophenecarbohydrazide(4f) allowed the  
30 coupling reaction and afforded the corresponding products (**6m-p**) (SI, Figures 61-68) in good  
31 isolated yields (52-76%).  
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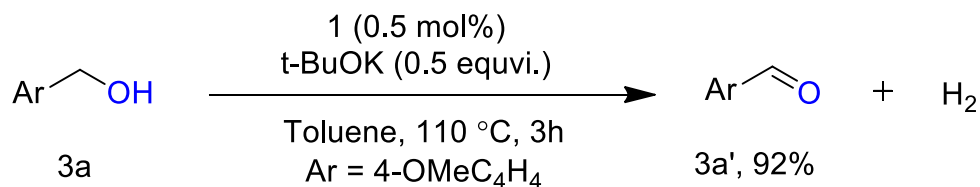
33  
34 In order to demonstrate the usefulness of the present protocol for an industrial application, we  
35 investigated the gram scale synthesis of (E)-N'-(4-methoxybenzylidene)benzohydrazide (**5a**) (SI,  
36 Figures 5-6) as a representative example (Scheme 4). After 12 hours in refluxing toluene, the  
37 targeted compound was isolated in 79% yield.  
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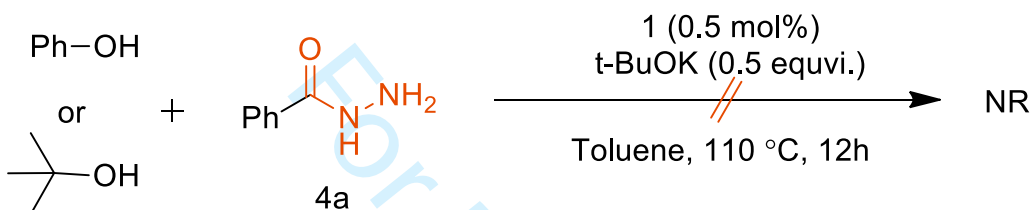
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3 In order to probe the mechanism, a series of control experiments have been carried out.  
4 Initially, 4-methoxybenzyl alcohol (3a) in the absence of benzohydrazide under the standard  
5 catalytic conditions resulted in the formation of the corresponding aldehyde (3a'). Thus, the  
6 formation of 3a' indicated that the reaction proceeds *via* selective acceptorless dehydrogenation of  
7 alcohols (**Scheme 5-i**). Further, to establish the dehydrogenation of alcohol, tests were carried out  
8 with phenol or *t*-butanol. As expected, no *N*-acylhydrazone formation was observed, which  
9 supports that the synthesis of *N*-acylhydrazone occurs *via* dehydrogenation of benzyl alcohol  
10 (**Scheme 5-ii**). On the basis of the previous reports,<sup>16</sup> we were interested in examining the product  
11 selectivity (**Scheme 5 iii**). In this purpose the catalytic transfer hydrogenation of *N*-acylhydrazone  
12 5a with alcohols such as 4-methoxybenzyl alcohol (3a) and isopropanol as hydrogen sources were  
13 carried out. In both the reactions, none of the *N*-alkylated products were observed. The results  
14 clearly indicate that *N*-acylhydrazones are stable and they did not undergo transfer hydrogenation  
15 in the presence of hydrogen sources, which are marked contrast with the literature reports where  
16 the *N*-alkylated products were produced from dehydrogenative coupling of alcohols and amine.  
17 Hence, the above observations supports for the selective synthesis of *N*-acylhydrazones without  
18 formation of any *N*-alkylated byproducts.  
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## Scheme 5. Control experiments

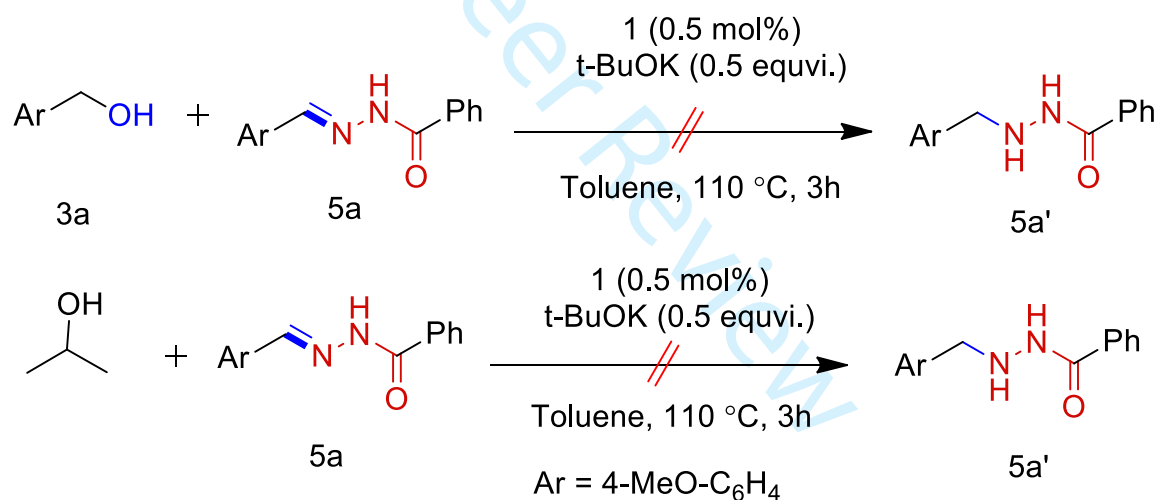
## (i) Dehydrogenation of alcohols



## (ii) Reaction of benzohydrazide with phenol or t-butanol



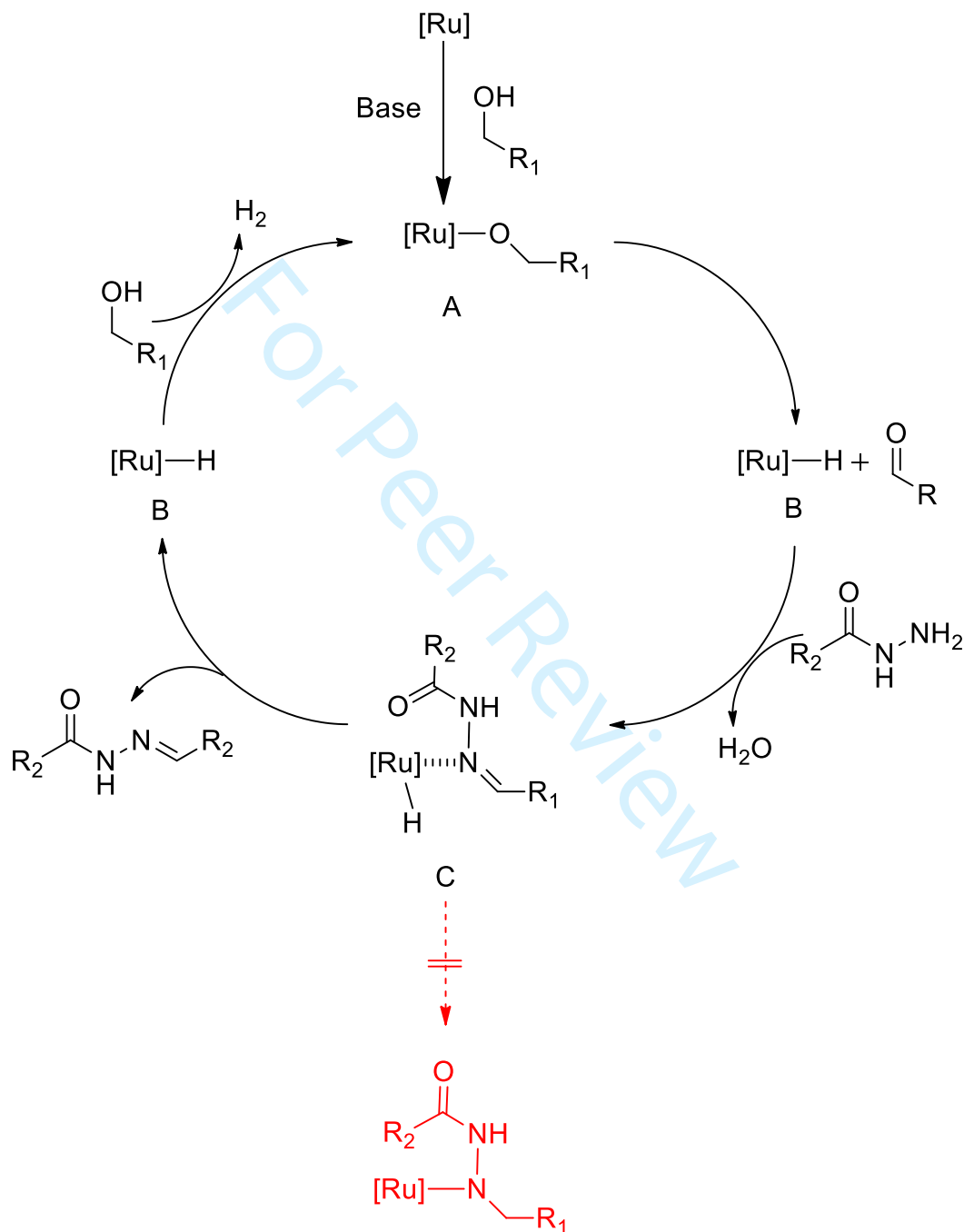
## (iii) Transfer hydrogenation of N-acylhydrazone



Encouraged by the literature reports<sup>15,16,17</sup> and results of the control experiments, we herein propose a mechanism for the synthesis of *N*-acylhydrazone catalyzed by arene-ruthenium(II) complex (**1**) via acceptorless dehydrogenative coupling of alcohols (**Scheme 6**). The initial step is presumed to be the formation of a ruthenium alkoxide species (A) which undergoes  $\beta$ -H elimination resulted in the formation of ruthenium hydride species (B) and aldehyde. Further, the condensation of aldehyde with acyllhydrazides results in ruthenium hydride species coordinated with aroylhydrazones (C). Subsequent dissociation of (C) releases the product aroylhydrazone and Ru-H species. Finally, the reaction of alcohol with ruthenium hydride species (B) regenerates the

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3 ruthenium alkoxide species (A) along with the liberation of hydrogen gas. (see **Supporting**  
4 **Information for more details**)

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7 **Scheme 6.** Plausible mechanism





## CONCLUSION

We herein report for the first time, an efficient strategy for the direct synthesis of *N*-acylhydrazones from acceptorless dehydrogenative coupling of alcohols and benzohydrazides catalyzed by a newly synthesized arene ruthenium(II) complex. The *N*-acylhydrazones products were isolated in good to excellent yields with a catalyst loading of only 0.5 mol%. Furthermore, the observation of aldehyde intermediate and the control experiments demonstrated that reaction mechanism involves dehydrogenation of alcohol as the initial step.

## EXPERIMENTAL SECTION

C, H, N and S analyses were carried out with a Vario EL III CHNS elemental analyzer. IR spectra were recorded on a JASCO 400 plus spectrometer. Electronic spectra in CH<sub>2</sub>Cl<sub>2</sub> were recorded with a CARY 300 Bio UV-visible Varian spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using Bruker Avance-400 NMR spectrometers in CDCl<sub>3</sub>, DMSO-*d*<sub>6</sub> and tetramethylsilane (TMS) as internal standard. Deuterated CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> were used as received. Chemical shifts were reported in units parts per million (ppm) by assigning TMS resonance as 0.00 ppm with reference to residual solvent signals. High Resolution Mass spectra were recorded on a Thermo Exactive Orbitrap mass spectrometer using electrospray ionization (ESI) technique. Ligands (HL1 and HL2) were prepared according to the literature procedure.<sup>16a</sup>

**General procedure for the synthesis and characterization of complexes 1 and 2:** 1-(Furan-5-carbonyl)-3-(thiazol-2-yl)thiourea (**HL1**) (50.66 mg, 0.20 mmol) or 1-(benzo[d]thiazol-2-yl)-3-benzoylthiourea (**HL2**) (62.68 mg, 0.20 mmol) were dissolved in 20 mL of benzene. To the solution, 0.10 mmol of the ruthenium precursor [RuCl<sub>2</sub>(*η*<sup>6</sup>-*p*-cymene)]<sub>2</sub> (61.23 mg, 0.10 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. The orange solid gets precipitated, which was filtered and dried in vacuum. The resulting complexes were recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/petroleum ether to afford pure desired ruthenium complex.

**[RuCl(HL1)(*η*<sup>6</sup>-*p*-cymene)]Cl (1):** Orange solid (85% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 12.31 (s, 1H, NH), 7.87 (s br, 1H, O-CH of furane), 7.76-7.75 (m, 2H, O-CH=CH-CH of furane and N-CH of thiazole), 7.31 (d, 1H, S-CH of thiazole, <sup>3</sup>*J* = 3.9 Hz), 6.64 (m, 1H, O-CH=CH of furane), 5.72 (d, 1H, arom. CH of *p*-cymene, <sup>3</sup>*J* = 5.9 Hz), 5.58 (d, 1H, arom. CH of *p*-cymene,

$^3J = 5.5$  Hz), 5.50 (d, 1H, arom. CH of *p*-cymene,  $^3J = 5.8$  Hz), 5.48 (d, 1H, arom. CH of *p*-cymene,  $^3J = 5.9$  Hz), 2.92 (hept, 1H, CH(CH<sub>3</sub>), 2.17 (s, 3 H, CH<sub>3</sub> of *p*-cymene), 1.33 (d, 3H, CH(CH<sub>3</sub>)<sub>2</sub>,  $^3J = 6.9$  Hz), 1.29 (d, 3H, CH(CH<sub>3</sub>)<sub>2</sub>,  $^3J = 6.9$  Hz); <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 126 MHz):  $\delta = 175.34$  (s, C=S), 158.30 (s, thiazole), 155.19 (s, HN-C=O), 147.83 (s, N-CH of thiazole), 145.19 (s, furane), 144.44 (s, O-CH=CH-CH of furane), 119.68 (s, O-CH of furane), 115.73 (s, S-CH of thiazole), 112.94 (s, O-CH=CH of furane), 106.91 (s, *p*-cymene), 101.42 (s, *p*-cymene), 87.38 (s, arom. CH of *p*-cymene), 85.56 (s, arom. CH of *p*-cymene), 85.41 (s, arom. CH of *p*-cymene), 85.29 (s, arom. CH of *p*-cymene), 30.79 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 22.57 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 22.14 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 18.57 (s, CH<sub>3</sub> of *p*-cymene) ppm. Elemental analysis calcd (%) for C<sub>19</sub>H<sub>21</sub>O<sub>2</sub>N<sub>3</sub>S<sub>2</sub>Cl<sub>2</sub>Ru: C, 40.79; H, 3.78; N, 7.51; S, 11.46. Found: C, 40.65; H, 3.80; N, 7.47; S, 11.40. FT-IR (cm<sup>-1</sup>): 3136, 2960, 1715, 1467, 1239. UV-Vis (CH<sub>2</sub>Cl<sub>2</sub>,  $\lambda_{\max}$  nm;  $\epsilon$  dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 381 (1000), 298 (4500), 227(3500).

**[RuCl(HL2)( $\eta^6$ -*p*-cymene)]Cl (2):** Orange solid (79% yield). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta = 12.89$  (s, 1H, NH), 8.15 (d, 2H, arom. CH,  $^3J = 7.5$  Hz), 8.02 (d, 1H, arom. CH,  $^3J = 7.8$  Hz), 7.93 (d, 1H, arom. CH,  $^3J = 7.6$  Hz), 7.79 (d, 1H, arom. CH,  $^3J = 8.3$  Hz), 7.66 (d, 1H, arom. CH,  $^3J = 7.3$  Hz), 7.58 (m, 2H, arom. CH), 7.34 (d, 1H, arom. CH,  $^3J = 7.2$  Hz), 5.81 (d, 2H, arom. CH of *p*-cymene,  $^3J = 6.2$  Hz, 1H), 5.77 (d, 2H, arom. CH of *p*-cymene,  $^3J = 6.2$  Hz), 2.90-2.76 (hept, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.09 (s, 3 H, CH<sub>3</sub> of *p*-cymene), 1.19 (d, 3H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (DMSO-*d*<sub>6</sub>, 100 MHz):  $\delta = 175.07$ (s, C=S), 151.36, 134.00, 132.87, 132.21, 128.64, 128.33, 128.29, 126.18, 123.69, 121.72, 121.44, 106.37 (s, *p*-cymene), 100.06 (s, *p*-cymene), 87.19 (arom. CH of *p*-cymene), 86.33 (arom. CH of *p*-cymene), 85.46 (arom. CH of *p*-cymene), 84.93 (arom. CH of *p*-cymene), 29.94 (CH(CH<sub>3</sub>)<sub>2</sub>), 21.46 (CH(CH<sub>3</sub>)<sub>2</sub>), 21.08 (CH(CH<sub>3</sub>)<sub>2</sub>), 17.83 (CH<sub>3</sub> of *p*-cymene) ppm. Elemental analysis calcd (%) for C<sub>25</sub>H<sub>24</sub>ClN<sub>3</sub>ORuS<sub>2</sub>: C, 51.49; H, 4.15; N, 7.21; S, 11.00. Found: C, 51.39; H, 4.09; N, 7.24; S, 11.05. FT-IR (cm<sup>-1</sup>): 3058, 1690, 1468, 1273. UV-Vis (CH<sub>2</sub>Cl<sub>2</sub>,  $\lambda_{\max}$  nm;  $\epsilon$  dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 400 (500), 304 (1500), 227 (4000).

**General procedure for the synthesis of *N*-acylhydrazones (5a-p and 6a-p):** The mixture of alcohol (1 mmol), substituted benzohydrazide (1 mmol), *t*-BuOK (0.5 mmol) and ruthenium complex (0.5 mol %) was stirred in toluene at 110°C under N<sub>2</sub> atmosphere. After 12 h, the solvent was evaporated under reduced pressure and the resulting crude product was subjected to column chromatography on silica gel (EtOAc/hexane, gradient from 20% to pure EtOAc) to afford *N*-acylhydrazones.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Complete details of crystal structure, data collection, crystallographic data, refinement parameters, selected bond lengths, and bond angles. Figures illustrating the  $^1\text{H}$  &  $^{13}\text{C}$  NMR spectra of ligands, complexes, *N*-Acylhydrazones catalytic products (see **supporting Information, Figures S8 – S39**). CIF for the complexes. CCDC numbers for complexes **1** and **2** are 2038566 and 2038567 respectively.

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## AUTHOR CONTRIBUTIONS

**Saranya Sundar:** Investigation, Methodology, Writing-original draft.

**Rengan Ramesh:** Conceptualization, Supervision, Validation, Writing-review and editing.

**Pennamuthiriyam Anandaraj:** Investigation, Methodology.

**Sémeril David:** Software.

## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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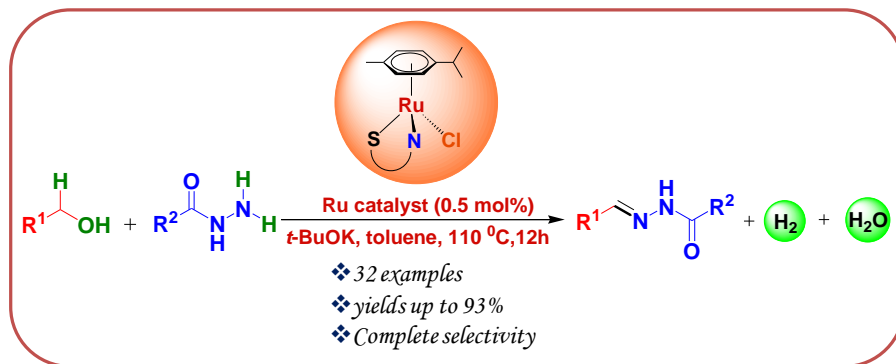
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4 A facile catalytic one-pot synthesis of *N*-acylhydrazones via acceptorless dehydrogenative  
5 coupling of readily available alcohols and benzohydrazides using arene ruthenium(II) catalysts  
6 have been described.  
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## Arene Ru(II)- Catalyzed Facile Synthesis of *N*-Acylhydrazones via ADC Strategy

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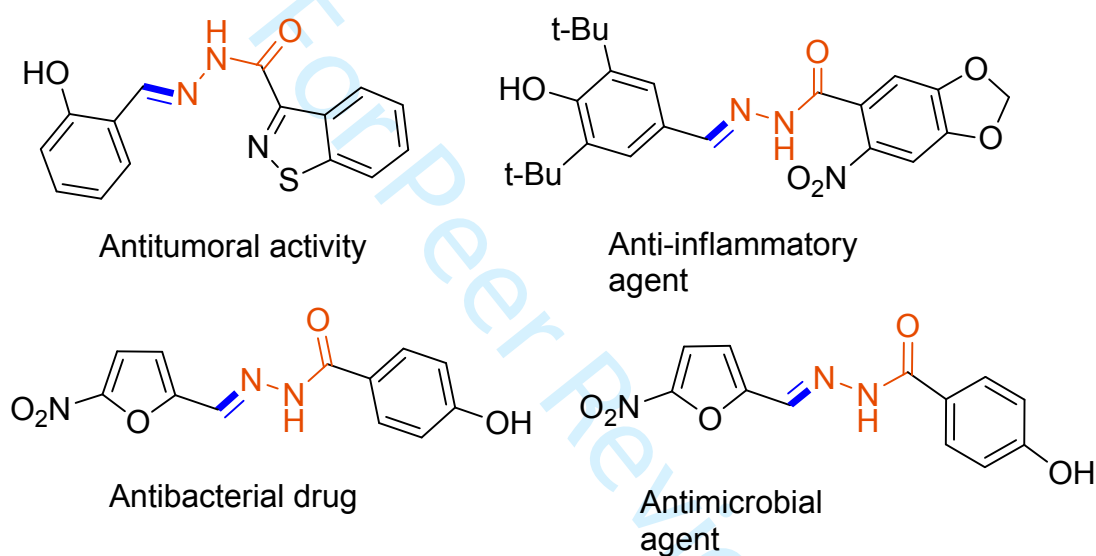
Laboratoire de Chimie Inorganique et Catalyse, Institut de Chimie, Université de Strasbourg, UMR 7177, CNRS, France. *Supporting Information Placeholder*

**Keywords:** benzohydrazides, ruthenium(II) complexes, acceptorless dehydrogenative coupling, alcohols, *N*-acylhydrazones

**ABSTRACT:** A facile catalytic one-pot synthesis of *N*-acylhydrazones (NAH) via acceptorless dehydrogenative coupling (ADC) of readily available alcohols and benzohydrazides ( $R_2CONHNH_2$ ) using arene ruthenium(II) complexes has been described. The coupling of alcohols with various benzohydrazides using ruthenium catalysts provide a wide range of *N*-acylhydrazones in good to excellent yields (63% - 93%; 32 examples). The present protocol offers high selectivity of hydrazones without any alkylated products and tolerates a range of functional groups. Control experiments indicate that the mechanism proceeds via acceptorless dehydrogenation of alcohols and hydrogen and water are the sole by-products. The gram scale synthesis illustrates the usefulness of the present strategy.

## INTRODUCTION

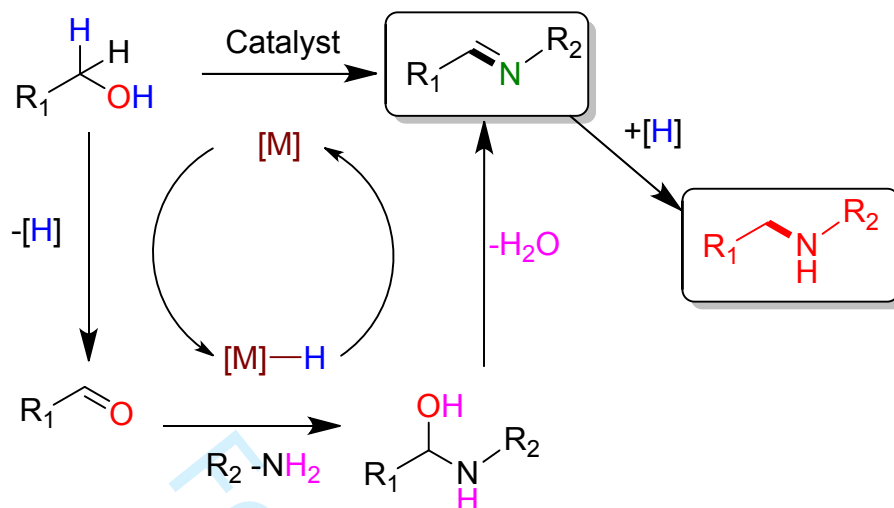
N-Acylhydrazones (NAHs) are influential class of compounds that demonstrate versatile reactivity and exhibit extensive applications in organic<sup>1</sup> and medicinal chemistry.<sup>2</sup> Because of their distinct structural and stereochemical reactivity, they act as electrophiles for the synthesis of valuable sort of nitrogen-containing compounds.<sup>3</sup> NAH scaffolds reveal significant biological activities, including antiviral<sup>4</sup> (influenza virus HSV-1<sup>5</sup>), antimicrobial,<sup>6</sup> antitubercular,<sup>7</sup> analgesic, anti-inflammatory,<sup>8</sup> antiproliferative,<sup>9</sup> anticonvulsant,<sup>10</sup> and antitrypanosomal<sup>11</sup> activities (**Figure 1**). Owing to these comprehensive biological applications, N-acylhydrazones are considered as ubiquitous structure which resulted in the development of new NAH based drugs.



**Figure 1.** Biologically active *N*-acylhydrazones

Traditionally, synthesis of *N*-acylhydrazones involves the condensation of carbonyl compounds and acylhydrazides.<sup>12</sup> Initially, alcohols are oxidized to the carbonyl compounds using toxic inorganic chemicals and further reaction with acylhydrazides yields the corresponding *N*-acylhydrazones. This conventional method for the synthesis of *N*-acylhydrazones, involves multistep process which produces waste and needs reaction workups, isolation and purification of the products. Metal-mediated direct synthesis of target molecules is a valuable approach in organic synthesis. Recently, Rassadin and co-workers reported gold(I) catalyzed hydrohydrazidation of terminal alkynes with acylhydrazides for the generation of keto-*N*-acylhydrazones, but the catalytic reaction requires high catalyst loading (6 mol%) and expensive alkynes. Unfortunately, the reaction is substrate specific which is limited to the synthesis of methylketone-*N*-acylhydrazones.<sup>13</sup>



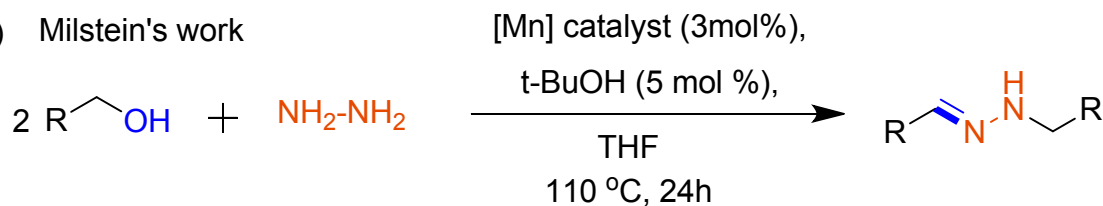
**Scheme 1.** Transition-metal catalyzed Acceptorless Dehydrogenative Coupling (ADC) strategy

The direct synthesis of substituted hydrazones from acceptorless dehydrogenative coupling (ADC) of alcohols has been received much attention recently (Scheme 1). This protocol is apparently attractive because of alcohols are abundant, inexpensive, commercially available, easy to store and have a low toxicity. Milstein and co-workers elegantly reported manganese pincer catalyst (3 mol %) for the synthesis of  $N$ -substituted hydrazones from alcohols and hydrazine hydrate via acceptorless dehydrogenative coupling using 5 mol % of  $t$ -BuOK (Scheme 2a).<sup>14</sup> Li, et al., demonstrated acceptorless dehydrogenative coupling of primary alcohols and arylhydrazine for the synthesis of arylhydrazones using 0.5 mol % of commercially available iridium catalyst in the presence of KOH at 130°C (Scheme 2b).<sup>15</sup> Despite the reports on substituted hydrazones, metal mediated synthesis of  $N$ -acylhydrazones from alcohols remains unexplored. In light of this, we have attempted to synthesize  $N$ -acylhydrazones by acceptorless dehydrogenative coupling of alcohols and benzohydrazides using ruthenium(II) arene catalysts. The reaction proceeded smoothly to yield the respective  $N$ -acylhydrazone products with complete selectivity and hydrogen and water are the only by-products. To the best of our knowledge, there is no report available on the metal mediated synthesis of  $N$ -acylhydrazones from alcohols and benzohydrazides. In continuation of our quest to develop new catalysts for the C-N bond forming reactions,<sup>16</sup> herein we report the direct synthesis of  $N$ -acylhydrazones using 0.5 mol% catalyst loading.

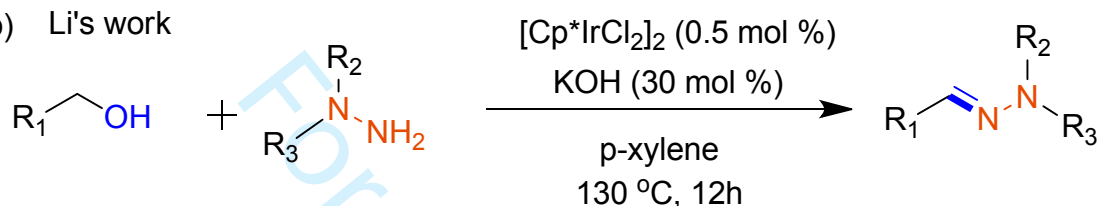
**Scheme 2.** Metal-mediated synthetic strategies for hydrazone synthesis via ADC

Previous work

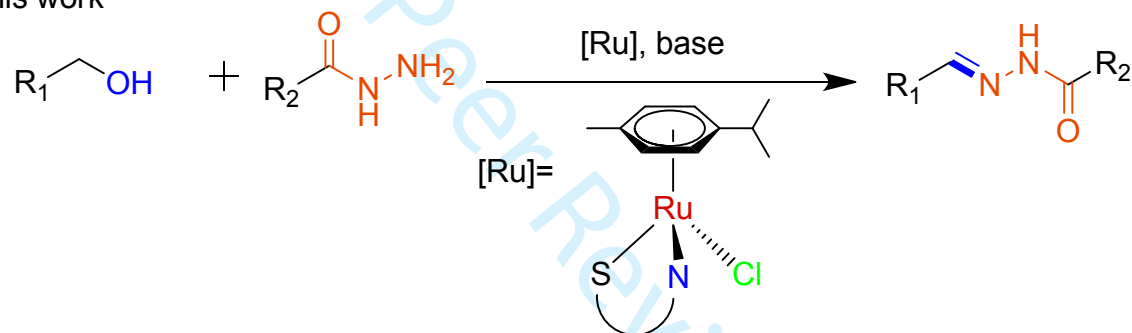
(a) Milstein's work



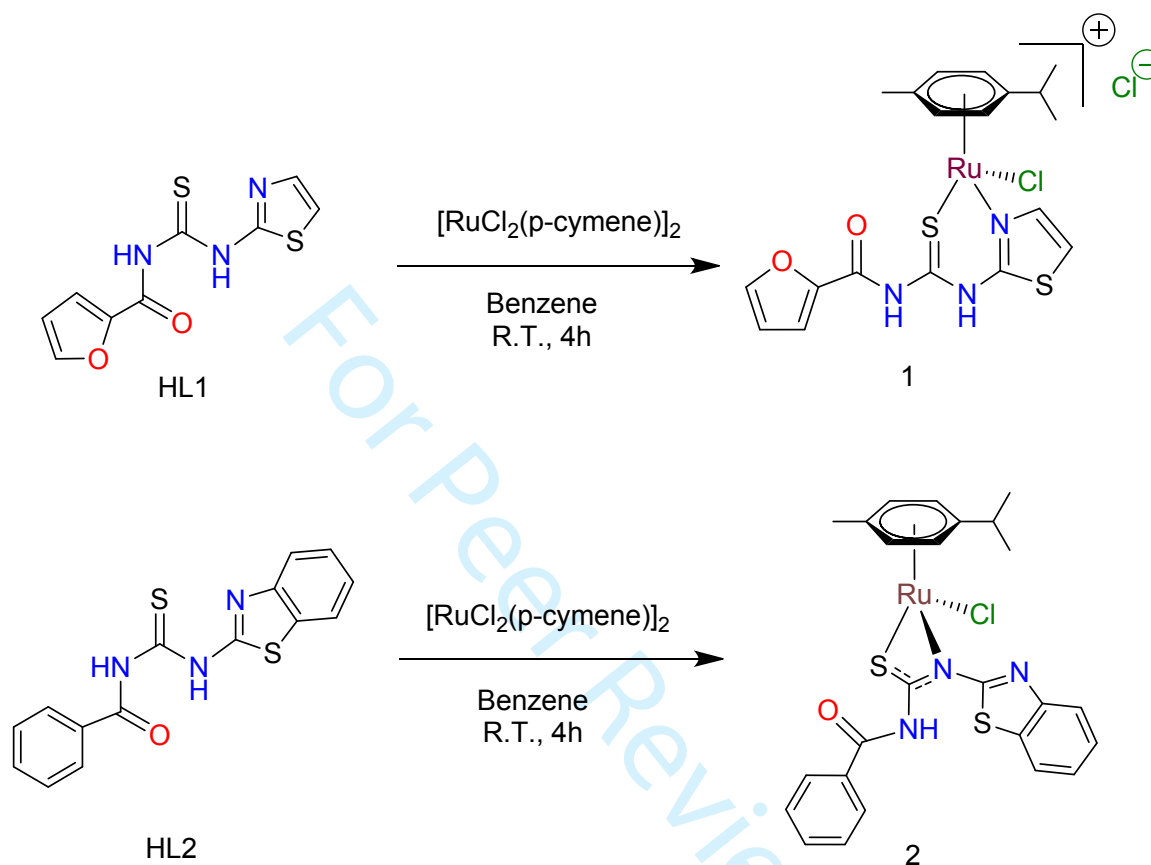
(b) Li's work



This work

**RESULTS AND DISCUSSION**

Treatment of Ru(II) arene precursor  $[\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})]_2$  with bidentate ligands 1-(furan-5-carbonyl)-3-(thiazol-2-yl)thiourea (HL1) and 1-(benzo[d]thiazol-2-yl)-3-benzoylthiourea (HL2) at room temperature resulted in two types of arene-Ru(II) complexes 1 and 2 in 85% and 79%, respectively (**Scheme 3**).

**Scheme 3.** Synthesis of arene-Ru(II) complexes **1** and **2**.

The FT-IR spectra of the complexes **1** and **2** were compared to that of the free ligands. In complex **1**, the bands corresponding to N-H and C=O groups of the ligands remain unaltered upon complexation, which confirms that they do not involve in coordination whereas in complex **2**, the disappearance of band corresponding to NH(thiocarbonyl) confirms that the nitrogen is coordinated to the ruthenium atom. On the other hand, the decrease in the C=S stretching frequency from  $1263$  to  $1217\text{ cm}^{-1}$  in complex **1**, suggests that the ligand is coordinated to ruthenium ion *via* neutral sulphur atom. Thus, the IR spectra of the complexes clearly indicated that ligand HL1 acts as a 4-electron (*N,S*)-chelator in contrast to ligand HL2 which turns out to be a 3-electron (*N,S*)-chelator.

In the  $^1\text{H}$  NMR spectra of complexes **1** and **2**, the resonances due to the aromatic protons of the coordinated ligand (HL1) and (HL2) were observed in the region  $\delta = 7.87\text{-}6.64$  ppm and  $\delta =$

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2  
3 8.15-7.36 ppm, respectively. The signals owing to *p*-cymene moiety of the complexes were found  
4 in the region of 5.82-5.47, 2.95-2.78, 2.17-2.08 and 1.33-1.18 ppm. The disappearance of signal  
5 due to thiocarbonyl attached NH in complex **2**, confirms the coordination of nitrogen atom in  
6 anionic form. Further, in the <sup>13</sup>C NMR spectra of complexes **1** and **2**, signals appeared in the region  
7 175.3–175.0 and 158.0–151.3 ppm attributed to the C=S and C=O carbons, respectively. The  
8 aromatic carbons of *p*-cymene moieties resonate in the expected range of 84.93–101.42 ppm.  
9 Further, the peaks corresponding to CH and CH<sub>3</sub> carbons of *p*-cymene moieties were observed in  
10 the region  $\delta = 30.79$ -29.94 ppm and  $\delta = 22.57$ -17.83 ppm, respectively.  
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17 The molecular structure of the complexes **1** and **2** were unambiguously confirmed with the  
18 aid of single crystal X-ray diffraction study. It is inferred from the XRD data that the complex **1**  
19 crystallizes as triclinic with the space group P-1 whereas complex **2** crystallizes as monoclinic  
20 with the space group P21/*c*. The molecular structure of complexes **1** and **2** exhibit a pseudo  
21 octahedral geometry with a “3-legged piano-stool” arrangement around the Ru(II) ion. In the  
22 cationic complex **1**, the seat was occupied by the *p*-cymene moiety and the legs by the thione  
23 sulphur (neutral form) and thiazole nitrogen of the ligand (HL1) and chlorine atom. In contrast, in  
24 the neutral complex **2**, the seat of piano-stool was occupied by the *p*-cymene moiety and the  
25 remaining sites by the nitrogen (anionic form) attached to thiocarbonyl, thione sulphur of the  
26 ligand (HL2) and a chloride ligand. The bond lengths of Ru(1)-Cl(1), Ru(1)-S(1) and Ru(1)-N(3)  
27 in complex **1** were found to be 2.411, 2.3585 and 2.0884 Å, respectively and in complex **2**, bond  
28 lengths of Ru(1)-Cl(1), Ru(1)-S(1) and Ru(1)-N(2) were found to be 2.3986, 2.3961 and 2.125 Å,  
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Figure 2. ORTEP plots of complexes 1. Thermal ellipsoids are shown at the 50% probability level.

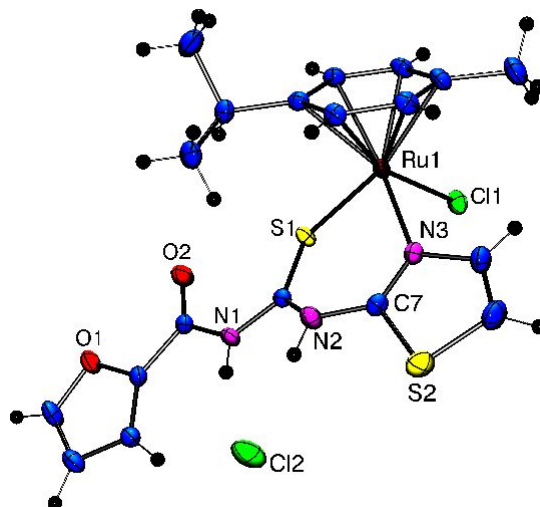


Figure 3. ORTEP plots of complexes 2. Thermal ellipsoids are shown at the 50% probability level.

