CHAPTER-4

Green and Efficient Iron-Catalysed Synthesis of Polyfunctionalized Benzofuran-4(5H)-one Derivatives via Cross-Dehydrogenative Coupling

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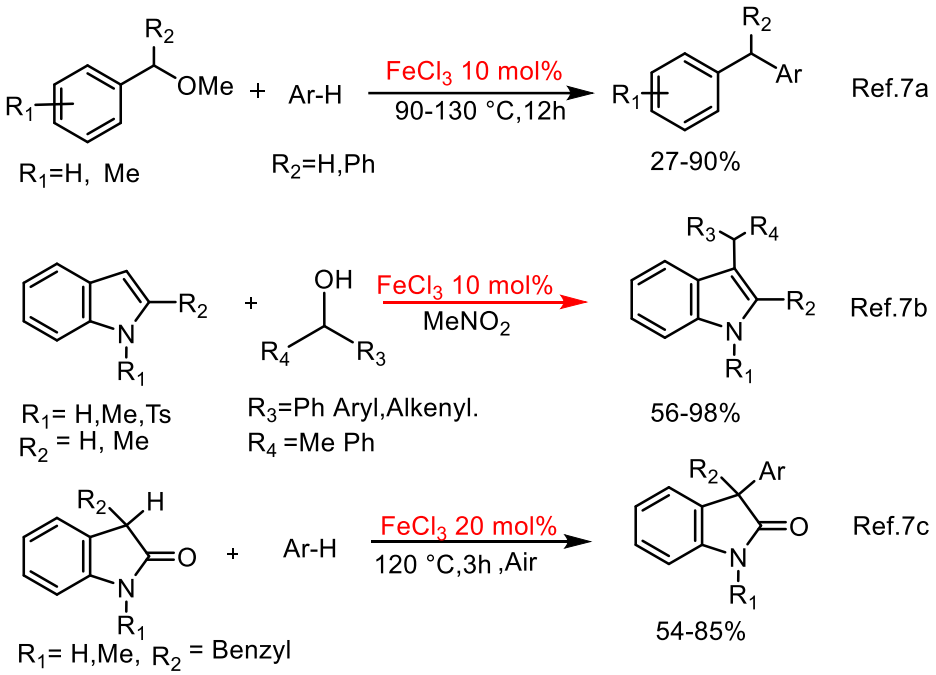
4.1 Introduction

In view of the environmentally concerns, researchers are moving towards synthetic strategies using green aspects [1–3]. According to the principles of green chemistry, a sustainable reaction condition should full fill several standards such as low toxicity, non-flammability, non-volatility and extensive availability of starting materials and catalytic system. Moreover, this greener reaction should be cost effective, easy to handle and recoverable [4]. In this aspect, attempts are being made to instead substitute the expensive and toxic catalyst with materials which are non-hazardous, cost-effective and environmentally benign. Catalyst, one of the most important parts which are overarching principles of green chemistry, and it is capable of producing substantial material and energy, time as well as economic benefits. Catalysis lies at the soul of uncounted chemical process and the chemical properties of the catalyst play a vital role for the chemical reactions [5–7]. Thus, the presence of a catalyst is necessary in the synthesis of organic compounds as well as in the chemical industries. Herein, we report iron catalysed to proceed cross-dehydrogenative coupling reaction between two C(sp3)-H bonds to form C-C double bonds. $FeCl_3$ is a very important catalyst for the formation of C-C coupling in various organic syntheses, which is described in the following **scheme 4.1 (a-c)**.



Scheme 4.1 Few $FeCl_3$ catalysed reactions in organic synthesis **(a-c)**.

Iron is the second most abundant metal which found in the Earth's crust. Iron salts are cheap and very low toxic in comparison other metal salts and which have also unified into biological systems. Low toxicity of iron salts played an important role as a catalyst in food and drugs industry [8], Due to these advantages iron salts highly attractive catalysts in chemical reactions [9-10]. Air is easily available and it use as a substitute of chemical oxidants is considered to be an ideal oxidation process due to its eco-friendly nature and economical profits [11–14]. Thus, the synthesis of novel series of benzofuran derivatives which have many biological significances of this well-designed moiety and their derivatives have made them conspicuous targets in research over many years [15–18]. Benzofuran ring systems are common structural units in many bioactive compounds which display numerous biological

and chemical activities such as antibacterial [19], antifungal [20-21] anti-inflammatory, [22-23], antioxidative [24], antiviral [25], antineoplastic [26], anthelminthic, anticoagulant, insecticide, hypnotic, and HIV protease inhibition properties [27]. These compounds play an important role in the metabolism of all living cells.

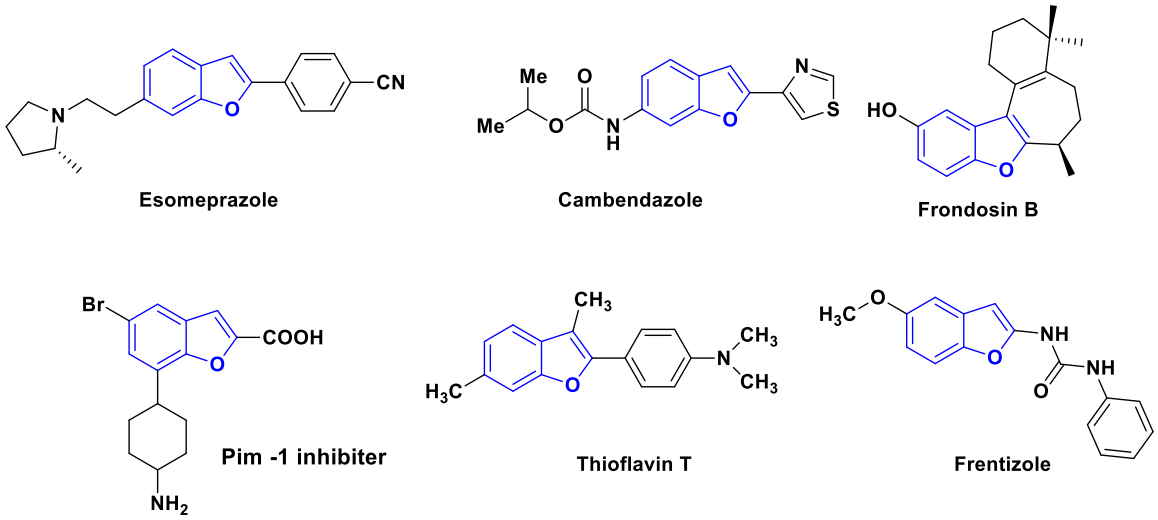
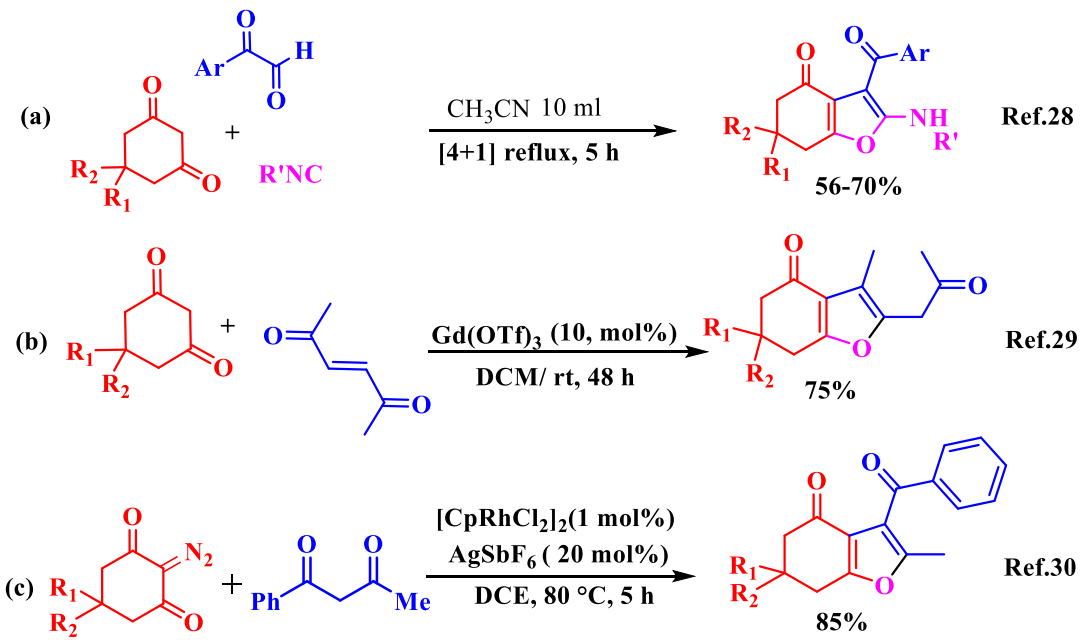


Figure 4.1 Some pharmacologically active benzimidazole and benzothiazole compounds

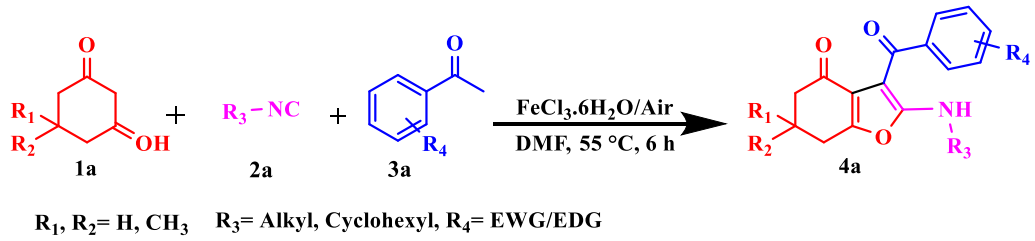
Several distinctive synthetic methods have been reported for achieving 6,7-dihydrobenzofuran-4(5H)-ones due to their wide range of applications in organic chemistry as intermediates and ligands for the asymmetric catalysis. Many methodologies for synthesizing these compounds have been developed [28-30], most of them involved arene diazonium salts [31], arylhydrazones [32], arylhydrazines [33], and nitriles [34], as well as aryl phenylallylidene hydrazone as the starting materials [35]. However, these synthetic procedures suffered from limitations involving poor yields, multiple steps, or metal catalysts.

