

## Supporting Information

### Alcohol mediated Isocyanide domino reactions toward 2-aminofuronaphthoquinones

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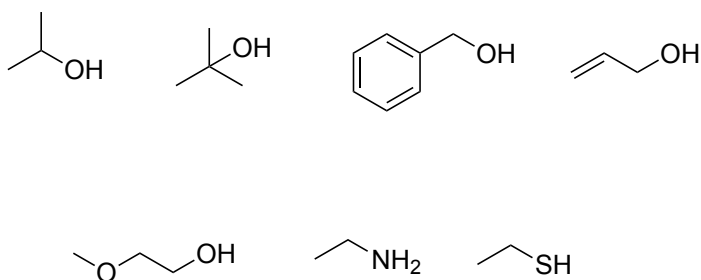
Table SI-1

Entry	Ratio (1:2)	Catalyst	Reaction conditions	Yield (%)
1	1:1.0	10 mol% InCl <sub>3</sub>	MW, 120 °C, 3h	36
2	1:1.5	10 mol% InCl <sub>3</sub>	MW, 150 °C, 30 min	34
3	1:1.5	10 mol% FeCl <sub>3</sub>	MW, 150 °C, 1.5 h	25
4	1:1.5	10 mol% BiCl <sub>3</sub>	MW, 150° C, 1h	13
5	1:1.5	10 mol% Cu(OTf) <sub>2</sub>	MW, 150° C, 1h	12
6	1:1.5	10 mol% Bi(OTf) <sub>3</sub>	MW, 150° C, 1h	9
7	1:1.5	10 mol% Sc(OTf) <sub>3</sub>	MW, 150° C, 30 min	31
8	1:1.5	10 mol% Yb(OTf) <sub>3</sub>	MW, 150° C, 30 min	48
9	1:1.5	30 mol% Yb(OTf) <sub>3</sub>	MW, 150° C, 30 min	7
<b>10</b>	<b>1:3.0</b>	<b>10 mol% Yb(OTf)<sub>3</sub></b>	<b>MW, 150° C, 30 min</b>	<b>63</b>
11	1:1.5	10 mol% Yb(OTf) <sub>3</sub>	Reflux, 24 h	-- <sup>a</sup>
12	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	Sealed tube, 120° C, 4h	37 <sup>b</sup>
13	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	Sealed tube, 100° C, 16h	31 <sup>b</sup>
14	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	Reflux, 30 min	-- <sup>a</sup>
15	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	Reflux, 24 h	-- <sup>a</sup>
16	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	MW, 150° C, 30 min	7 <sup>c</sup>
17	1:3.0	10 mol% InCl <sub>3</sub>	MW, 150° C, 30 min	59
18	1:3.0	10 mol% CeCl <sub>3</sub>	MW, 150° C, 2h	38
19	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	MW, 170° C, 10 min	62
20	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	MW, 120° C, 3h	65
21	1:1.5	10 mol% InCl <sub>3</sub>	MW, 170 °C, 30 min	-- <sup>d</sup>
22	1:1.5	10 mol% NiCl <sub>2</sub>	MW, 150° C, 1h	-- <sup>a</sup>
23	1:1.5	10 mol% AgOTf	MW, 150° C, 1h	-- <sup>d</sup>
24	1:1.5	10 mol% BF <sub>3</sub> ·Et <sub>2</sub> O	MW, 150° C, 30 min	-- <sup>d</sup>
25	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	MW, 150° C, 1h	48 <sup>e</sup>
26	1:3.0	10 mol% Yb(OTf) <sub>3</sub>	MW, 150° C, 1h	57 <sup>f</sup>
27	1:3.0	10 mol% Yb(OTf) <sub>3</sub> /Et <sub>3</sub> N	MW, 150° C, 1h	58
28	1:3.0	10 mol% Yb(OTf) <sub>3</sub> /InCl <sub>3</sub>	MW, 150° C, 30 min	61
29	1:3.0	10 mol% CAN	MW, 150° C, 30 min	45
30	1:3.0	10 mol% SmI <sub>2</sub>	MW, 150° C, 1h	35
31	1:3.0	10 mol% Zn(OTf) <sub>2</sub>	MW, 150° C, 50 min	38
32	1:3.0	--	MW, 150° C, 30 min	-- <sup>a</sup>

<sup>a</sup>no reaction; <sup>b</sup>oven heating in a sealed tube; <sup>c</sup> using argon atmosphere and previously degassed ethanol; <sup>d</sup>complex reaction mixture; <sup>e</sup>2 mL DCE/EtOH (3:1); <sup>f</sup>2 mL (toluene/EtOH) (3:1)

The marked differences observed in yields upon small changes in reaction conditions reflect the sensitivity of the reaction to temperature, catalyst and MW irradiation time. Productive conversion appears to require a narrow window that enables efficient ether formation and subsequent isocyanide addition, while slight deviations, particularly increased temperature or extended reaction times, lead to product decomposition pathways becoming more significant and diminishing yields.