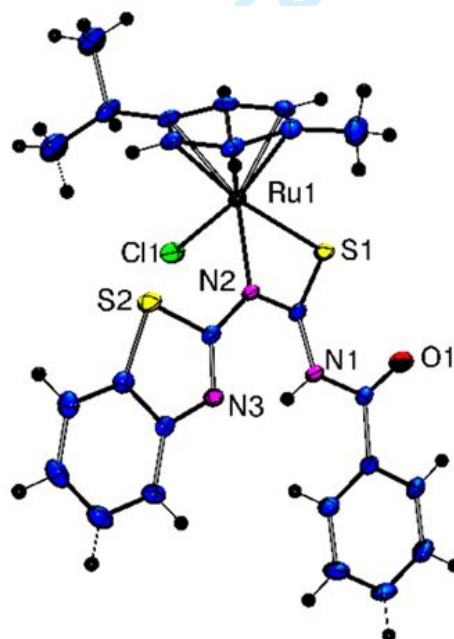
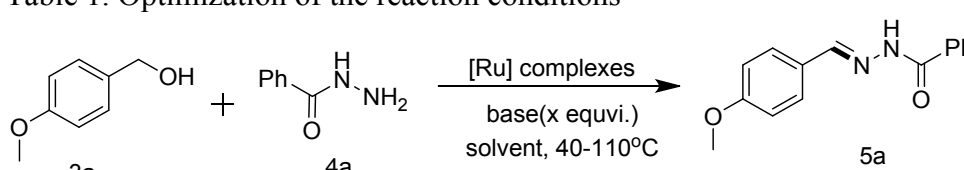


Table 1. Optimization of the reaction conditions<sup>a</sup>



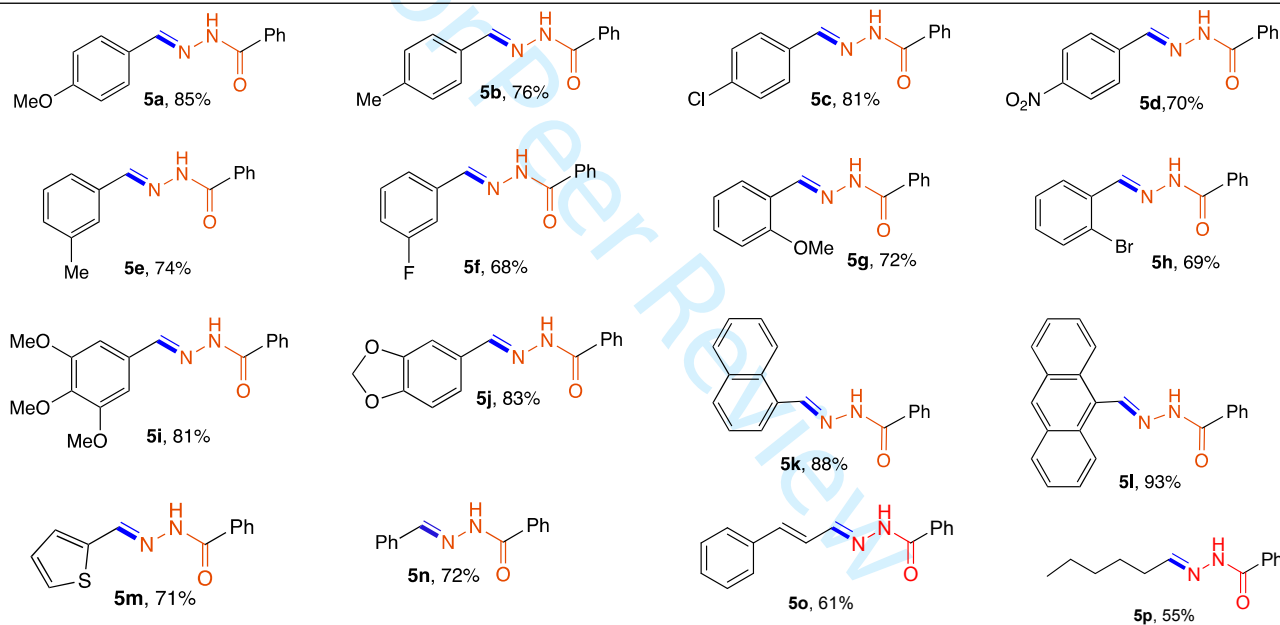
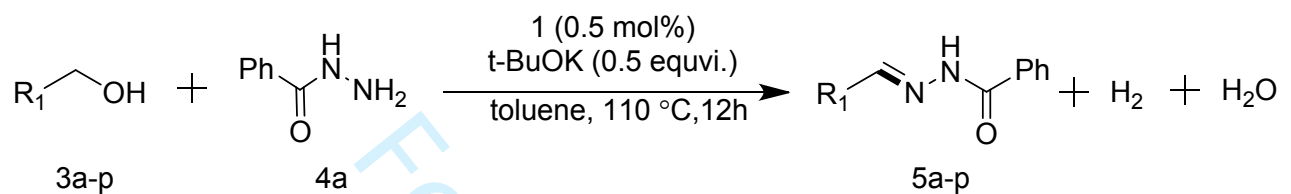
Complexes	Solvent	Base	T (°C)	Yield (%) <sup>b</sup>
1	THF	<i>t</i> -BuOK	66	48
2	CH <sub>2</sub> Cl <sub>2</sub>	<i>t</i> -BuOK	40	46
3	PhCH <sub>3</sub>	<i>t</i> -BuOK	80	65
4	<i>t</i> -BuOH	<i>t</i> -BuOK	83	<10
5	PhCH <sub>3</sub>	<i>t</i> -BuOK	110	85
6	PhCH <sub>3</sub>	KOH	110	79
7	PhCH <sub>3</sub>	LiOH.H <sub>2</sub> O	110	<15
8	PhCH <sub>3</sub>	<i>t</i> -BuOK	110	67
9 <sup>c</sup>	PhCH <sub>3</sub>		110	NR
10 <sup>d</sup>	PhCH <sub>3</sub>	<i>t</i> -BuOK	110	NR
11 <sup>e</sup>	PhCH <sub>3</sub>	<i>t</i> -BuOK	110	51

<sup>a</sup>Reaction conditions: Complex 1 (0.5 mol %), 4-methoxybenzyl alcohol 3a (1 mmol), benzohydrazide 4a (1 mmol), *t*-BuOK (0.5 mmol), solvent (3 mL) for 12 h; <sup>b</sup>yield of the isolated product; <sup>c</sup>in the absence of base; <sup>d</sup>in the absence of catalyst 1; <sup>e</sup>0.25 mol% of complex 1.

For optimization of the catalytic synthesis of *N*-acylhydrazones, an equimolar ratio of 4-methoxybenzyl alcohol (**3a**) and benzohydrazide (**4a**) were employed as model substrates in the presence of 0.5 mol% of complex **1**. We began the optimization using *t*-BuOK (0.5 mmol) as a base in THF medium at 66°C, after 12 hours, the corresponding product was isolated in 48% yield (**Table 1, entry 1**). A few common solvents such as THF, CH<sub>2</sub>Cl<sub>2</sub>, PhCH<sub>3</sub> and *t*-BuOH were employed and we found that the higher isolated yield was obtained in toluene at 80°C (**Table 1, entries 1-4**). Interestingly, repeated the run at the reflux temperature of toluene favored the formation of the desired product and **5a** was isolated in 85% yield (**Table 1, entry 5**). Among all the bases, *t*-BuOK was found to be the most suitable base (**Table 1, entry 5**). However, using KOH as the base under the same reaction conditions gave **5a** in 79% yield (**Table 1, entry 6**). The isolated yields of **5a** dropped off to <15% when LiOH.H<sub>2</sub>O was employed as the base (**Table 1,**

entry 7). It is interesting to note that among complexes **1** and **2**, the cationic ruthenium complex **1** gave the highest isolated yield (Table 1, entries 5 and 8). As expected, the reaction did not occur in the absence of base or catalyst (Table 1, entries 9 and 10). The decreasing of the catalyst loading resulted in a lower formation of **5a** (Table 1, entry 11).

**Table 2.** Scope of the ruthenium-catalyzed coupling of benzohydrazides with substituted aromatic alcohols.<sup>a</sup>



<sup>a</sup>Reaction conditions: Complex **1** (0.5 mol %), substituted benzyl alcohols **3a-p** (1 mmol), benzohydrazide **4a** (1 mmol), *t*-BuOK (0.5 mmol), and toluene (3 mL) were heated at 110 °C for 12 h; <sup>b</sup> Yield of the isolated product.

After optimizing the catalytic conditions, in order to explore the generality of the protocol various primary alcohols were tested. We can see that the introduction of substituents on the aromatic ring of the benzyl alcohol does not inhibit the coupling reaction (Table 2). The use of alcohols bearing electron-rich (4-MeO-C<sub>6</sub>H<sub>4</sub> (**3a**), 4-Me-C<sub>6</sub>H<sub>4</sub> (**3b**)) and electron-deficient (4-Cl-C<sub>6</sub>H<sub>4</sub> (**3c**), 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub> (**3d**)) substituents only slightly affects the amounts of *N*-acylhydrazones **5a-5d** formed (SI, Figures 5-12) Conversely, the presence of a fluorine atom at the *meta*-position

(3f) affects the formation of the corresponding *N*-acylhydrazone **5f** (SI, Figures 13-14) the product is isolated in 68% yield, while the 3-methylbenzyl alcohol (3e) gave a 74% yield of product **5e** (SI, Figures 14-15). Surprisingly, good isolated yields were observed when benzyl alcohols bearing sterically hindered substituents at *ortho*-position (2-MeO-C<sub>6</sub>H<sub>4</sub> (**5g**), 2-Br-C<sub>6</sub>H<sub>4</sub> (**5h**)) (SI, Figures 16-20) were employed. Similarly, 81% of the corresponding *N*-acylhydrazone **5i** (SI, Figures 21-22) was obtained using 3,4,5-trimethoxybenzyl alcohol (3i). Using piperonyl alcohol (3j), led to the formation the corresponding product **5j** (SI, Figures 23-24) in 83% yield. We can note that 1-naphthalenemethanol (3k) and 9-anthracenemethanol (3l) were also found to be reactive substrates as they gave 88% and 93% of the products **5k** and **5l**, (SI, Figures 25-28) respectively. The reaction of a heteroaromatic alcohol such as 2-thiophenemethanol (3m) gave 71% of the corresponding *N*-acylhydrazone **5m** (SI, Figures 29-30). Further, the present protocol works well with cinnamyl alcohol and *n*-hexanol to render the hydrazone products **5o** and **5p** (SI, Figures 31-36) in good to moderate yields respectively.

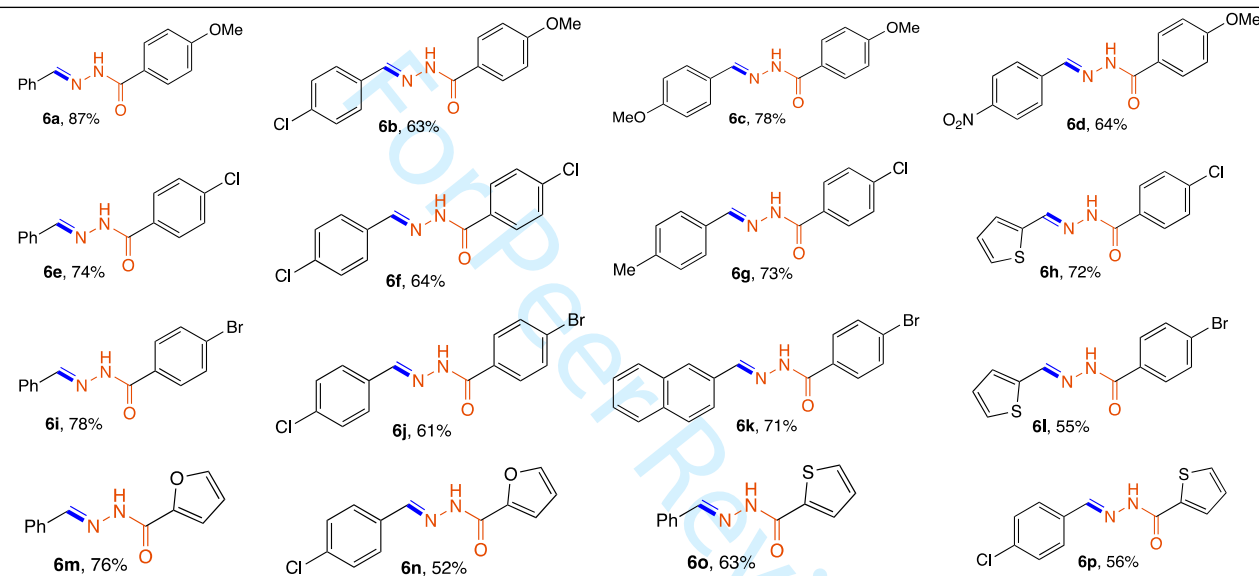
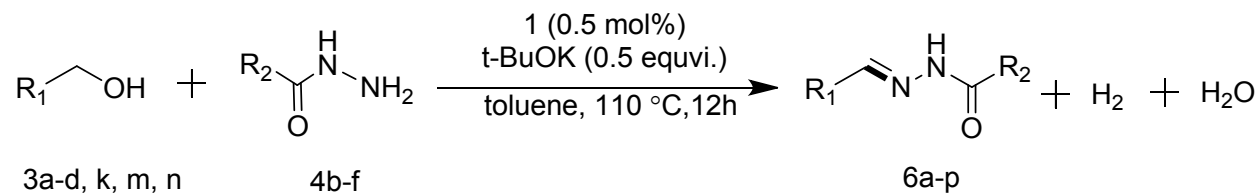
The substrate scope was further extended to the substituent of benzohydrazide (4b-f) (**Table 3**). The reaction of 4-methoxybenzohydrazide (4b) with benzyl alcohol (3n) delivered the corresponding *N*-acylhydrazone **6a** (SI, Figures 37-38) in 87% yield. Similarly, the reactions of 4-methoxybenzohydrazide (4b) with both electron poor (-Cl (3c) and -NO<sub>2</sub> (3d)) or electron rich (-MeO (3a)) arylmethyl alcohols led to the formation of the desired products **6b-6d** (SI, Figures 39-44) with yield up to 78%. Further, the benzohydrazide reaction with 4-chlorobenzyl alcohol to give **6e** in 74% isolated yield (SI, Figures 45-46). Expectedly, 4-chlorobenzohydrazide (4c) reacted with chloro- and methyl- substituted aryl alcohols and the corresponding products were isolated in 64% (**6f**) and 73% (**6g**) (SI, Figures 47-50) yields, respectively. Furthermore, the reaction of 2-thiophenemethanol (3m) with 4- chlorobenzohydrazide (4c) led to compound **6h** (SI, Figures 51-52) in 72% yield. It is gratifying to note that the benzohydrazide bearing weakly deactivating -Br group (4d) provided of *N*-acylhydrazones (**6i-6l**) (SI, Figures 53-60) with good yields (55-78%). Interestingly, furan-2-carbohydrazide (4e) and 2-thiophenecarbohydrazide(4f) allowed the coupling reaction and afforded the corresponding products (**6m-p**) (SI, Figures 61-68) in good isolated yields (52-76%).

In order to demonstrate the usefulness of the present protocol for an industrial application, we investigated the gram scale synthesis of (*E*)-*N'*-(4-methoxybenzylidene)benzohydrazide (**5a**) (SI,



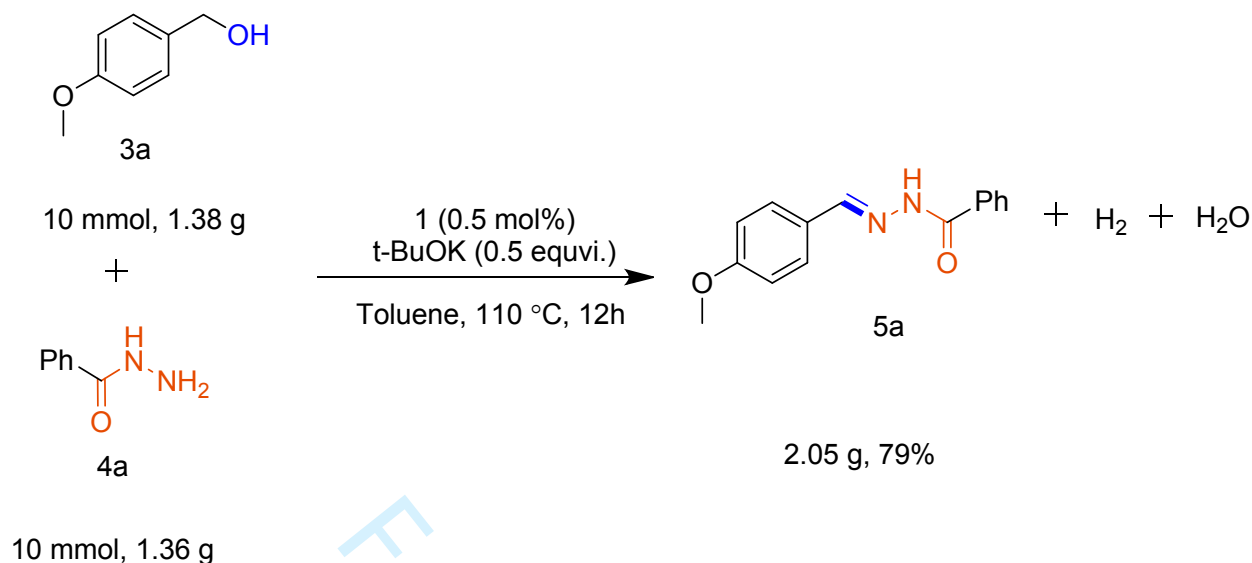
Figures 5-6) as a representative example (Scheme 4). After 12 hours in refluxing toluene, the targeted compound was isolated in 79% yield.

**Table 3.** Scope of the ruthenium-catalyzed coupling of substituted benzohydrazides with primary benzyl alcohols<sup>a</sup>



<sup>a</sup>Reaction conditions: Complex **1** (0.5 mol %), primary alcohols **3a-d,k,m,n** (1 mmol), substituted benzohydrazides **4b-f** (1 mmol), *t*-BuOK (0.5 mmol), and toluene (3 mL) were heated at 110°C for 12 h; <sup>b</sup>Yield of the isolated product

**Scheme 4.** Gram scale synthesis of (*E*)-*N'*-(4-methoxybenzylidene)benzohydrazide



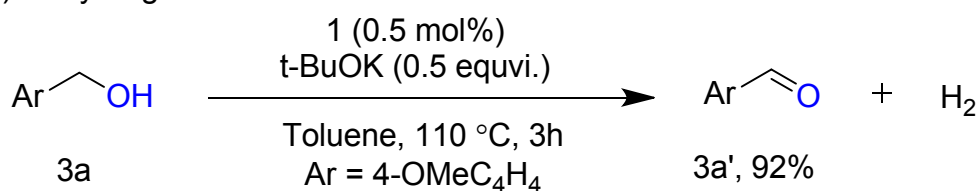
In order to probe the mechanism, a series of control experiments have been carried out. Initially, 4-methoxybenzyl alcohol (3a) in the absence of benzohydrazide under the standard catalytic conditions resulted in the formation of the corresponding aldehyde (3a'). Thus, the formation of 3a' indicated that the reaction proceeds *via* selective acceptorless dehydrogenation of alcohols (**Scheme 5-i**). Further, to establish the dehydrogenation of alcohol, tests were carried out with phenol or *t*-butanol. As expected, no *N*-acylhydrazone formation was observed, which supports that the synthesis of *N*-acylhydrazone occurs *via* dehydrogenation of benzyl alcohol (**Scheme 5-ii**). On the basis of the previous reports,<sup>16</sup> we were interested in examining the product selectivity (**Scheme 5 iii**). In this purpose the catalytic transfer hydrogenation of *N*-acylhydrazone 5a with alcohols such as 4-methoxybenzyl alcohol (3a) and isopropanol as hydrogen sources were carried out. In both the reactions, none of the *N*-alkylated products were observed. The results clearly indicate that *N*-acylhydrazones are stable and they did not undergo transfer hydrogenation in the presence of hydrogen sources, which are marked contrast with the literature reports where the *N*-alkylated products were produced from dehydrogenative coupling of alcohols and amine. Hence, the above observations supports for the selective synthesis of *N*-acylhydrazones without formation of any *N*-alkylated byproducts.

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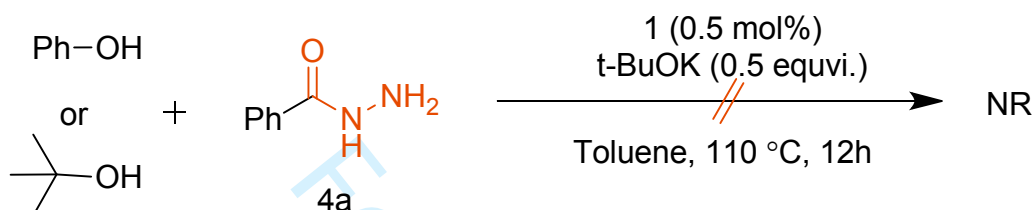
**Scheme 5.** Control experiments

For Peer Review

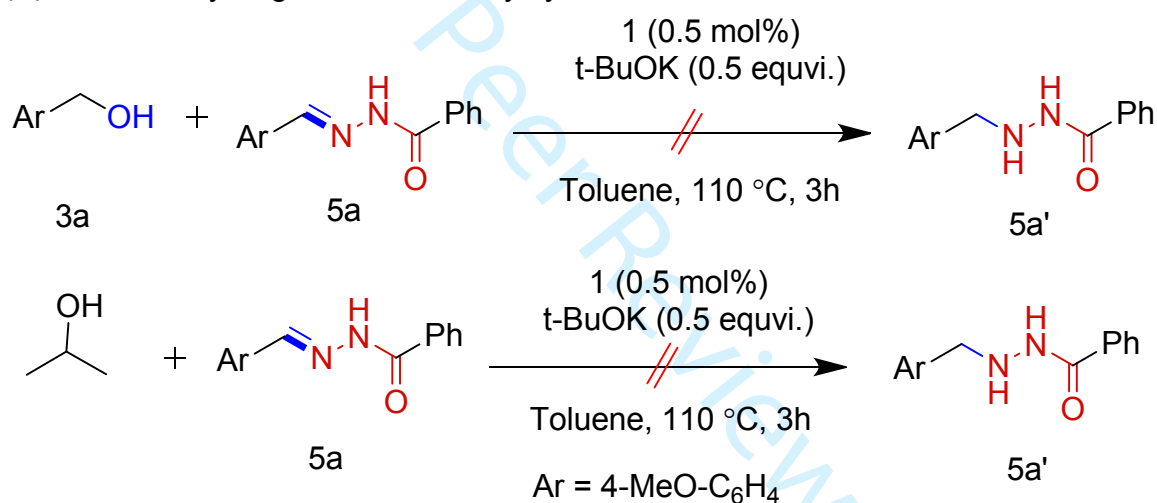
## (i) Dehydrogenation of alcohols



## (ii) Reaction of benzohydrazide with phenol or t-butanol



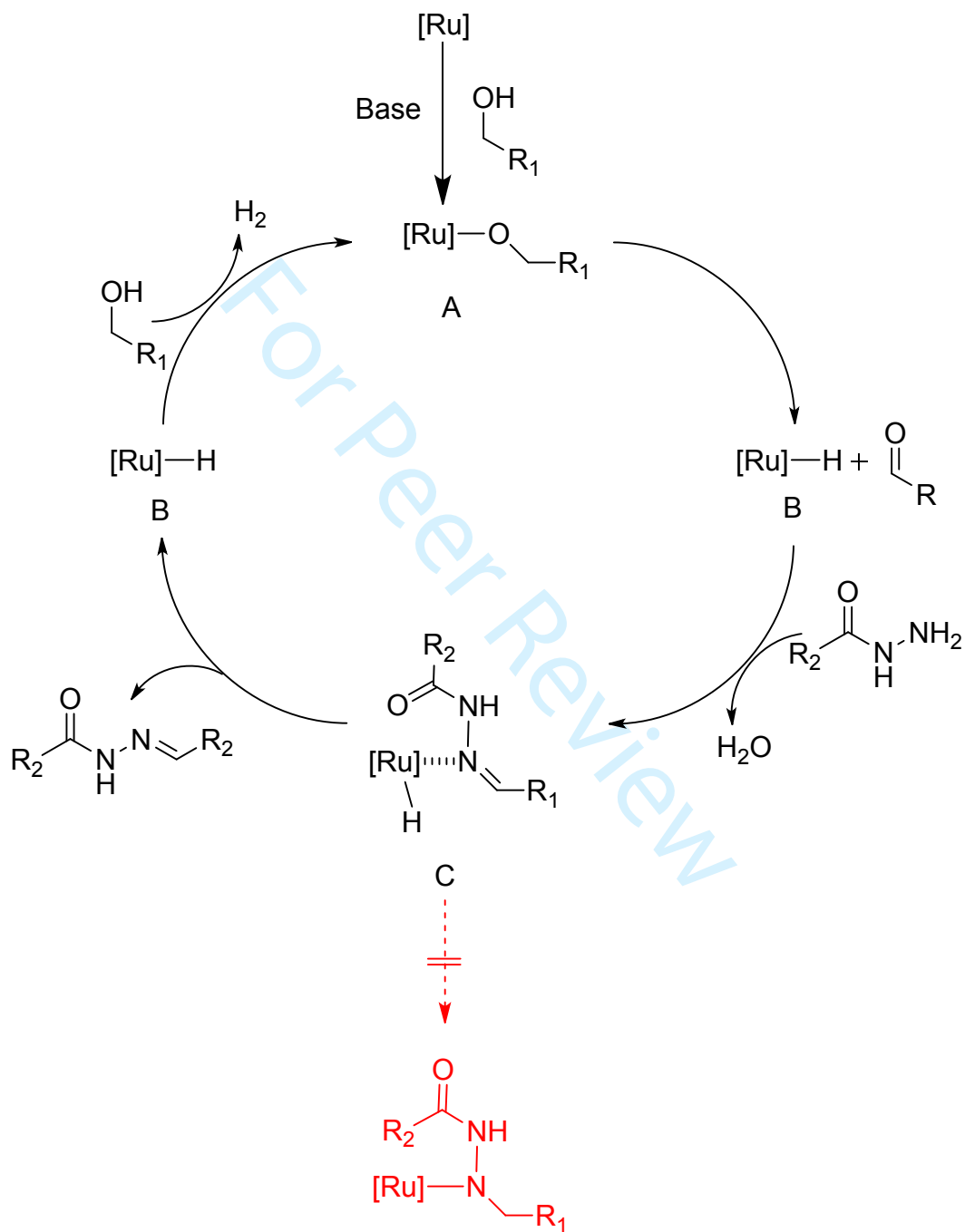
## (iii) Transfer hydrogenation of N-acylhydrazone



Encouraged by the literature reports<sup>15,16,17</sup> and results of the control experiments, we herein propose a mechanism for the synthesis of *N*-acylhydrazone catalyzed by arene-ruthenium(II) complex (**1**) via acceptorless dehydrogenative coupling of alcohols (**Scheme 6**). The initial step is presumed to be the formation of a ruthenium alkoxide species (A) which undergoes  $\beta$ -H elimination resulted in the formation of ruthenium hydride species (B) and aldehyde. Further, the condensation of aldehyde with acyllhydrazides results in ruthenium hydride species coordinated with aroylhydrazones (C). Subsequent dissociation of (C) releases the product aroylhydrazone and Ru-H species. Finally, the reaction of alcohol with ruthenium hydride species (B) regenerates the

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3 ruthenium alkoxide species (A) along with the liberation of hydrogen gas. (see **Supporting**  
4  
5 **Information for more details**)

6  
7 **Scheme 6.** Plausible mechanism



## CONCLUSION

We herein report for the first time, an efficient strategy for the direct synthesis of *N*-acylhydrazones from acceptorless dehydrogenative coupling of alcohols and benzohydrazides catalyzed by a newly synthesized arene ruthenium(II) complex. The *N*-acylhydrazones products were isolated in good to excellent yields with a catalyst loading of only 0.5 mol%. Furthermore, the observation of aldehyde intermediate and the control experiments demonstrated that reaction mechanism involves dehydrogenation of alcohol as the initial step.

## EXPERIMENTAL SECTION

C, H, N and S analyses were carried out with a Vario EL III CHNS elemental analyzer. IR spectra were recorded on a JASCO 400 plus spectrometer. Electronic spectra in CH<sub>2</sub>Cl<sub>2</sub> were recorded with a CARY 300 Bio UV-visible Varian spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using Bruker Avance-400 NMR spectrometers in CDCl<sub>3</sub>, DMSO-*d*<sub>6</sub> and tetramethylsilane (TMS) as internal standard. Deuterated CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> were used as received. Chemical shifts were reported in units parts per million (ppm) by assigning TMS resonance as 0.00 ppm with reference to residual solvent signals. High Resolution Mass spectra were recorded on a Thermo Exactive Orbitrap mass spectrometer using electrospray ionization (ESI) technique. Ligands (HL1 and HL2) were prepared according to the literature procedure.<sup>16a</sup>

**General procedure for the synthesis and characterization of complexes 1 and 2:** 1-(Furan-5-carbonyl)-3-(thiazol-2-yl)thiourea (**HL1**) (50.66 mg, 0.20 mmol) or 1-(benzo[d]thiazol-2-yl)-3-benzoylthiourea (**HL2**) (62.68 mg, 0.20 mmol) were dissolved in 20 mL of benzene. To the solution, 0.10 mmol of the ruthenium precursor [RuCl<sub>2</sub>(*η*<sup>6</sup>-*p*-cymene)]<sub>2</sub> (61.23 mg, 0.10 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. The orange solid gets precipitated, which was filtered and dried in vacuum. The resulting complexes were recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/petroleum ether to afford pure desired ruthenium complex.

**[RuCl(HL1)(*η*<sup>6</sup>-*p*-cymene)]Cl (1):** Orange solid (85% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 12.31 (s, 1H, NH), 7.87 (s br, 1H, O-CH of furane), 7.76-7.75 (m, 2H, O-CH=CH-CH of furane and N-CH of thiazole), 7.31 (d, 1H, S-CH of thiazole, <sup>3</sup>*J* = 3.9 Hz), 6.64 (m, 1H, O-CH=CH of furane), 5.72 (d, 1H, arom. CH of *p*-cymene, <sup>3</sup>*J* = 5.9 Hz), 5.58 (d, 1H, arom. CH of *p*-cymene,

$^3J = 5.5$  Hz), 5.50 (d, 1H, arom. CH of *p*-cymene,  $^3J = 5.8$  Hz), 5.48 (d, 1H, arom. CH of *p*-cymene,  $^3J = 5.9$  Hz), 2.92 (hept, 1H, CH(CH<sub>3</sub>), 2.17 (s, 3 H, CH<sub>3</sub> of *p*-cymene), 1.33 (d, 3H, CH(CH<sub>3</sub>)<sub>2</sub>,  $^3J = 6.9$  Hz), 1.29 (d, 3H, CH(CH<sub>3</sub>)<sub>2</sub>,  $^3J = 6.9$  Hz);  $^{13}\text{C}\{^1\text{H}\}$  NMR (CDCl<sub>3</sub>, 126 MHz):  $\delta = 175.34$  (s, C=S), 158.30 (s, thiazole), 155.19 (s, HN-C=O), 147.83 (s, N-CH of thiazole), 145.19 (s, furane), 144.44 (s, O-CH=CH-CH of furane), 119.68 (s, O-CH of furane), 115.73 (s, S-CH of thiazole), 112.94 (s, O-CH=CH of furane), 106.91 (s, *p*-cymene), 101.42 (s, *p*-cymene), 87.38 (s, arom. CH of *p*-cymene), 85.56 (s, arom. CH of *p*-cymene), 85.41 (s, arom. CH of *p*-cymene), 85.29 (s, arom. CH of *p*-cymene), 30.79 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 22.57 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 22.14 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 18.57 (s, CH<sub>3</sub> of *p*-cymene) ppm. Elemental analysis calcd (%) for C<sub>19</sub>H<sub>21</sub>O<sub>2</sub>N<sub>3</sub>S<sub>2</sub>Cl<sub>2</sub>Ru: C, 40.79; H, 3.78; N, 7.51; S, 11.46. Found: C, 40.65; H, 3.80; N, 7.47; S, 11.40. FT-IR (cm<sup>-1</sup>): 3136, 2960, 1715, 1467, 1239. UV-Vis (CH<sub>2</sub>Cl<sub>2</sub>,  $\lambda_{\text{max}}$  nm;  $\epsilon$  dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 381 (1000), 298 (4500), 227(3500).

**[RuCl(HL2)( $\eta^6$ -*p*-cymene)]Cl (2):** Orange solid (79% yield).  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta = 12.89$  (s, 1H, NH), 8.15 (d, 2H, arom. CH,  $^3J = 7.5$  Hz), 8.02 (d, 1H, arom. CH,  $^3J = 7.8$  Hz), 7.93 (d, 1H, arom. CH,  $^3J = 7.6$  Hz), 7.79 (d, 1H, arom. CH,  $^3J = 8.3$  Hz), 7.66 (d, 1H, arom. CH,  $^3J = 7.3$  Hz), 7.58 (m, 2H, arom. CH), 7.34 (d, 1H, arom. CH,  $^3J = 7.2$  Hz), 5.81 (d, 2H, arom. CH of *p*-cymene,  $^3J = 6.2$  Hz, 1H), 5.77 (d, 2H, arom. CH of *p*-cymene,  $^3J = 6.2$  Hz), 2.90-2.76 (hept, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.09 (s, 3 H, CH<sub>3</sub> of *p*-cymene), 1.19 (d, 3H, CH(CH<sub>3</sub>)<sub>2</sub>);  $^{13}\text{C}\{^1\text{H}\}$  NMR (DMSO-*d*<sub>6</sub>, 100 MHz):  $\delta = 175.07$ (s, C=S), 151.36, 134.00, 132.87, 132.21, 128.64, 128.33, 128.29, 126.18, 123.69, 121.72, 121.44, 106.37 (s, *p*-cymene), 100.06 (s, *p*-cymene), 87.19 (arom. CH of *p*-cymene), 86.33 (arom. CH of *p*-cymene), 85.46 (arom. CH of *p*-cymene), 84.93 (arom. CH of *p*-cymene), 29.94 (CH(CH<sub>3</sub>)<sub>2</sub>), 21.46 (CH(CH<sub>3</sub>)<sub>2</sub>), 21.08 (CH(CH<sub>3</sub>)<sub>2</sub>), 17.83 (CH<sub>3</sub> of *p*-cymene) ppm. Elemental analysis calcd (%) for C<sub>25</sub>H<sub>24</sub>ClN<sub>3</sub>ORuS<sub>2</sub>: C, 51.49; H, 4.15; N, 7.21; S, 11.00. Found: C, 51.39; H, 4.09; N, 7.24; S, 11.05. FT-IR (cm<sup>-1</sup>): 3058, 1690, 1468, 1273. UV-Vis (CH<sub>2</sub>Cl<sub>2</sub>,  $\lambda_{\text{max}}$  nm;  $\epsilon$  dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 400 (500), 304 (1500), 227 (4000).

**General procedure for the synthesis of *N*-acylhydrazones (5a-p and 6a-p):** The mixture of alcohol (1 mmol), substituted benzohydrazide (1 mmol), *t*-BuOK (0.5 mmol) and ruthenium complex (0.5 mol %) was stirred in toluene at 110°C under N<sub>2</sub> atmosphere. After 12 h, the solvent was evaporated under reduced pressure and the resulting crude product was subjected to column

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3 chromatography on silica gel (EtOAc/hexane, gradient from 20% to pure EtOAc) to afford *N*-  
4 acylhydrazones.  
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## 6 7 **ASSOCIATED CONTENT**

### 8 9 Supporting Information

10  
11 The Supporting Information is available free of charge on the ACS Publications website.

12  
13 Complete details of crystal structure, data collection, crystallographic data, refinement parameters,  
14 selected bond lengths, and bond angles. Figures illustrating the <sup>1</sup>H & <sup>13</sup>C NMR spectra of ligands,  
15 complexes, *N*-Acylhydrazones catalytic products (**see supporting Information, Figures S8 –**  
16 **S39**). CIF for the complexes. CCDC numbers for complexes **1** and **2** are 2038566 and 2038567  
17 respectively.  
18  
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### 30 31 **AUTHOR CONTRIBUTIONS**

32  
33 **Saranya Sundar:** Investigation, Methodology, Writing-original draft.

34  
35 **Rengan Ramesh:** Conceptualization, Supervision, Validation, Writing-review and editing.

36  
37 **Pennamuthiriyam Anandaraj:** Investigation, Methodology.

38  
39 **Sémeril David:** Software.  
40  
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## 42 43 **DATA AVAILABILITY STATEMENT**

44  
45 The data that supports the findings of this study are available in the supplementary material of this  
46 article.  
47

## 48 49 **ACKNOWLEDGMENT**

50  
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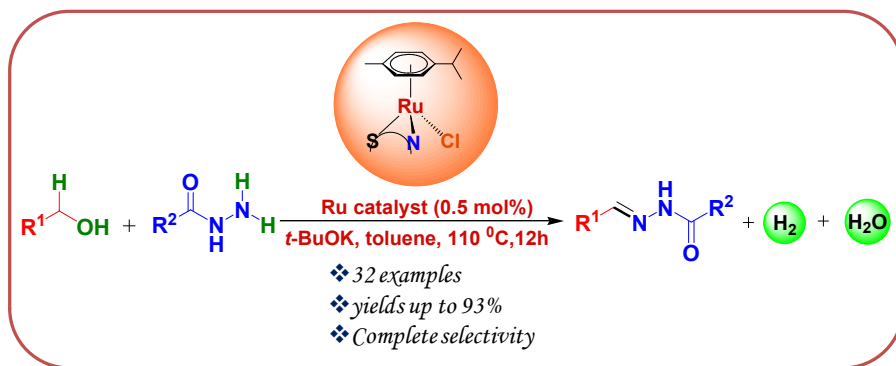


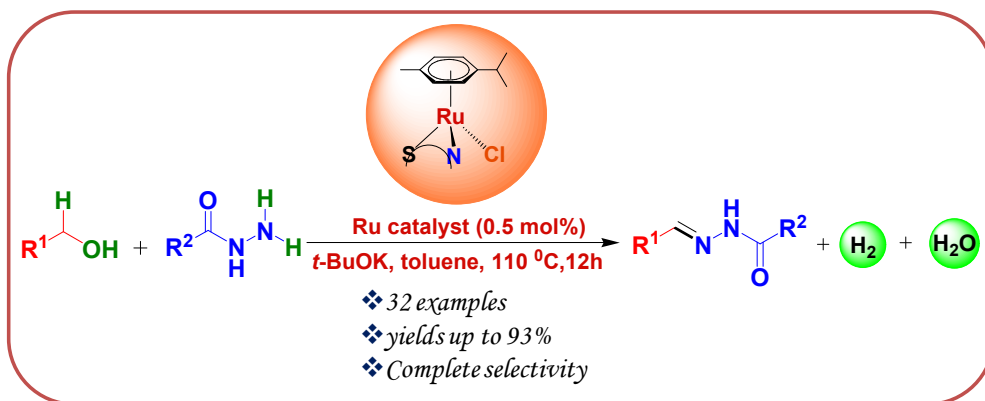
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A facile catalytic one-pot synthesis of *N*-acylhydrazones via acceptorless dehydrogenative coupling of readily available alcohols and benzohydrazides using arene ruthenium(II) catalysts have been described.