These undesirable conditions encouraged us to develop a new methodology for their syntheses. Hence, it is very necessary to develop more convenient and eco-friendly protocol for the construction of biologically potent heterocycles. In this methodology, three-component initial substances are employed to improve the production of multi-functionalized 6,7-dihydrobenzofuran-4(5H)-ones and their analogues. The utilization of iron salts in conjunction with air and DMF as the solvent in this procedure leads to effective outcomes in a brief time frame. A comparison of the previous and present methodologies is illustrated in **Scheme 4.2**.

4.1A Previous approaches



4.1B Present approach

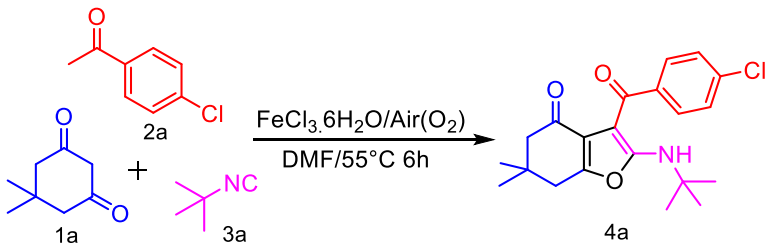


Scheme 4.2 An illustration of the previous (4.2 A) and present (4.2 B) approaches for the synthesis of 6,7-dihydrobenzofuran-4(5H)-one's derivatives.

4.2 Results and discussion

4.2.1 Optimization of Reaction Conditions

We have designed an improved, assisted synthesis of clean and efficient one-pot synthesis of 6,7-dihydrobenzofuran-4(5H)-ones. To investigate the feasibility of our envisioned protocol, we commenced our analysis with dimedone 1a (1.0mmol), 4'chloroacetophenone 2a (1.0 mmol) and tertiary butyl isocyanide 3a (1.0 mmol) using iron salt as a catalyst in the presence air and DMF as promoting medium. As model substrates which is documented herein (**Scheme 4.3**). Various reaction parameters were optimized like solvent, amount of catalyst, reaction temperature on the model reaction.

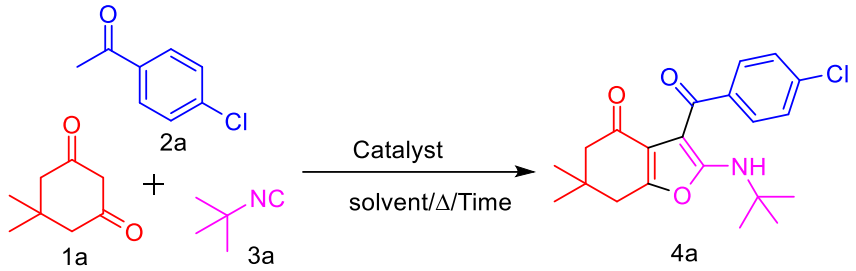


Scheme 4.3. Model reaction for the synthesis of benzofuran-4(5H)-ones.

At the outset, the optimization experiments were carried out with the model reaction at room temperature by stirring in different polar and non-polar solvents and the progress of the reaction was monitored by TLC. Polar solvents (H_2O, EtOH) gave negligible amount of product even after 6 h stirring at room temperature (**Table 4.1, entry 1 and 2**). However non-polar solvents like xylene and toluene give trace amount of product even after 6 h stirring at 40 °C (**Table 4.1, entry 3 and 4)** for better yield we optimization in the presence of polar

aprotic solvent such as chloroform, acetonitrile and 1,4-dioxane gave the product (**4a**) but the yield was low to good yield (25-60%) (**Table 4.1, entries 5-7**). However polar aprotic solvents like THF and DMSO also gave desired product in better yield (70-92%) (**Table 4.1, entries 8-9).** In order to improve the yield of the product an attempt was made under in the presence of DMF surprise it gave 92% yield of product in shorter reaction time 6 h (**Table 4.1, entry 10**). Both solvents DMF and DMSO are good aprotic solvents. DMF is better than DMSO in the present methods due to DMF is more nucleophilic than DMSO which increase the rate of reaction. However, DMSO is more polar than DMF, but some are based on our reaction condition. In that case, we prefer DMF rather than DMSO. One other advantageous property is that DMF is very easily removed at the end of the reaction due to the low boiling point. After the optimization of solvent, we investigate next parameter such as catalyst system. When the reaction was carried out in the presence of Eosin Y **(Table 4.1, Entry 11)**, and Eosin Y into visible light **(Table 4.1, Entry 12)** there is no yields of the product was obtained in a longer reaction time. Further in the presence of $InCl_3$ then it was trace of the reaction and no yield was observed (**Table 4.1, Entry 13).** $FeBr_3$/ Air (O2) **(Table 4.1, entry 14)** provided a better yield of products. To our delight a noticeable improvement in the yields of the product was observed when the reaction proceeds in the presence of $FeCl_3.6H_2O$ in air and DMF as reaction medium. Finally, we observed that $FeCl_3.6H_2O$ was the most effective promoter for the formation of the corresponding product in terms of both the reaction time and yield **(Table 4.1, entry 15-17)**.

Table 4.1. Optimization of catalyst system for the synthesis of compound 4a[a].



S. No	Solvent	Catalyst system	Temperature (°C)	Time (h)	Yield [%] [b]
1	H_2O	$FeCl_3.6H_2O/Air(O_2)$	rt	6	NA
2	EtOH	$FeCl_3.6H_2O/Air(O_2)$	rt	6	NA
3	Xylene	$FeCl_3.6H_2O/Air(O_2)$	40	6	Trace
4	Toluene	$FeCl_3.6H_2O/Air(O_2)$	50	6	Trace
5	$CHCl_3$	$FeCl_3.6H_2O/Air(O_2)$	55	6	25
6	CH_3CN	$FeCl_3.6H_2O/Air(O_2)$	55	6	40
7	1, 4 Dioxane	$FeCl_3.6H_2O/Air(O_2)$	55	6	60
8	THF	$FeCl_3.6H_2O/Air(O_2)$	55	6	70
9	DMSO	$FeCl_3.6H_2O/Air(O_2)$	55	6	85
10	DMF	$FeCl_3.6H_2O/Air(O_2)$	55	6	92
11	DMF	Eosin Y/Air	55	6	NR
12	DMF	Eosin Y/Visible	55	6	Trace
13	DMF	$InCl_3$	55	6	Trace

14	DMF	$FeBr_3$/Air (O2)	55	6	82
15	DMF	Fe $(NO_3)_3.9H_2O$	55	6	68
16	DMF	$FeCl_3.6H_2O$/Air(O_2)	55	10	92
17	DMF	$FeCl_3.6H_2O$/Air(O_2)	55	10	92
[a]**Reaction conditions:** dimedone 1a (1.0 mmol), 4'-Chloroacetophenone 2a (1.0 mmol) and tertiary butyl isocyanide 3a (1.0 mmol). [b]Yields of isolated pure product.					

Next, the model reaction was investigated the amount of catalyst to make the synthesis cost effective, several attempts has also been made to scale down the amount of iron salt and found that the use of 10 mole % of $FeCl_3.6H_2O$ was sufficient for better yield of product for this reaction **(Table 4.2, Entry 2).**

Table 4.2. Study of the effect of catalyst amount for the synthesis of compound 4a[a]

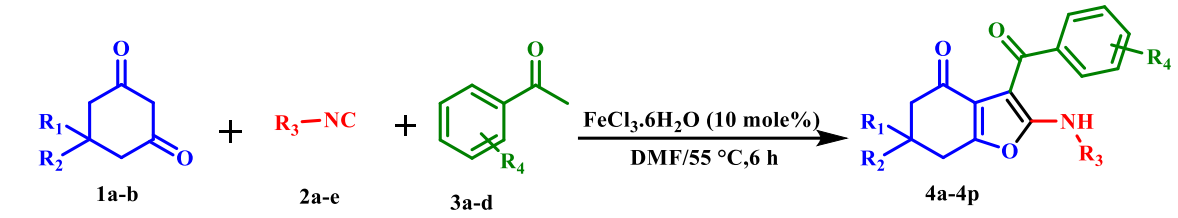
Entry	**Mole% of catalyst system**	**Yield (%)[b]**
1.	$FeCl_3.6H_2O$ (05 mole %)	78
2.	$FeCl_3.6H_2O$ (10 mole %)	92
3.	FeCl3.6H2O (15 mole %)	92
[a]**Reaction conditions:** dimedone1a (1.0 mmol), 4'-chloroacetophenone 2a (1.0 mmol) and tertiary butyl isocyanide 3a (1.0 mmol). [b]Yields of isolated pure product**.**		

4.2.2 Substrates scope for benzofuran-4(5H)–ones.

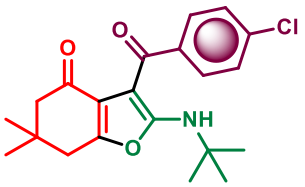
After optimization of reaction condition, we next investigate substrate scopes for the synthesis of benzofuran-4(5H)-one's derivatives. There are total of sixteen derivatives of

benzofuran-4(5H)–ones 4a–4p were synthesized in good yields. Several acetophenone derivatives (2a–e) (contain electron donating and electron withdrawing substitute) with dimedone derivatives (1a and 1b) and isocyanide derivatives were studied under optimized reaction conditions. Results were summarized in **Table 4.3**.