### List of unreactive substrates:



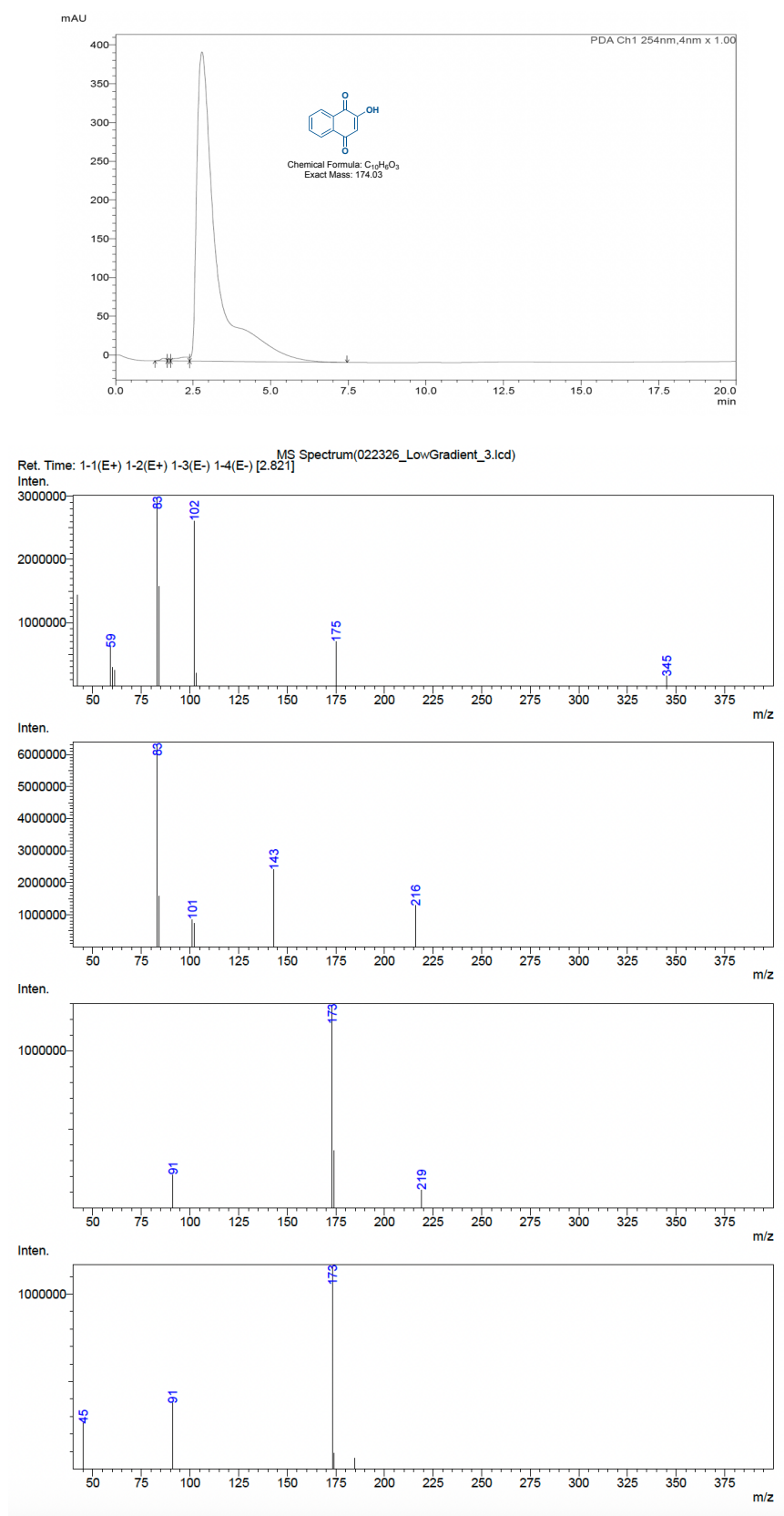
### LCMS Analysis:

General LCMS experimental conditions:

LC-MS and MS/MS experiments were performed on a Shimadzu LCMS-8030 triple quadrupole mass spectrometer instrument equipped with an electrospray ionization (ESI) source operating in both positive and negative ion modes. Reaction mixtures obtained under optimized conditions were diluted in acetonitrile (1 mL) prior to analysis. A 1  $\mu$ L aliquot of the diluted solution was injected for LCMS analysis.