For Peer Review

## Supporting Information

### Arene Ru(II)- Catalyzed Facile Synthesis of *N*-Acylhydrazones via ADC Strategy

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#### CONTENTS

1. X-ray crystallography .....	S2-S3
2. <sup>1</sup> H NMR and <sup>13</sup> C NMR spectra of Complexes <b>1</b> and <b>2</b> .....	S4-S7
3. Characterization data for <i>N</i> -acylhydrazones .....	S8-S13
4. <sup>1</sup> H NMR and <sup>13</sup> C NMR spectra of <i>N</i> -acylhydrazones .....	S14-S45
5. Experimental confirmation for the hydrogen gas liberation using GC-TCD detector.....	S46
6. References.....	S47

#### 1. X-ray crystallography

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2 Crystals of complexes **1** and **2** were grown by the slow evaporation of a dichloromethane-  
3 acetonitrile solution. A single crystal of a suitable size complex **1** or **2** was covered with Paratone oil,  
4 mounted on the top of a glass fiber, and moved to a Bruker APEX II DUO Kappa-CCD single-crystal  
5 X-ray Diffractometer. The monochromated Mo-K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) was used and data were  
6 collected at 173(2) K. The absorption corrections were performed by the multiscan method using  
7 SADABS in APEX2 software.<sup>1</sup> Structure of the complexes were solved by SHELXS-2014 and refined  
8 by SHELXL-2014 with full-matrix least-squares on F2.<sup>2</sup> All non-hydrogen atoms were refined with  
9 anisotropy thermal parameters, and the hydrogen atoms were constrained to the ideal positions in the  
10 refinement procedure. The unit cell parameters were determined by the method of difference vectors  
11 using reflections scanned from three different zones of the reciprocal lattice. The intensity data were  
12 measured using a  $\omega$  and  $\Phi$  scan with a frame width of  $0.5^\circ$ . Frame integration and data reduction were  
13 performed using Bruker SAINT-Plus (Version 7.06a) software.<sup>3</sup> The CCDC numbers for the complexes  
14 **1** and **2** are 2038566 and 2038567, respectively.  
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58 **Table S1: Crystal data of complexes 1 and 2**

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Crystal data
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CCDC Number	2038566	2038567
Chemical formula	$C_{19}H_{21}ClN_3O_2RuS_2 \cdot Cl$	$C_{25}H_{24}ClN_3ORuS_2$
$M_r$	559.48	583.11
Crystal system, space group	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$
Temperature (K)	173	173
$a, b, c$ (Å)	9.8424 (4), 10.7289 (4), 12.2627 (5)	13.5712 (4), 7.0433 (2), 24.7967 (8)
$\alpha, \beta, \gamma$ (°)	66.011 (1), 86.303 (1), 66.362 (1)	91.069 (1)
$V$ (Å <sup>3</sup> )	1076.27 (7)	2369.81 (12)
$Z$	2	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$
$\mu$ (mm <sup>-1</sup> )	1.19	0.98
Crystal size (mm)	0.30 × 0.22 × 0.16	0.30 × 0.12 × 0.10
Diffractometer	Bruker APEX-II CCD diffractometer	Bruker APEX-II CCD diffractometer
Absorption correction	Multi-scanSADABS	Multi-scanSADABS
$T_{min}, T_{max}$	0.680, 0.746	0.626, 0.746
No. of measured, independent and observed [ $I > 2\sigma(I)$ ] reflections	30240, 7545, 6475	34597, 6337, 5698
$R_{int}$	0.031	0.041
$(\sin \theta/\lambda)_{max}$ (Å <sup>-1</sup> )	0.748	0.683
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.027, 0.054, 1.08	0.065, 0.137, 1.31
No. of reflections	7545	6337
No. of parameters	273	295
$\Delta\rho_{max}, \Delta\rho_{min}$ (e Å <sup>-3</sup> )	0.93, -0.73	1.42, -2.29

## 2. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of complexes 1 and 2

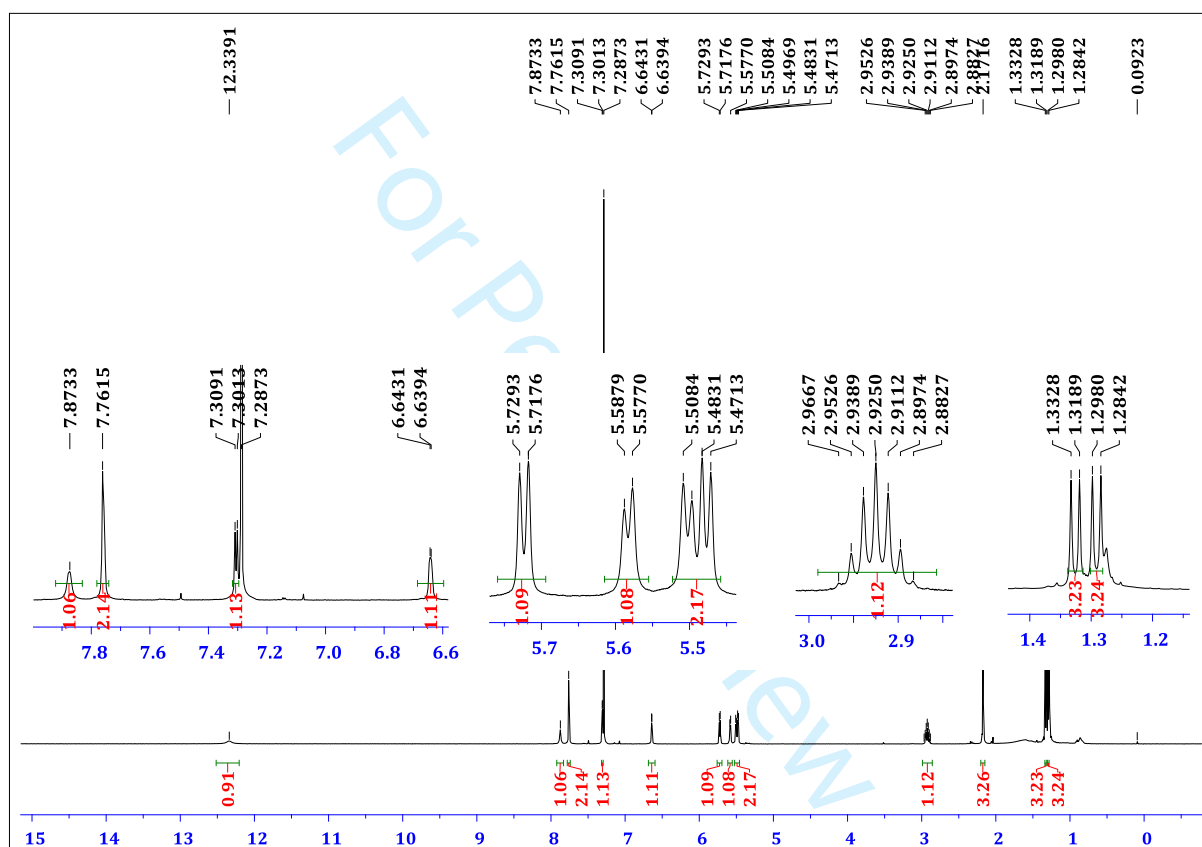


Figure S1:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of complex 1



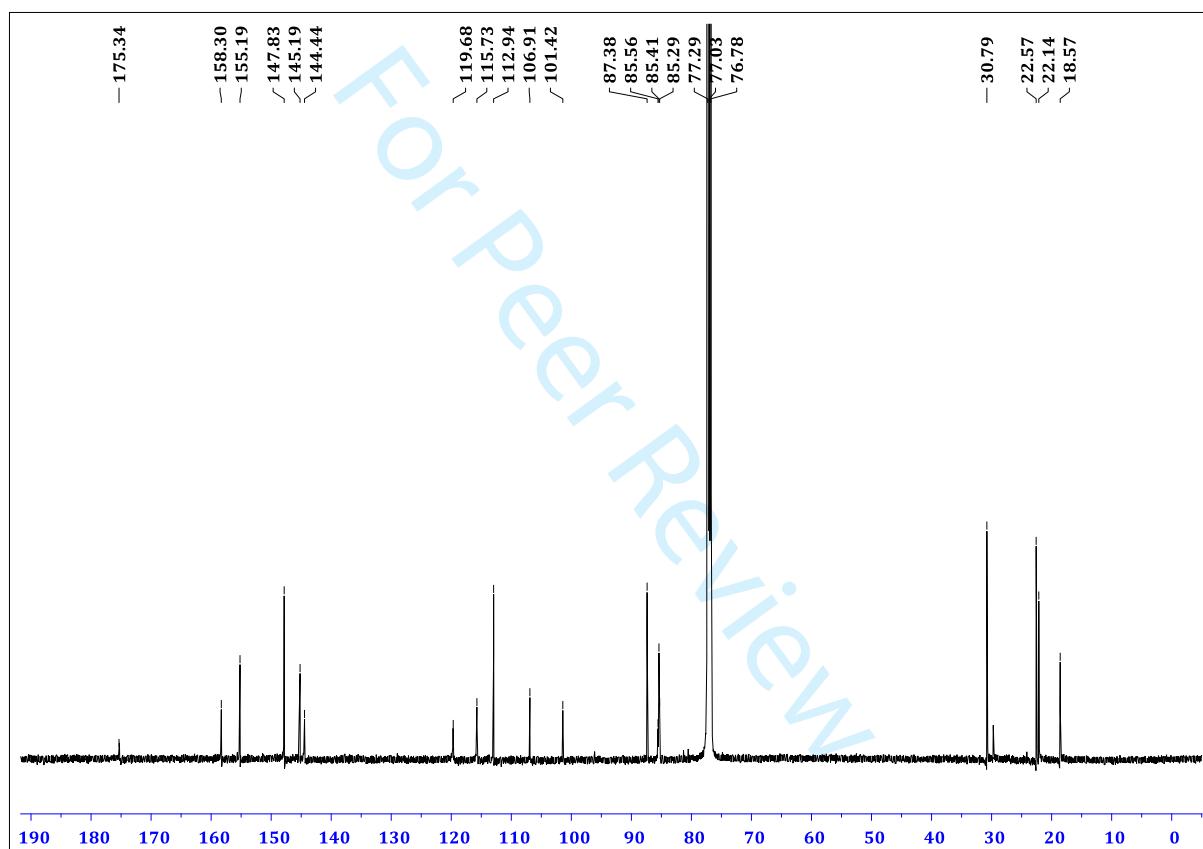


Figure S2:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of complex 1

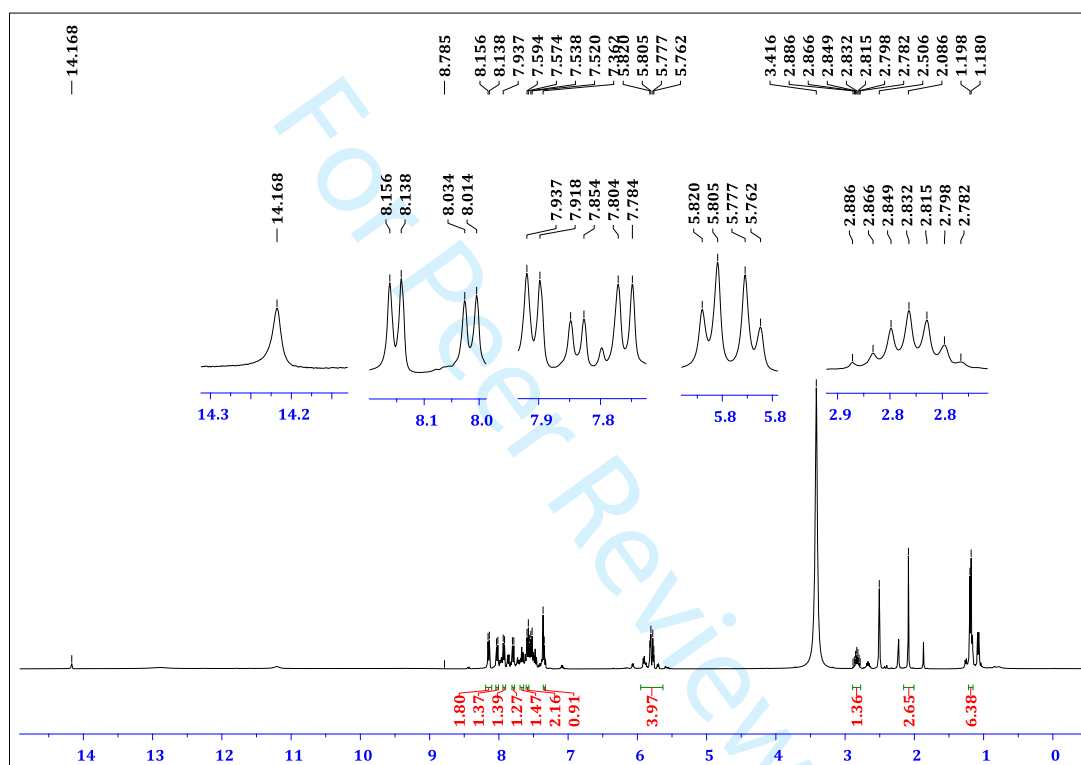


Figure S3:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of complex 2

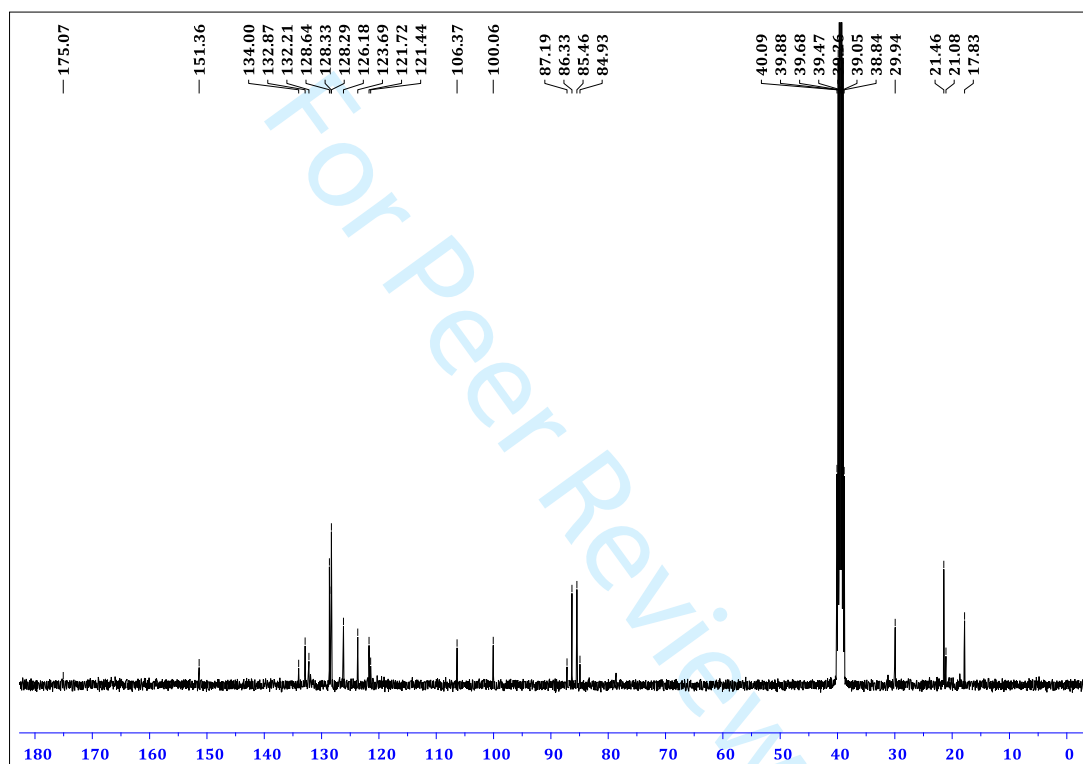


Figure S4:  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of complex 2

**Characterization data for N-acylhydrazones**

**(E)-N'-(4-methoxybenzylidene)benzohydrazide (5a):**<sup>4</sup> From 4-methoxybenzyl alcohol (3a) (138 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5a** (216 mg, 85%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.75 (s, 1H), 8.41 (s, 1H), 7.91 (d, 2H, <sup>3</sup>*J* = 7.4 Hz), 7.68 (d, 2H, <sup>3</sup>*J* = 8.3 Hz), 7.56 (m, 3H), 7.03 (d, 2H, <sup>3</sup>*J* = 8.3 Hz), 3.81 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 162.94, 160.81, 147.66, 133.54, 131.59, 128.67, 128.42, 127.52, 126.85, 114.31, 55.26 ppm.

**(E)-N'-(4-methylbenzylidene)benzohydrazide (5b):** From 4-methylbenzyl alcohol (3b) (122 mg, 1.00 mmol) and benzohydrazide (3a) (136 mg, 1.00 mmol), compound **5b** (181 mg, 76%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.80 (s, 1H), 8.42 (s, 1H), 8.32 (s, 1H), 7.91 (d, 2H, <sup>3</sup>*J* = 6.9 Hz), 7.65-7.53 (m, 4H), 7.28 (d, 2H, <sup>3</sup>*J* = 7.2 Hz), 2.35 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.58, 158.25, 148.29, 140.18, 133.05, 131.88, 131.32, 129.43, 128.54, 127.18, 20.94 ppm. HRMS (ESI), *m/z*: [M+H]<sup>+</sup>calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O: 239.1184; found: 239.1183.

**(E)-N'-(4-chlorobenzylidene)benzohydrazide (5c):**<sup>4</sup> From 4-chlorobenzyl alcohol (3c) (143 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5c** (209 mg, 81%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.95 (s, 1H), 8.45 (s, 1H), 7.93 (m, 2H), 7.77 (d, 2H, <sup>3</sup>*J* = 8.4 Hz), 7.62-7.51 (m, 5H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 166.46, 163.18, 146.42, 134.49, 133.24, 131.81, 131.11, 128.92, 128.60, 127.61 ppm.

**(E)-N'-(4-nitrobenzylidene)benzohydrazide (5d):**<sup>4</sup> From 4-nitrobenzyl alcohol (3d) (122 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5d** (188 mg, 70%) was obtained as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.18 (s, 1H), 8.56 (s, 1H), 8.30 (d, 2H, <sup>3</sup>*J* = 6.4 Hz), 7.97 (m, 4H), 7.62-7.55 (m, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.40, 147.80, 145.20, 140.62, 133.03, 132.01, 128.51, 127.96, 127.71, 124.05 ppm.

**(E)-N'-(3-methylbenzylidene)benzohydrazide (5e):** From 3-methylbenzyl alcohol (3e) (122 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5e** (176 mg, 74%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.87 (s, 1H), 8.43 (s, 1H), 7.93 (m, 3H), 7.75 (m, 2H), 7.55 (m, 5H), 7.38 (m, 2H), 7.25 (m, 1H), 2.35 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.14, 147.82, 138.04, 134.24, 133.36, 131.73, 130.78, 129.69, 128.45, 127.59, 126.42, 124.50, 20.84 ppm. HRMS (ESI), *m/z*: [M+H]<sup>+</sup>calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O: 239.1184; found: 239.1177.

**(E)-N'-(3-fluorobenzylidene)benzohydrazide (5f):**<sup>5</sup> From 3-fluorobenzyl alcohol (3f) (126 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5f** (164 mg, 68%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.00 (s, 1H), 8.47 (s, 1H), 8.31 (s, 1H), 7.93 (t, 2H, <sup>3</sup>*J* = 8.8 Hz), 7.60-7.47 (m, 5H), 7.28 (t, 1H, <sup>3</sup>*J* = 7.6 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.59, 146.39, 136.92, 131.85, 130.94, 129.21, 128.81, 128.47, 127.63, 125.35, 123.46 ppm.

**(E)-N'-(2-methoxybenzylidene)benzohydrazide (5g):**<sup>6</sup> From 2-methoxybenzyl alcohol (3g) (138 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5g** (183 mg, 72%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.87 (s, 1H), 8.82 (s, 1H), 7.94 (d, 2H, <sup>3</sup>*J* = 7.2 Hz), 7.89 (d, 1H, <sup>3</sup>*J* = 7.6 Hz), 7.56-7.52 (m, 4H), 7.42 (t, 1H, <sup>3</sup>*J* = 7.2 Hz), 7.11 (d, 1H, <sup>3</sup>*J* = 8.0 Hz), 7.03 (t, 1H, <sup>3</sup>*J* = 7.2 Hz), 3.87 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 162.92, 157.72, 143.20, 133.32, 131.69, 131.55, 128.42, 127.57, 125.48, 122.27, 120.72, 111.80, 55.64 ppm.

**(E)-N'-(2-bromobenzylidene)benzohydrazide (5h):** From 2-bromobenzyl alcohol (3h) (122 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5h** (209 mg, 69%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.14 (s, 1H), 8.84 (s, 1H), 8.02 (d, 1H, <sup>3</sup>*J* = 7.6 Hz), 7.95 (d, 2H, <sup>3</sup>*J* = 7.2 Hz), 7.70 (d, 1H, <sup>3</sup>*J* = 8.0 Hz), 7.53-7.46 (m, 4H), 7.37 (t, 1H, <sup>3</sup>*J* = 7.2 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.18, 145.99, 133.14, 133.05, 131.92, 131.72, 128.47, 128.08, 127.65, 127.24, 123.55 ppm. HRMS (ESI), *m/z*: [M+H]<sup>+</sup>calcd. for C<sub>14</sub>H<sub>11</sub>BrN<sub>2</sub>O: 303.0133; found: 303.0134.

**(E)-N'-(3,4,5-trimethoxybenzylidene)benzohydrazide (5i):** From 3,4,5-trimethoxybenzyl alcohol (3i) (198 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5i** (254 mg, 81%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.81 (s, 1H), 8.65 (s, 1H), 7.93 (d, 2H, <sup>3</sup>*J* = 7.2 Hz), 7.66-7.51 (m, 4H), 6.95 (d, 1H, <sup>3</sup>*J* = 8.8 Hz), 3.78 (s, 3H), 3.39 (s, 6H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 162.83, 155.11, 152.61, 143.32, 141.50, 133.44, 131.63, 128.40, 127.53, 120.52, 120.38, 108.70, 61.81, 60.44, 55.93 ppm. HRMS (ESI), *m/z*: [M+H]<sup>+</sup>calcd. for C<sub>17</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub>: 315.1345; found: 315.1342.

**(E)-N'-(benzo[d][1,3]dioxol-5-ylmethylene)benzohydrazide (5j):**<sup>21</sup> From piperonyl alcohol (3j) (152 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5j** (222 mg, 83%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.77 (s, 1H), 8.38 (s, 1H), 7.91 (d, 2H, <sup>3</sup>*J* = 7.6 Hz), 7.55 (m, 3H), 7.31 (s, 1H), 7.18 (d, 1H, <sup>3</sup>*J* = 7.6 Hz), 7.01 (d, 1H, <sup>3</sup>*J* = 7.6 Hz), 6.11 (s, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.00, 149.08, 147.96, 147.59, 133.44, 131.65, 128.69, 128.43, 127.53, 123.35, 108.44, 105.07, 101.53 ppm.

**(E)-N'-(naphthalen-1-ylmethylene)benzohydrazide (5k):** From 1-naphthalenemethanol (3k) (122 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5k** (241 mg, 88%) was obtained as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.01 (s, 1H), 9.16 (s, 1H), 8.90 (s, 1H), 8.34 (s, 1H), 8.00-7.96 (m, 5H), 7.63-7.57 (m, 6H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.07, 147.65, 133.53, 133.37, 131.80, 130.54, 130.20, 129.55, 128.78, 128.52, 127.72, 127.61, 127.31, 126.26, 125.56, 124.19 ppm. HRMS (ESI), *m/z*: [M+H]<sup>+</sup>calcd. for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O: 275.1184; found: 275.1177.

**(E)-N'-(anthracen-9-ylmethylene)benzohydrazide (5l):**<sup>8</sup> From 9-anthracenemethanol (3l) (308 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5l** (301 mg, 93%) was obtained as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.51 (s, 1H), 9.77 (s, 1H), 8.88 (d, 2H, <sup>3</sup>*J* = 8.8), 8.72 (s, 1H), 8.33 (m, 1H), 8.15 (d, 2H, <sup>3</sup>*J* = 8 Hz), 8.10 (d, 2H, <sup>3</sup>*J* = 7.2), 7.65-7.57 (m, 6H); <sup>13</sup>C NMR (100

MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.16, 147.08, 133.45, 131.79, 130.91, 129.61, 129.54, 128.96, 128.51, 127.72, 127.11, 125.52, 125.23, 124.96 ppm.

**(*E*)-*N'*-(thiophen-2-ylmethylene)benzohydrazide (5m):**<sup>9</sup> From 2-thiophenemethanol (3m) (114 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5m** (163 mg, 71%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.83 (s, 1H), 8.66 (s, 1H), 7.89 (d, 2H, <sup>3</sup>*J* = 7.2 Hz), 7.68 (d, 1H, <sup>3</sup>*J* = 4.4 Hz), 7.60-7.48 (m, 4H), 7.16 (m, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 162.98, 142.89, 139.08, 133.34, 131.73, 130.94, 128.95, 128.47, 127.86, 127.53 ppm.

**(*E*)-*N'*-benzylidenebenzohydrazide (5n):**<sup>10</sup> From benzyl alcohol (3n) (108 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5n** (161 mg, 71%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.89 (s, 1H), 8.46 (s, 1H), 7.92 (d, 2H, <sup>3</sup>*J* = 7.6 Hz), 7.75 (d, 2H, <sup>3</sup>*J* = 7.6 Hz), 7.61 (t, 1H, <sup>3</sup>*J* = 7.6 Hz), 7.54 (t, 2H, <sup>3</sup>*J* = 7.6 Hz), 7.47 (m, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.20, 147.82, 134.24, 131.79, 130.11, 128.84, 128.49, 127.57, 127.08 ppm.

**(*E*)-*N'*-((*E*)-3-phenylallylidene)benzohydrazide (5o):**<sup>11</sup> From cinnamyl alcohol (3o) (129 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5o** (153 mg, 61%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.80 (s, 1H), 8.29 (d, *J* = 7.3 Hz, 1H), 7.93 (d, *J* = 7.0 Hz, 2H), 7.68 – 7.46 (m, 5H), 7.45 – 7.26 (m, 3H), 7.23 – 6.84 (m, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.03, 149.77, 139.00, 135.88, 133.40, 131.69, 128.79, 128.42, 127.61, 127.06, 125.65, 40.11, 39.90, 39.69, 39.49, 39.17, 38.88, 38.86 ppm.

**(*E*)-*N'*-hexylidenebenzohydrazide (5p):**<sup>10</sup> From *n*-hexyl alcohol (3p) (126 mg, 1.00 mmol) and benzohydrazide (4a) (136 mg, 1.00 mmol), compound **5p** (120 mg, 55%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 9.50 (s, 1H), 7.81 (d, *J* = 6.5 Hz, 2H), 7.62 (s, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 2.35 (m, 2H), 1.51-1.48 (m, 2H), 1.39 – 1.21 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 164.23, 153.06, 133.26, 131.86, 128.62, 127.33, 77.38, 77.06, 76.74, 32.44, 31.43, 26.34, 22.42, 13.95 ppm.

**(*E*)-*N'*-benzylidene-4-methoxybenzohydrazide (6a):** From benzyl alcohol (3n) (108 mg, 1.00 mmol) and 4-methoxybenzohydrazide (4b) (166 mg, 1.00 mmol), compound **6a** (221 mg, 87%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 11.77 (s, 1H), 8.47 (s, 1H), 7.94 (d, 2H, <sup>3</sup>*J* = 8.4 Hz), 7.73 (d, 2H, <sup>3</sup>*J* = 6.4 Hz), 7.50-7.46 (m, 3H), 7.07 (d, 2H, <sup>3</sup>*J* = 8.8 Hz), 3.84 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 162.52, 161.99, 147.13, 134.44, 129.89, 129.52, 128.80, 126.96, 125.40, 113.68, 55.39 ppm. HRMS (ESI), *m/z*: [M+H]<sup>+</sup> calcd. for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: 255.1134; found: 255.1126.

**(*E*)-*N'*-(4-chlorobenzylidene)-4-methoxybenzohydrazide (6b):**<sup>12</sup> From 4-chlorobenzyl alcohol (3c) (143 mg, 1.00 mmol) and 4-methoxybenzohydrazide (4b) (166 mg, 1.00 mmol), compound **6b** (182 mg, 63%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.05 (s, 1H), 8.50 (s, 1H), 8.32 (s, 1H), 7.95 (d, 2H, <sup>3</sup>*J* = 8.5 Hz), 7.74 (s, 1H), 7.51 (d, 2H, <sup>3</sup>*J* = 8.4 Hz), 7.05 (d, 2H, <sup>3</sup>*J* = 8.8 Hz), 3.84 (s,

3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 161.98, 145.82, 134.24, 133.49, 129.60, 128.86, 128.54, 125.37, 113.64, 79.15, 55.38$  ppm.

**(E)-N'-(4-methoxybenzylidene)-4-methoxybenzohydrazide (6c):**<sup>13</sup> From 4-methoxybenzyl alcohol (3a) (138 mg, 1.00 mmol) and 4-methoxybenzohydrazide (4b) (166 mg, 1.00 mmol), compound **6c** (222 mg, 78%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d$ ):  $\delta = 11.95$  (s, 1H), 8.46 (s, 1H), 7.95 (d, 2H,  $^3J = 8.3$  Hz), 7.66 (d, 2H,  $^3J = 8.0$  Hz), 7.03 (t, 4H,  $^3J = 8.7$  Hz), 3.83 (s, 3H), 3.81 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 161.82, 160.64, 147.12, 129.51, 128.51, 127.15, 125.67, 114.28, 113.58, 55.31, 55.26, 25.87$  ppm.

**(E)-N'-(4-nitrobenzylidene)-4-methoxybenzohydrazide (6d):** From 4-nitrobenzyl alcohol (3d) (138 mg, 1.00 mmol) and 4-methoxybenzohydrazide (4b) (166 mg, 1.00 mmol), compound **6d** (191 mg, 64%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 12.05$  (s, 1H), 8.53 (s, 1H), 8.29 (d, 2H,  $^3J = 8.4$  Hz), 8.03-7.88 (m, 4H), 7.07 (d, 2H,  $^3J = 8.6$  Hz), 3.84 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 162.20, 147.66, 144.57, 140.76, 129.68, 127.82, 124.98, 124.02, 113.73, 55.41$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_4$ : 300.0986; found: 300.0981.

**(E)-N'-benzylidene-4-chlorobenzohydrazide (6e):** From benzyl alcohol (3n) (108 mg, 1.00 mmol) and 4-chlorobenzohydrazide (4c) (170 mg, 1.00 mmol), compound **6e** (191 mg, 74%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 11.94$  (s, 1H), 8.46 (s, 1H), 7.96 (d, 2H,  $^3J = 8.4$  Hz), 7.74 (m, 2H), 7.62 (d, 2H,  $^3J = 8.4$  Hz), 7.47 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 162.31, 148.28, 136.64, 134.05, 131.93, 130.26, 129.51, 128.85, 128.59, 127.16$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{O}$ : 259.0638; found: 259.0638.

**(E)-N'-4-chlorobenzylidene-4-chlorobenzohydrazide (6f):** From 4-chlorobenzyl alcohol (3c) (122 mg, 1.00 mmol) and 4-chlorobenzohydrazide (4c) (170 mg, 1.00 mmol), compound **6f** (174 mg, 64%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 12.00$  (s, 1H), 8.44 (s, 1H), 7.95 (d, 2H,  $^3J = 8.4$  Hz), 7.77 (d, 2H,  $^3J = 8.4$  Hz), 7.62 (d, 2H,  $^3J = 8.4$  Hz), 7.54 (d, 2H,  $^3J = 8.4$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 162.42, 146.96, 136.73, 134.68, 132.96, 131.74, 129.49, 128.88, 128.78, 128.57$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{14}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}$ : 293.0248; found: 293.0241.

**(E)-N'-(4-methylbenzylidene)-4-chlorobenzohydrazide (6g):** From 4-methylbenzyl alcohol (3b) (143 mg, 1.00 mmol) and 4-chlorobenzohydrazide (4c) (170 mg, 1.00 mmol), compound **6g** (214 mg, 73%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 11.86$  (s, 1H), 8.42 (s, 1H), 7.95 (d, 2H,  $^3J = 8.4$  Hz, 2H), 7.64 (d, 2H,  $^3J = 8.4$  Hz), 7.29 (d, 2H,  $^3J = 7.6$  Hz), 2.35 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 162.42, 148.51, 140.22, 136.64, 131.88, 131.26, 129.43, 128.56, 127.19, 20.96$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}$ : 273.0795; found: 273.0786.

**(E)-4-chloro-N'-(thiophen-2-ylmethylene)benzohydrazide (6h):** From 2-thiophenemethanol (3m) (114 mg, 1.00 mmol) and 4-chlorobenzohydrazide (4c) (170 mg, 1.00 mmol), compound **6h** (191 mg, 72%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 11.93$  (s, 1H), 8.62 (s, 1H), 7.89 (d,



2H,  $^3J = 8.4$  Hz), 7.65 (d, 1H,  $^3J = 4.9$  Hz), 7.58 (d, 2H,  $^3J = 8.3$  Hz), 7.46 (d, 1H,  $^3J = 3.2$  Hz), 7.18-7.08 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta = 162.17, 143.34, 138.76, 136.63, 131.87, 131.22, 129.44, 129.13, 128.58, 127.94$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{12}\text{H}_9\text{ClN}_2\text{OS}$ : 265.0204; found: 265.0199.

**(E)-N'-benzylidene-4-bromobenzohydrazide (6i)**: From benzyl alcohol (3n) (108 mg, 1.00 mmol) and 4-bromobenzohydrazide (4d) (215 mg, 1.00 mmol), compound **6i** (236 mg, 78%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 11.96$  (s, 1H), 8.47 (s, 1H), 7.89 (d, 2H,  $^3J = 8.3$  Hz), 7.82-7.68 (m, 4H), 7.48 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta = 162.16, 148.11, 134.18, 132.42, 131.50, 130.16, 129.70, 128.83, 127.12, 125.53$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{14}\text{H}_{11}\text{BrN}_2\text{O}$ : 303.0135; found: 303.0130.

**(E)-N'-(4-chlorobenzylidene)-4-bromobenzohydrazide (6j)**: From 4-chlorobenzyl alcohol (3c) (143 mg, 1.00 mmol) and 4-bromobenzohydrazide (4d) (215 mg, 1.00 mmol), compound **6j** (205 mg, 61%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 12.02$  (s, 1H), 8.46 (s, 1H), 7.89 (d, 2H,  $^3J = 8.2$  Hz), 7.77 (dd,  $J = 7.6, 4.0$  Hz, 4H), 7.54 (d, 2H,  $^3J = 8.2$  Hz);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta = 162.21, 146.75, 134.59, 133.12, 132.30, 131.50, 129.71, 128.82, 125.61$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{14}\text{H}_{10}\text{BrClN}_2\text{O}$ : 336.9745; found: 336.9742.

**(E)-4-bromo-N'-(naphthalen-2-ylmethylene)benzohydrazide (6k)**: From 1-naphthalenemethanol (3k) (122 mg, 1.00 mmol) and 4-bromobenzohydrazide (4d) (215 mg, 1.00 mmol), compound **6k** (251 mg, 71%) was obtained as a yellow solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 12.05$  (s, 1H), 9.13 (s, 1H), 8.90 (d, 1H,  $^3J = 8.4$  Hz), 8.11-8.02 (m, 2H), 8.00-7.92 (m, 3H), 7.80 (d, 2H,  $^3J = 8.4$  Hz), 7.74-7.55 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta = 162.10, 148.05, 133.52, 132.41, 131.57, 130.66, 130.18, 129.70, 129.43, 128.80, 127.91, 127.36, 126.29, 125.56, 124.20$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{18}\text{H}_{13}\text{BrN}_2\text{O}$ : 353.0291; found: 353.0284.

**(E)-4-bromo-N'-(thiophen-2-ylmethylene)benzohydrazide (6l)**: From 2-thiophenemethanol (3m) (114 mg, 1.00 mmol) and 4-bromobenzohydrazide (4d) (215 mg, 1.00 mmol), compound **6l** (170 mg, 55%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 11.91$  (s, 1H), 8.67 (s, 1H), 7.86 (d, 2H,  $^3J = 8.4$  Hz), 7.76 (d, 2H,  $^3J = 8.4$  Hz), 7.70 (d, 1H,  $^3J = 4.9$  Hz), 7.50 (d, 1H,  $^3J = 3.2$  Hz), 7.19-7.13 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta = 161.99, 143.20, 138.96, 132.39, 131.50, 131.14, 129.65, 129.10, 127.87, 125.50$  ppm. HRMS (ESI), m/z:  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{12}\text{H}_9\text{BrN}_2\text{OS}$ : 308.9699; found: 308.9690.

**(E)-N'-benzylidenefuran-2-carbohydrazide (6m)**: From benzyl alcohol (3n) (108 mg, 1.00 mmol) and furan-2-carbohydrazide (4e) (126 mg, 1.00 mmol), compound **6m** (163 mg, 76%) was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 11.88$  (s, 1H), 8.47 (s, 1H), 7.96 (s, 1H), 7.72 (d, 2H,  $^3J = 6.2$  Hz), 7.45 (d, 3H,  $^3J = 6.5$  Hz), 7.32 (s, 1H), 6.71 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta =$



154.21, 147.84, 146.59, 145.84, 134.20, 130.06, 128.82, 127.05, 114.94, 112.06 ppm. HRMS (ESI), m/z: [M+H]<sup>+</sup>calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: 215.0822; found: 215.0819.

**(E)-N'-(4-chlorobenzylidene)furan-2-carbohydrazide (6n)**: From 4-chlorobenzyl alcohol (3c) (143 mg, 1.00 mmol) and furan-2-carbohydrazide (4e) (126 mg, 1.00 mmol), compound **6n** (129 mg, 52%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 11.95 (s, 1H), 8.44 (s, 1H), 7.95 (s, 1H), 7.74 (d, 2H, <sup>3</sup>J = 8.4 Hz), 7.52 (d, 2H, <sup>3</sup>J = 8.4 Hz), 7.32 (s, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 154.24, 146.49, 145.92, 134.50, 133.13, 128.92, 128.68, 115.11, 112.09 ppm. HRMS (ESI), m/z: [M+H]<sup>+</sup>calcd. for C<sub>12</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>2</sub>: 249.0433; found: 249.0428.

**(E)-N'-benzylidenethiophene-2-carbohydrazide (6o)**: From benzyl alcohol (3n) (108 mg, 1.00 mmol) and 2-thiophenecarbohydrazide (4f) (142 mg, 1.00 mmol), compound **6o** (145 mg, 63%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 11.90 (s, 1H), 8.44 (s, 1H), 8.10 (m, 1H), 8.02-7.68 (m, 4H), 7.46 (s, 3H), 7.23 (s, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 161.32, 157.79, 147.56, 144.08, 138.14, 134.95, 134.07, 132.80, 131.91, 130.03, 128.90, 128.14, 127.18, 126.67 ppm. HRMS (ESI), m/z: [M+H]<sup>+</sup>calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>OS: 231.0594; found: 231.0589.