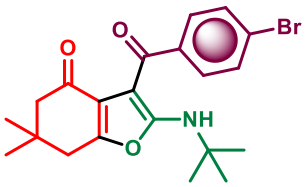
Table 4.3 Synthesis of benzofuran-4(5H)–ones **4a–4p**[a, b].



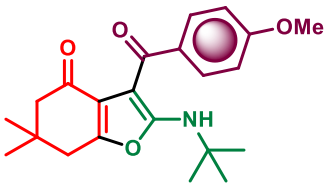
R_1, R_2= H, CH_3 R_3= Alkyl, Cyclohexyl, R_4= EWG/EDG



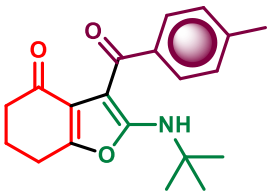
4a; 92%



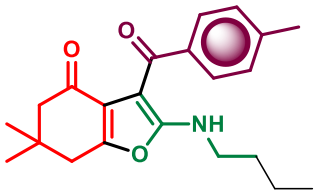
4b; 90%



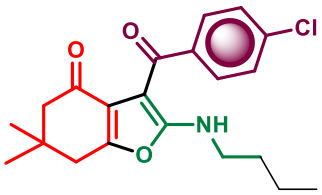
4c; 90%



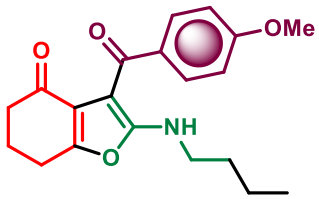
4d; 88%



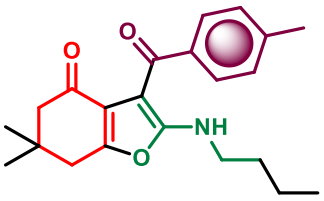
4e; 85%



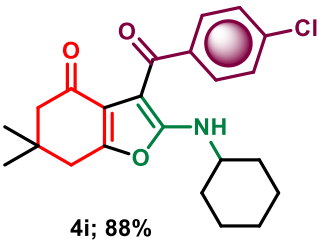
4f; 91%



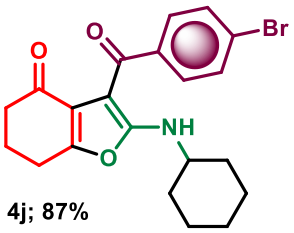
4g; 86%



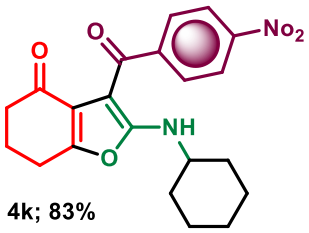
4h; 85%



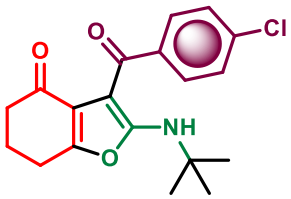
4i; 88%



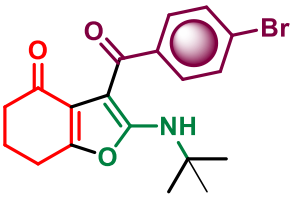
4j; 87%



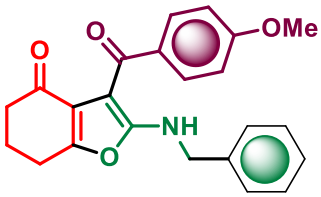
4k; 83%



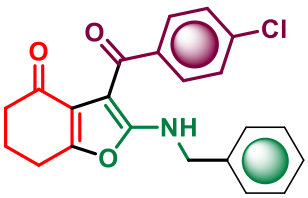
4l; 91%



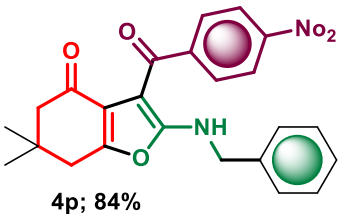
4m; 90%



4n; 89%



4o; 89%



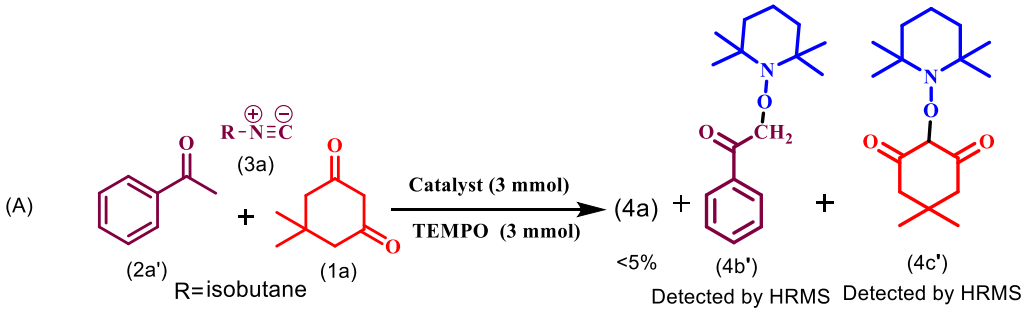
4p; 84%

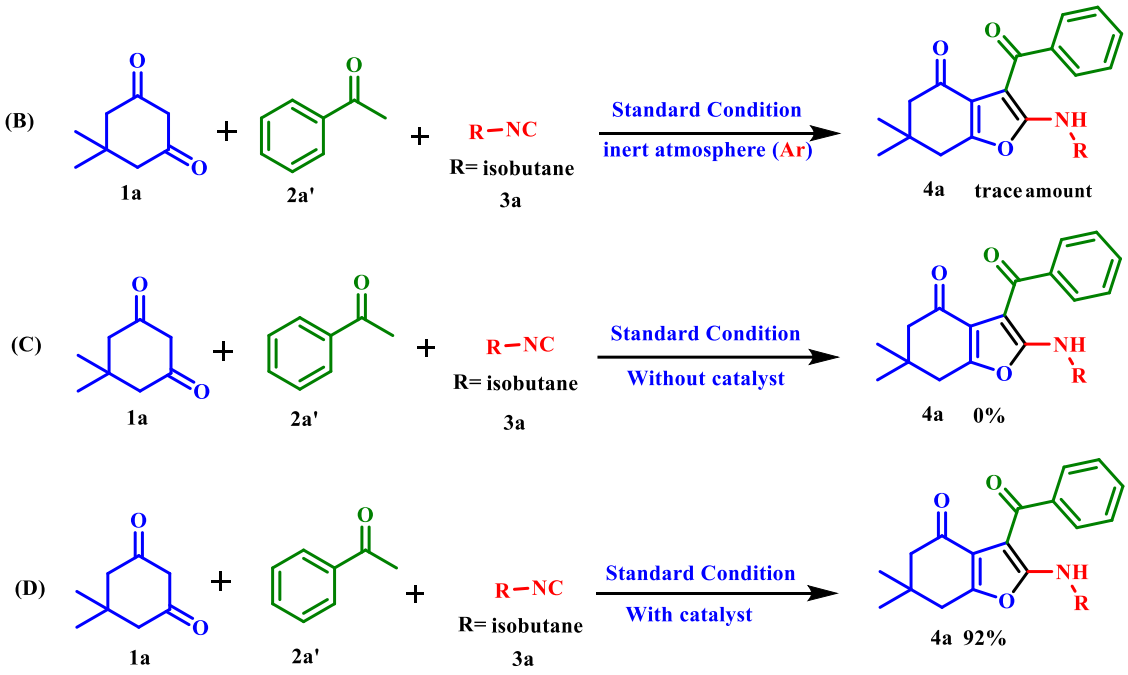
[a]**Reaction condition**: dimedone1a–b (1.0 mmol), acetophenone derivatives 2a–e (1.0 mmol) and isocyanide3a–d (1.0 mmol). Catalysed by $FeCl_3.6H_2O$ in presence of air and DMF as reaction medium at 55°C. [b]Isolated yield of product.

4.2.3 Mechanistic Study and Controlled experiments

In order to establish the reaction mechanism, a controlled experiment was performed with radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl **(Scheme 4.4.A)** under the same optimized reaction conditions with **3** mmol of TEMPO, less than **5%** of the desired

product **(4a)** was obtained. This observation shows that the reaction proceedsthrough radical pathway which is confirmed by the HRMS spectra. Next control reaction was performed between dimedone **1a (1.0 mmol),** acetophenone **2a' (1.0 mmol)** and tertiary butyl isocyanide **3a (1.0 mmol),** The reaction was conducted under an argon atmosphere, resulting in only a trace amount of **4a** was obtained (**Scheme 4.4.B**). This result signifies the importance of air (molecular oxygen). Air can be considering as diluted oxygen, thus help the oxidation of Fe(II) to Fe(III) [**36**]. On the other hand next control reaction was performed without catalyst which failed to give the product (**Scheme 4.4.C**). This indicates that dimedone is not converted into dimedone radical intermediate without iron salt as a catalyst in the presence air and DMF as promoting medium. when the same reaction was carried out in the presence of iron salt as a catalyst to give desired product was obtained in 92% yield (**Scheme 4.4, D**). These results indicate that catalyst to take part not only in the oxidation of acetophenone to alpha β unsaturated carbonyl compound through Michale addition reaction.