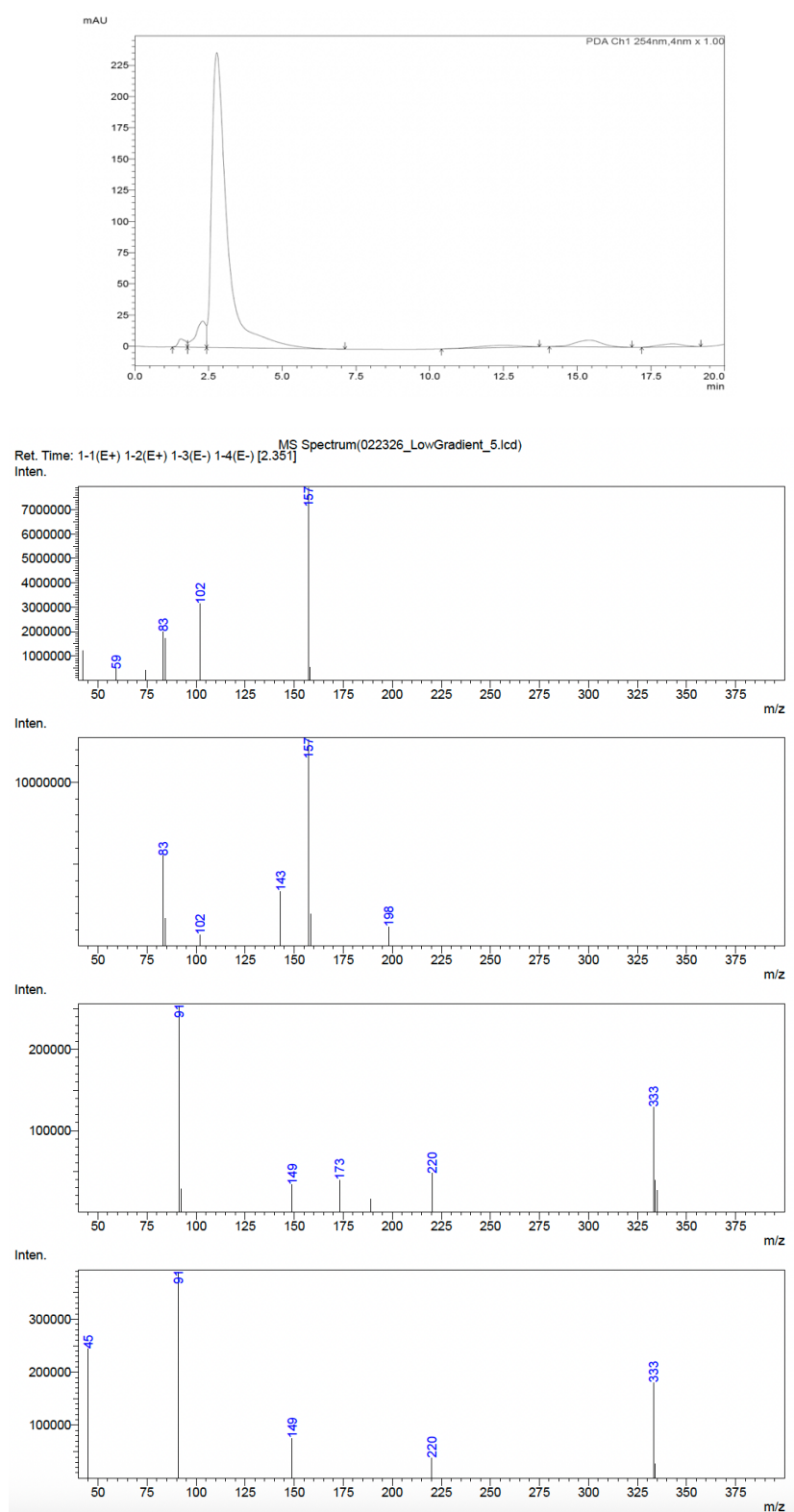
Separations were carried out on a reversed-phase column (Waters XBridge C18 3.5 $\mu$ m, 4.6mm x 50mm) using a gradient of solvent A (H<sub>2</sub>O + 0.1% formic acid) and solvent B (MeCN + 0.1% formic acid), from 15% to 45% B over 20 min at a flow rate of 0.3 mL/min. Injection volume was 1  $\mu$ L. Data were acquired in both positive and negative ion modes. Q1 and Q3 scans were performed over an  $m/z$  range of 40–400. Collision energies for MS/MS experiments were varied between 5 and 30 eV, depending on the fragmentation behavior of the precursor ions. Data acquisition and analysis were performed using LabSolutions software (Shimadzu).