**(E)-N'-(4-chlorobenzylidene)thiophene-2-carbohydrazide (6p)**: From 4-chlorobenzyl alcohol (3c) (143 mg, 1.00 mmol) and 2-thiophenecarbohydrazide (4f) (142 mg, 1.00 mmol), compound **6p** (148 mg, 56%) was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 11.96 (s, 1H), 8.43 (s, 1H), 8.09 (m, 1H), 8.02-7.86 (m, 2H), 7.79 (m, 2H), 7.55 (d, 2H, <sup>3</sup>J = 6.2 Hz), 7.30-7.19 (m, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 161.30, 157.73, 146.14, 142.79, 138.12, 134.95, 134.46, 133.09, 132.72, 132.00, 128.99, 128.76, 128.15, 126.71 ppm. HRMS (ESI), m/z: [M+H]<sup>+</sup>calcd. for C<sub>12</sub>H<sub>9</sub>ClN<sub>2</sub>OS: 265.0204; found: 265.0201.

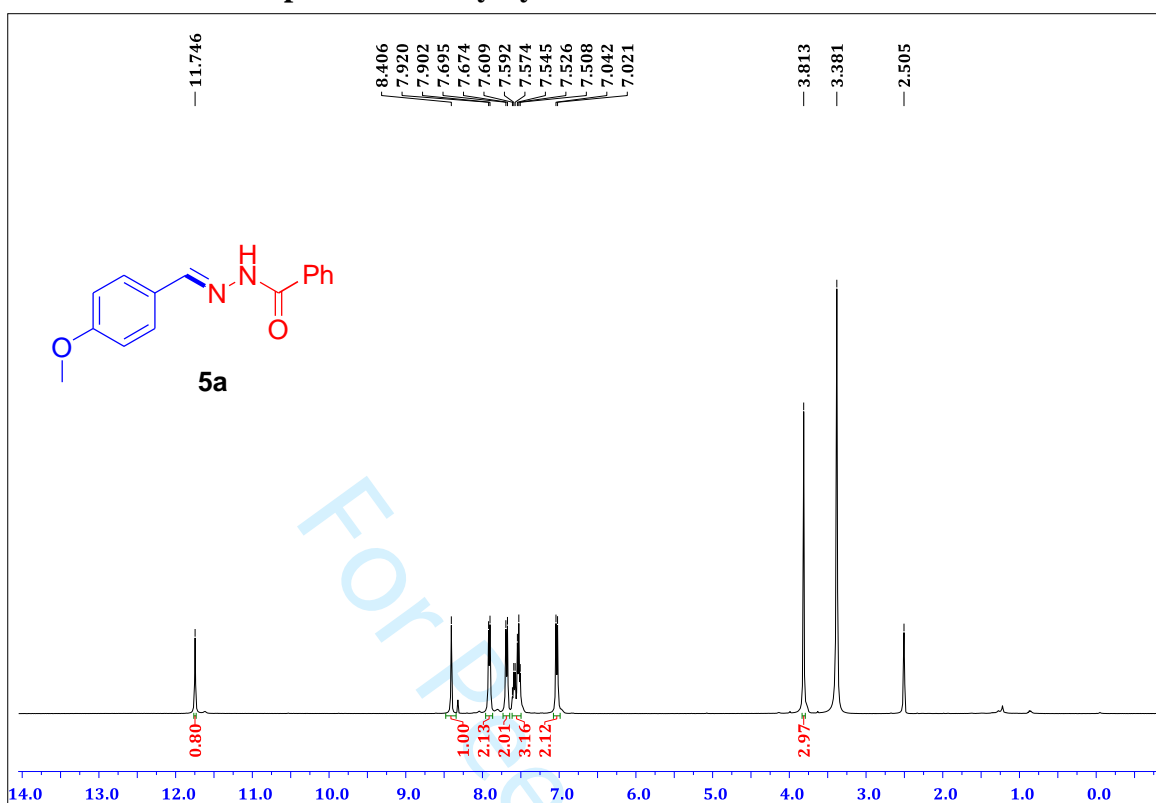
3.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of *N*-acylhydrazones

Figure S5:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5a** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)

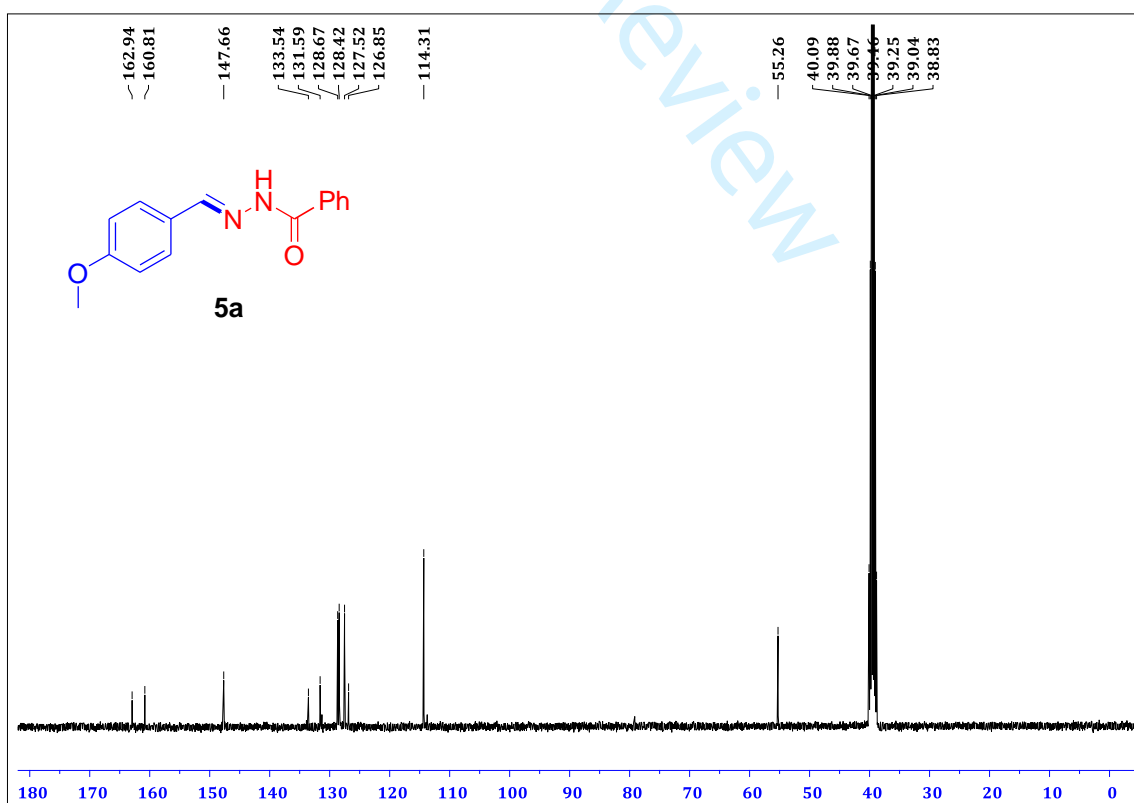
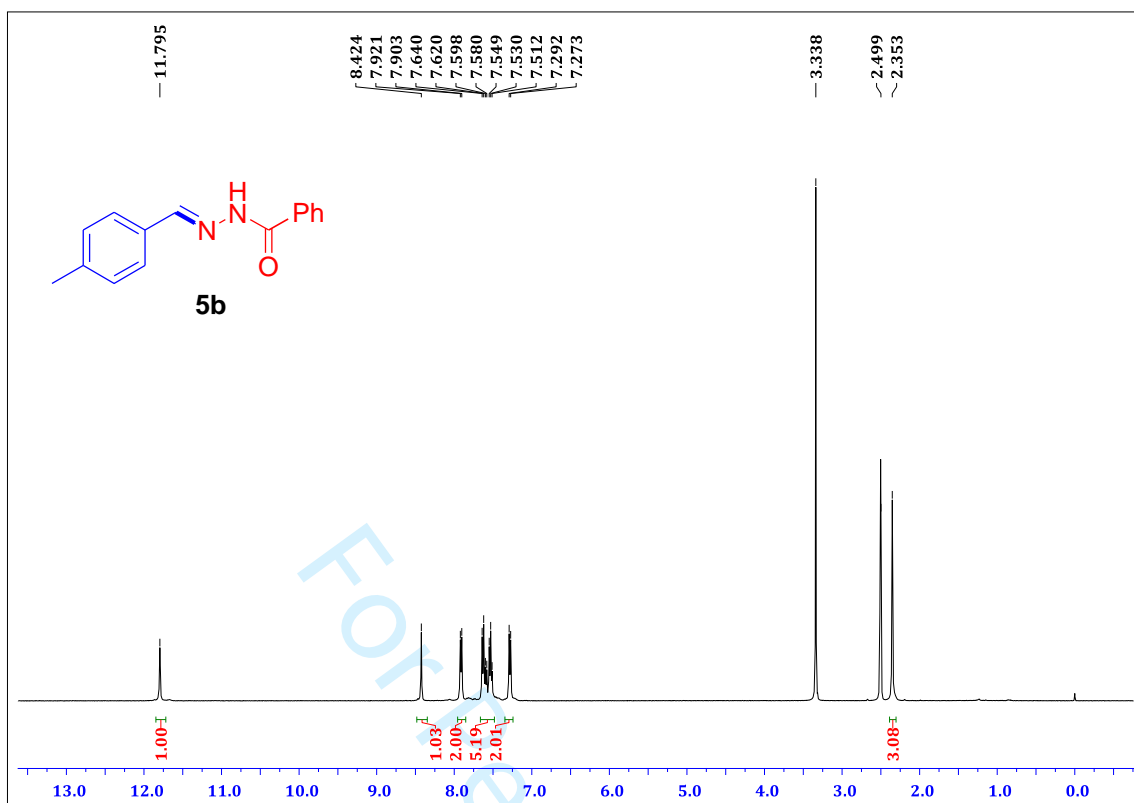


Figure S6:  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5a**



30  
31  
32  
33

Figure S7:  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5b** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)

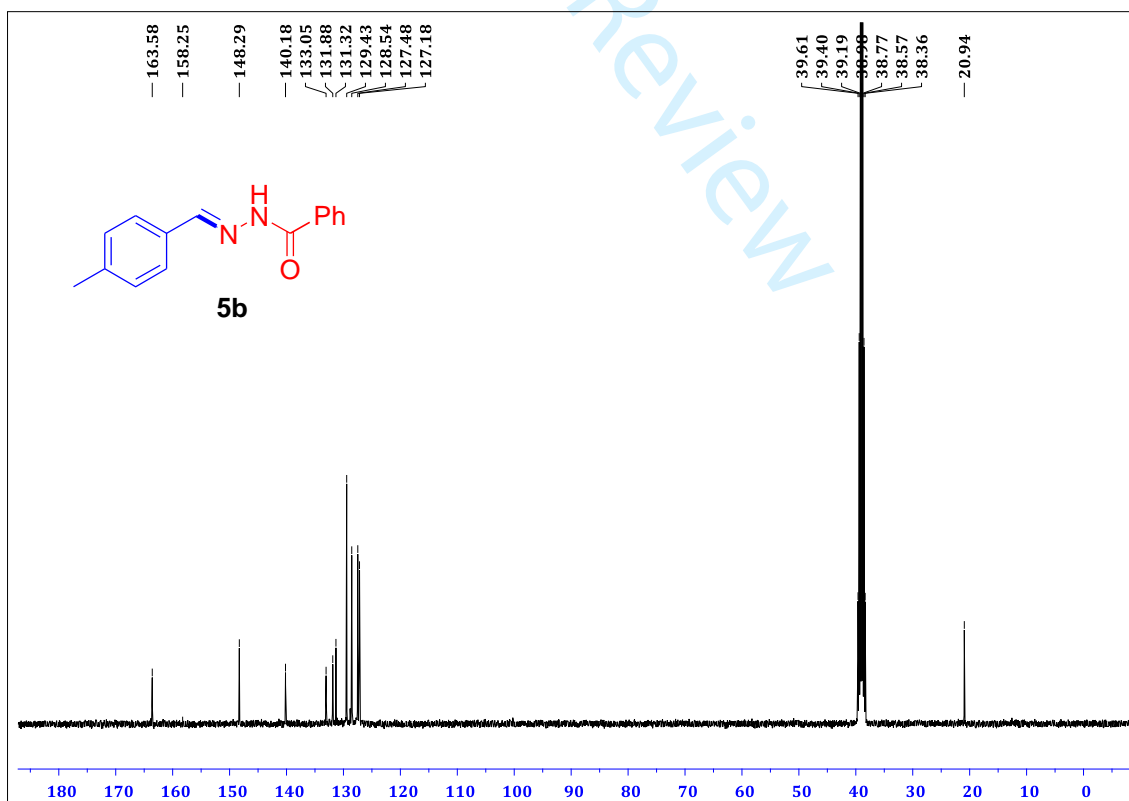
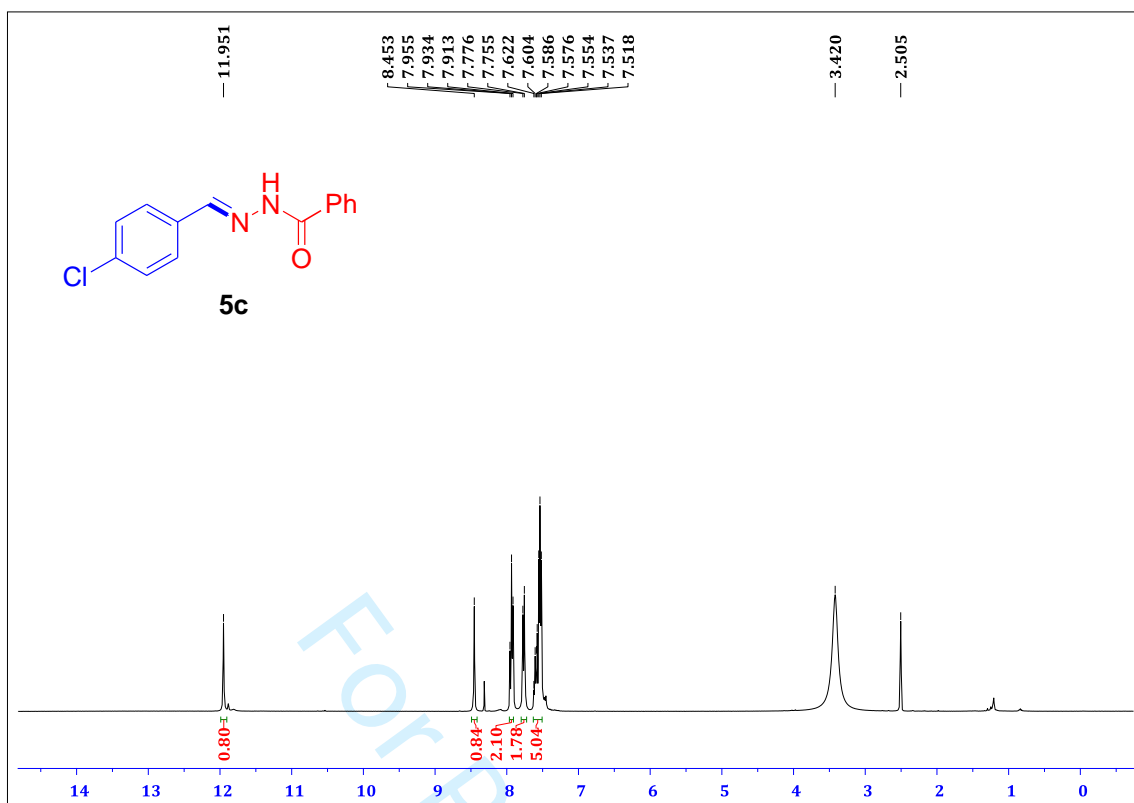
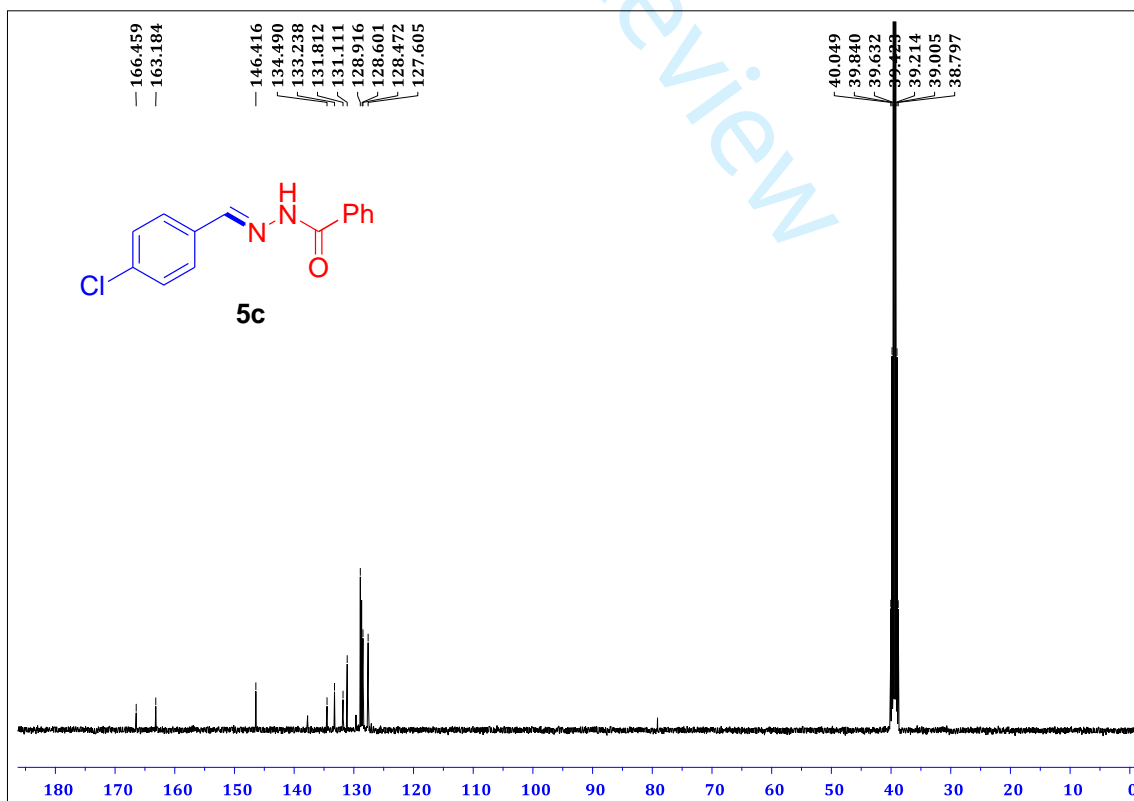


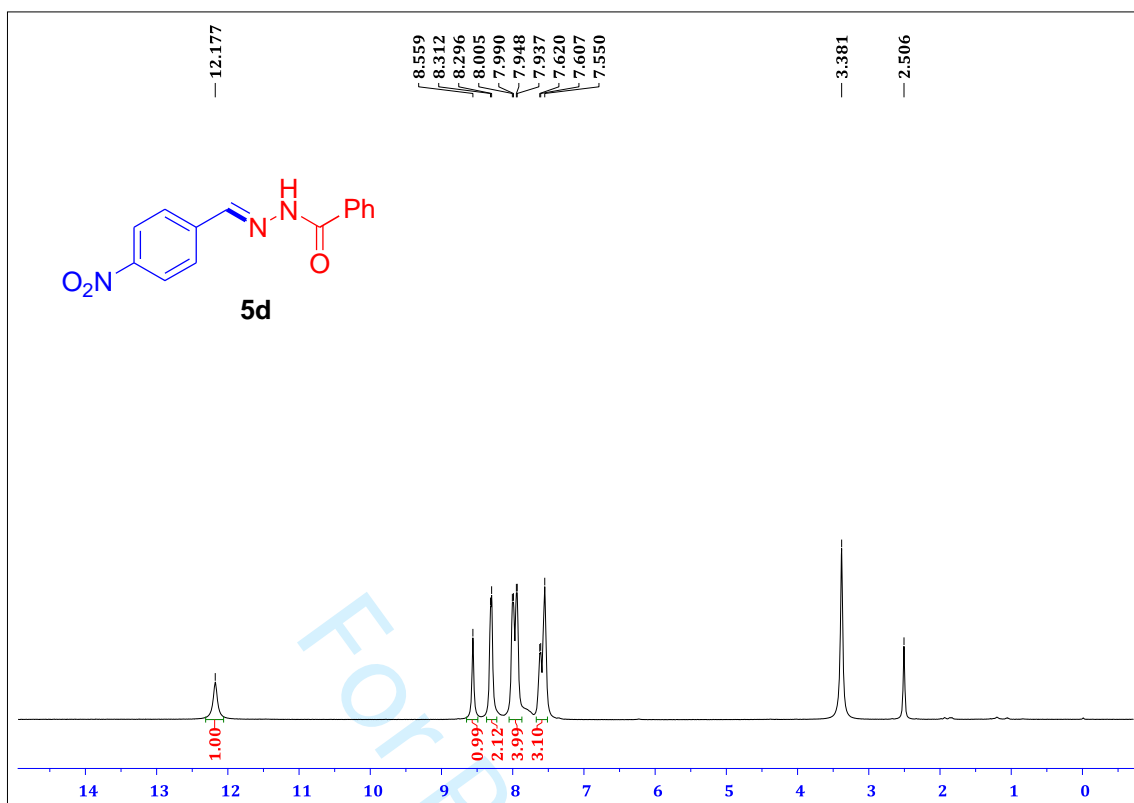
Figure S8:  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5b**



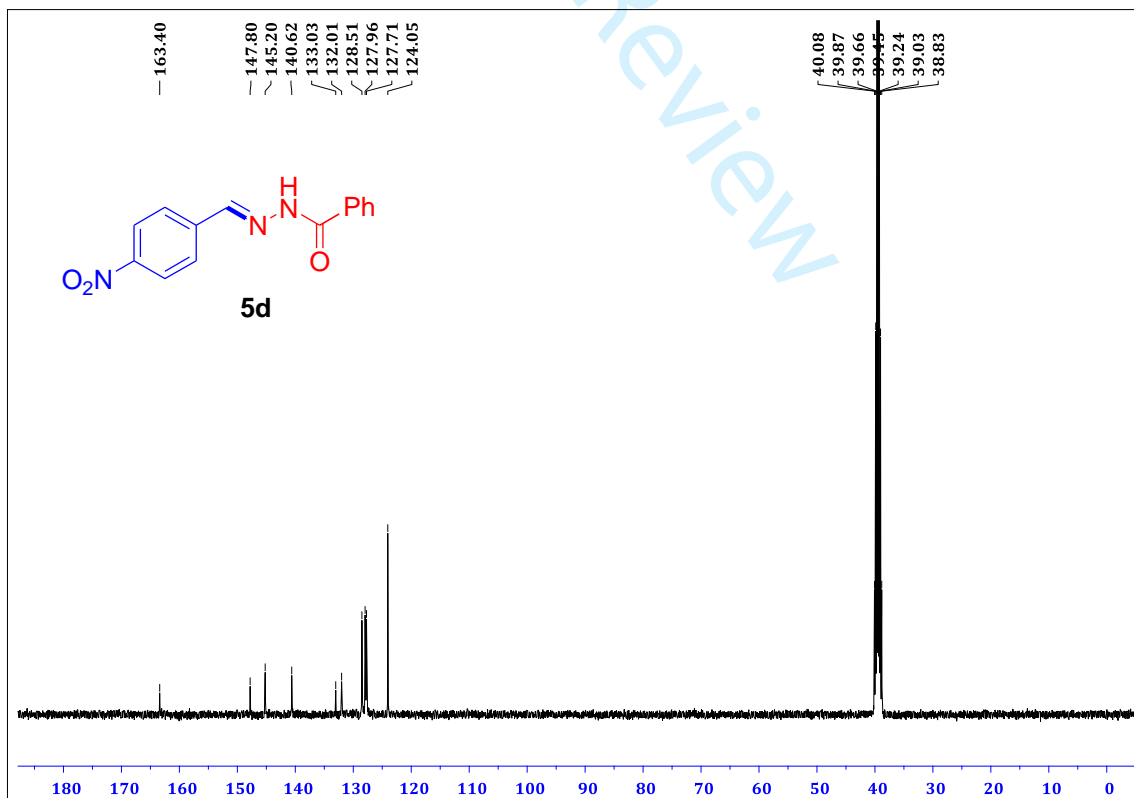
28 **Figure S9:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5c** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



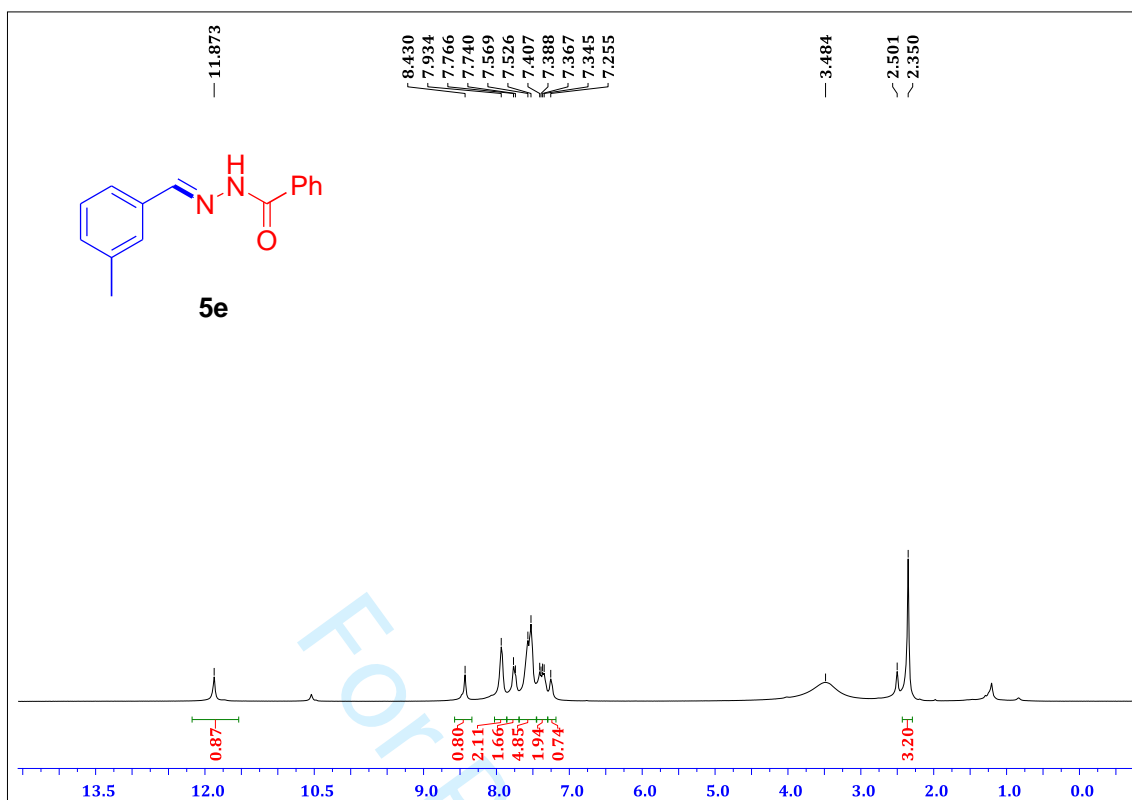
**Figure S10:** <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5c**



27 **Figure S11:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5d** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)

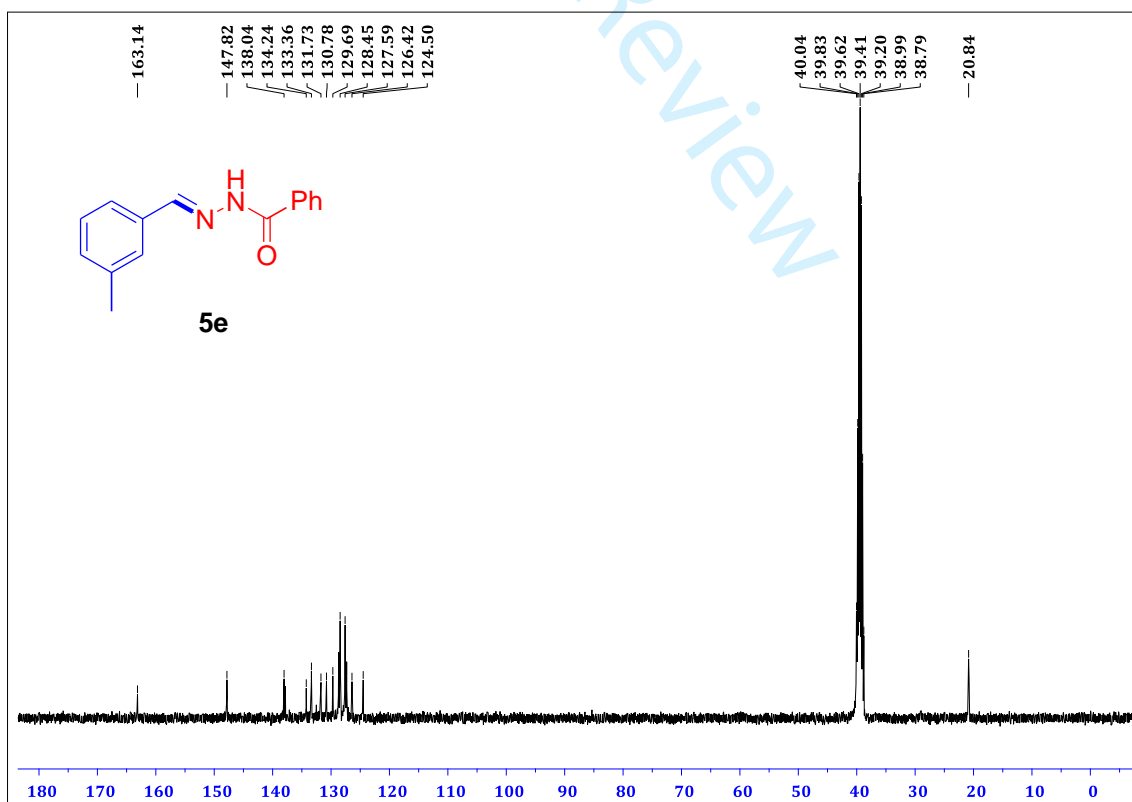


**Figure S12:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5d**

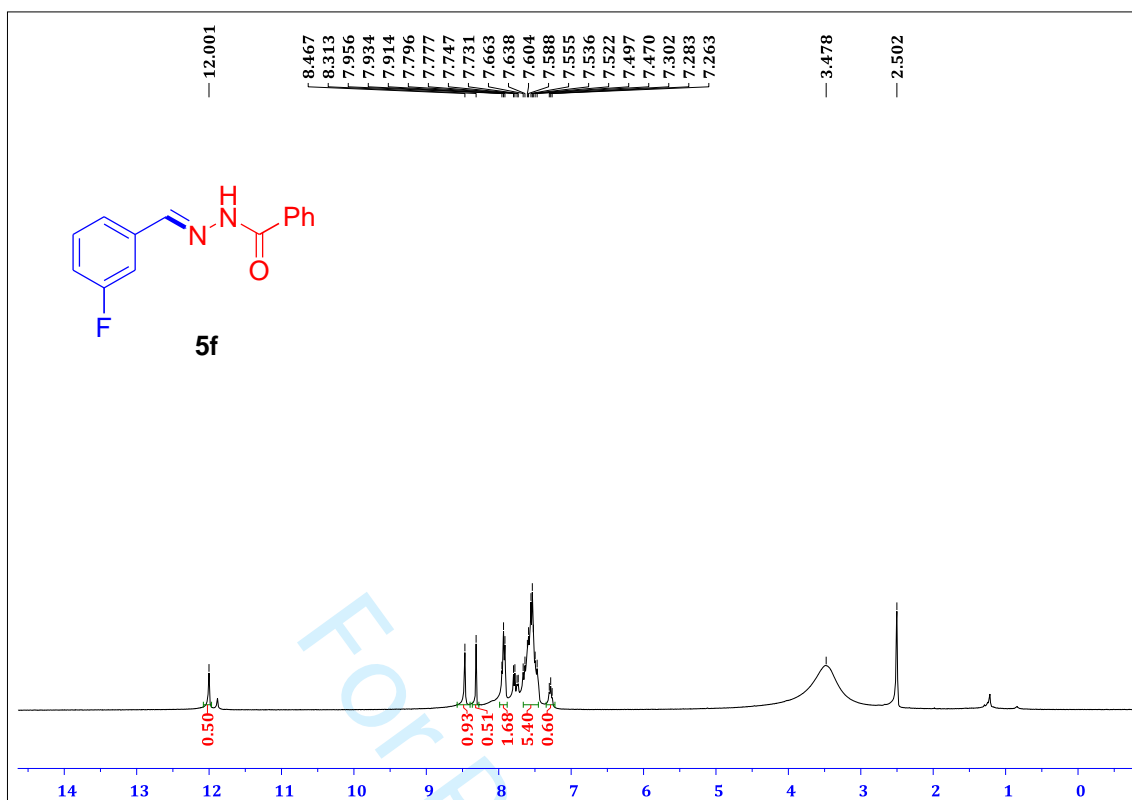


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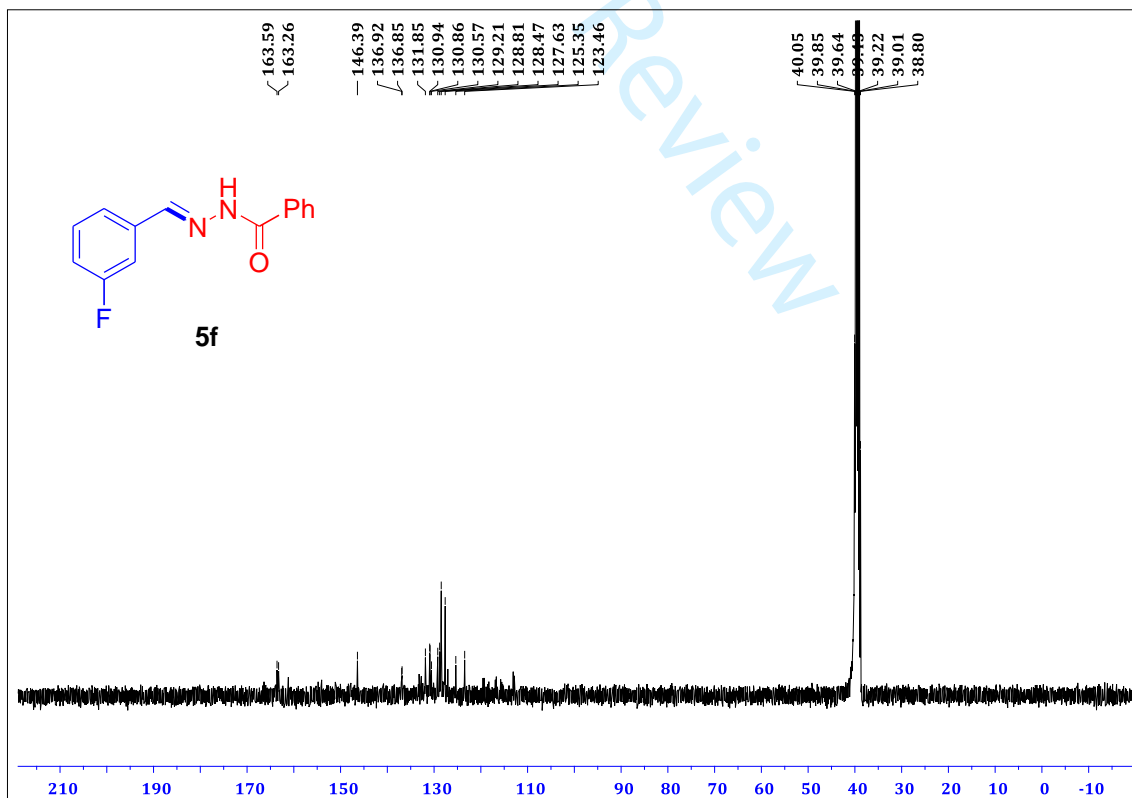
**Figure S13:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5e** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)



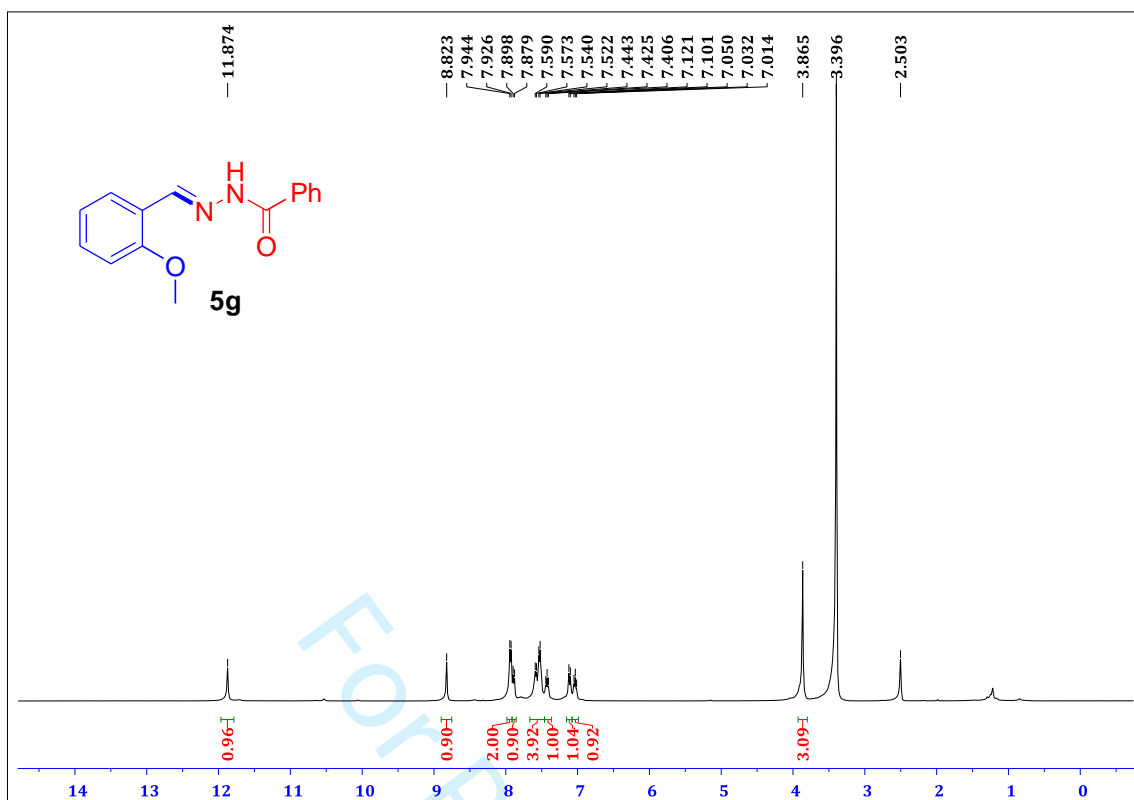
**Figure S14:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5e**



27 **Figure S15:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5f** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)