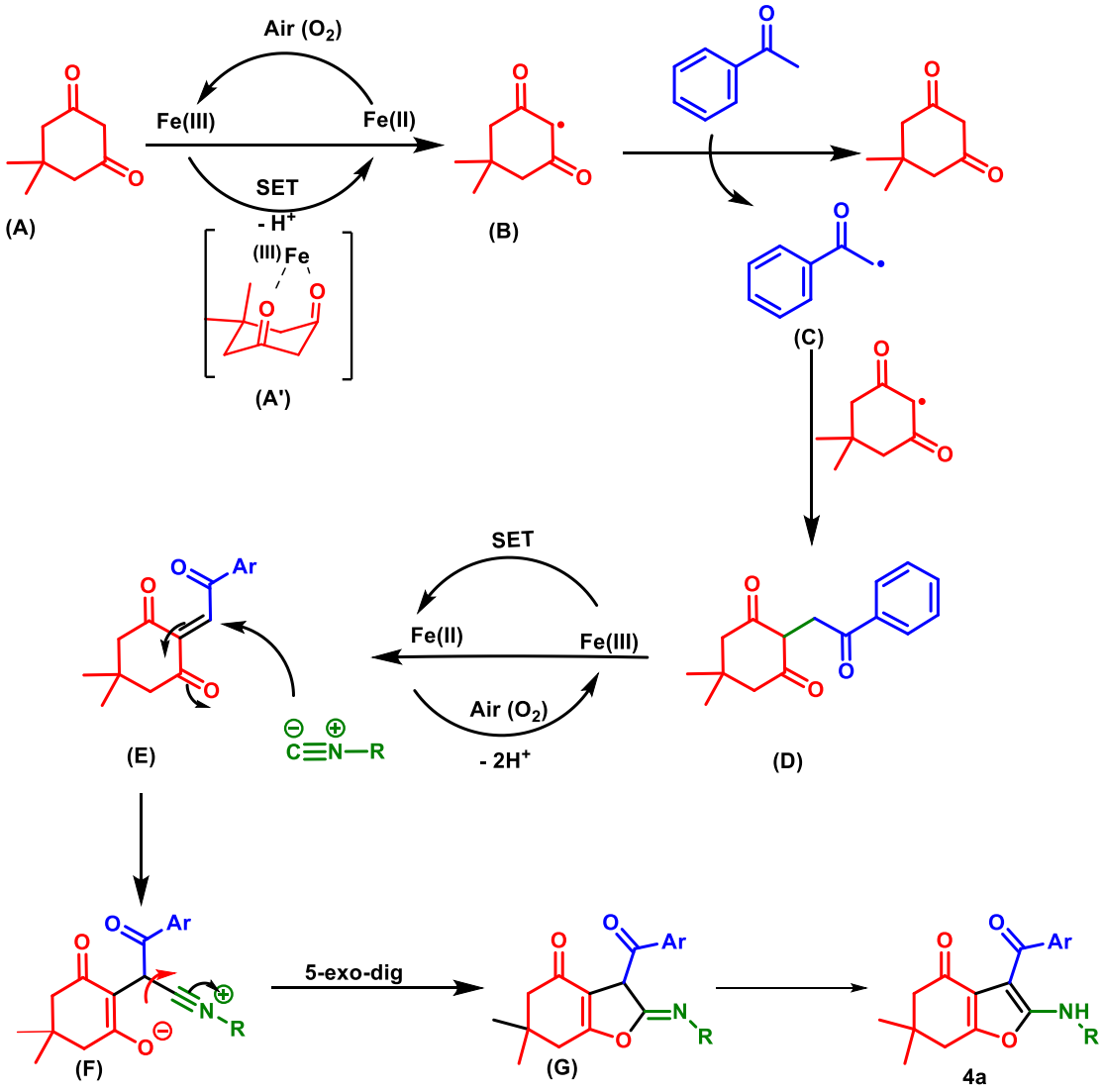


Scheme 4.4 Control experiment for mechanistic investigation.

4.2.4. Plausible Reaction Mechanism

On the basis of above control experiment and previous reports [**8, 37-38**], a plausible mechanism was proposed, as shown in (**scheme 4.4**). In the presence of air with Fe(III) the *sp*3 carbon of dimedone converted into carbon radical of dimedone (B) *via* SET (single electron transfer) reaction and removal of H^+ while at the same time Fe(II) is formed[**38**]. In this step, the substrate (A) act as auxiliary ligand with Fe(III) to a chelate Fe complex (**A'**) which may play a key role in the oxidation step (A) to (B). Dimedone radical (B) abstract hydrogen from acetophenone to form acetophenone radical (C). Then acetophenone radical (C) coupled with dimedone radical (B) to form an intermediate (D) [**8**] and finally, (D) was oxidized to provide the product (E) [**8**] *via* two single electron transfers (SET) and loss of

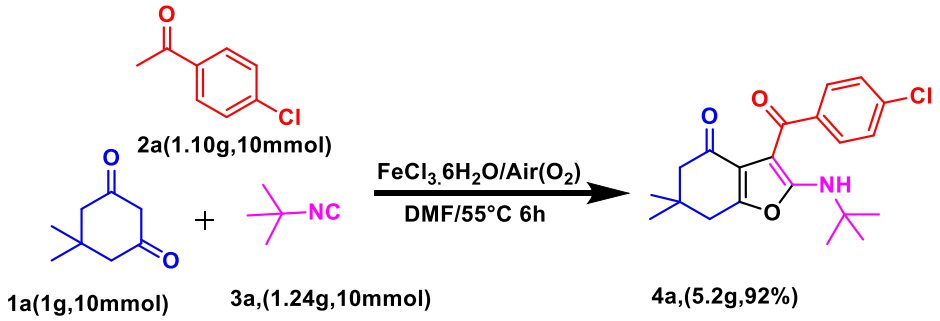
two H^+ [**36-37**]. (E) molecule act as Michael accepter and isocyanide nucleophile attack on conjugate position then oxygen nucleophile undergoes 5-exo-dig cyclization reaction (F-G) to give the product **4a**.



Scheme 4.5. Plausible mechanism for the synthesis of Benzofuran-4(5H)-one's derivatives 4a.

4.3 Gram-scale synthesis of Benzofuran-4(5H)-one's derivatives.

To establish the potential synthetic application of this methodology the synthesis of Benzofuran-4(5H)-one's (**4a**) was carried out on gram scale with dimedone (**1a**) (1.10 g, 10 mmol), 4'-chloroacetophenone (**2a**) (1.20 g, 10 mmol) and tertiary butyl isocyanide **(3a) (1.24** g,10 mmol) using of iron salt (5mg,10 mmol) under optimized reaction conditions it gave desired products (**4a**) in 92% yield (5.2 g). at **55** °C using iron salt as a catalyst in the presence air and DMF as promoting medium. As model substrates which is documented herein (**Scheme 4.6)**.



Scheme 4.6 Gram-scale synthesis of Benzofuran-4(5H)-one's.

4. 4 Experimental Section

4.4.1 Materials and methods

All chemical were purchased from Aldrich and Alfa Assar and were used without purification. IR spectra were recorded on a Perkin Elmer spectrum RX-IFTIR spectrometer. NMR spectra were recorded on a BRUKER AVANCE II-400 FT spectrometer (400 for ^{1}HNMR,) using DMSO as solvent and TMS as an internal reference. Mass spectra were

recorded on a JEOL SX-102 (FAB) mass spectrometer at 70 eV. Elemental analyses were carried out in a coleman automatic carbon, hydrogen and nitrogen analyzer. All the reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254). Melting points were determined by open glass capillary method and were uncorrected.

4.4.2 Typical Procedure for the Synthesis of Benzofuran-4(5H)-one's derivatives. (4a-4o) Preparation of Compound 4a Typically, 5,5-dimethylcyclohexane-1,3-dione (1.0 mmol) and 4'- Chloroacetophenone (1.0 mmol) were stirred in a 50-ml round bottom flask at 55 ^{o}C using $FeCl_3.6H_2O$ (10 mmol) as a catalyst in DMF. After four-hour tertiary butyl isocyanide (1.0 mmol) were then successively added. Subsequently, the reaction was completed in next two hour. The reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. The crude products were purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluentThe ^{1}H NMR and ^{13}C NMR of the Benzofuran-4(5H)-one's derivatives were compared with literature reports.

4.5. Analytical data

2-(tert-Butylamino)-3-(4-chlorobenzoyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (4a) Yellow solid, mp: 131– 132^{o}C **IR** (KBr, v, cm^{-1}): 2968, 2875, 1671, 1630, 1541, 1365, 1278, 1234, 1022, 966, 840, 754**. ^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.83(s, 1H, NH), 7.46 (d, J = 7.6 Hz, 2H, ArH), 7.30(d, J =7.6 Hz, 2H, ArH), 2.71 (s, 2H, CH_2), 2.34 (s, 2H, CH_2), 1.47 (s, 9H, CH_3), 1.10 (s,6H, CH_3).**^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 190.3,

186.8, 165.6, 156.8, 140.5, 135.5, 130.8, 128.4, 118.2, 92.4, 52.2, 51.7, 36.9, 34.8, 28.4, 27.2. **HRMS**(ESI) m/z: Calc. for $C_21H_{24}ClNNaO_3$: 396.1342 $[M+Na]^+$; Obser.: 396.1339.

3-(4-Bromobenzoyl)-2-(tert-butylamino)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (4b) Yellow solid, mp: 112 – 115ºC **IR** (KBr, v, cm^{-1}) 2966, 2878,1673,1631, 1542, 1382, 1280, 1225, 1018, 962, 890, 576. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.84 (s, 1H, NH), 7.43 (d, J = 8.0 Hz, 2H, ArH), 7.36 (d, J = 8.2 Hz, 2H, ArH), 2.72 (s, 2H, CH_2), 2.34 (s, 2H, CH_2), 1.45 (s, 9H, CH_3), 1.12 (s, 6HCH_3). **^{13}C NMR** (100 MHz, DMSO) (δ, ppm) 185.8, 180.7, 160.3, 151.2, 134.8, 124.5, 123.4 ,118.5 ,110.8, 87.2, 46.7, 46.1, 30.4, 29.0, 25.2, 22.8. **HRMS**(ESI) m/z: Calc. for $C_{21}H_{24}BrNNaO_3$: 440.0837 $[M+Na]^+$; Obser.: 440.0875.

2-(tert-Butylamino)-3-(4-methoxybenzoyl)-6,6-dimethyl-6,7-dihydrobenzofuran4(5H)-one (4c) Yellow solid, mp: 185 – 186ºC **IR** (KBr, v, cm^{-1}): 2956, 2878, 2830, 1675, 1630, 1541, 1380, 1240, 1175, 839, 770. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.64 (s, 1H, NH), 7.51 (d, J = 8.4 Hz, 2H, ArH), 6.82 (d, J= 4 8.4Hz,2H, ArH), 3.81 (s, 3H, OCH_3), 2.72 (s, 2H, CH_2), 2.36 (s, 2H, CH^2), 1.45 (s, 9H, CH_3) 1.12 (s, 6H, CH_3).**^{13}C NMR** (100 MHz, DMSO) (δ, ppm) 185.3, 182.6, 160.8, 157.2,153.5, 127.2, 124.7, 110.5,106.3, 87.2, 48.8, 47.3, 46.4, 30.8, 30.7, 25.5, 24.1. **HRMS**(ESI) m/z: Calc. for $C_{22}H_{27}NNaO_4$: 392.1838 $[M+Na]^+$; Obser.: 376.1865.

2-(tert-Butylamino)-3-(4-methylbenzoyl)-6,7-dihydrobenzofuran-4(5H)-one(4d)

Yellow solid, mp: 157 – 159oC **IR** (KBr, v, cm^{-1}): 2964, 2889, 1670, 1638, 1547, 1474, 1172,

976, 938, 758. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.68 (s, 1H, NH), 7.47 (d, J = 7.5 Hz, 2H, ArH), 7.18 (d, J = 7.2 Hz, 2H, ArH), 2.85 – 2.81 (m, 2H, CH_2), 2.47 – 2.34 (m, 5H, CH_2 and CH_3), 2.27 – 2.12 (m,2H, CH_2), 1.44 (s, 9H, CH_3).**^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 190.3, 188.6, 165.4, 157.6, 141.6, 139.5, 129.8, 127.2, 118.5, 92.6, 79.3, 77.2, 76.5, 51.5, 37.6, 28.2, 24.6, 22.5, 22.4.**HRMS**(ESI) m/z: Calc. for $C_{20}H_{23}NNaO_3$: 348.1576 $[M+Na]^+$; Obser.:348.1538.

3-(4-Bromobenzoyl)-2-(butylamino)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one

(4e) White solid, mp: 152-153^{o}C. **IR** (KBr, v, cm^{-1}): 2957, 2934, 1674, 1647, 1540, 1454, 1382, 1328, 1090, 1018, 774.**^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.42 (t, J = 11.2 Hz, 1H, NH), 7.46 (d, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 8.0 Hz, 2H, ArH), 3.54 – 3.49 (m, 2H, CH_2), 2.72 (s, 2H, CH_2), 2.31 (s, 2H, CH_2),1.66 – 1.60 (m, 2H, CH_2), 1.44 – 1.40 (m, 2H, CH_2), 1.10 (s, 6H, CH_3), 0.95 (t, 3H, J = 14.4 Hz,CH_3).**^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 191.8, 188.6, 164.5, 158.8, 141.2, 129.8, 130.4, 124.6, 119.4, 94.7, 51.3, 43.2, 38.8, 36.9, 32.2, 29.6, 18.5, 14.1. **HRMS**(ESI) m/z: Calc. for $C_{21}H_{24}BrNNaO_3$: 440.0837 $[M+Na]^+$; Obser.: 440.0844.

2-(Butylamino)-3-(4-chlorobenzoyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one

(4f). Yellow solid, mp: 151- 153oC **IR** (KBr, v, cm^{-1}): 2965, 2948, 1676, 1640, 1541, 1462, 1380, 1075, 1024, 837, 780.**^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.41 (t, J = 11.1 Hz, 1H, NH), 7.42 (d, J = 8.0 Hz, 2H,ArH) 7.36 (d, J = 8.0 Hz, 2H, ArH), 3.53 – 3.48 (m, 2H, CH_2), 2.72 (s, 2H, CH_2), 2.32 (s, 2H, CH_2), 1.72 – 1.65 (m, 2H, CH_2), 1.45 – 1.40 (m, 2H, CH_2), 1.16 (s, 6H, CH_3), 0.96 (t, 3H, J = 14.8 Hz, CH3).**^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm)

192.4, 189.6, 166.5, 158.8, 140.2, 137.2, 130.2, 129.5,119.8, 92.5, 51.2, 43.6, 38.2, 36.8, 30.5, 27.8, 18.3, 12.4.**HRMS** (ESI) m/z: Calc. for $C_{21}H_{24}ClNNaO_3$: 396.1342 [M+Na]+; Obser.: 396.1364.

2-(Butylamino)-3-(4-methoxybenzoyl)-6,7-dihydrobenzofuran-4(5H)-one (4g) Yellow solid, mp: 123 – 124 ^oC **IR** (KBr, v, cm^{-1}): 2953, 2870, 1689, 1649, 1608, 1548, 1459, 1260, 1109, 995, 798.**^{1}HNMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.27 (t, J = 11.2 Hz, 1H, NH), 7.66 (d, J = 8.6 Hz, 2H, ArH), 6.87 (d, J = 8.6 Hz, 2H, ArH), 3.85 (s, 3H, OCH_3), 3.46 – 3.41 (m, 2H, CH_2), 2.82 – 2.80 (m, 2H, CH_2), 2.39 – 2.33 (m, 2H, CH_2), 2.23 – 2.16 (m, 2H, CH_2), 1.68 – 1.63 (m, 2H, CH_2), 1.43 – 1.40 (m, 2H, CH_2), 0.98 (t, 3H, J = 14.4 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 193.4, 187.0, 165.8, 162.3, 159.8, 134.0, 131.2, 118.4, 113.7, 91.0, 54.3, 44.6, 37.8, 33.5, 24.8, 21.5, 20.8, 14.3. **HRMS** (ESI)/z: Calc. for $C_{20}H_{23}NNaO_4$: 364.1525 $[M+Na]^+$; Obser.: 364.1558.

2-(Butylamino)-6,6-dimethyl-3-(4-methylbenzoyl)-6,7-dihydrobenzofuran-4(5H)-one (4h) Yellow solid, mp: 131 – 133 ^oC 6 **IR** (KBr, v, cm^{-1}): 2952, 2937, 1672, 1641, 1550, 1470, 1378, 1230, 1091, 1042, 757.**^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.35 (t, J = 11.2 Hz, 1H, NH), 7.46 (d, J = 8.0 Hz, 2H, ArH), 7.18 (d, J = 8.0 Hz, 2H, ArH), 3.45 – 3.40 (m, 2H, CH_2), 2.71 (s, 2H, CH_2), 2.41 (s, 3H, CH_3),2.31 (s, 2H, CH_2), 1.68 – 1.64 (m, 2H, CH_2), 1.46 – 1.42 (m, 2H, CH_2), 1.16 (s, 6H, CH_3), 0.98 (t,3H, J = 14.8 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 193.2, 190.7, 165.4, 158.7, 141.5, 132.8, 129.2, 127.8, 119.5, 98.2, 92.8, 54.5, 51.2, 42.9, 38.5, 36.4, 33.8, 27.6, 23.8, 18.3, 14.2. **HRMS** (ESI) m/z: Calc. for $C_{22}H_{27}NNaO_3$: 376.1889 $[M+Na]^+$; Obser.: 376.1826.

3-(4-Chlorobenzoyl)-2-(cyclohexylamino)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (4i) Yellow solid, mp: 155–157 ^{o}C. IR (KBr, v, cm^{-1}): 2933, 2924, 2844, 1766, 1622, 1564, 1448, 1365, 1243, 1042, 882, 771. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.46 (d, J = 8.2 Hz, 1H, NH), 7.46–7.38 (m, 2H, ArH), 7.38 – 7.24 (m, 2H, ArH), 3.72–3.66 (m, 1H, CH), 2.68 (s, 2H, CH_2), 2.26 (s, 2H, CH_2), 2.06– 2.03 (m, 2H, CH_2), 1.78–1.73(m, 2H, CH_2), 1.60–1.56 (m, 1H, CH_2), 1.45– 1.34 (m, 4H, CH_2), 1.33 – 1.24 (m, 1H, CH_2), 1.12 (s, 6H, CH_3) **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 190.6, 184.1, 162.3, 158.3, 140.5, 137.9, 130.4, 128.4, 115.5, 91.7, 51.2, 52.8, 36.4, 34.9, 32.2, 27.6, 24.8, 23.6.**HRMS** (ESI) m/z: Calc. for $C_{23}H_{26}ClNNaO_3$: 422.1499 [M+Na]+; Obser.: 422.1443.