**Figure S16:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5f**



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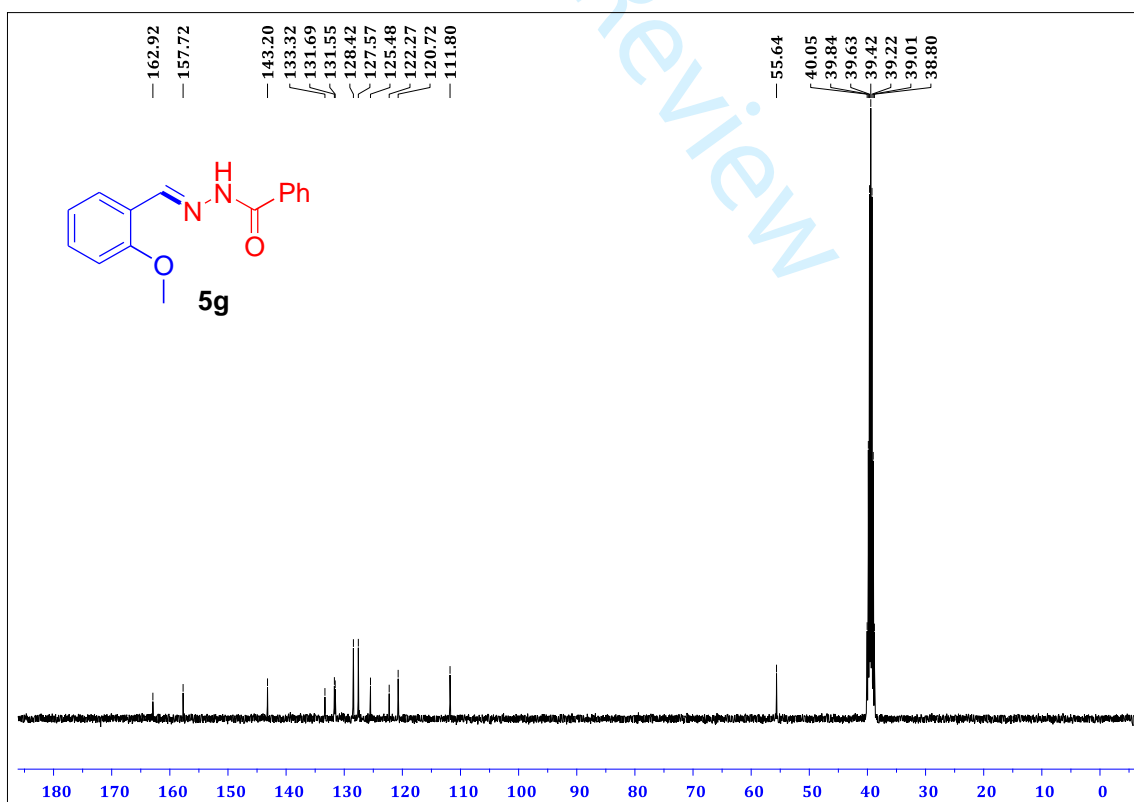
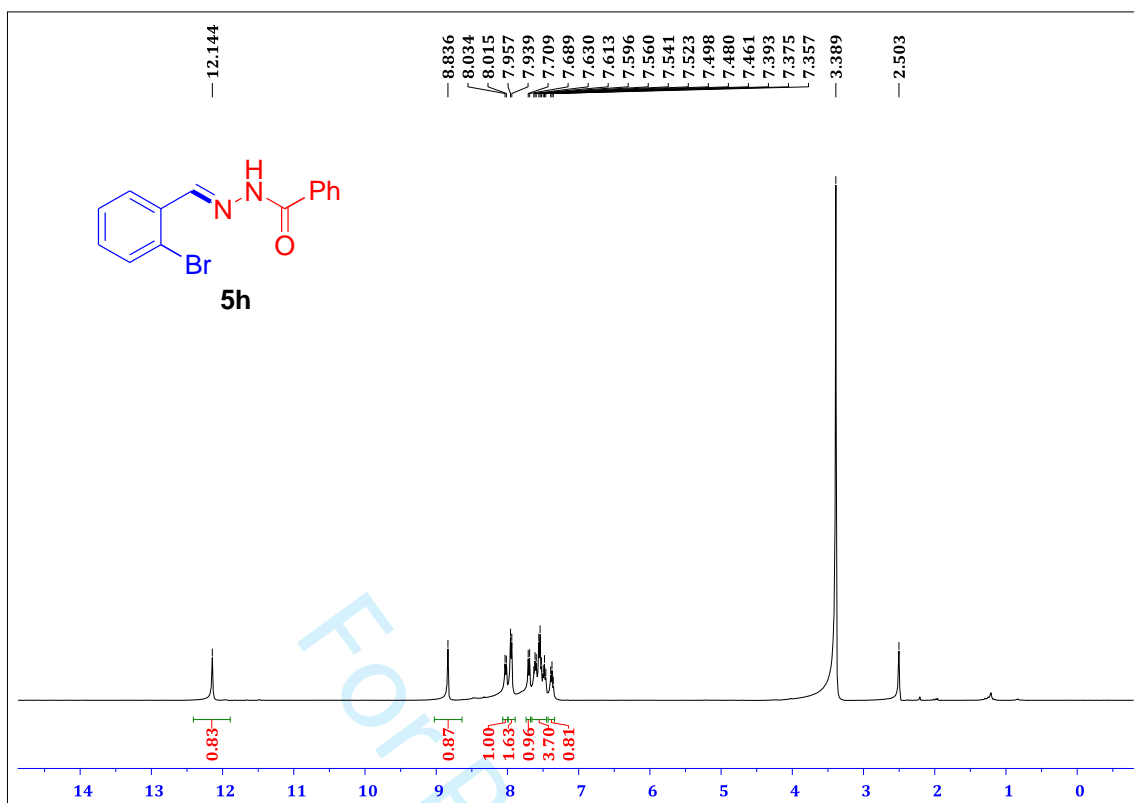
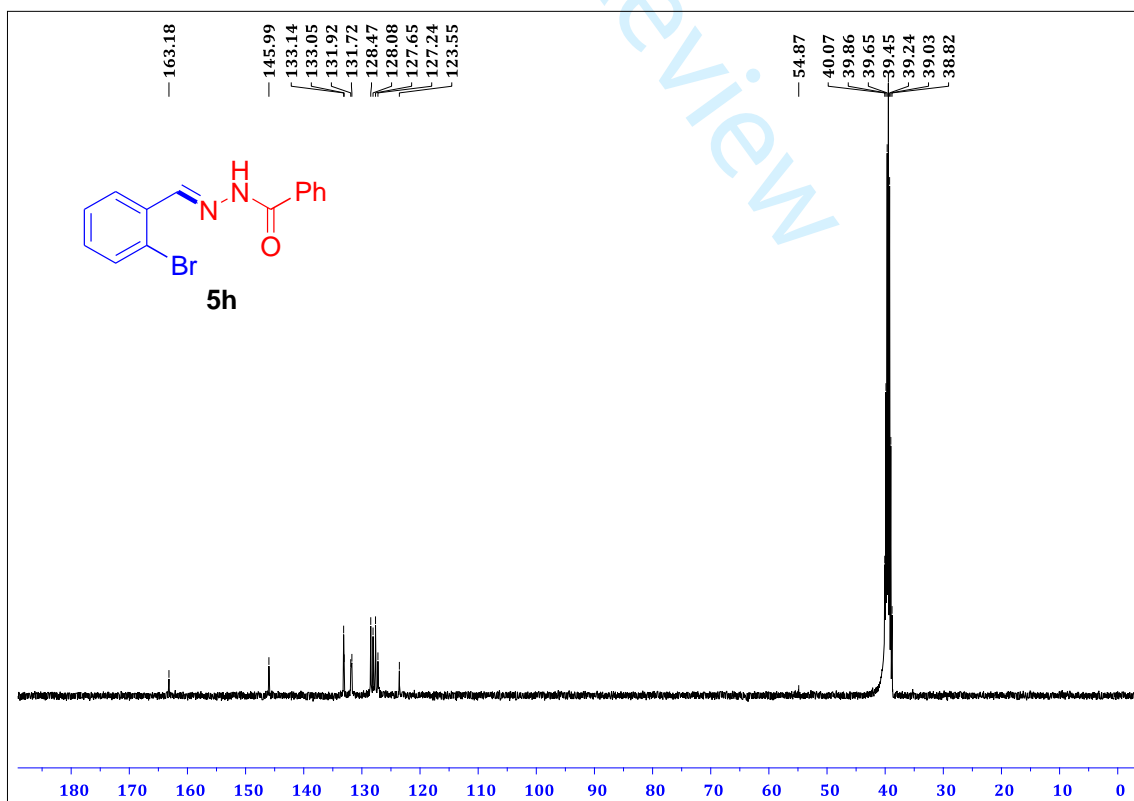


Figure S18:  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5g**

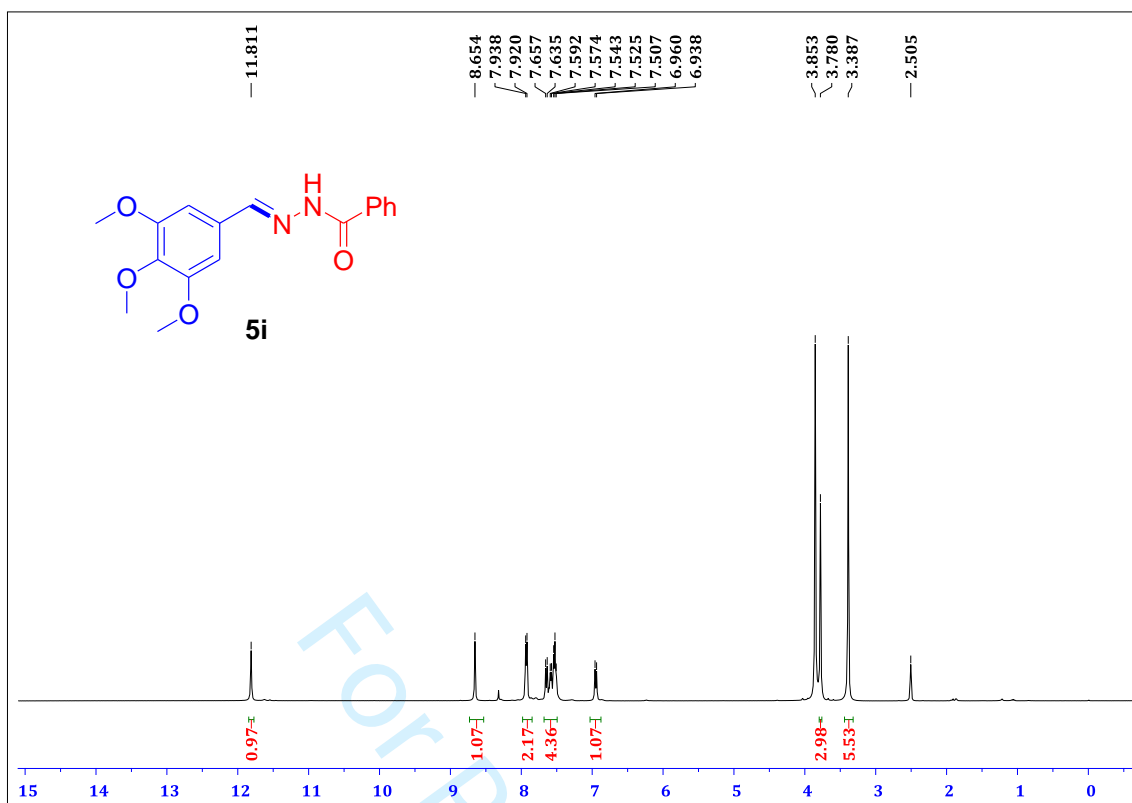




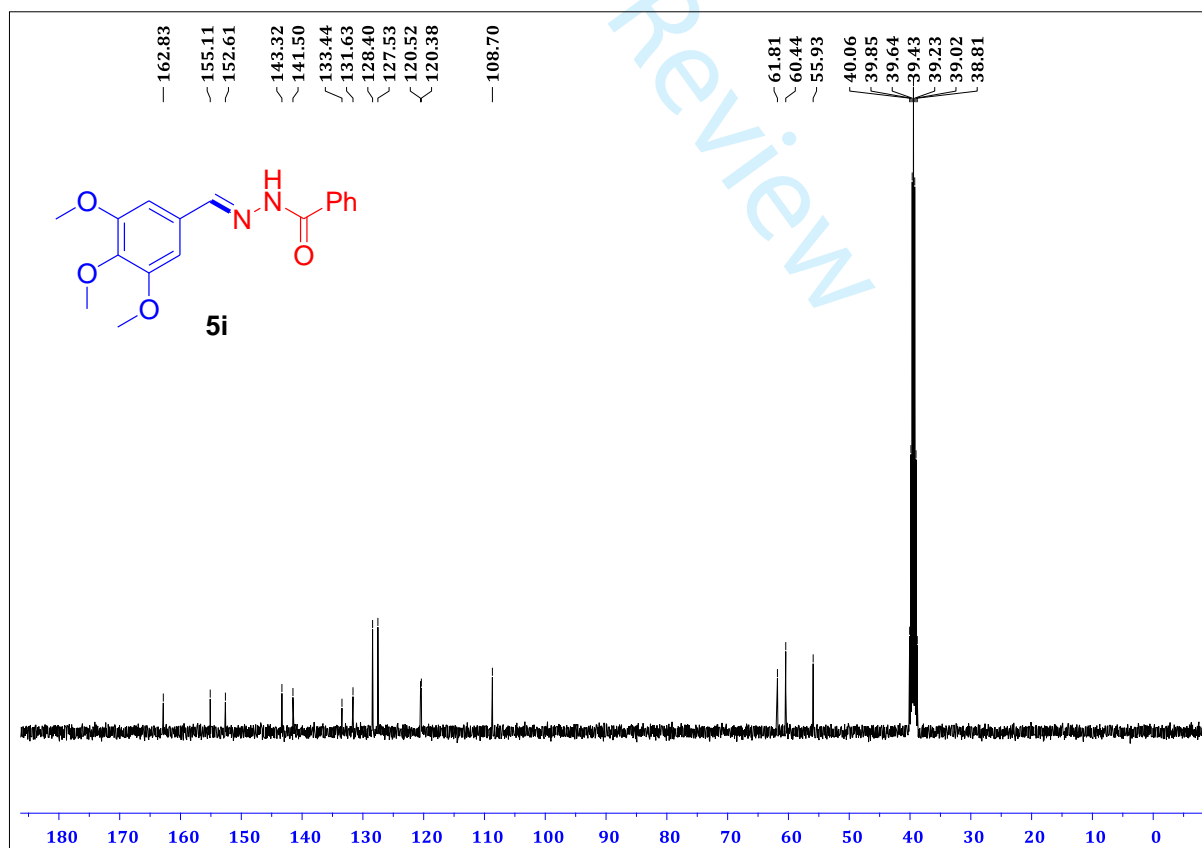
28 **Figure S19:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of 5h (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



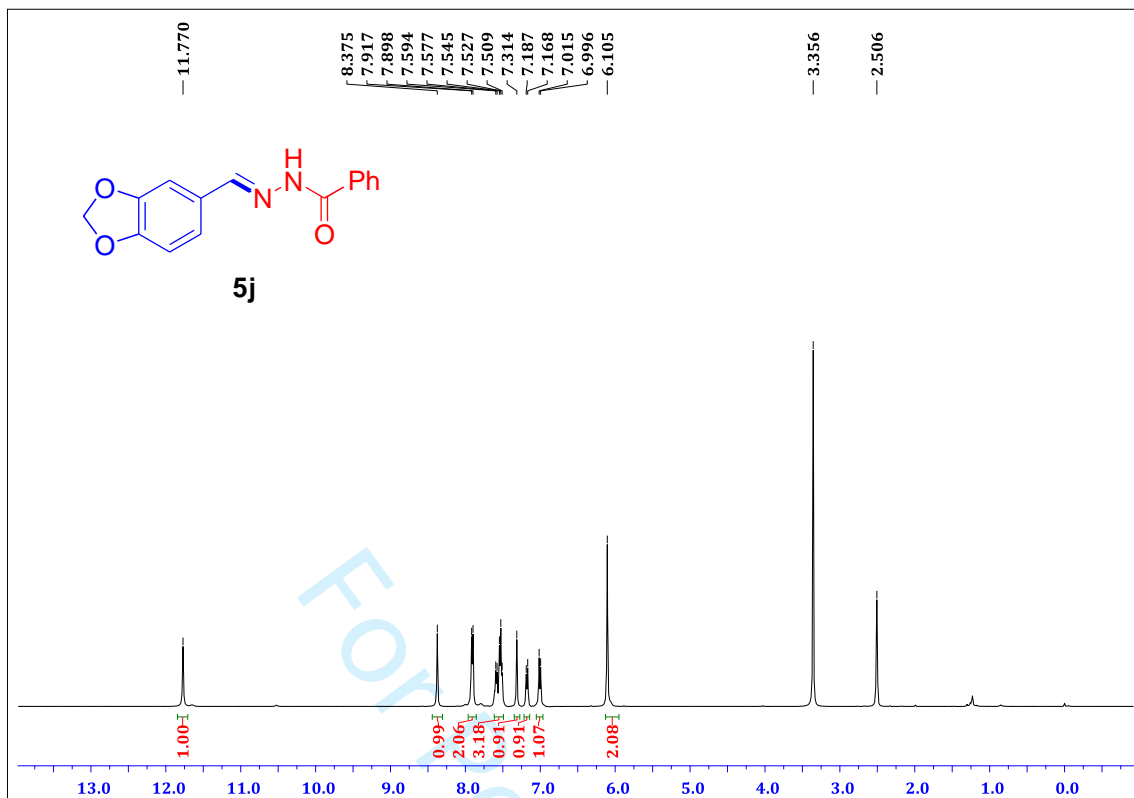
**Figure S20:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of 5h



27 **Figure S21:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5i** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)

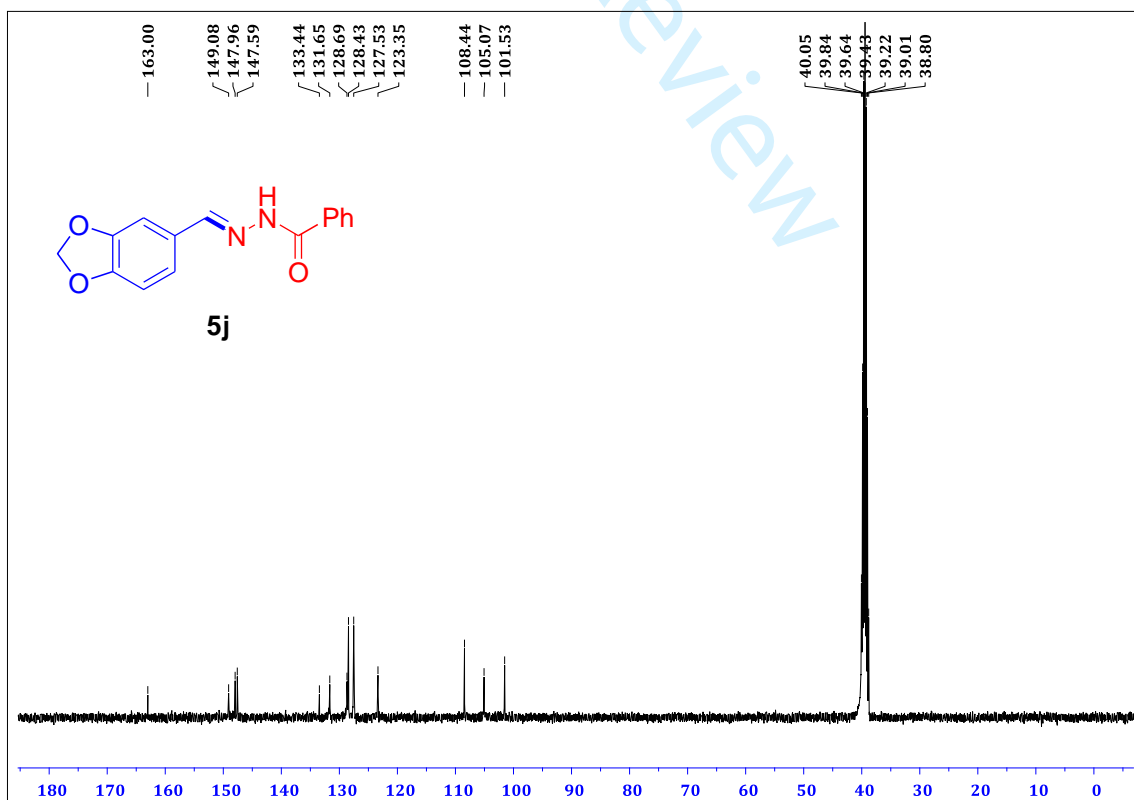


**Figure S22:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5i**

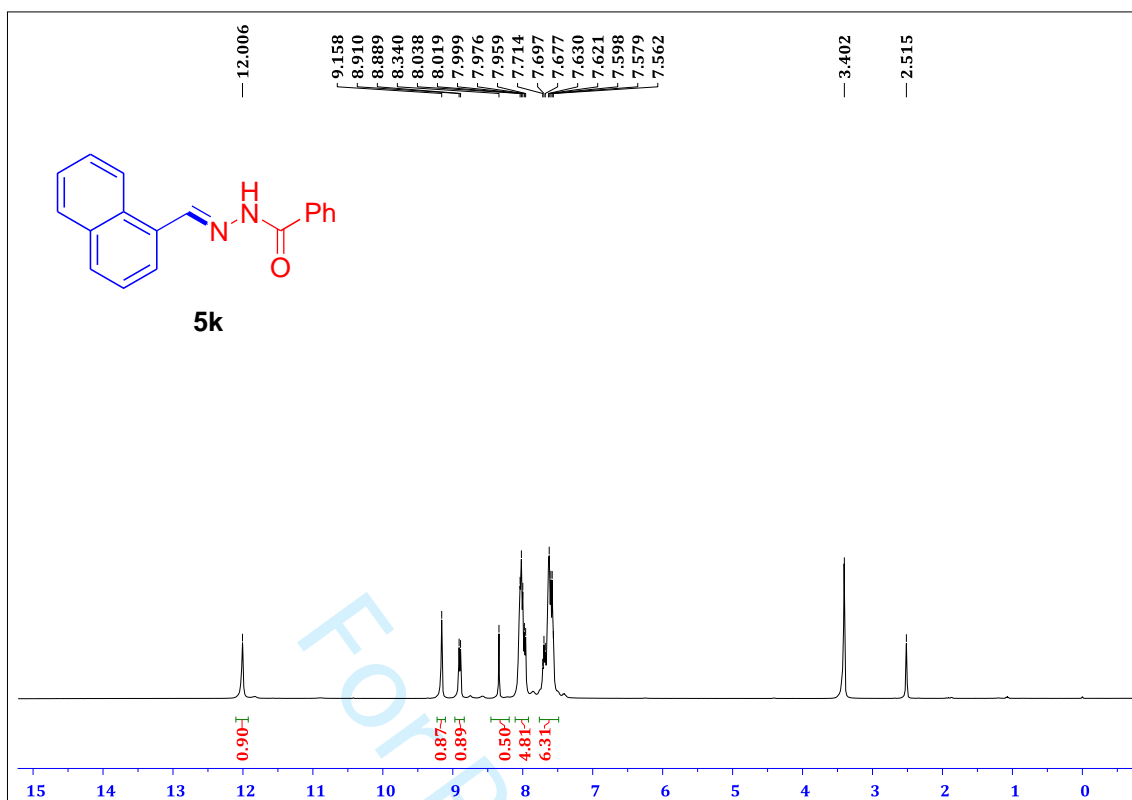


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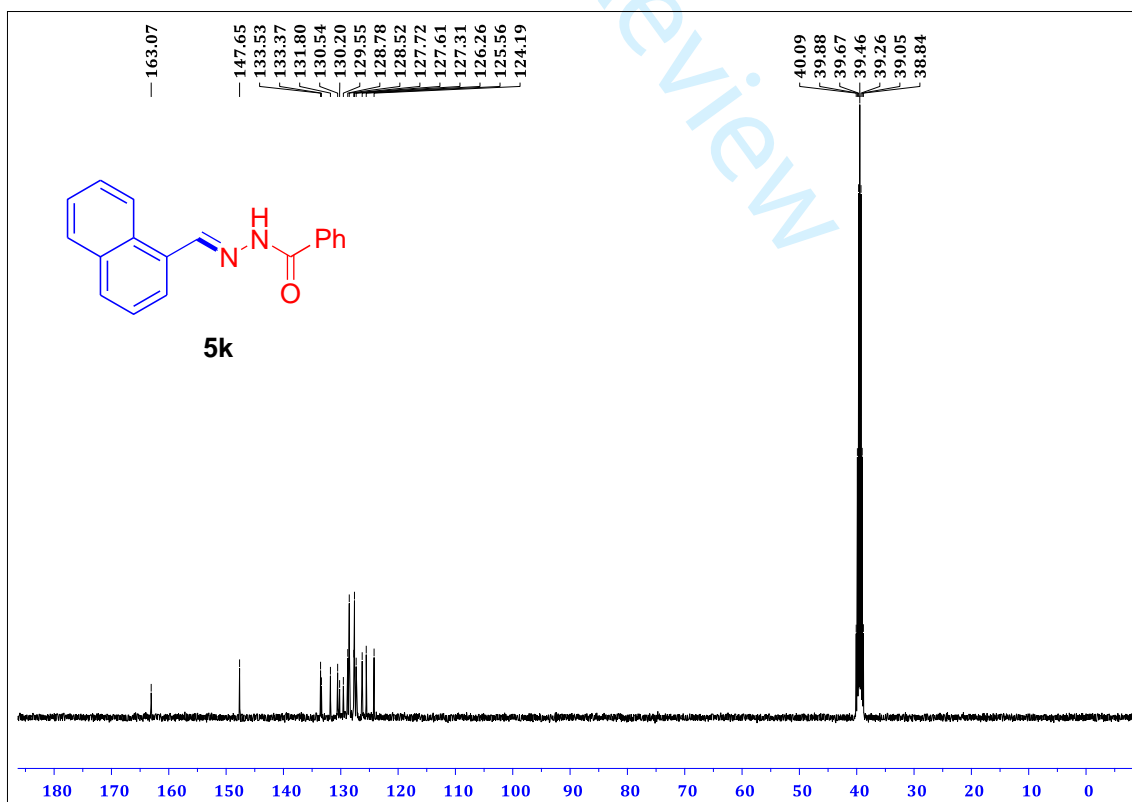
**Figure S23:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5j** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)



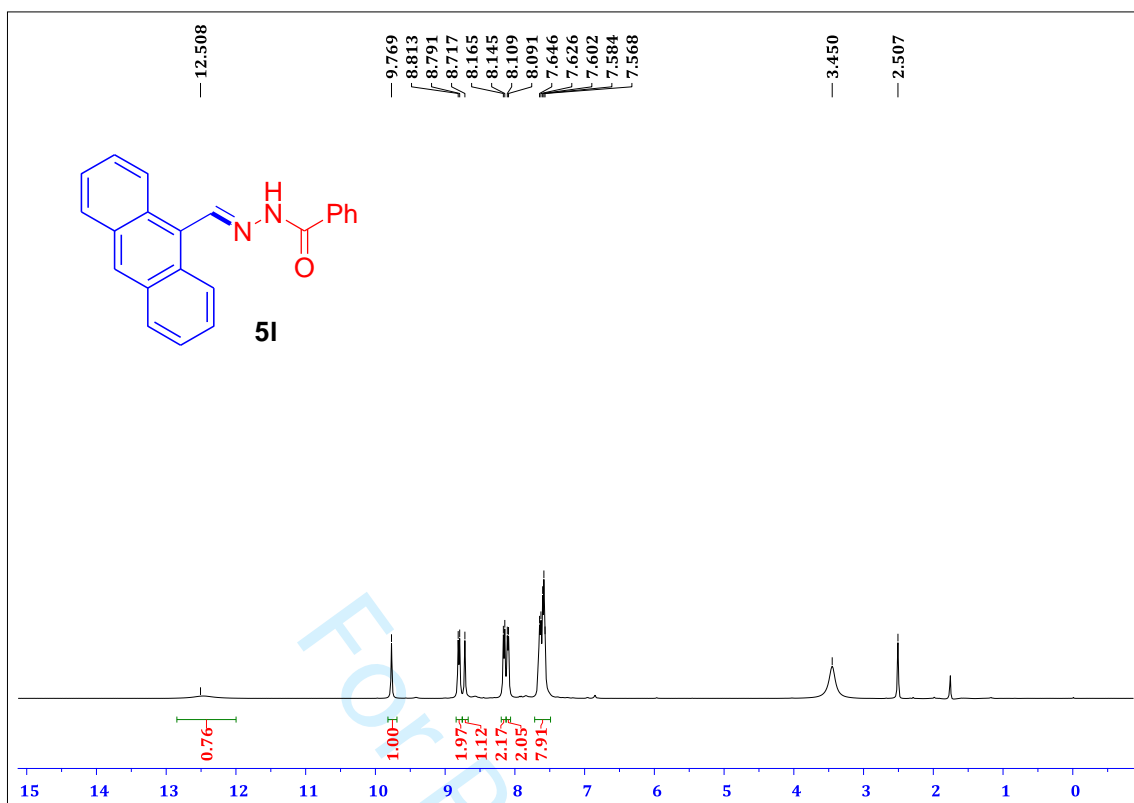
**Figure S24:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5j**



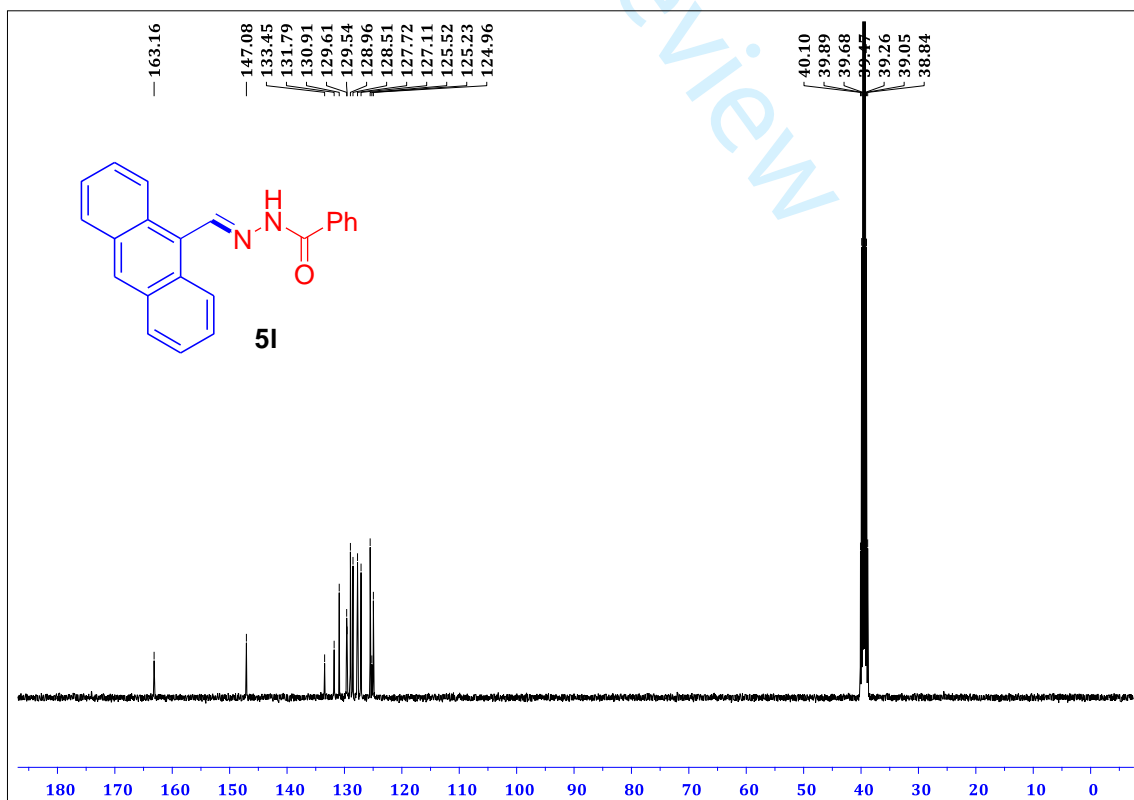
27 **Figure S25:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5k** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)



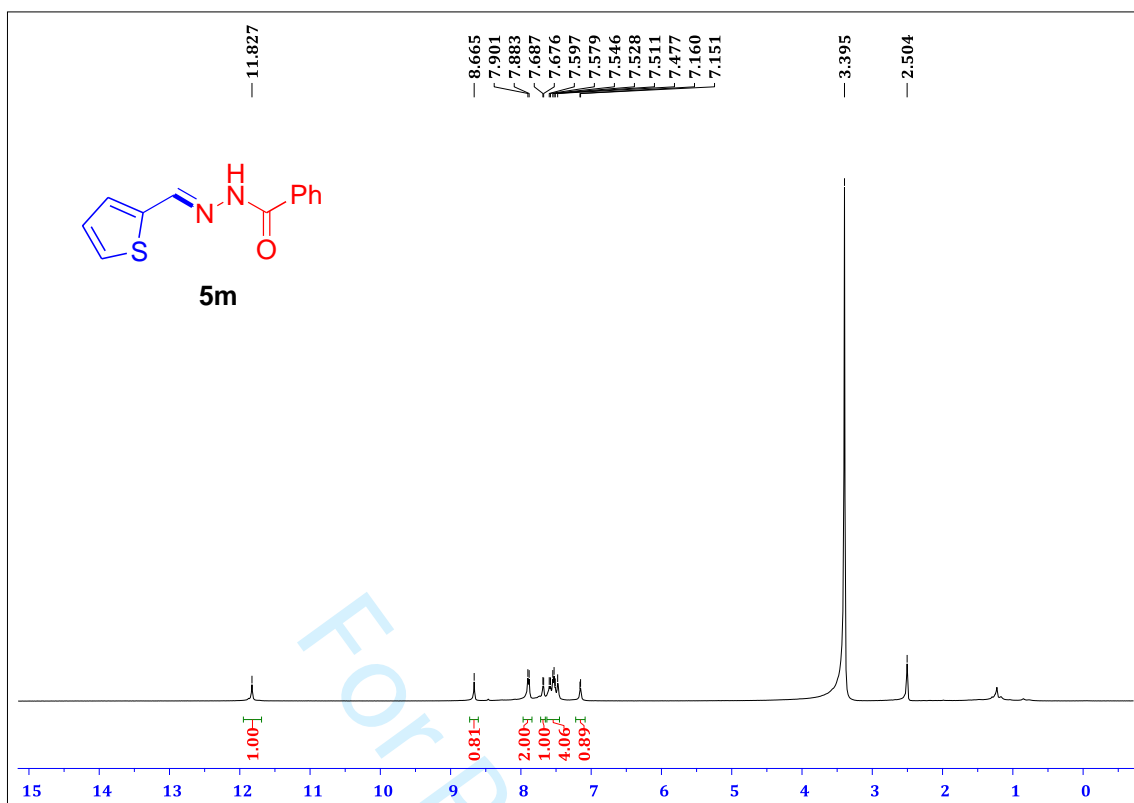
**Figure S26:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **5k**



28 **Figure S27:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5l** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)

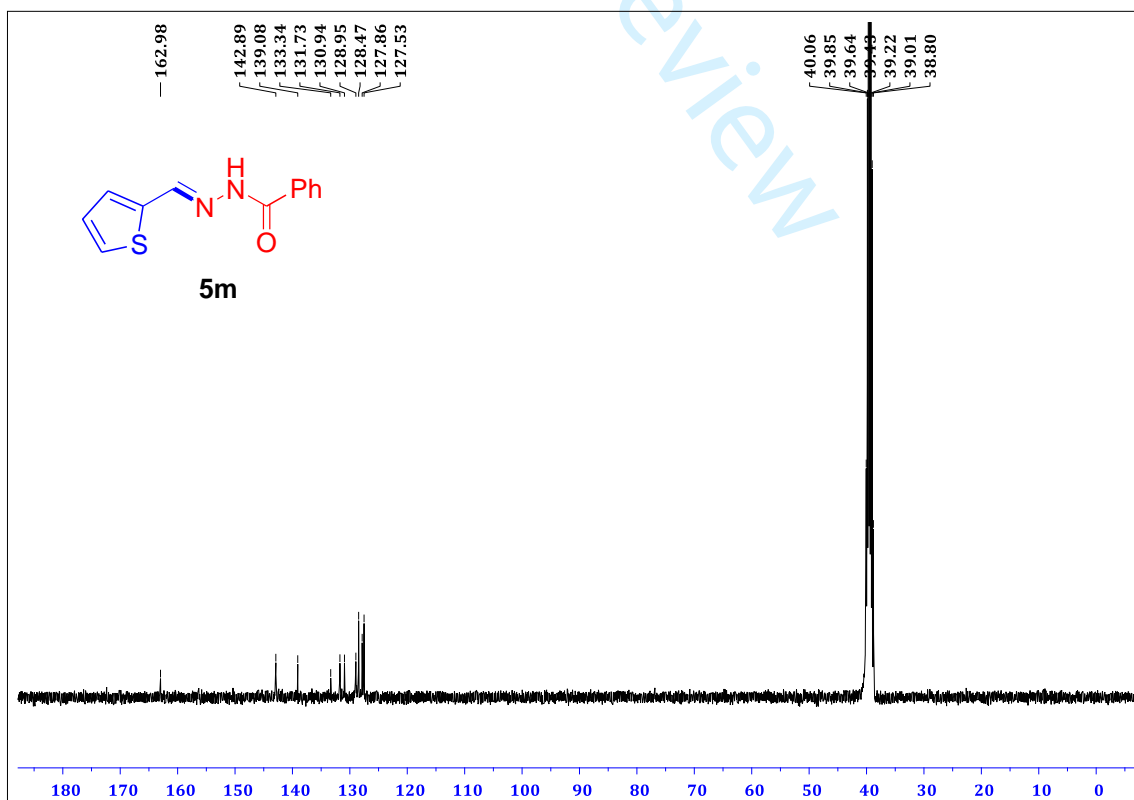


**Figure S28:** <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5l**

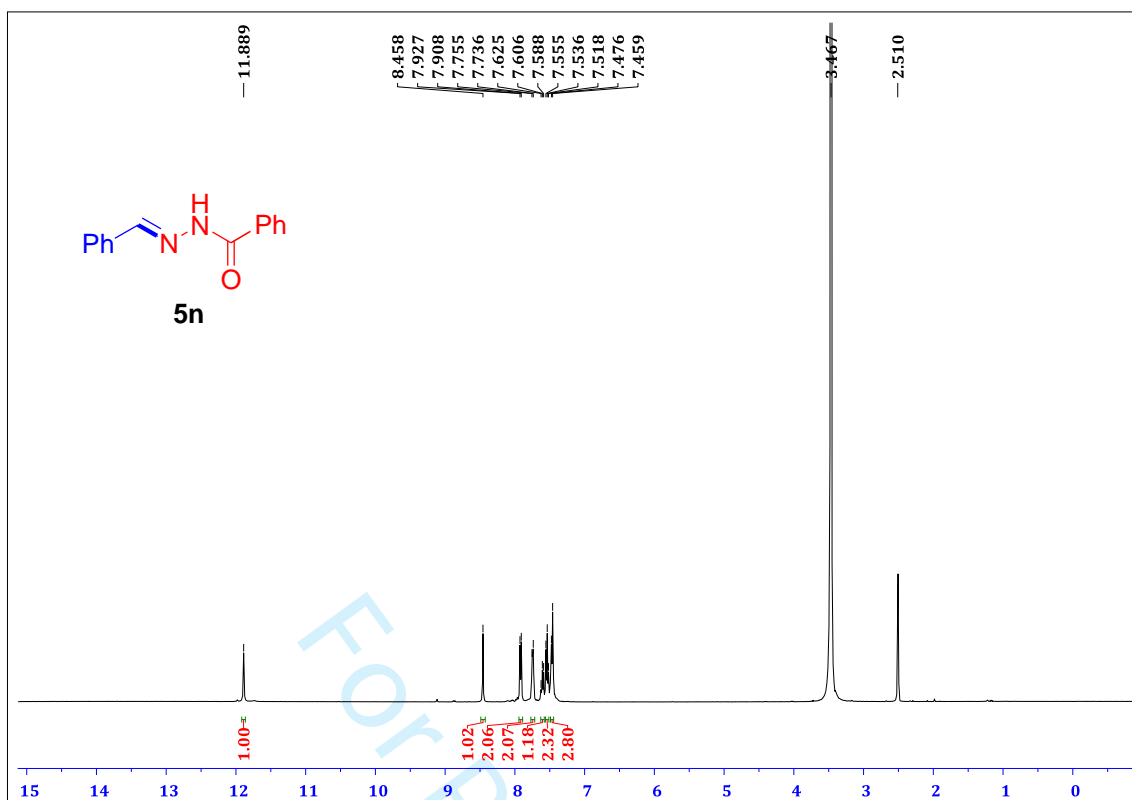


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**Figure S29:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5m** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)