3-(4-Bromobenzoyl)-2-(cyclohexylamino)-6,7-dihydrobenzofuran-4(5H)-one 4j Yellow solid, mp: 127 – 128 °C **IR** (KBr, v, cm^{-1}): 2947, 1638, 1554, 1448, 1365, 1285, 1065, 990, 938, 758. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.37 (d, J = 8.2 Hz, 1H, NH), 7.48 – 7.39 (m, 2H, ArH), 7.31 – 7.26 (m, 7 2H, ArH), 3.72 – 3.69 (m, 1H, CH), 2.74 (s, 2H, CH_2), 2.32 (s, 2H, CH_2), 2.04 – 2.02 (m, 2H, CH_2), 1.83 – 1.77 (m, 2H, CH_2), 1.62 (d, J = 12.4 Hz, 1H, CH_2), 1.43–1.34 (m, 4H, CH_2), 1.35 – 1.28 (m, 1H, CH_2), 1.16 (s, 6H, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 190.8, 185.8, 165.8, 157.3, 141.7, 131.4, 129.4, 124.6, 120.5, 90.6, 50.8, 39.4, 32.8, 24.9, 24.0, 23.1, 22.0 **HRMS** (ESI) m/z: Calc. for $C_{21}H_{22}BrNNaO_3$: 438.0631 $[M+Na]^+$; Obser.: 438.0621.

2-(Cyclohexylamino)-3-(4-nitrobenzoyl)-6,7-dihydrobenzofuran-4(5H)-one (4k).

Orange solid, mp: 130– 132^{o}C. **IR** (KBr, v, cm^{-1}): 2930, 2858, 1654, 1530, 1460, 1334, 1245, 1076, 926, 866. **^{1} HNMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.61 (d, J = 8.2 Hz, 1H, NH), 8.25 (d,

J = 8.8 Hz, 2H, ArH), 7.64 (d, J = 8.8 Hz, 2H, ArH), 3.85 – 3.76 (m, 1H, CH), 2.82 – 2.80 (m, 2H, CH_2), 2.42 – 2.30 (m, 2H, CH_2), 2.25 – 2.16 (m, 2H, CH_2), 2.06 – 2.03 (m, 2H, CH_2), 1.80 (d, J = 4.0 Hz, 2H, CH_2),1.62– 1.60 (m, 1H, CH_2), 1.55 – 1.41 (m, 4H, CH_2), 1.32 – 1.25 (m, 1H, CH_2).**^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 192.5, 185.7, 166.8, 160.8, 149.6, 146.2, 130.7, 120.4, 115.6, 92.2, 50.8, 39.5, 32.5, 24.8, 25.2, 22.8, 20.5.**HRMS** (ESI) m/z: Calc. for $C_{21}H_{22}N_2NaO_5$: 405.1426 $[M+Na]^+$; Obser.: 405.1455.

2-(tert-Butylamino)-3-(4-chlorobenzoyl)-6,7-dihydrobenzofuran-4(5H)-one (4l)

Yellow solid, mp: 192 – 193 ^oC **IR** (KBr, v, cm^{-1}): 2965, 1671, 1638, 1539, 1468, 1388, 1245, 1165, 1070 945 756.**^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.76 (s, 1H, NH), 7.45 (d, J = 8.4 Hz, 2H, ArH), 7.35(d, J= 8.4 Hz, 2H, ArH), 2.84 – 2.81 (m, 2H, CH_2), 2.42 – 2.34 (m, 2H, CH_2), 2.20–2.14 (m, 2H,CH_2),1.48 (s, 9H, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ, ppm)192.7, 187.1 ,165.7,157.8, 140.7, 135.8, 129.2, 8 126.3, 117.2, 92.4, 52.6, 36.4, 30.2, 24.8, 22.4. **HRMS** (ESI) m/z: Calc. for $C_{19}H_{20}ClNNaO_3$: 368.1029 $[M+Na]^+$; Obser.: 368.1075.

3-(4-Bromobenzoyl)-2-(tert-butylamino)-6,7-dihydrobenzofuran-4(5H)-one (4m)

Yellow solid, mp: 184 – 185 ^oC IR (KBr, v, cm^{-1}): 2970, 2876, 1676, 1634, 1548, 1458, 1378, 1246, 1168, 946, 762. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.81 (s, 1H, NH), 7.46 (d, J = 8.2 Hz, 2H, ArH), 7.41 (d, J= 8.2 Hz, 2H, ArH), 2.84 – 2.79 (m, 2H, CH_2), 2.44 - 2.40 (m, 2H, CH_2), 2.16– 2.12 (m, 2H, CH_2), 1.48 (s, 9H, CH_3). **^{13}C NMR** (100 MHz, DMSO-d6) (δ, ppm) 185.2, 181.8, 160.8, 154.4, 136.5, 124.8, 123.2, 118.5, 112.8, 87.4, 45.4, 33.8, 23.2,

18.5, 17.5. **HRMS** (ESI) m/z: Calc. for $C_{19}H_{20}BrNNaO_3$: 412.0524 $[M+Na]^+$; Obser.: 412.0565.

2-(Benzylamino)-3-(4-methoxybenzoyl)-6,7-dihydrobenzofuran-4(5H)-one (4n)

Yellow solid, mp: 155– 156 ^oC **IR** (KBr, v, cm^{-1}): 2958, 2844, 1683, 1640, 1608, 1465, 1371, 1258, 1058, 840, 769. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.53 (t, J = 12.0 Hz, 1H, NH), 7.58 (d, J = 8.4 Hz, 2H, ArH), 7.35 – 7.29 (m, 5H, ArH), 6.84 (d, J = 8.4 Hz, 2H, ArH), 4.62 (d, J = 6.4 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 2.81 (d, J = 12.4 Hz, 2H, CH_2), 2.45 (d, J = 12.8 Hz, 2H, CH_2), 2.15 – 2.10 (m, 2H, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 193.7, 189.0, 165.5, 162.7, 156.5, 138.5, 132.2, 130.0, 129.2, 128.0, 127.6, 118.5, 111.5, 92.5, 55.0, 44.6, 39.5, 24.8, 21.7. **HRMS** (ESI) m/z: Calc. for $C_{23}H_{21}NNaO_4$: 398.1368 $[M+Na]^+$; Obser.: 398.1341.

2-(Benzylamino)-3-(4-chlorobenzoyl)-6,7-dihydrobenzofuran-4(5H)-one (4o)

Yellow solid, mp: 157-158 ^oC **IR** (KBr, v, cm^{-1}): 2945, 2875, 1680, 1648, 1557, 1474, 1386, 1235, 1082, 980, 758. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm) 8.71 (t, J = 12.0 Hz, 1H, NH), 7.45 (d, J = 7.8 Hz, 2H, ArH), 7.39 – 7.34 (m, 7H, ArH), 4.65 (d, J = 6.4 Hz, 2H, CH_2), 2.85 – 2.81 (m, 2H, CH_2), 2.43 – 2.40 (m, 2H, CH_2), 2.18 – 2.14 (m, 2H, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 194.2, 187.8, 163.8, 157.4, 141.6, 138.8, 137.0, 130.5, 129.5, 128.6, 127.9, 126.8, 118.6, 92.8, 46.5, 36.0, 22.6, 20.3. **HRMS** (ESI) m/z: Calc. for $C_{22}H_{18}ClNNaO_3$:402.0873 $[M+Na]^+$; Obser.: 402.0823.

2-(Benzylamino)-6,6-dimethyl-3-(4-nitrobenzoyl)-6,7-dihydrobenzofuran-4(5H)-one(4p) Orange solid, mp: 170 – 172 ^oC. **IR** (KBr, v, cm^{-1}): 2963, 1678, 1644, 1640, 1557,

1534, 1338, 1218, 1045, 841, 754. **^{1}H NMR** (400 MHz, $CDCl_3$) (δ, ppm) 8.87 (t, J = 12.0 Hz, 1H, NH), 8.26 (d, J = 8.8 Hz, 2H, ArH), 7.66 (d, J = 8.6 Hz, 2H, ArH), 7.45 – 7.38 (m, 5H, ArH), 4.72 (d, J = 5.2 Hz, 2H, CH_2), 2.75 (s, 2H, CH_2), 2.24 (s, 2H, CH_2), 1.16 (s, 6H, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) (δ, ppm) 192.5, 185.2, 162.5, 156.5, 144.2, 141.4, 135.0, 130.2, 128.9, 128.1, 126.9, 123.2, 118.0, 94.5, 57.2, 54.8, 47.1, 34.8, 35.0, 28.4, 18.7. **HRMS** (ESI) m/z: Calc. for $C_{24}H_{22}N_2NaO_5$: 441.1426 $[M+Na]^+$; Obser.: 441.1476.

4.6 Some spectrum of intermediate and Benzofuran-4(5H)-one's derivatives of ^{1}HNMR,^{13}CNMR and HRMS.

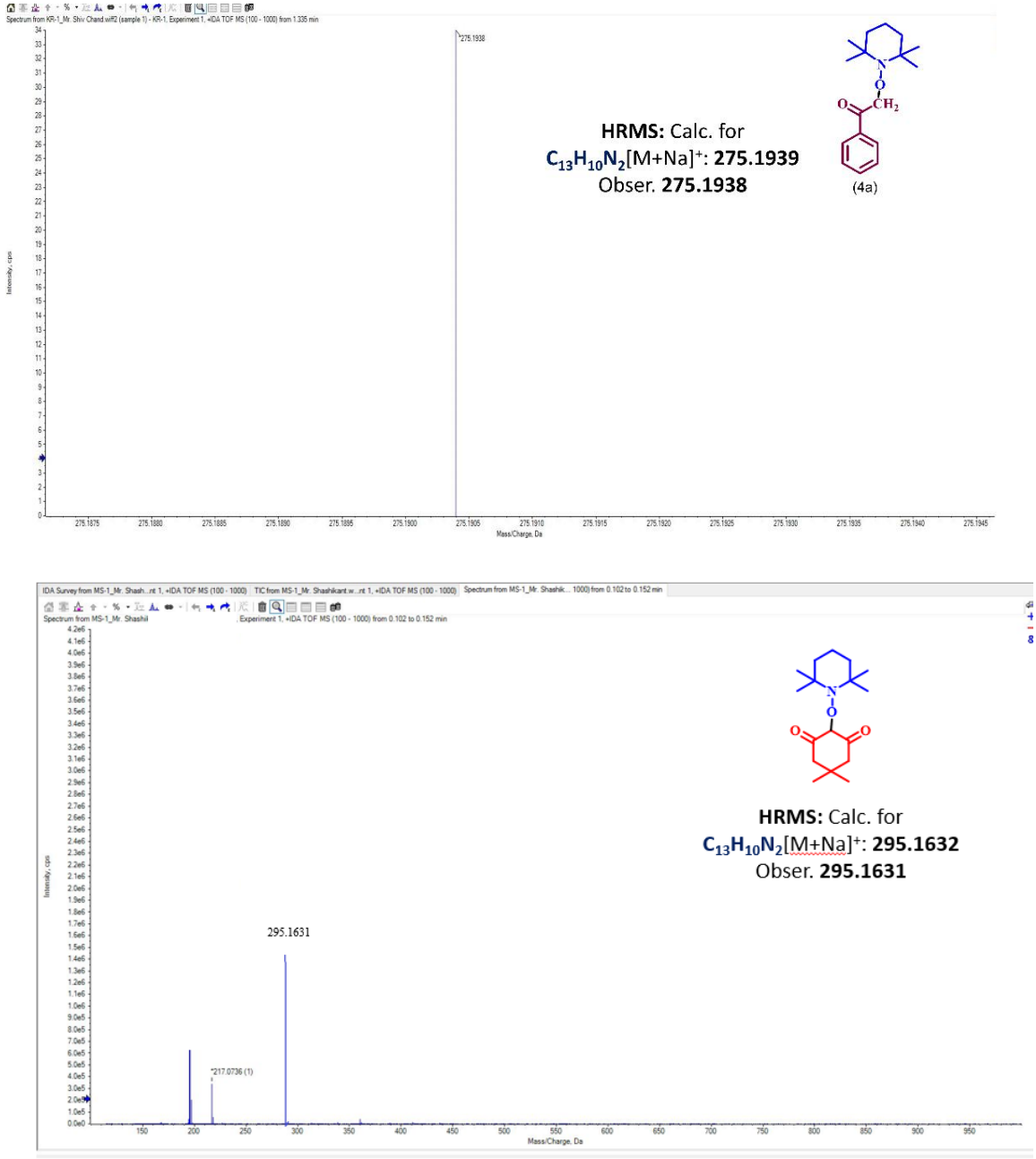


Figure 4.2 HRMS products of **4b'** and **4c'** compounds.

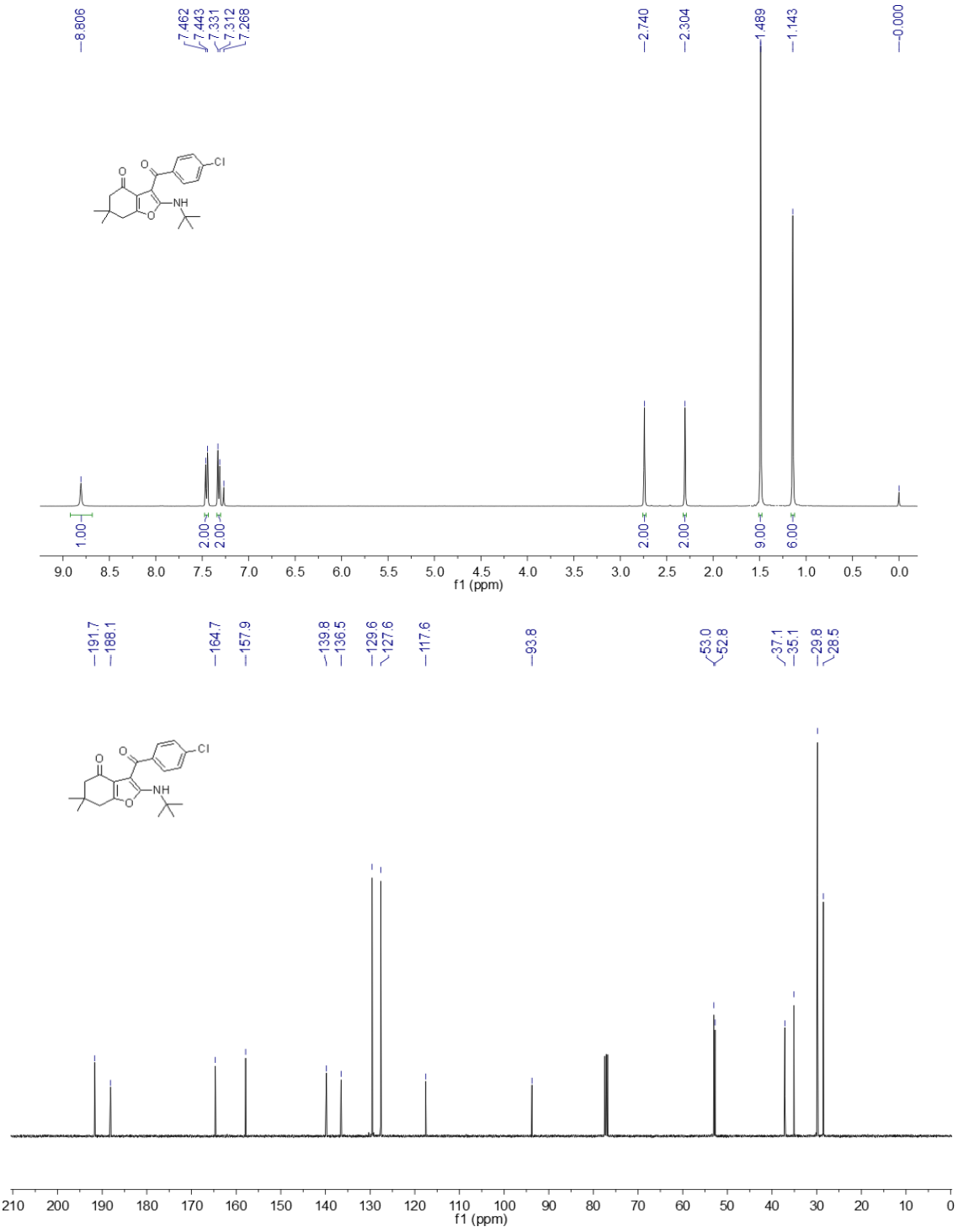


Figure 4.3 ^{1}H NMR and ^{13}C NMR of Benzofuran-4(5H)-one's derivatives **4a** in $CDCl_3$.