**Figure S30:** <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5m**



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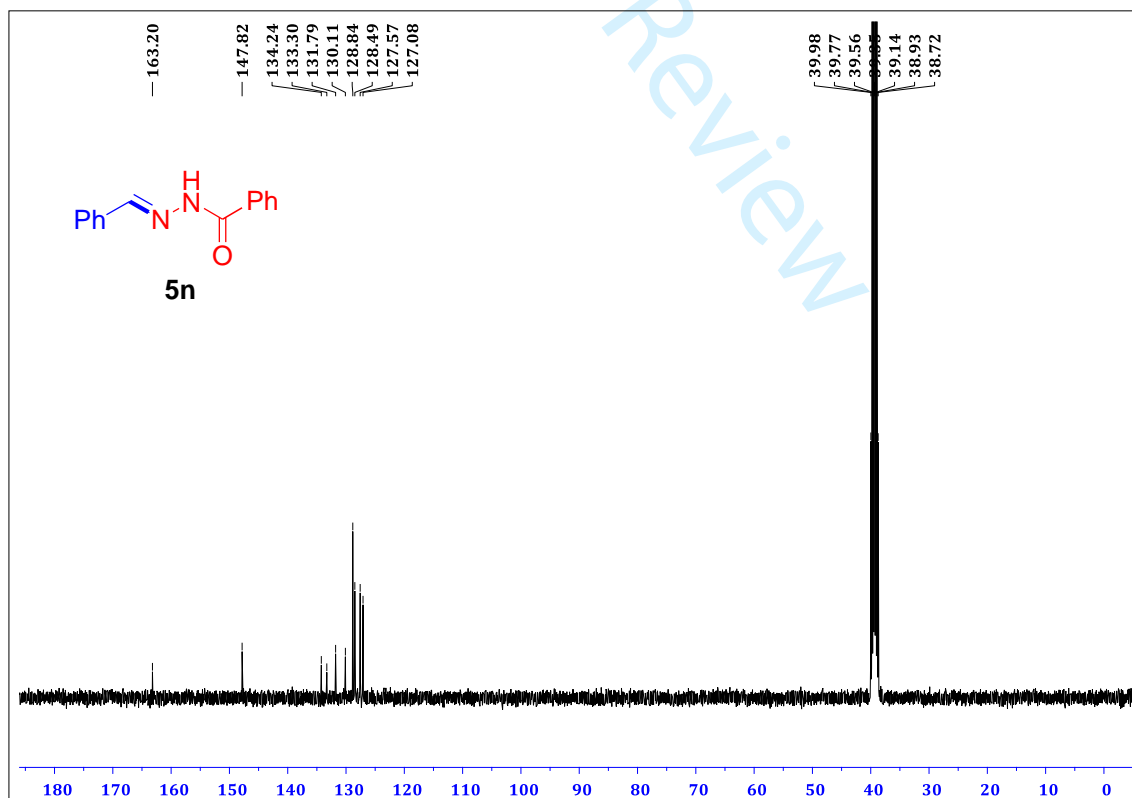
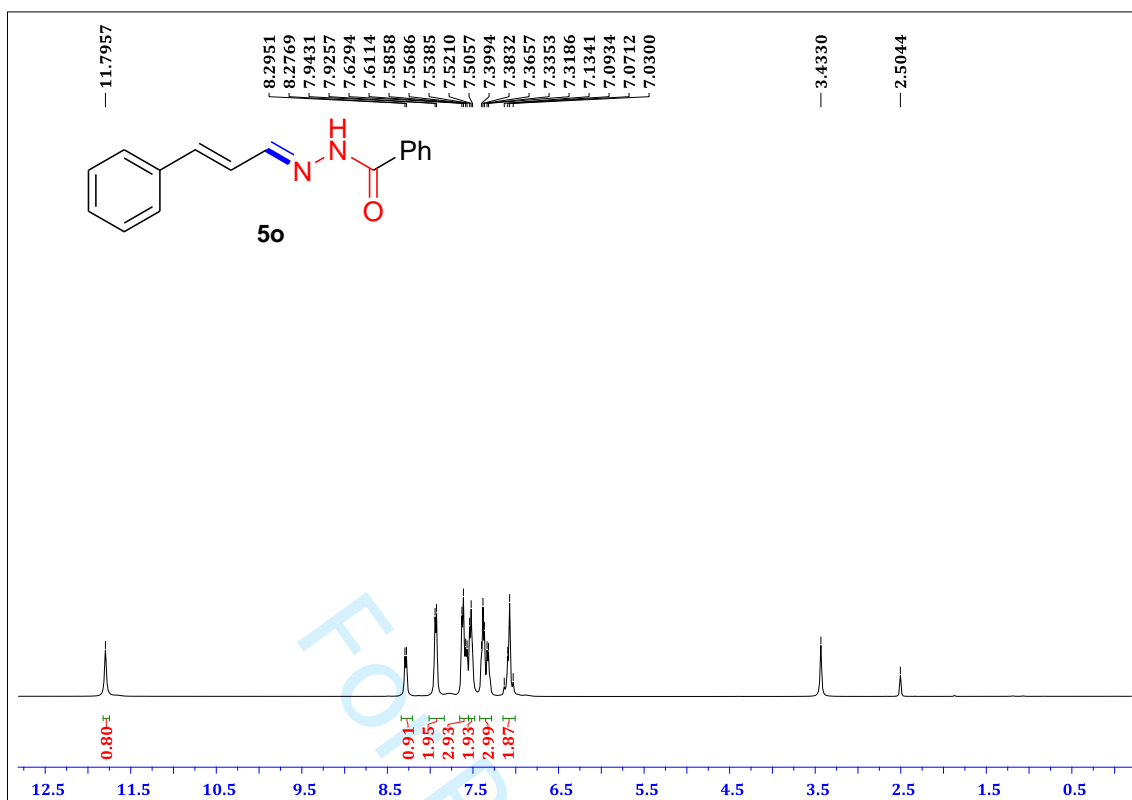
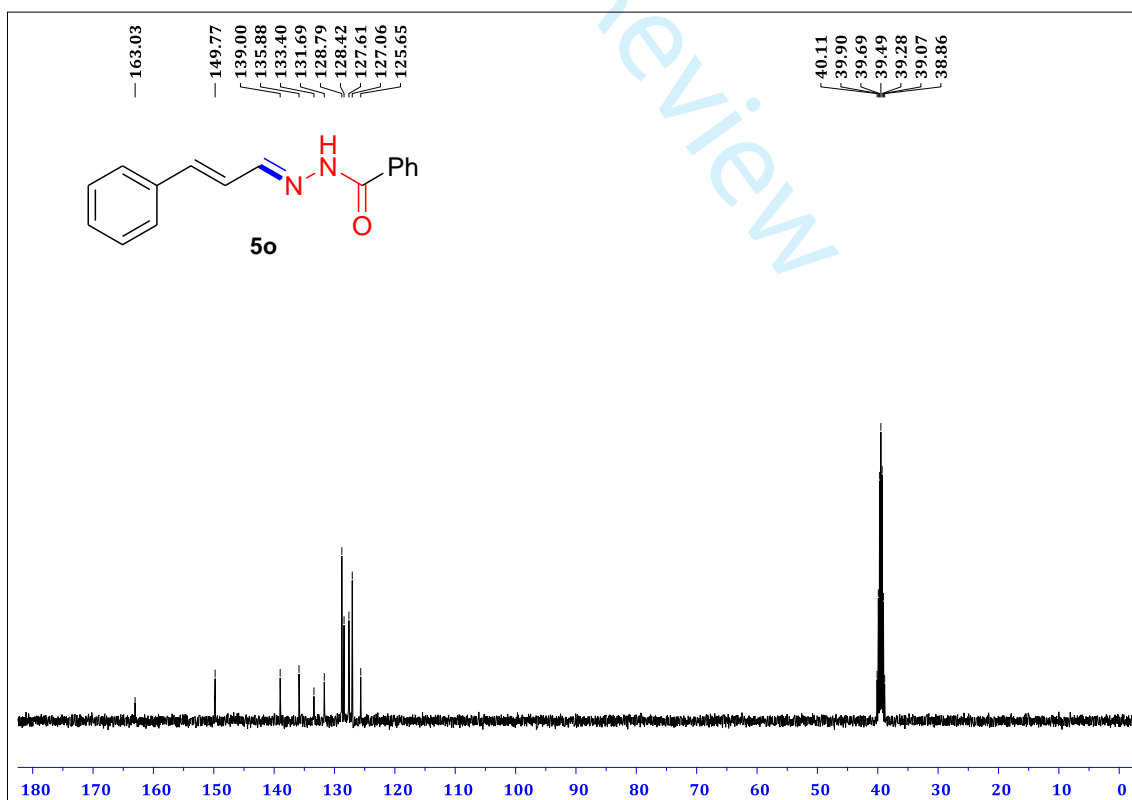


Figure S32: <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5n**



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**Figure S33:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5o** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)



**Figure S34:** <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **5o**



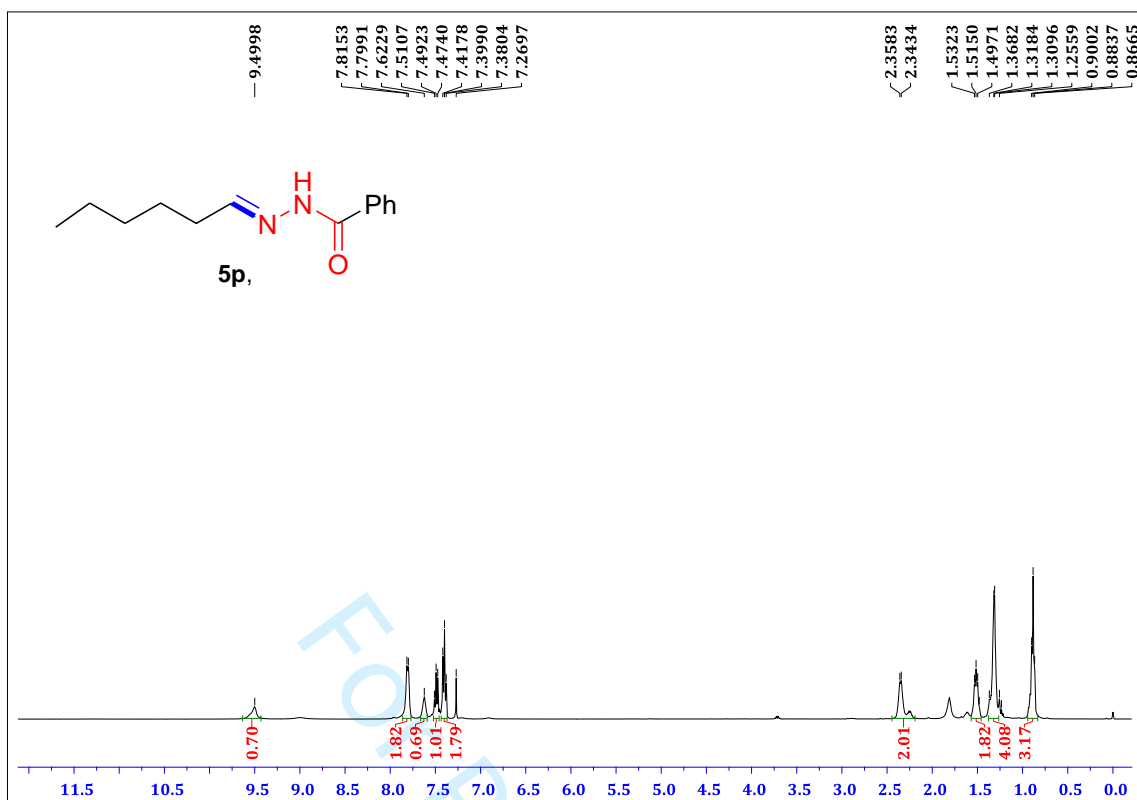


Figure S35: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of **5p**

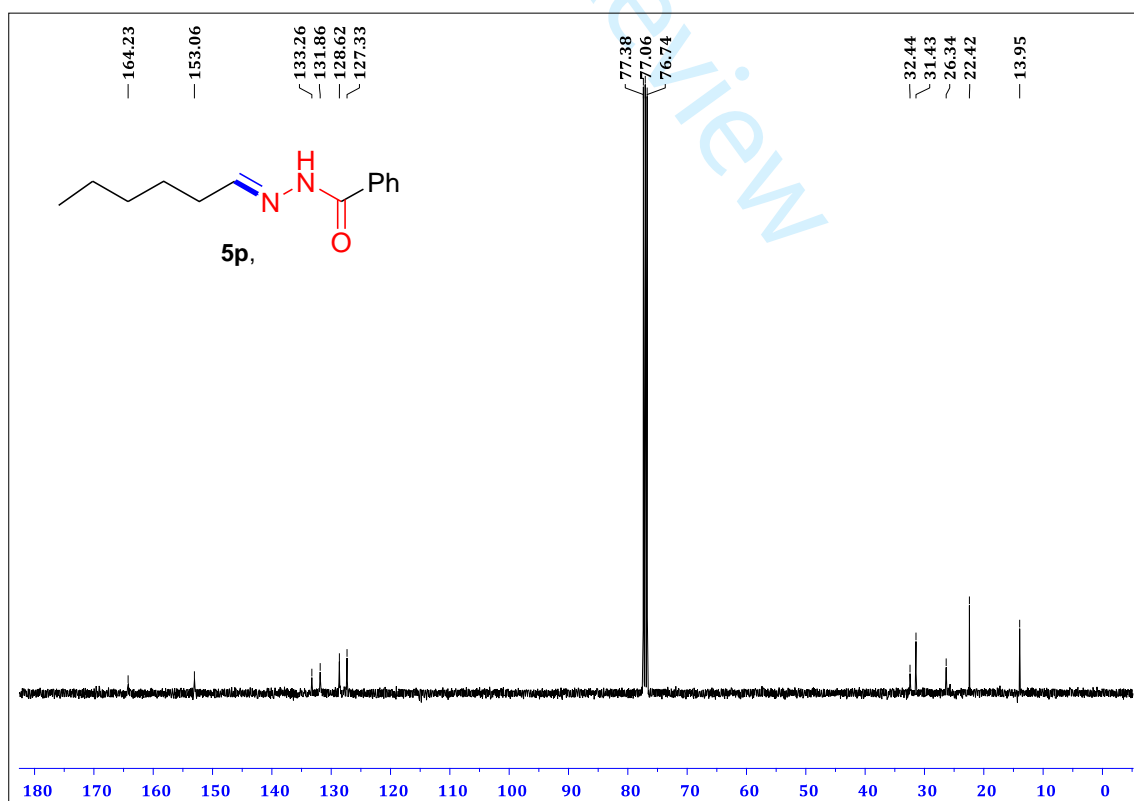
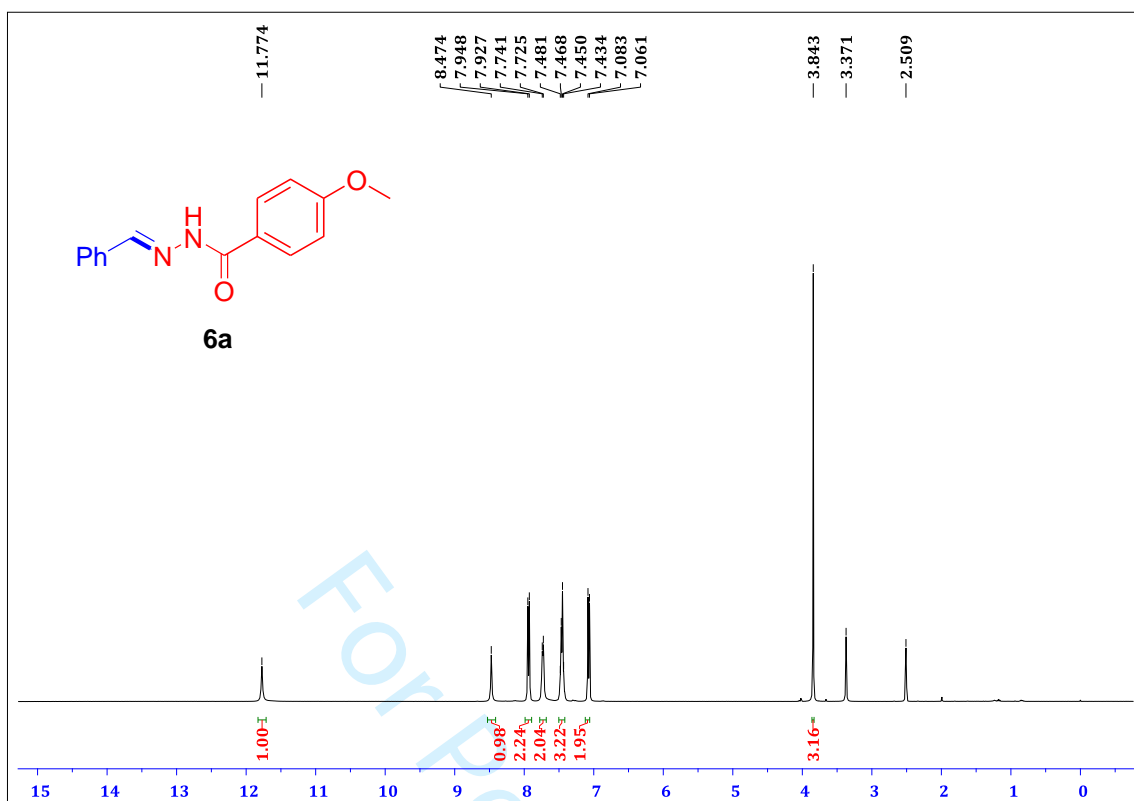


Figure S36: <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) spectrum of **5p**



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Figure S37:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of 6a (peaks at 3.3 and 2.5 ppm are solvent and water peaks)

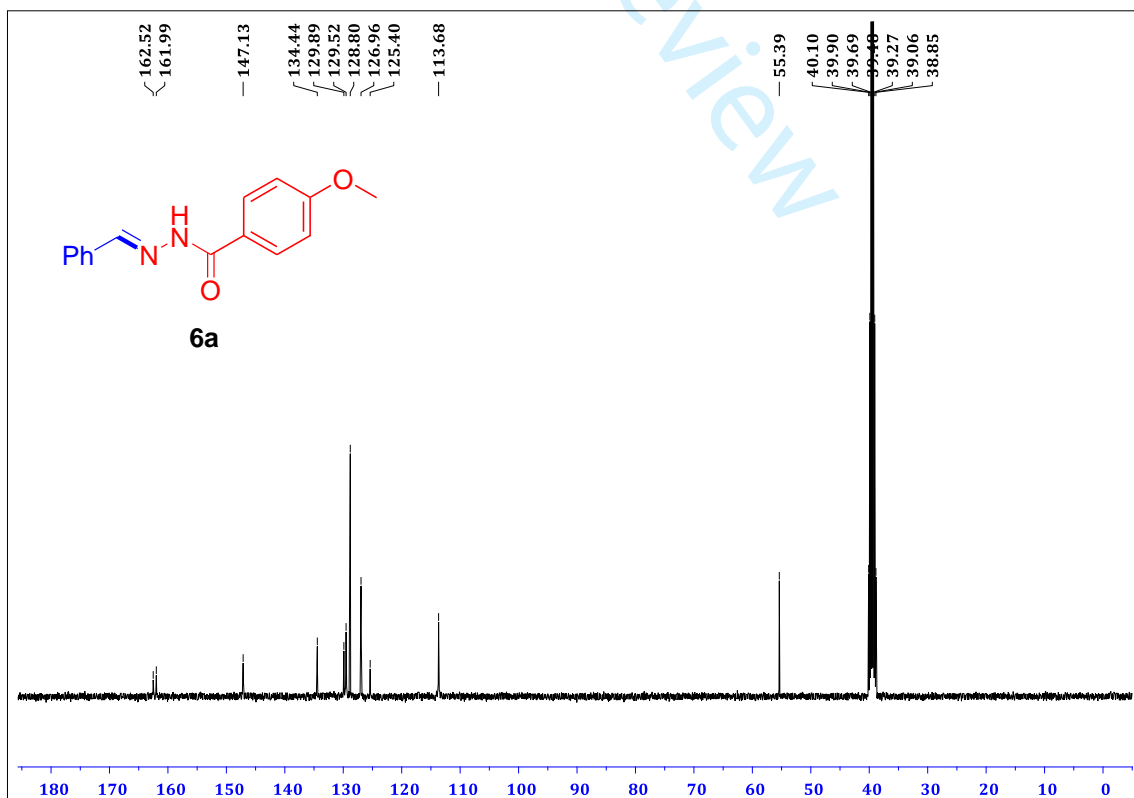
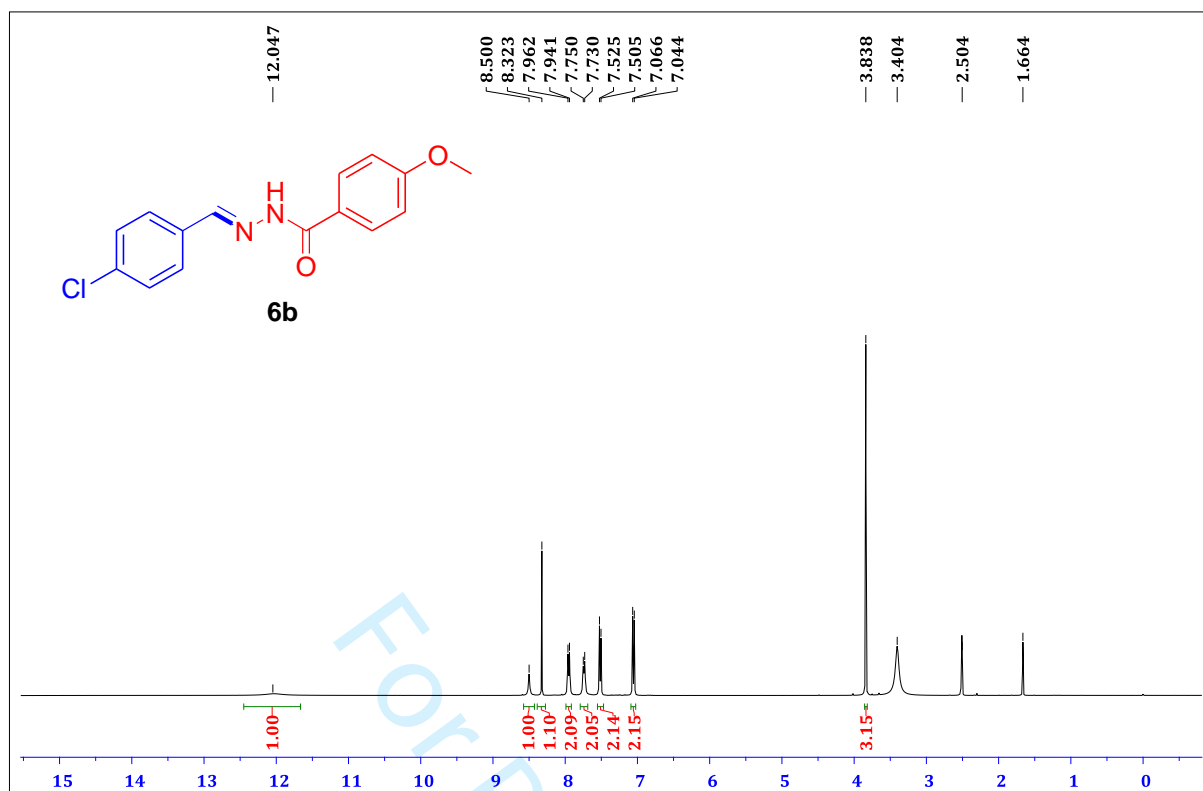
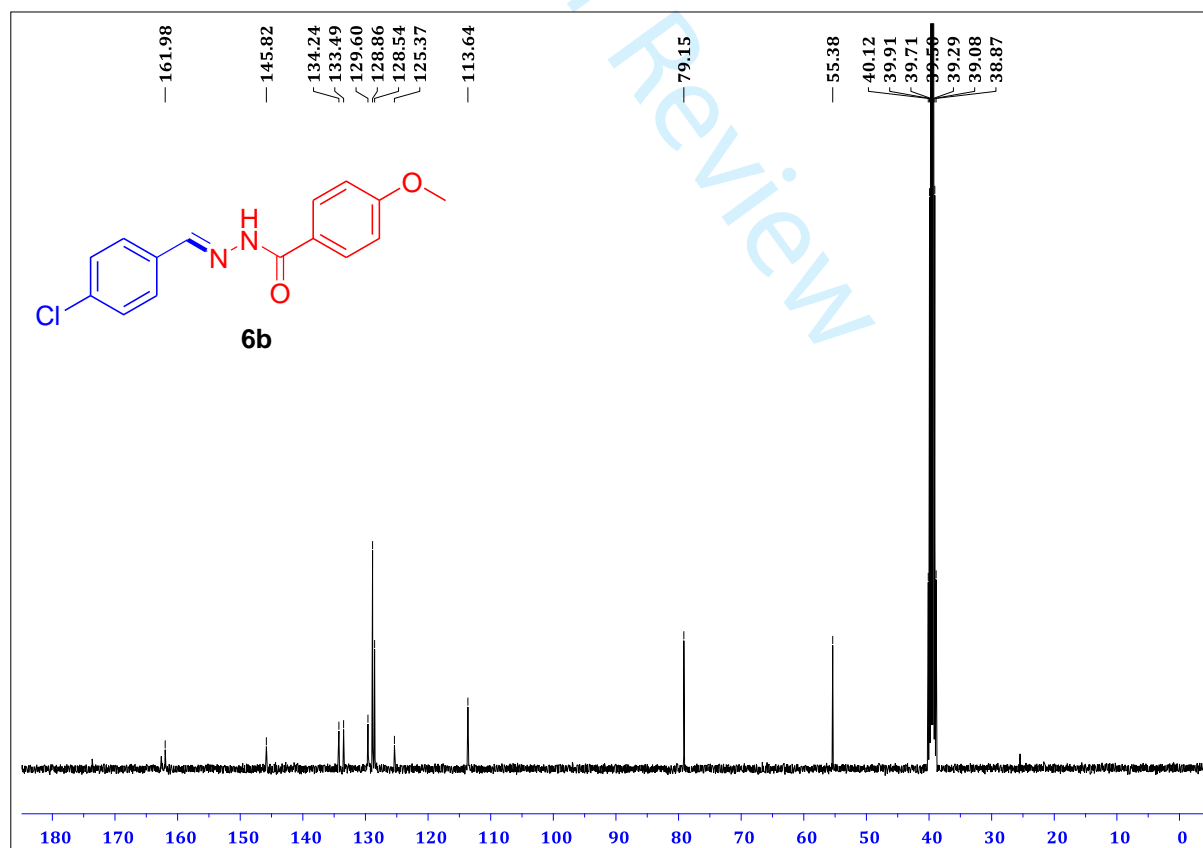


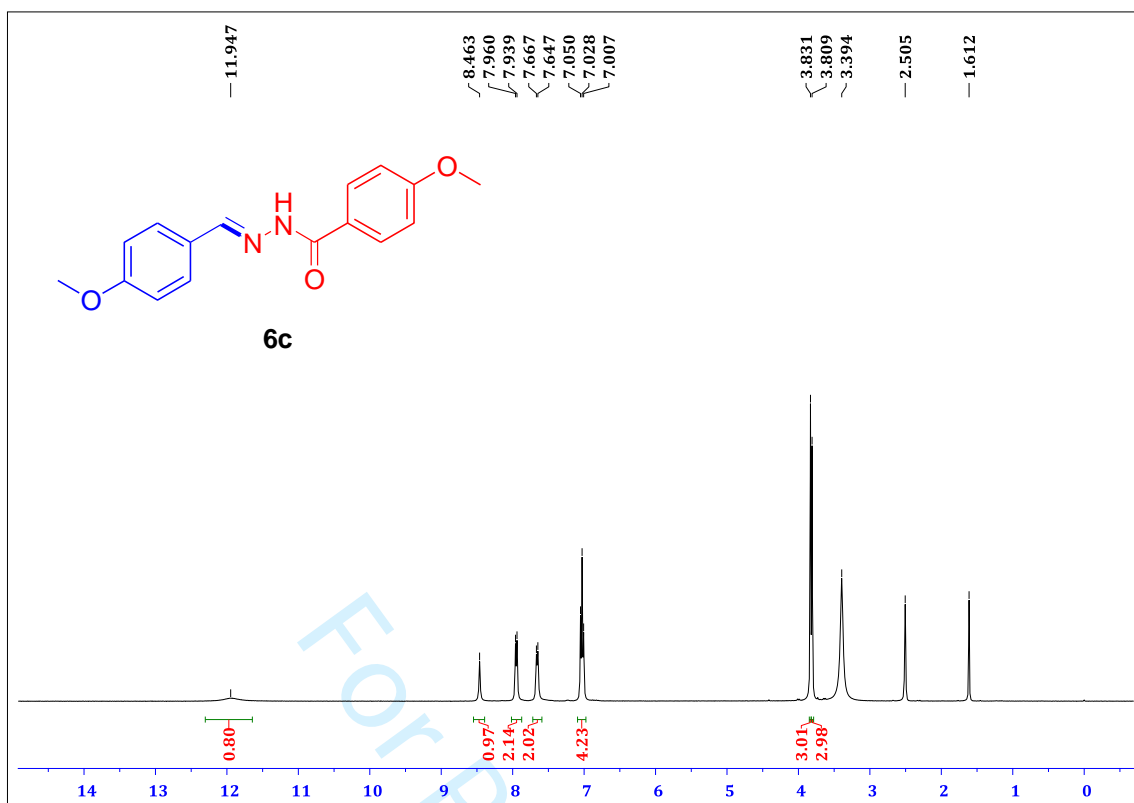
Figure S38:  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of 6a



28 **Figure S39:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6b** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)



**Figure S40:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6b**



27 **Figure S41:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6c** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)

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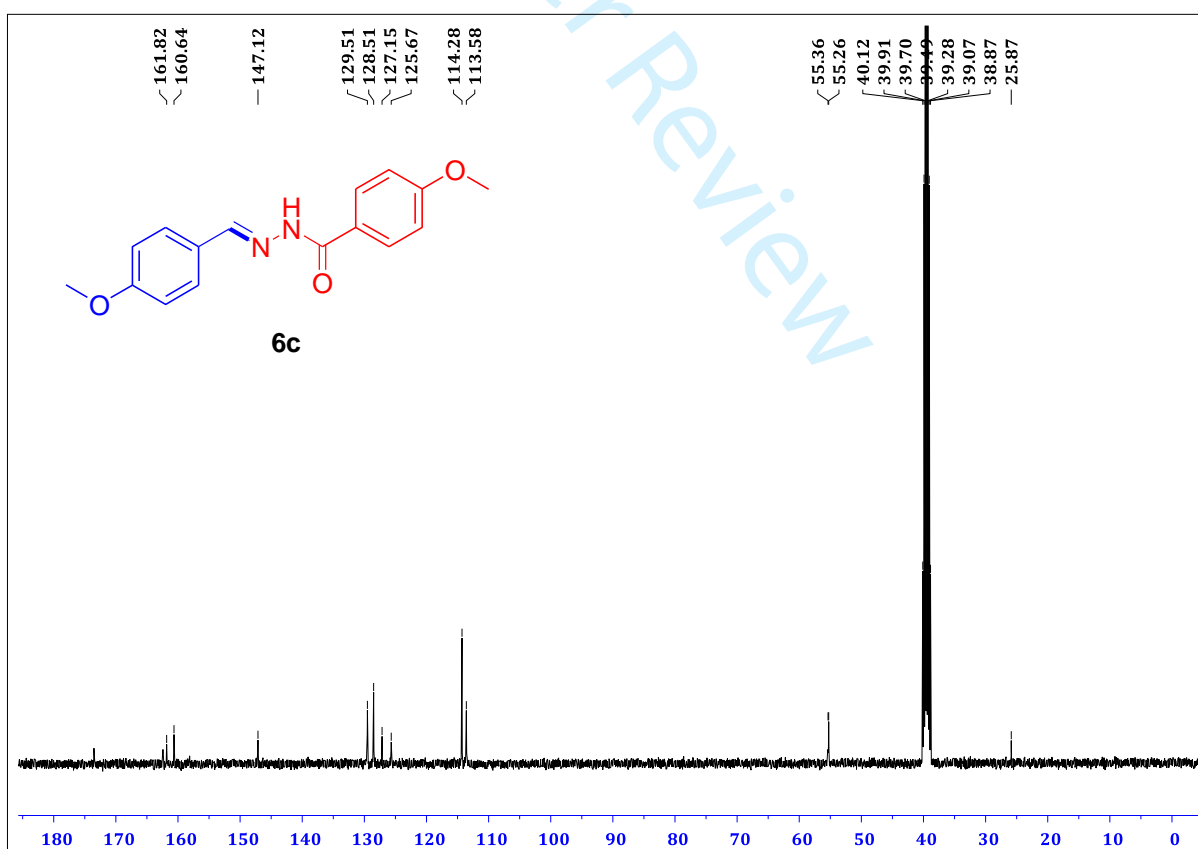
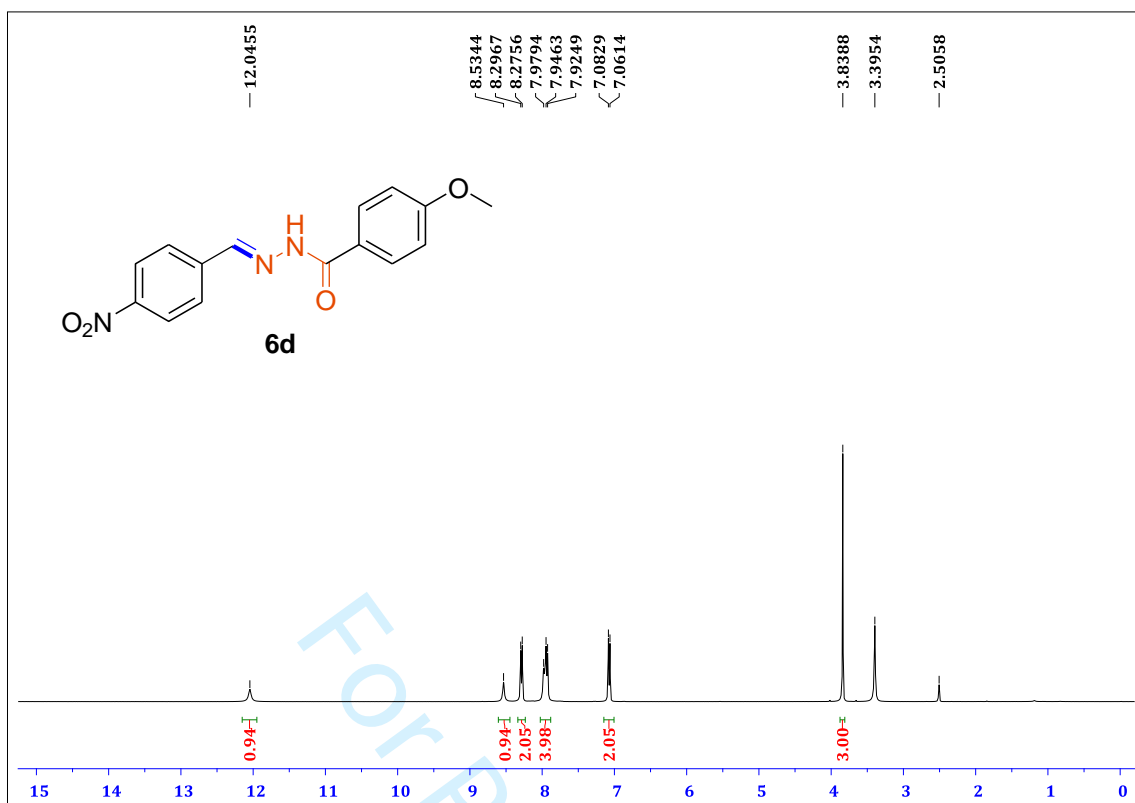
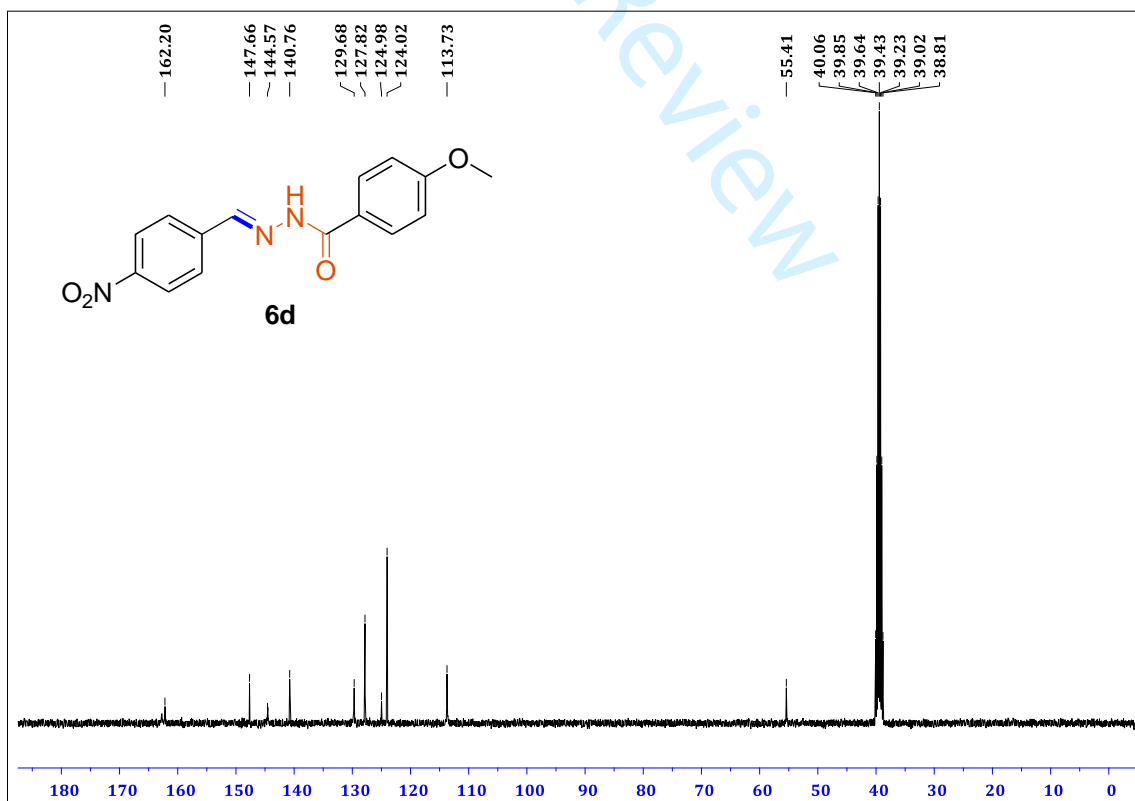