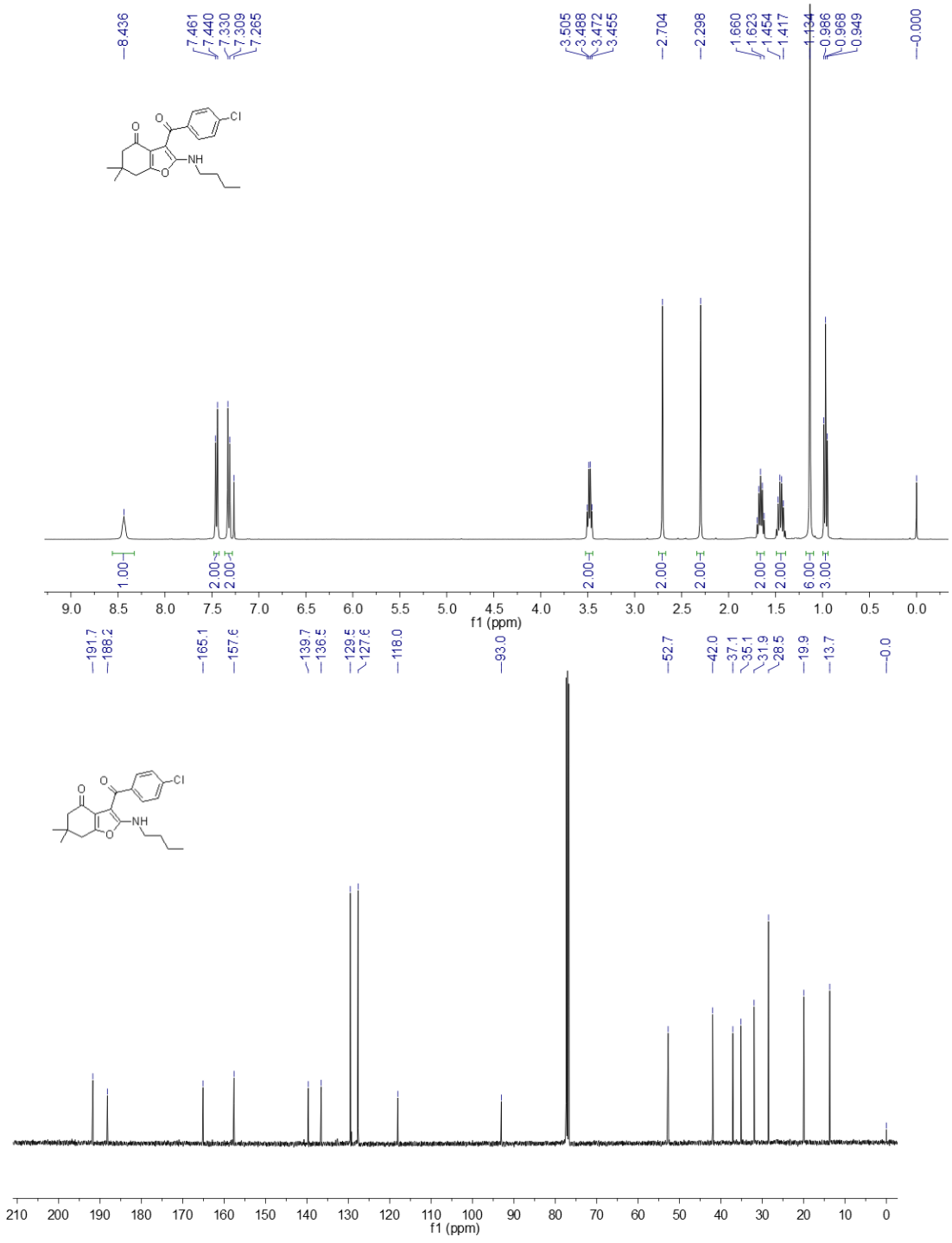


Figure 4.4 ^{1}H NMR and ^{13}C NMR of Benzofuran-4(5H)-one's derivatives **4f** in $CDCl_3$.

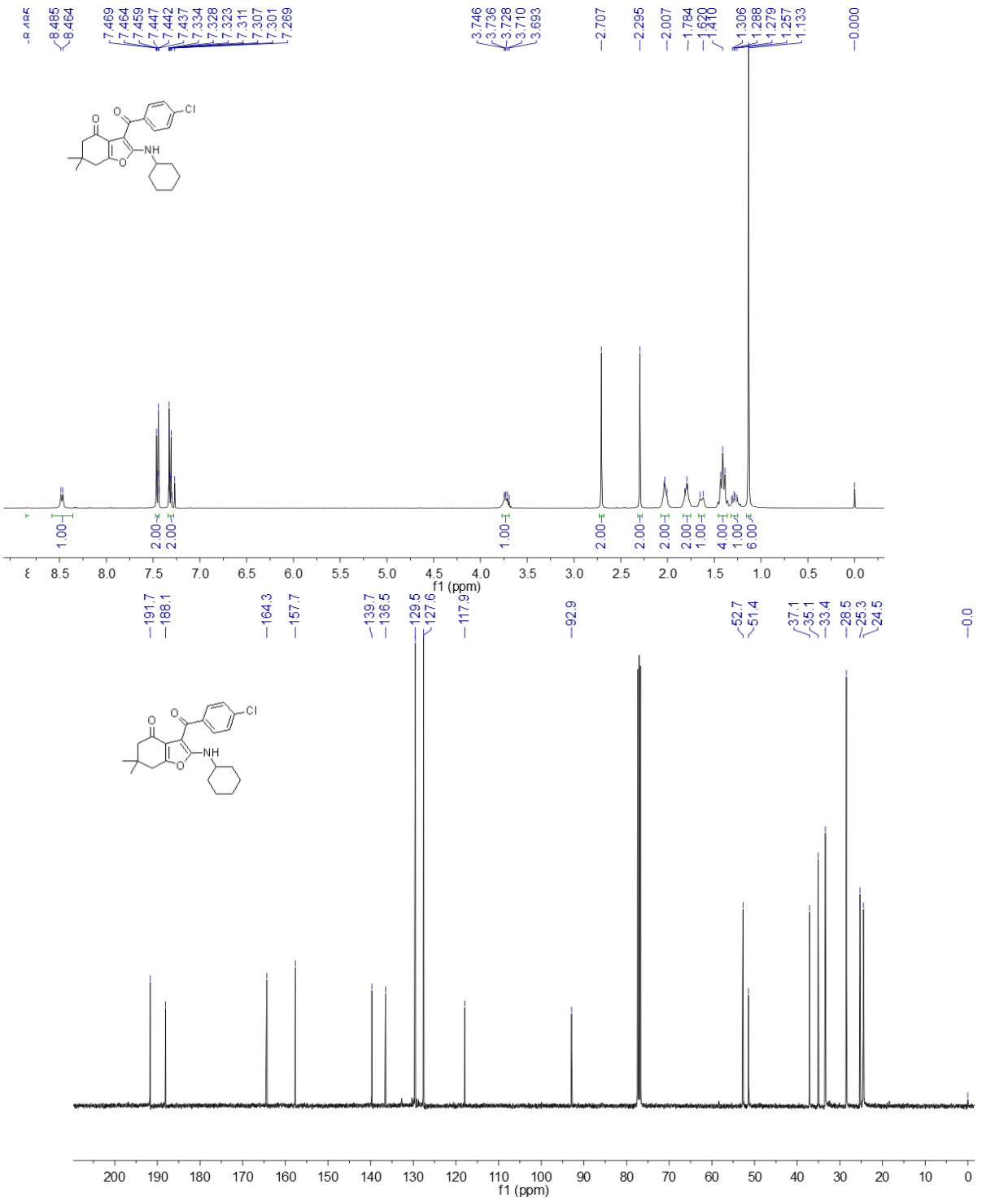


Figure 4.5 ^{1}H NMR and ^{13}C NMR of Benzofuran-4(5H)-one's derivatives **4i** in $CDCl_3$.

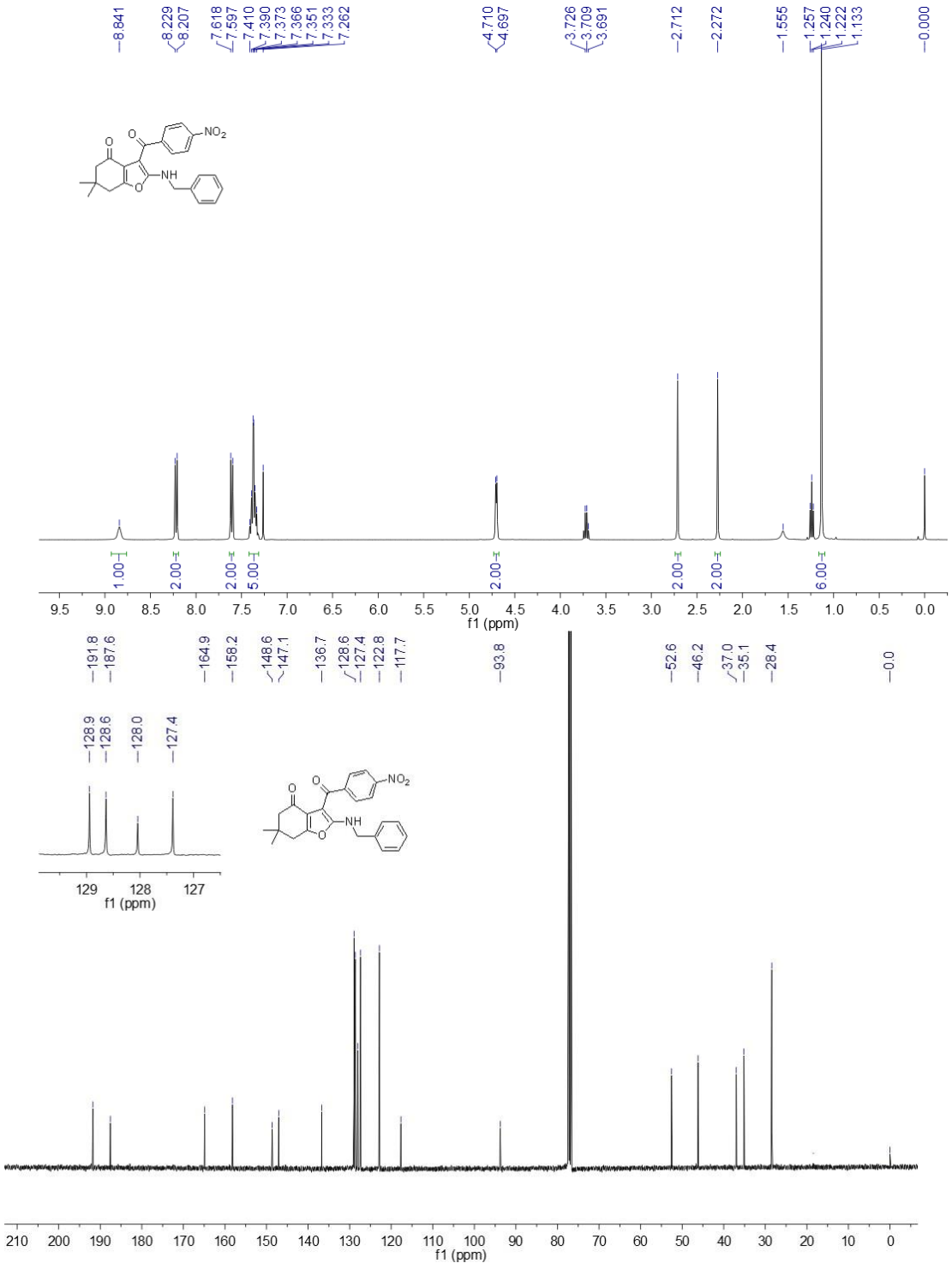


Figure 4.6 ^{1}H NMR and ^{13}C NMR of Benzofuran-4(5H)-one's derivatives **4p** in $CDCl_3$.

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