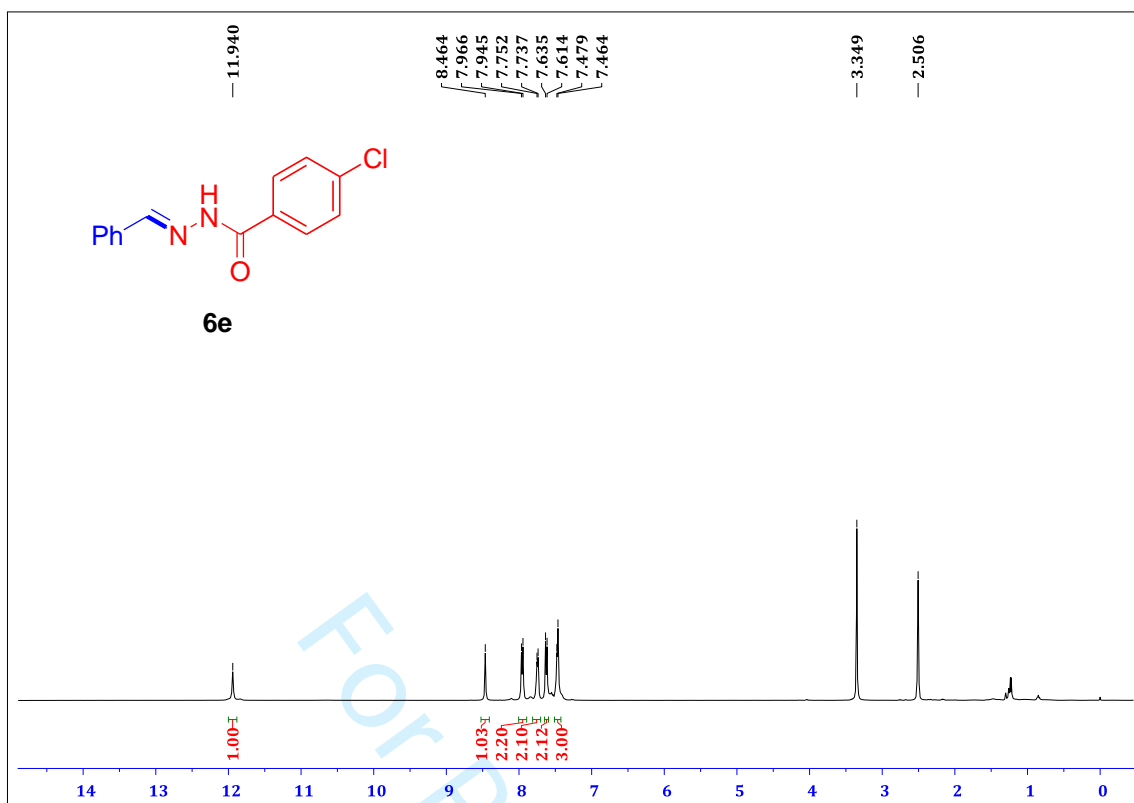
Figure S42:  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6c**



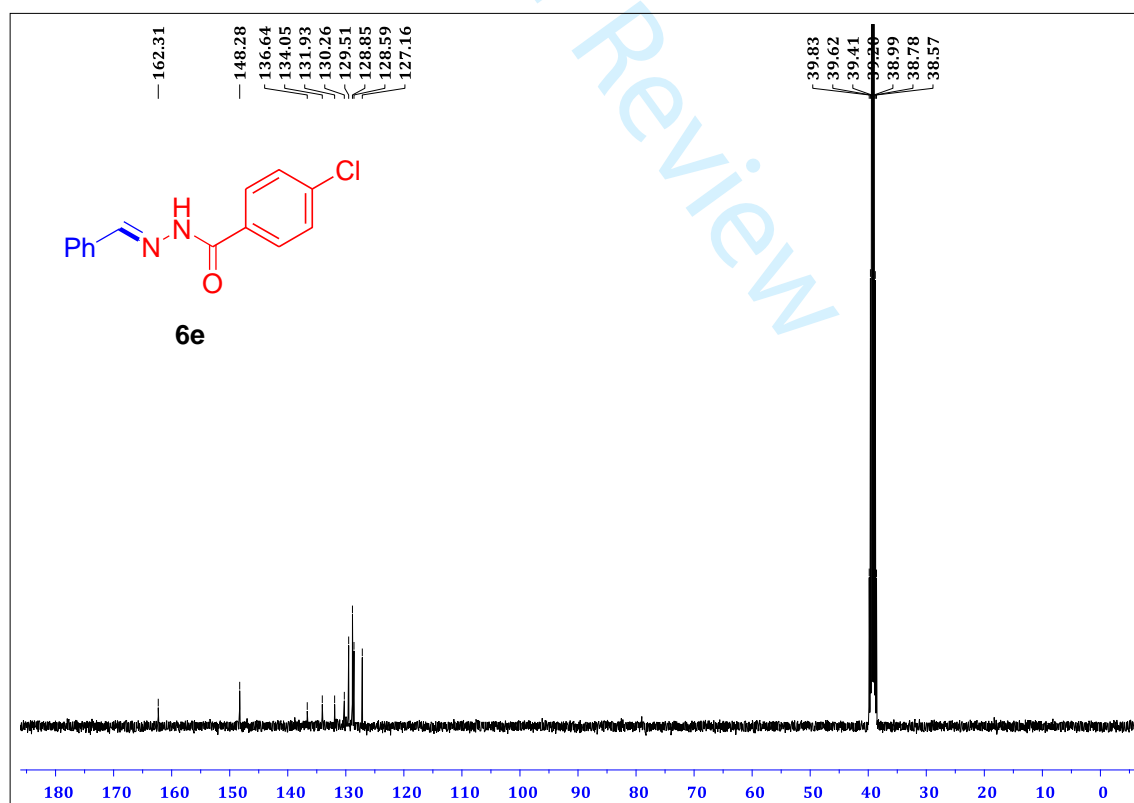
28 **Figure S43:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6d** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



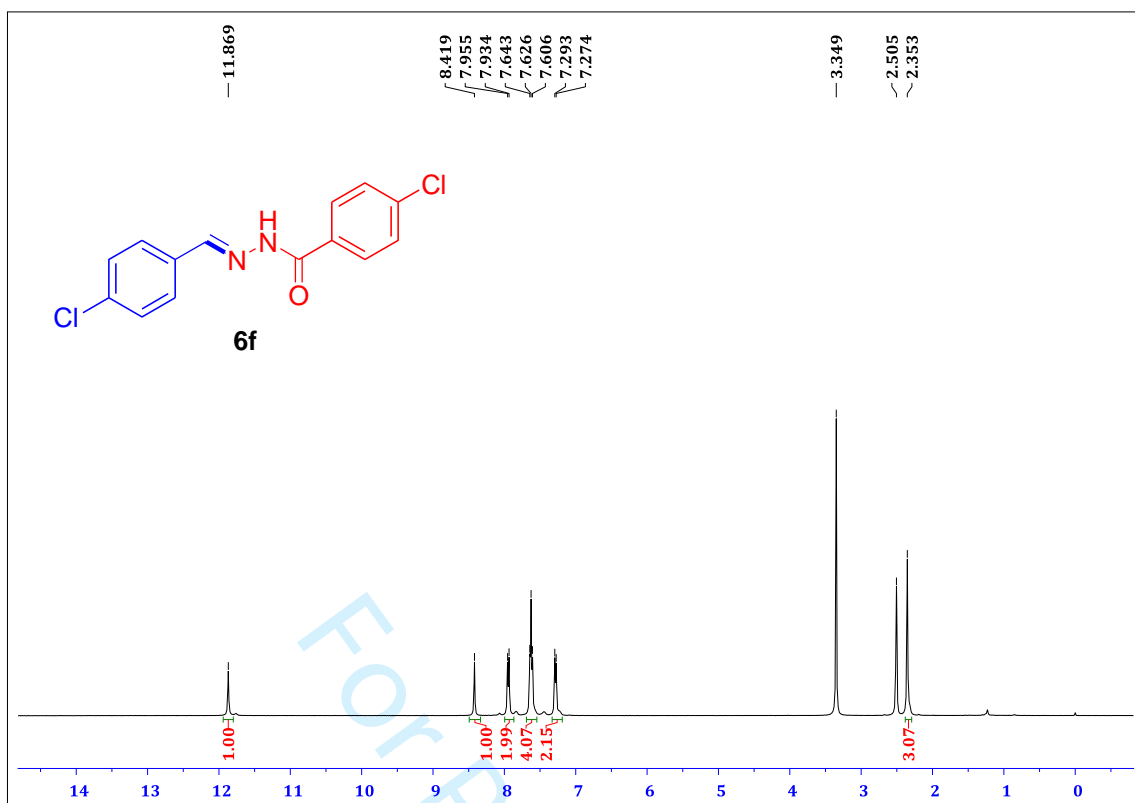
**Figure S44:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6d**



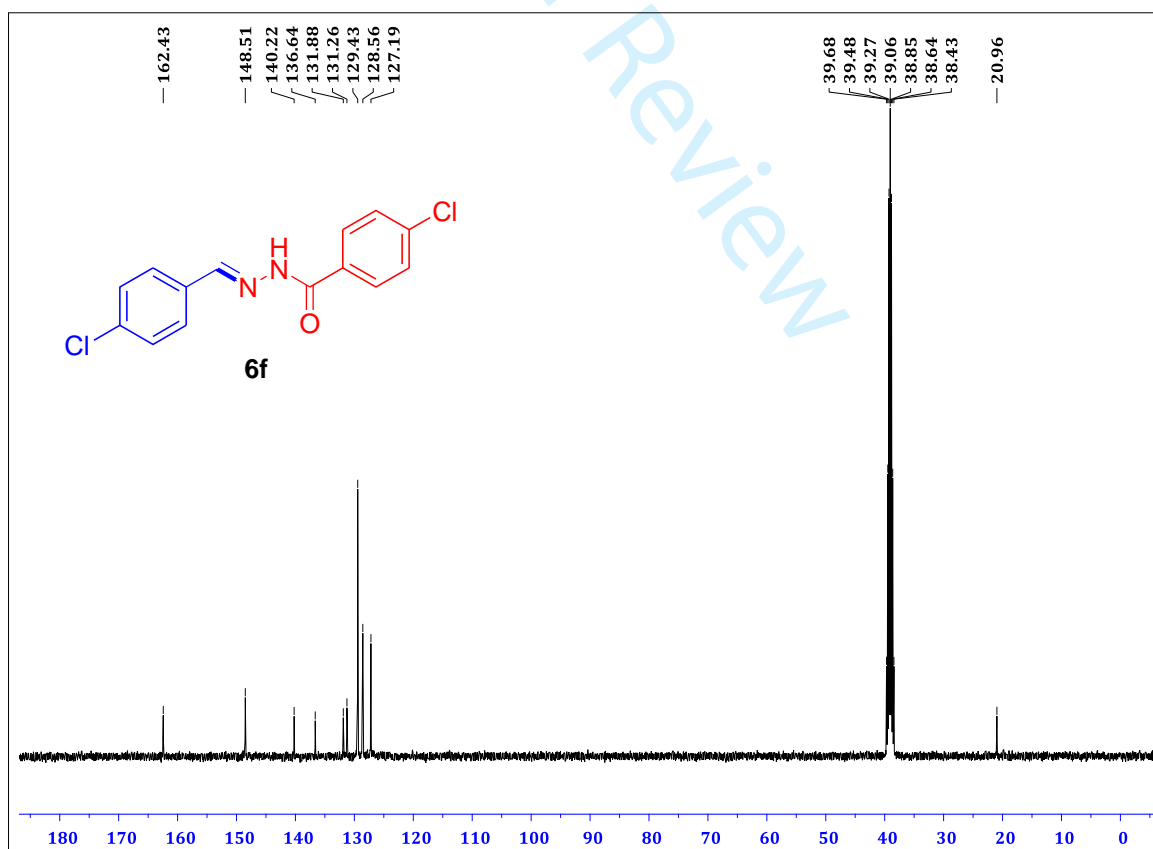
28 **Figure S45:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6e**(peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



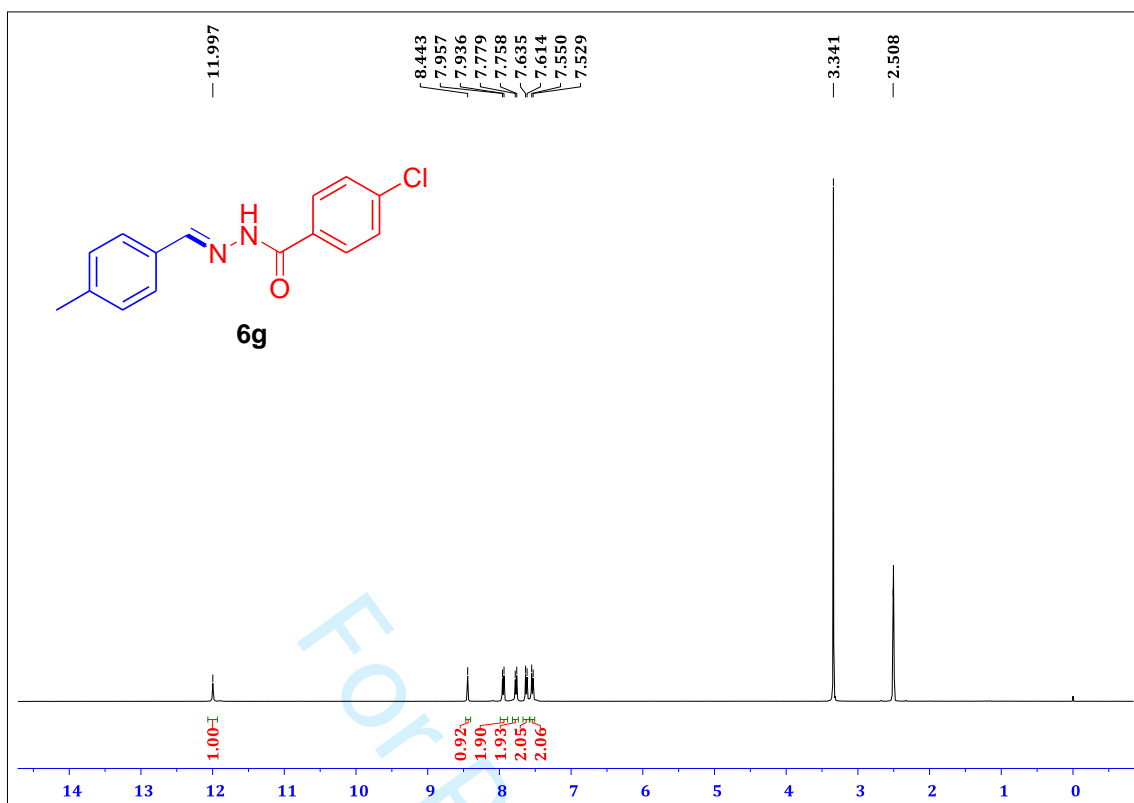
58 **Figure S46:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6e**



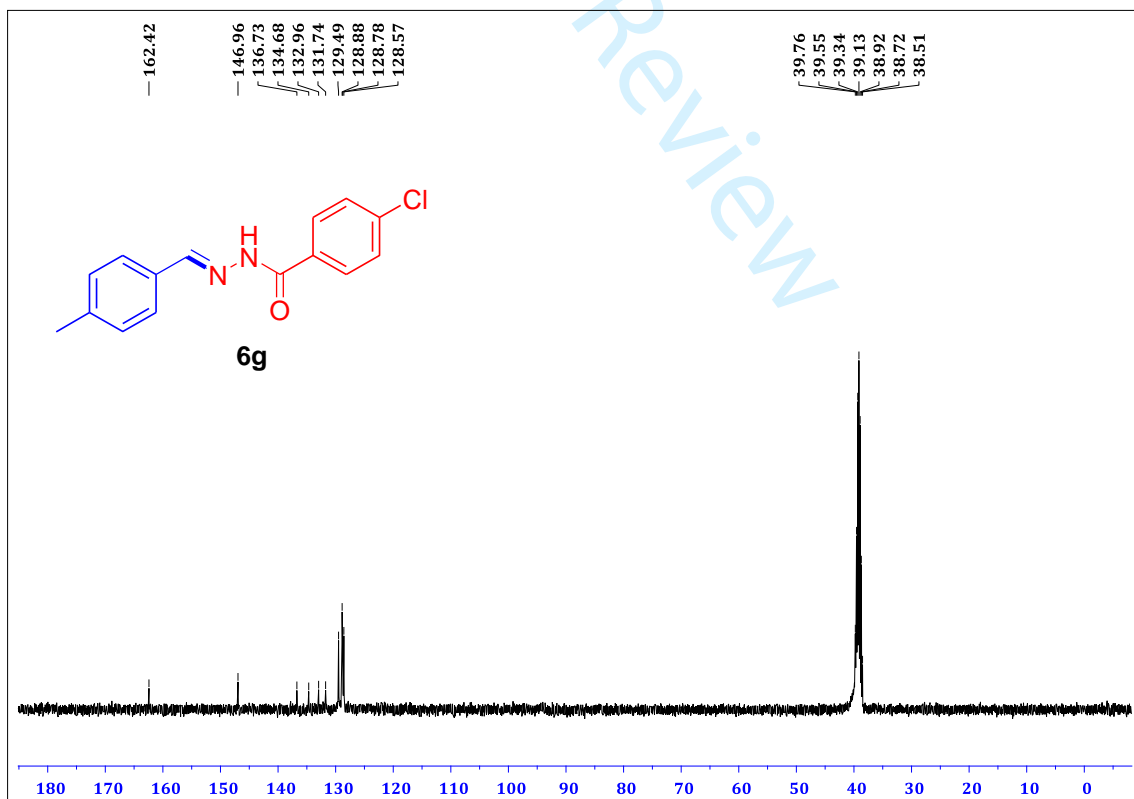
28 **Figure S47:**  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6f** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



**Figure S48:**  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6f**

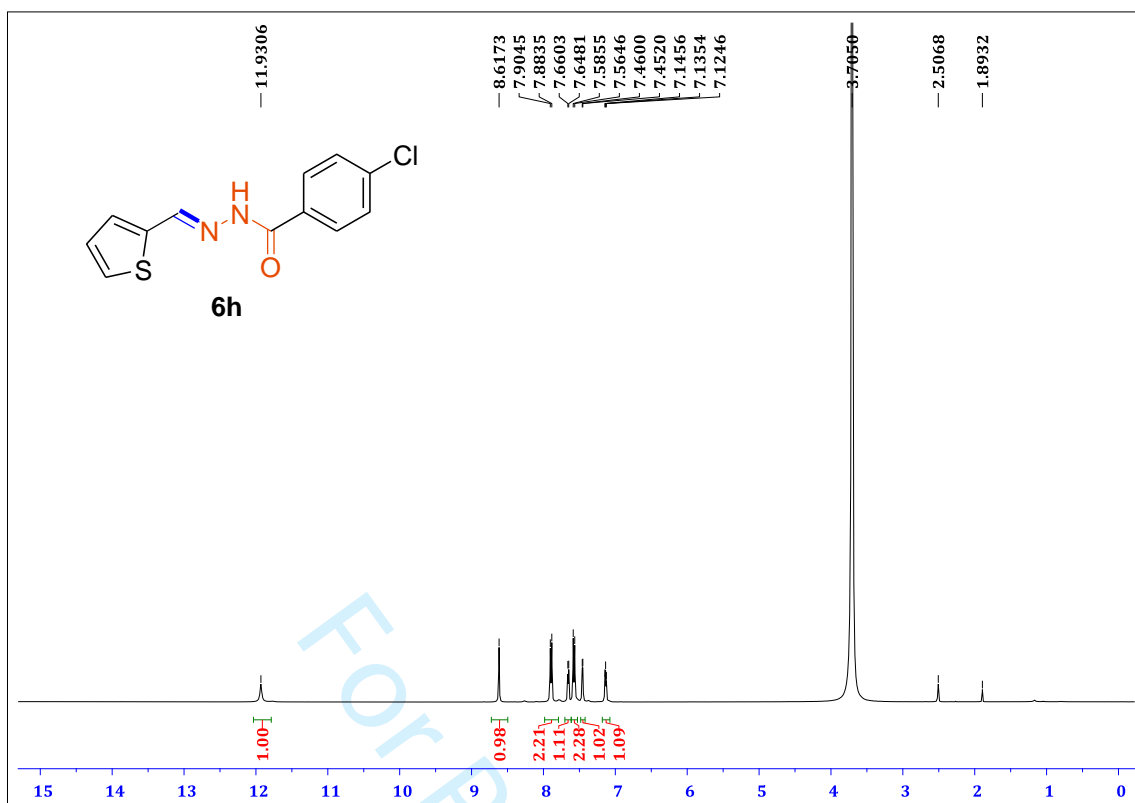


28 **Figure S49:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6g** (peaks at 3.3 and 2.5 ppm are solvent and water peaks)

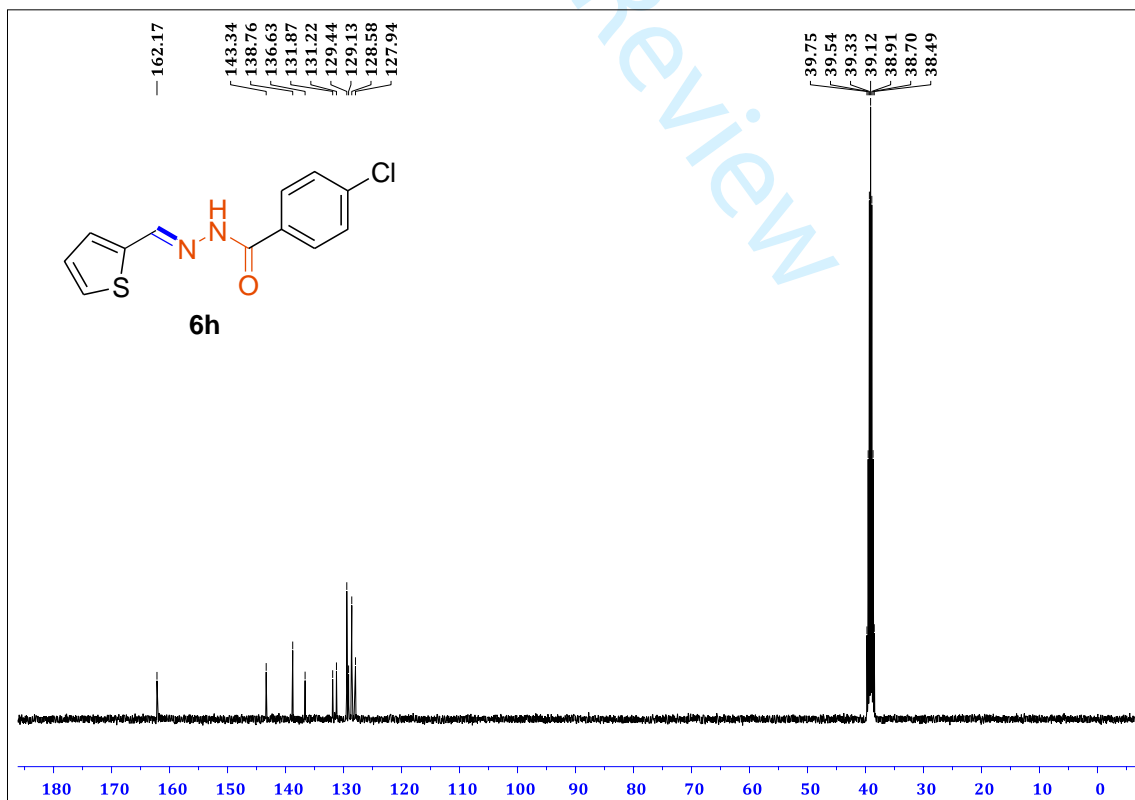


**Figure S50:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6g**

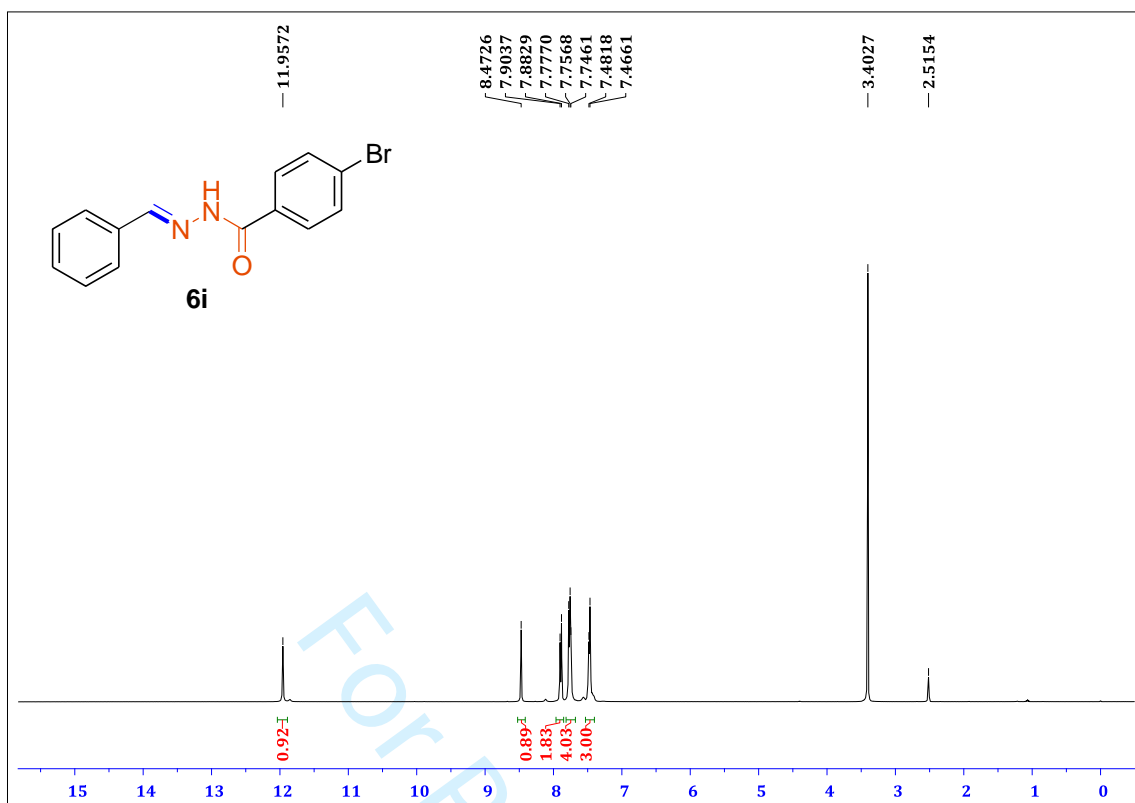




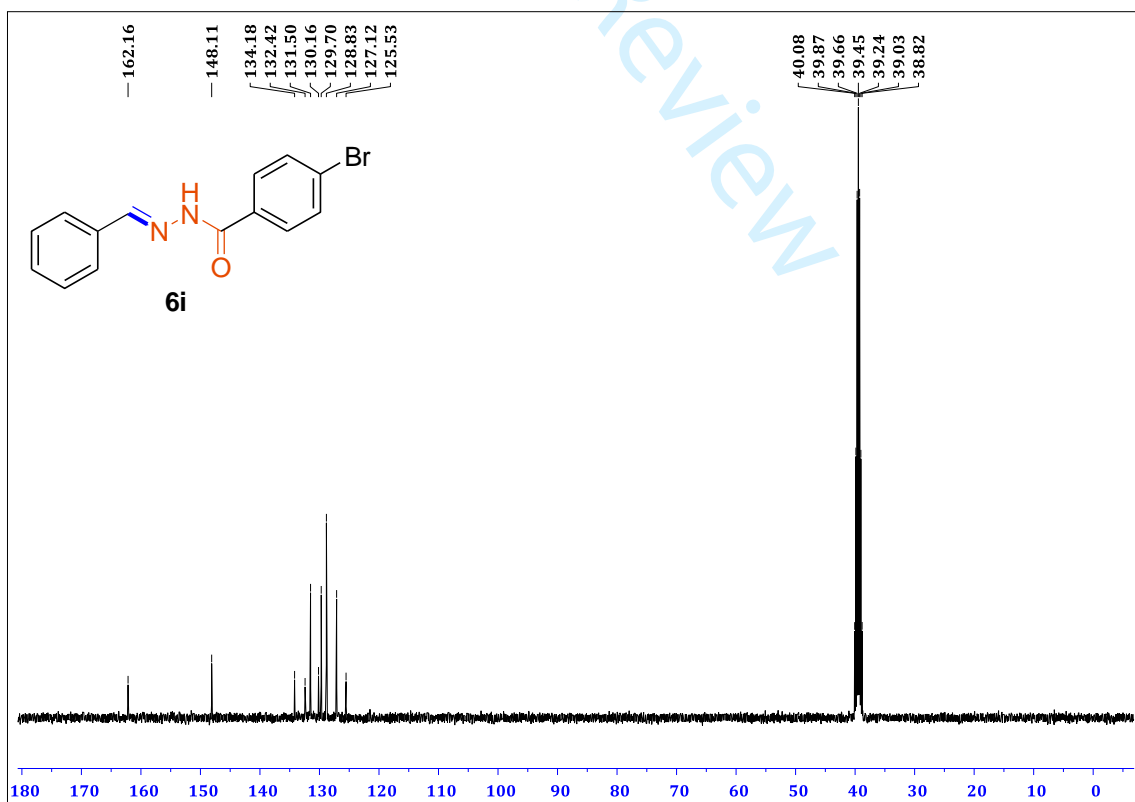
28 **Figure S51:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6h** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



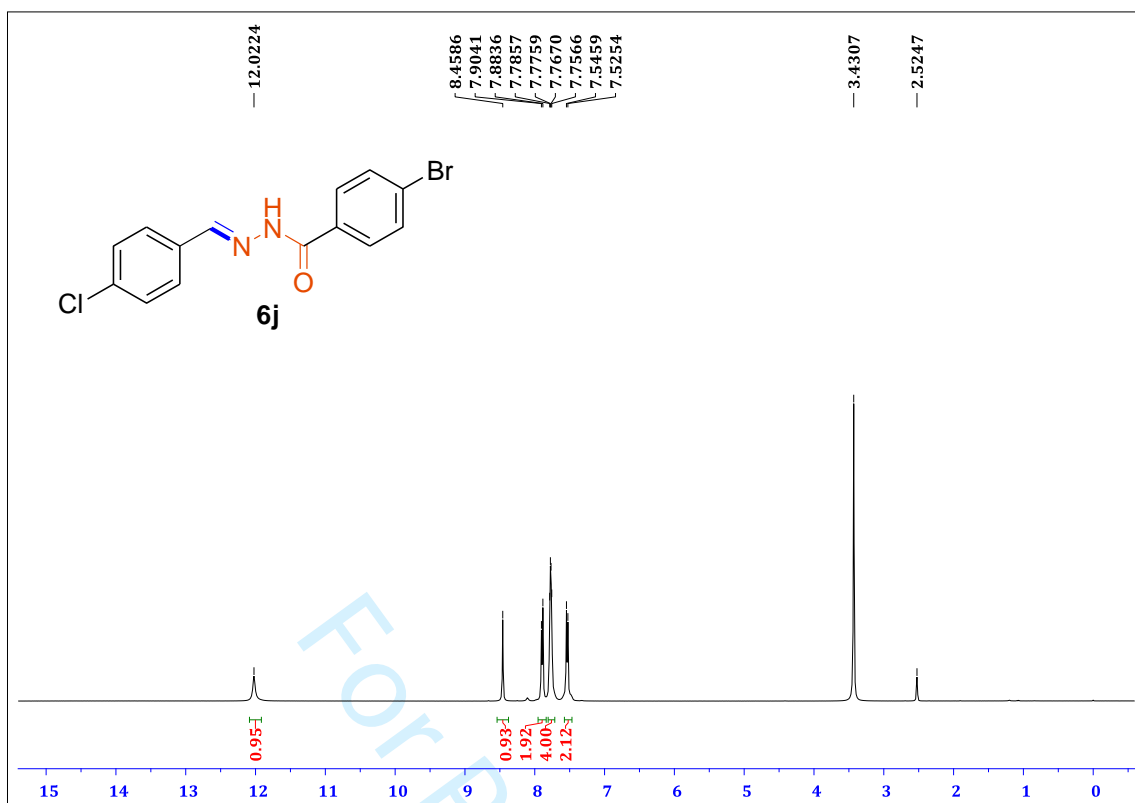
**Figure S52:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6h**



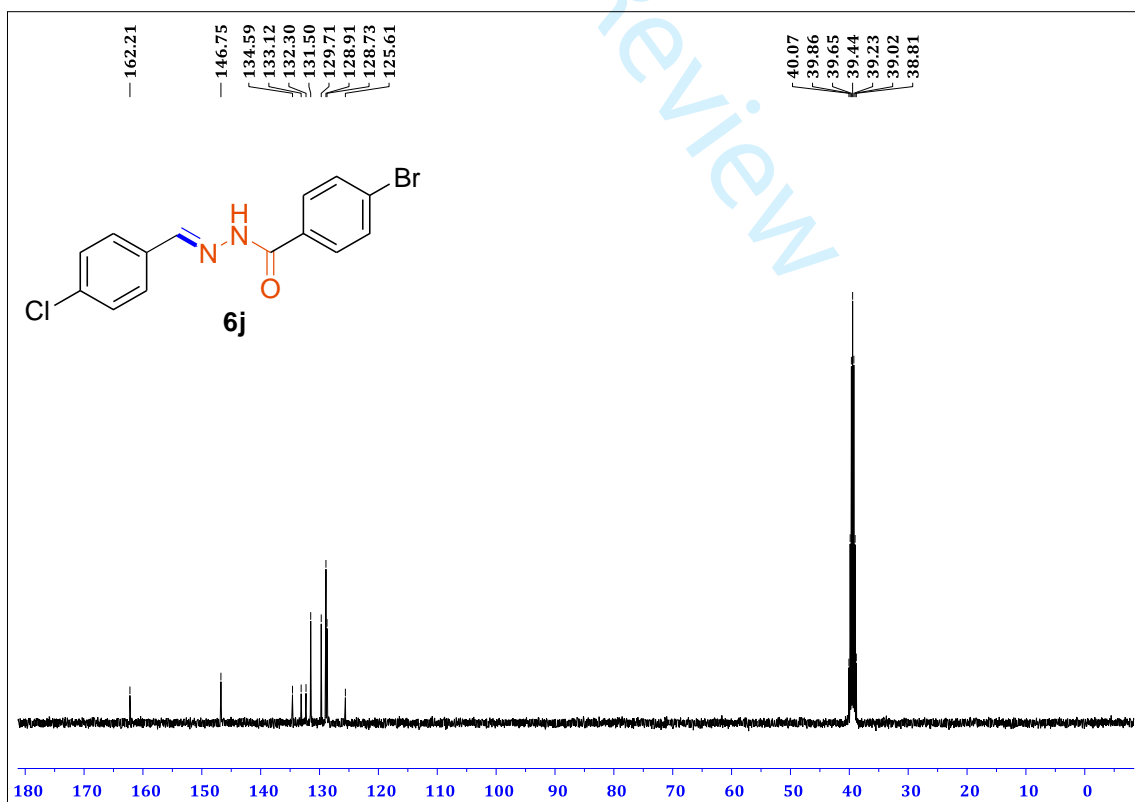
28 **Figure S53:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **6i** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



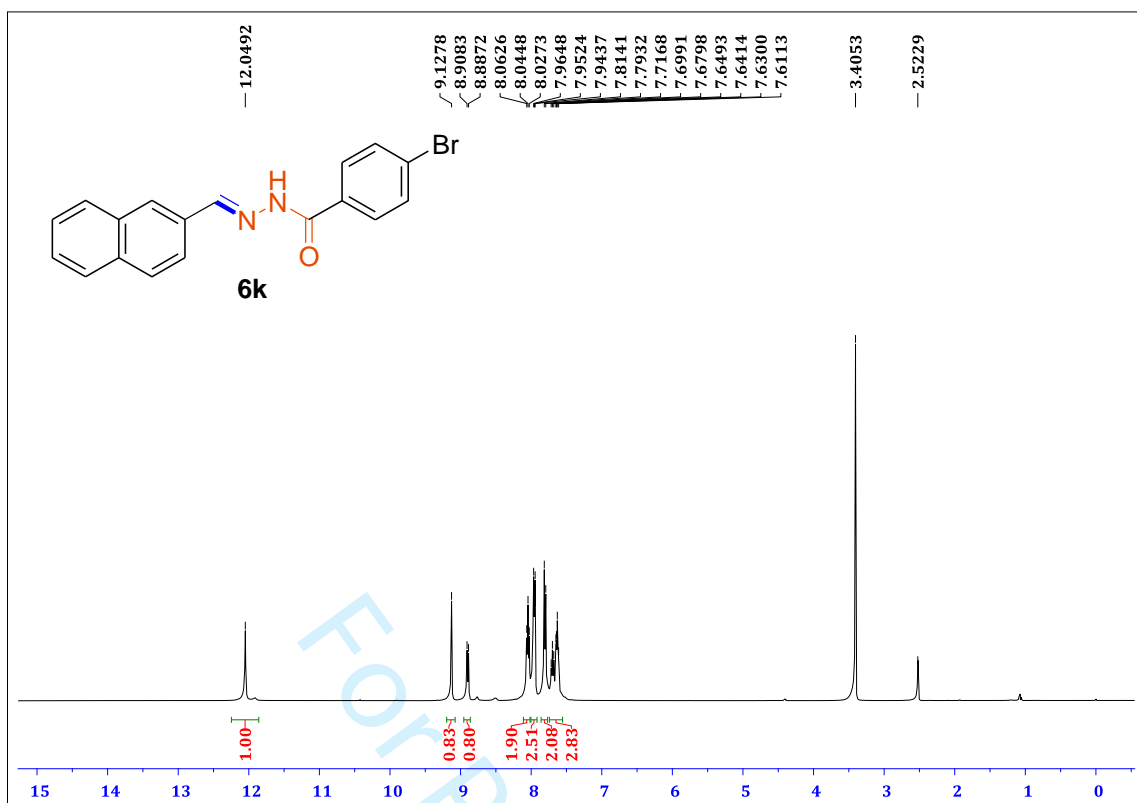
**Figure S54:** <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **6i**



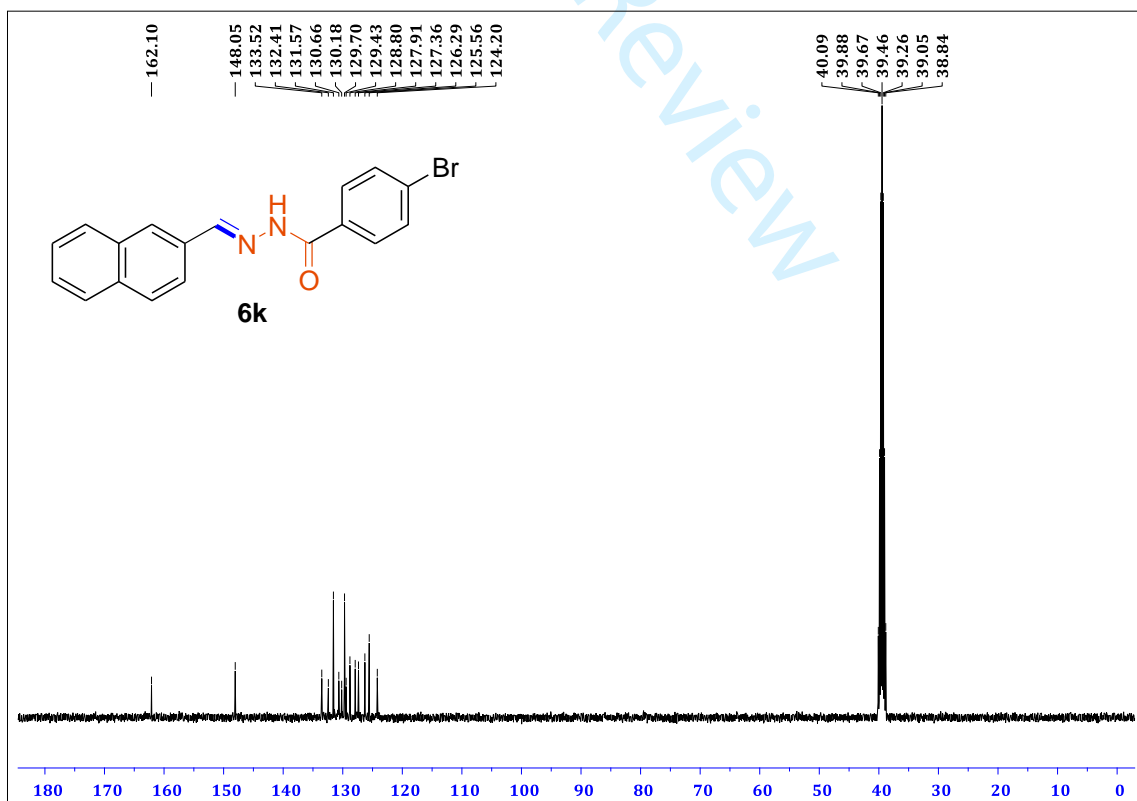
28 **Figure S55:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **6j** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



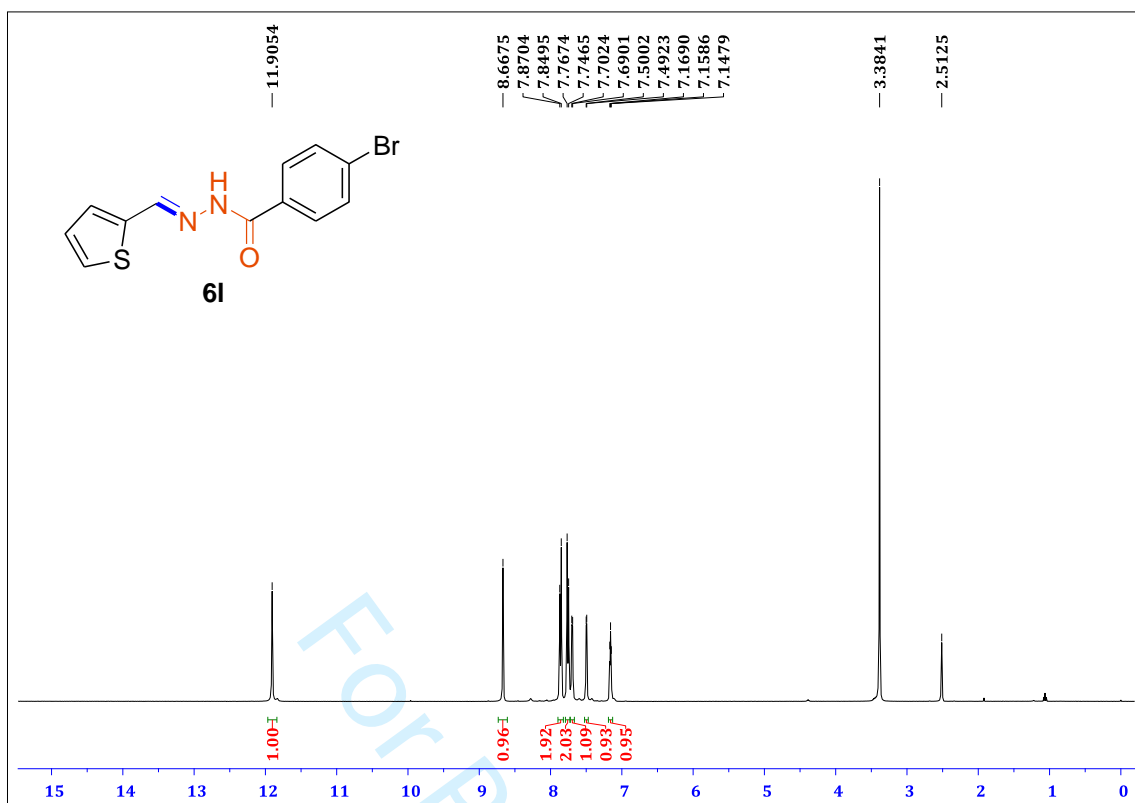
**Figure S56:** <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **6j**



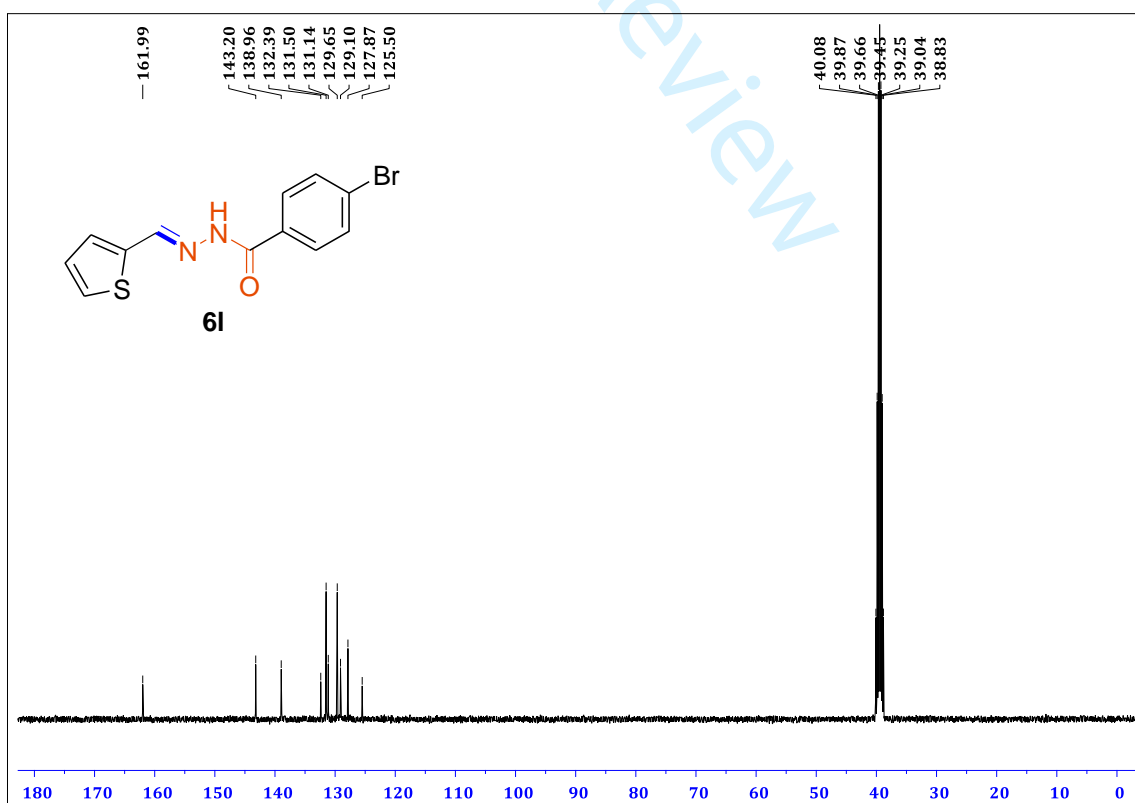
28 **Figure S57:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **6k** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



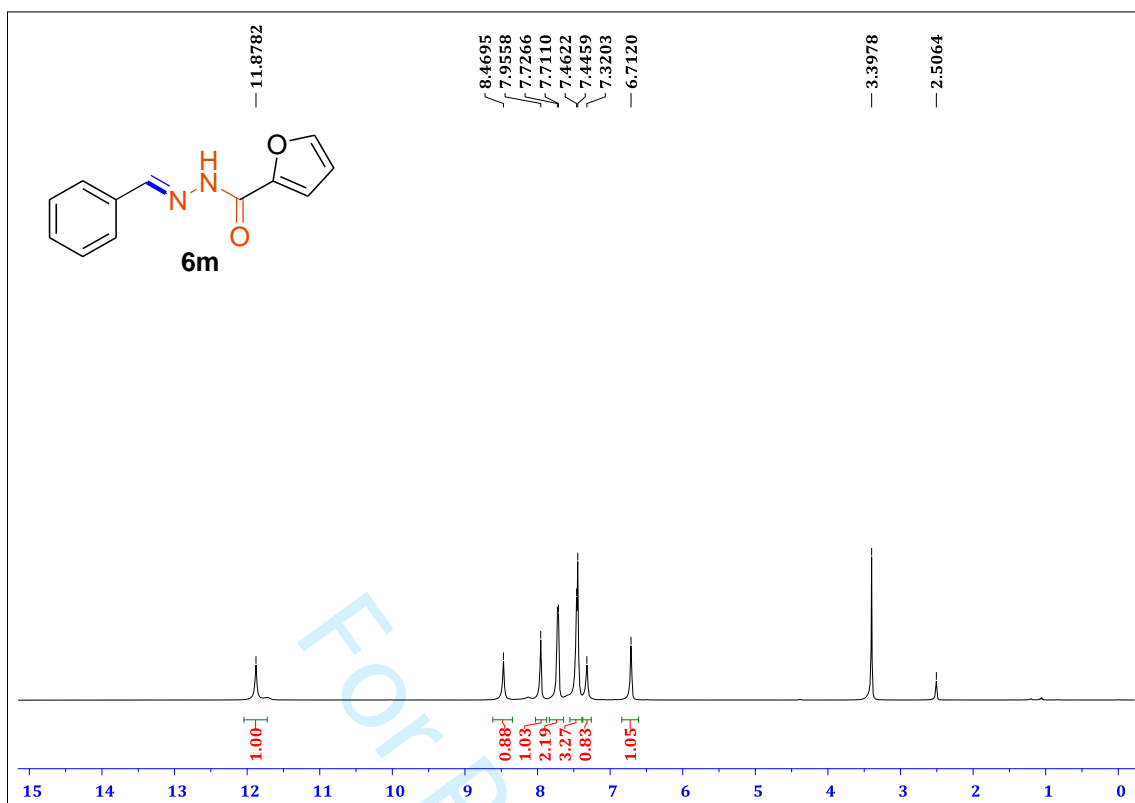
**Figure S58:** <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **6k**



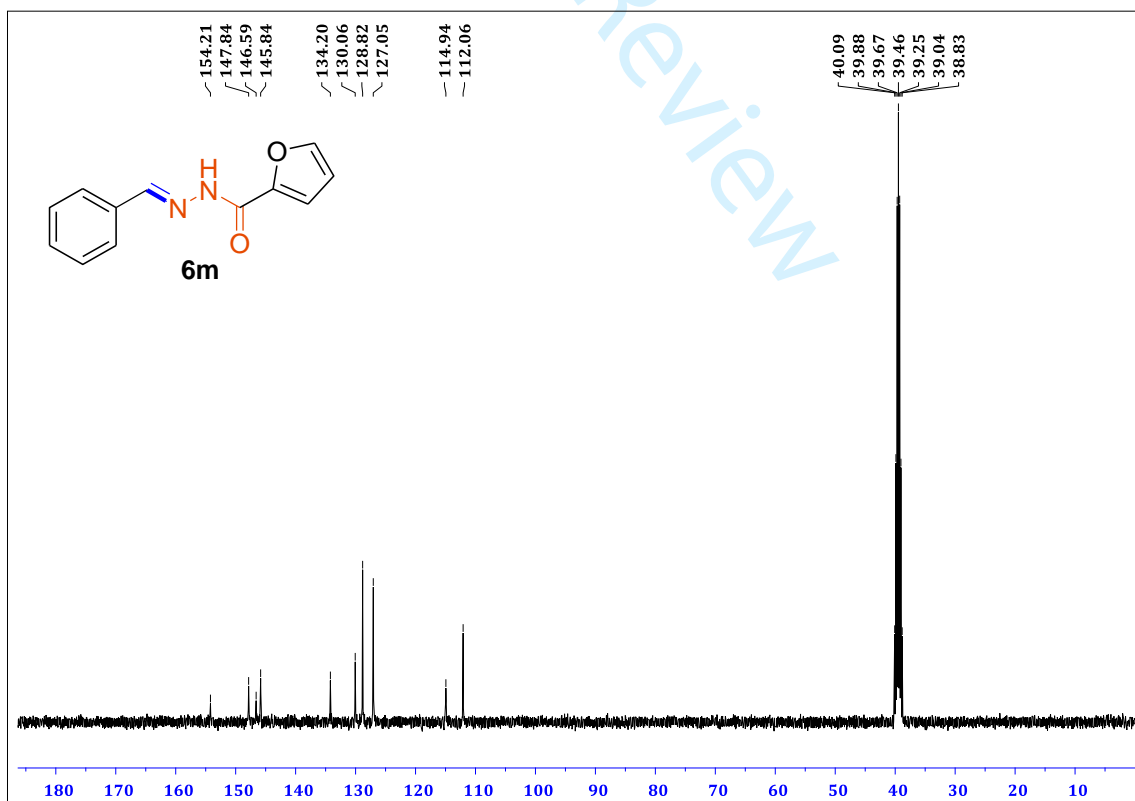
28 **Figure S59:**  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6l** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



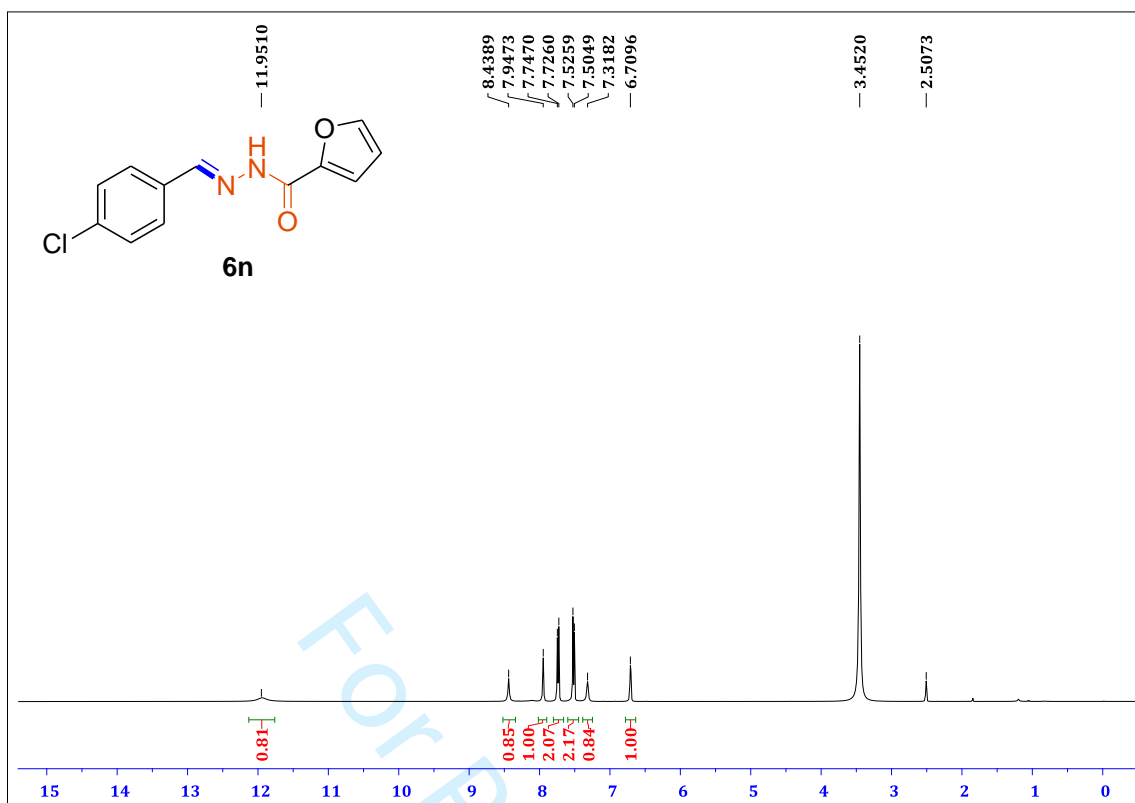
**Figure S60:**  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6l**



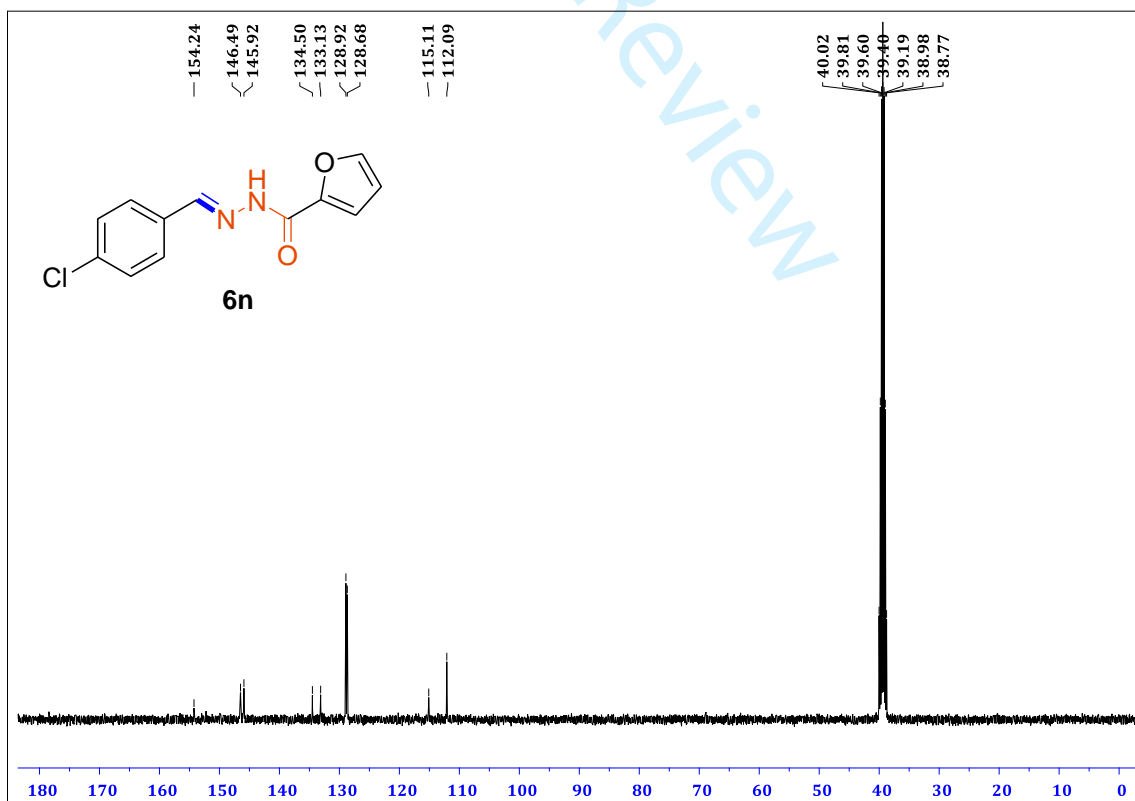
28 **Figure S61:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of **6m** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



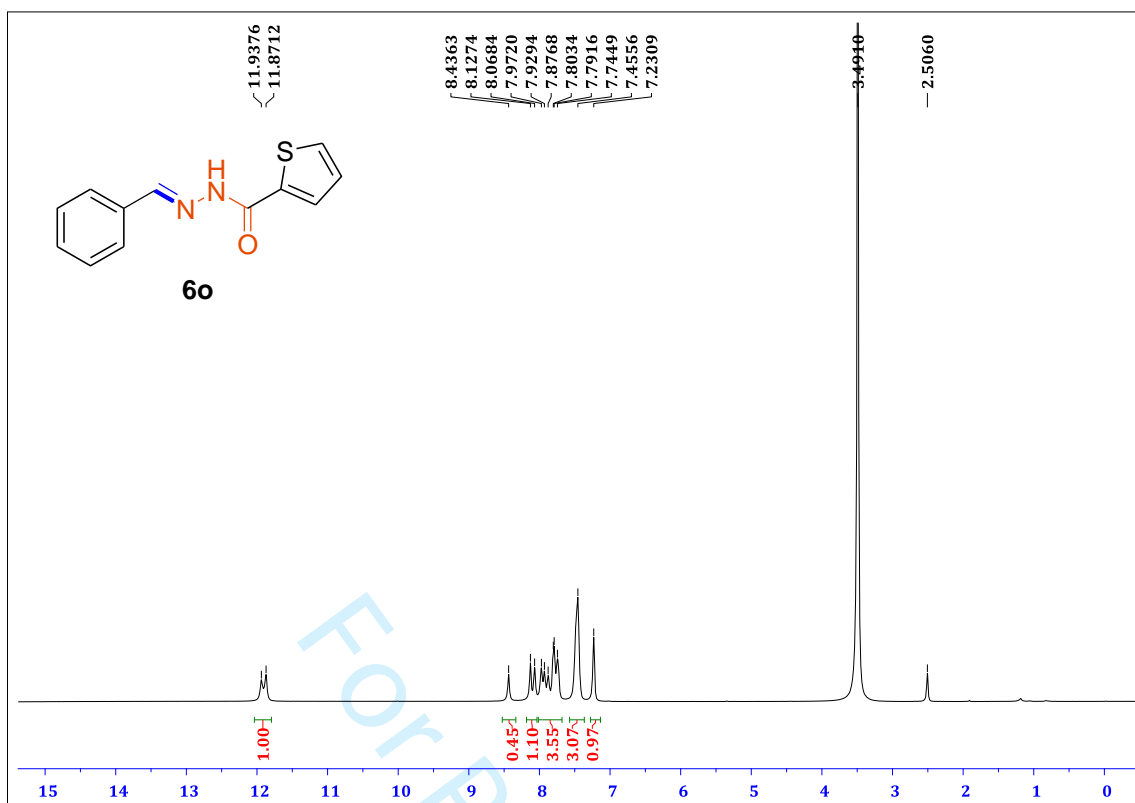
**Figure S62:** <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) spectrum of **6m**



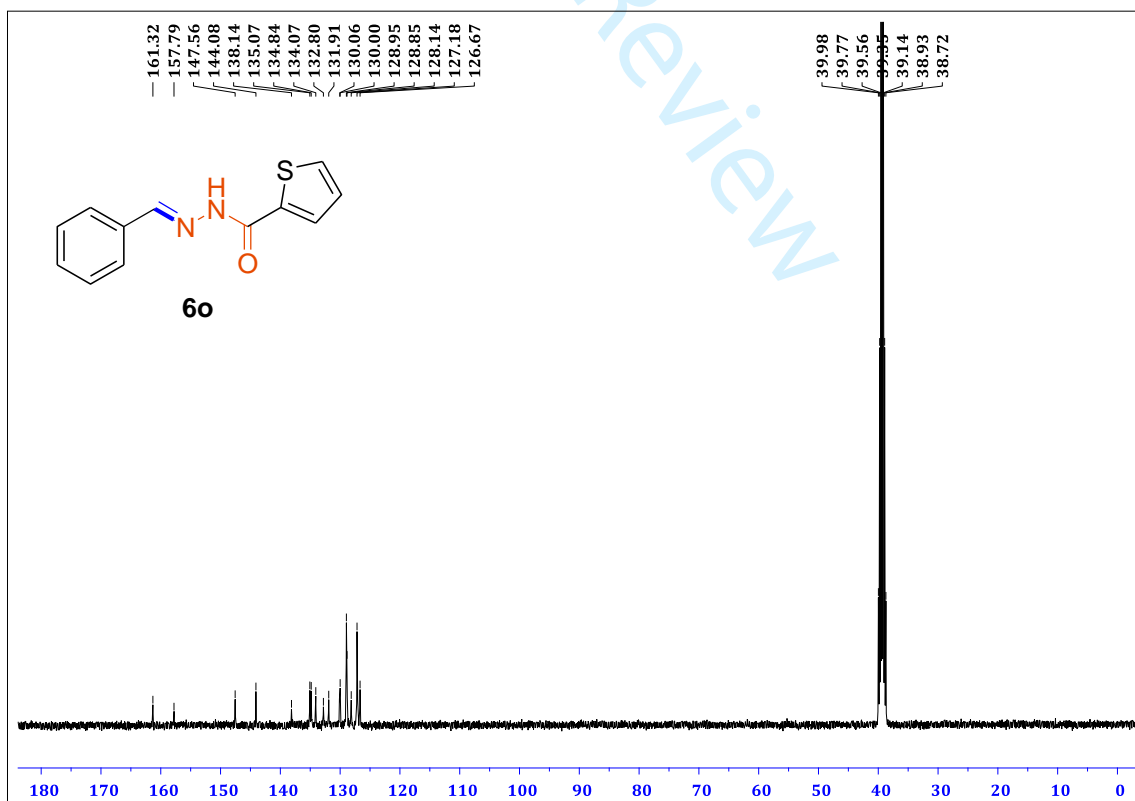
28 **Figure S63:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6n** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)



**Figure S64:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6n**

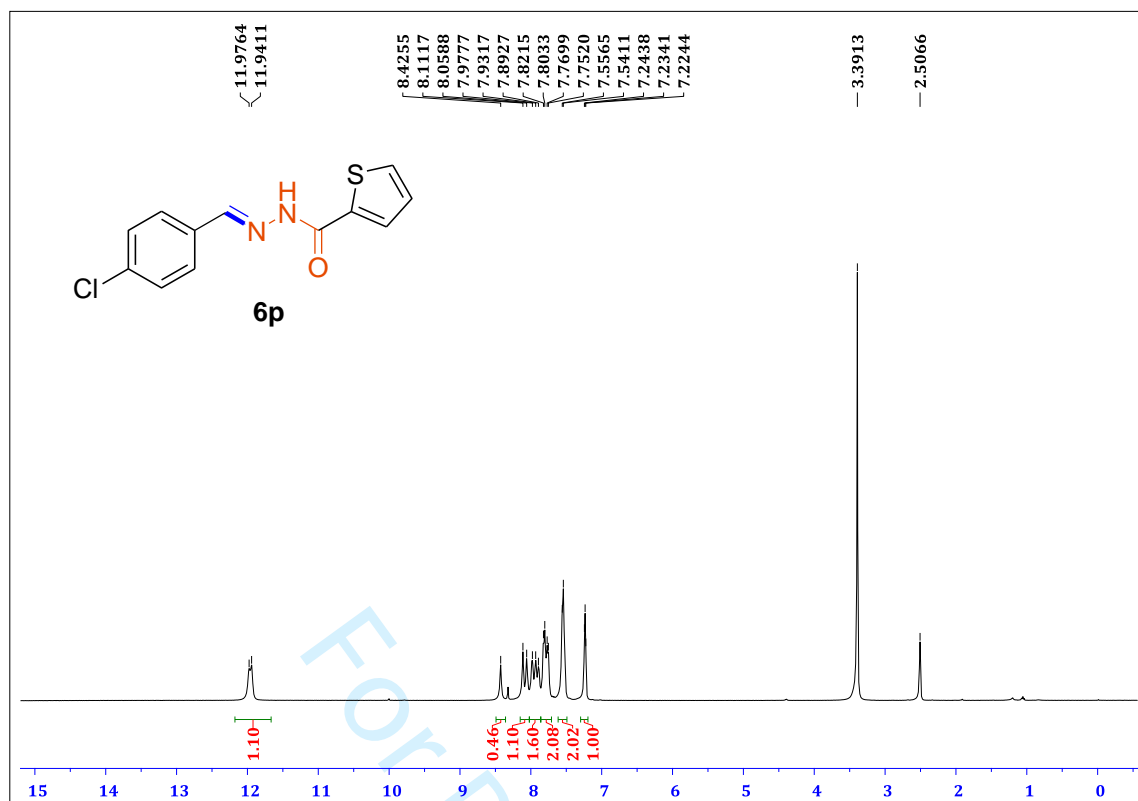


28 **Figure S65:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6o** (peaks at 3.3 and 2.5 ppm are solvent  
29 and water peaks)

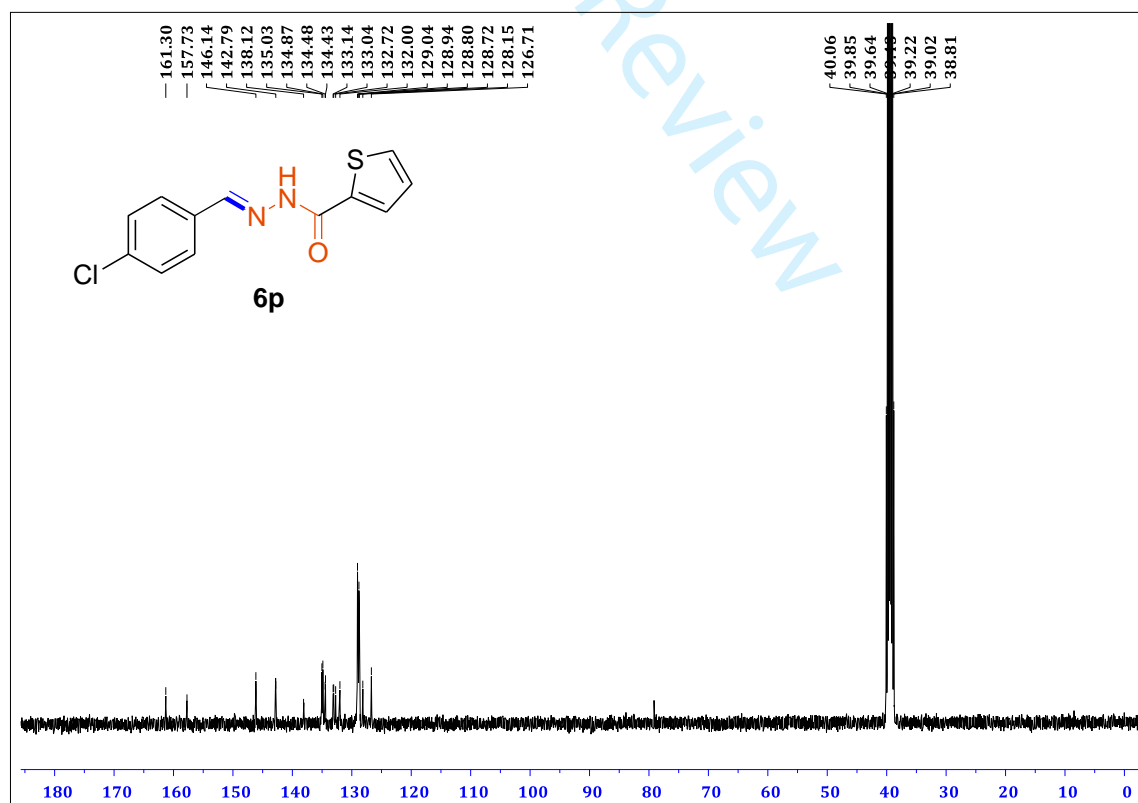


**Figure S66:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6o**





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29 **Figure S67:**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6p** (peaks at 3.3 and 2.5 ppm are solvent  
30 and water peaks)



**Figure S68:**  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ) spectrum of **6p**

#### 4. Experimental confirmation for the hydrogen gas liberation using GC-TCD detector

Under N<sub>2</sub> atmosphere, a mixture of complex **1** (0.5 mol%), *t*-BuOK (0.5 equiv.), 4-methoxybenzyl alcohol (1.0 mmol), and benzyl alcohol (1.0 mmol) was dissolved in 3 mL of toluene, and the mixture was heated at 110°C under N<sub>2</sub> atmosphere for 5 h. Then, the gaseous reaction mixture has been analyzed on GC-TCD detector to witness the liberation of hydrogen gas.

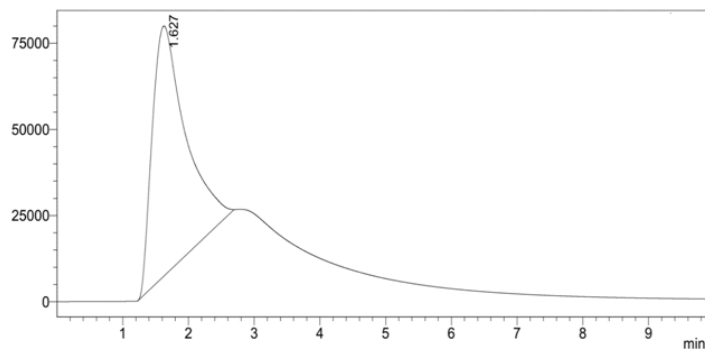


Figure S69. Chromatogram of H<sub>2</sub>

## 5. References

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**Alert level C**

PLAT220_ALERT_2_C	NonSolvent	Resd 1	C	Ueq(max)/Ueq(min) Range	3.2	Ratio
PLAT414_ALERT_2_C	Short Intra	D-H..H-X		H1N	..H5	1.95 Ang.
				x,y,z =	1_555	Check

**Alert level G**

PLAT007_ALERT_5_G	Number of Unrefined Donor-H Atoms	.....				1 Report
PLAT083_ALERT_2_G	SHELXL Second Parameter in WGHT	Unusually Large			11.03	Why ?
PLAT169_ALERT_4_G	The CIF-Embedded .res File Contains	AFIX 1 Recds				1 Report
PLAT171_ALERT_4_G	The CIF-Embedded .res File Contains	EADP Records				1 Report

0 **ALERT level A** = Most likely a serious problem - resolve or explain  
 0 **ALERT level B** = A potentially serious problem, consider carefully  
 2 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight  
 4 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data  
 3 ALERT type 2 Indicator that the structure model may be wrong or deficient  
 0 ALERT type 3 Indicator that the structure quality may be low  
 2 ALERT type 4 Improvement, methodology, query or suggestion  
 1 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special\_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

**Publication of your CIF in IUCr journals**

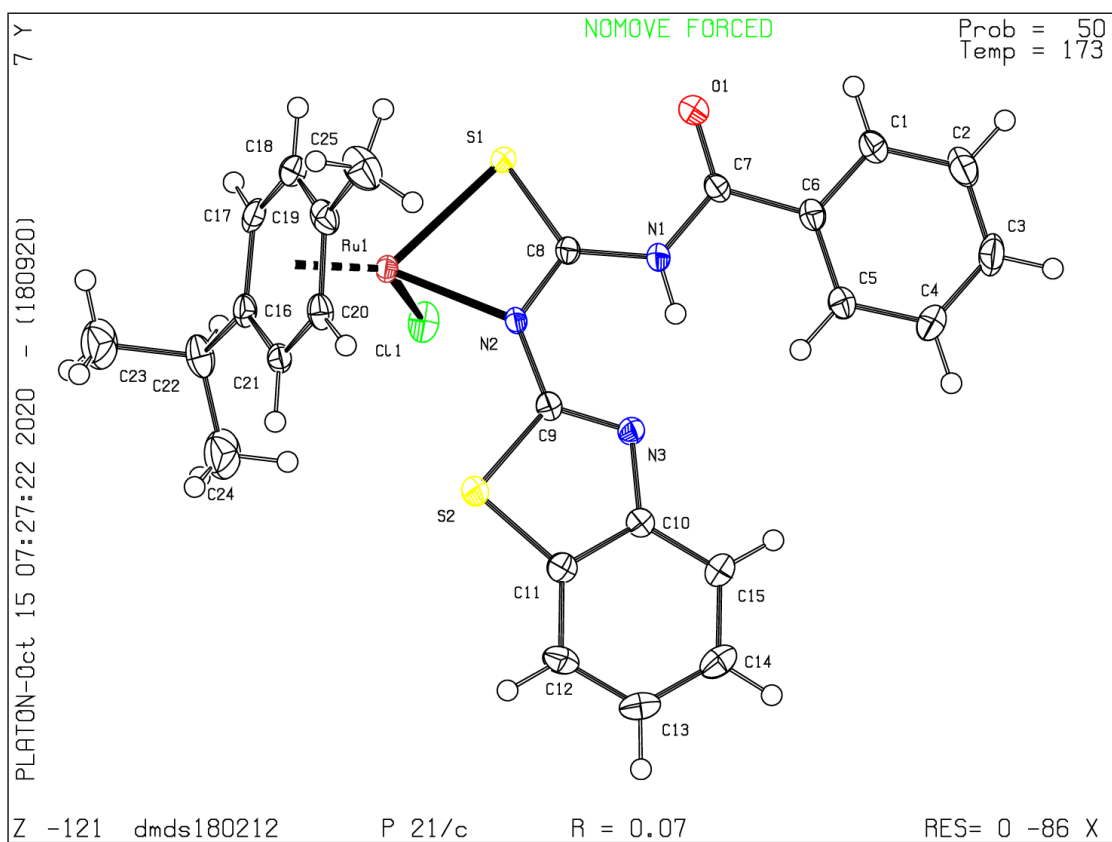
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

**Publication of your CIF in other journals**

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Datablock dmds180212 - ellipsoid plot





**Alert level C**

PLAT416\_ALERT\_2\_C Short Intra D-H..H-D H1N ..H2N . 1.97 Ang.  
 x,y,z = 1\_555 Check

**Alert level G**

PLAT154\_ALERT\_1\_G The s.u.'s on the Cell Angles are Equal ..(Note) 0.001 Degree  
 PLAT398\_ALERT\_2\_G Deviating C-O-C Angle From 120 for O1 106.2 Degree  
 PLAT941\_ALERT\_3\_G Average HKL Measurement Multiplicity ..... 4.0 Low

- 
- 0 **ALERT level A** = Most likely a serious problem - resolve or explain  
 0 **ALERT level B** = A potentially serious problem, consider carefully  
 1 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight  
 3 **ALERT level G** = General information/check it is not something unexpected
- 1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data  
 2 ALERT type 2 Indicator that the structure model may be wrong or deficient  
 1 ALERT type 3 Indicator that the structure quality may be low  
 0 ALERT type 4 Improvement, methodology, query or suggestion  
 0 ALERT type 5 Informative message, check
- 

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special\_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

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