LCMS of the reaction mixture before irradiation (RT = 3 min):



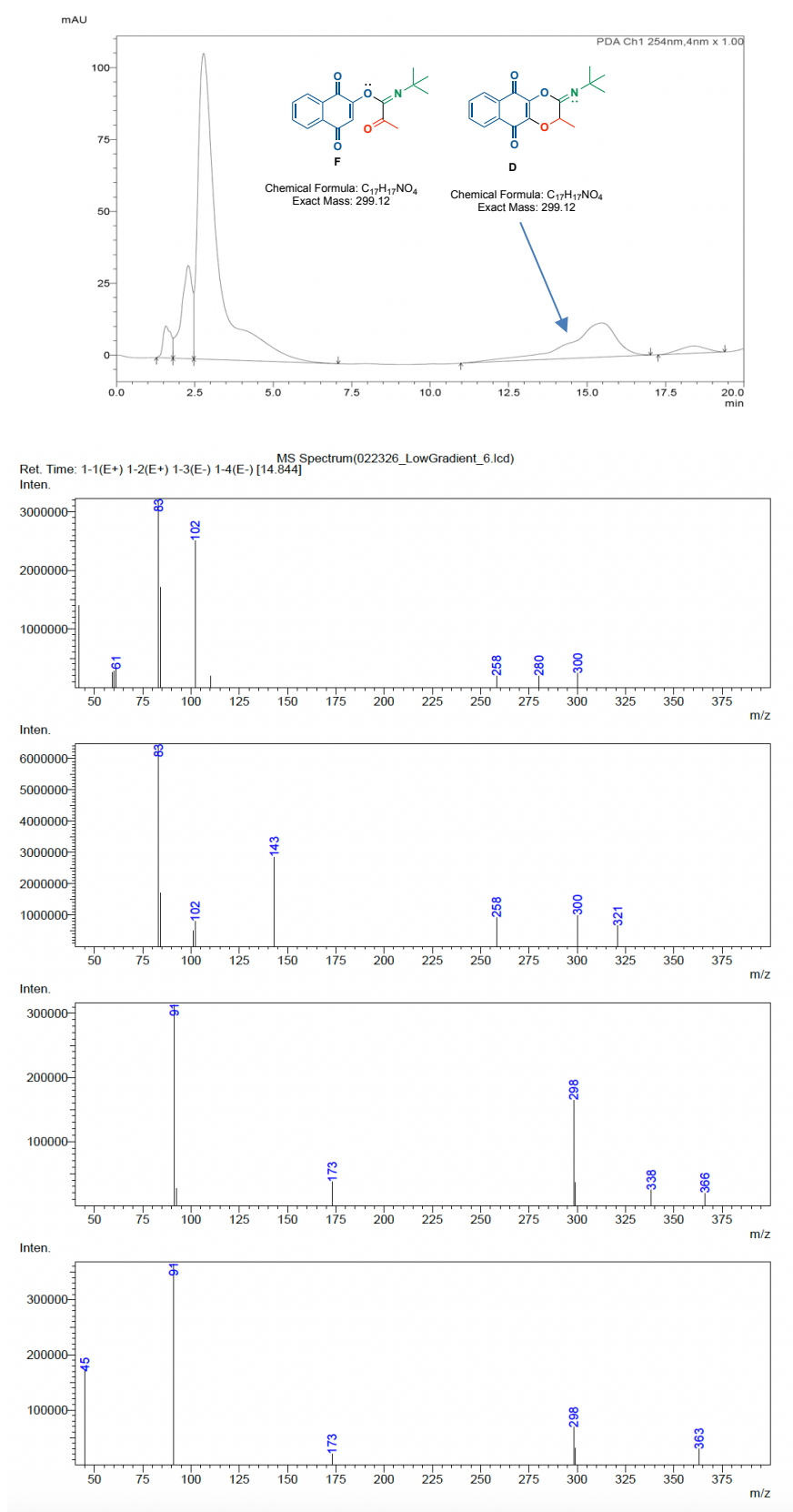
**Figure S1.** A) LC-UV spectra of the reaction mixture before irradiation. B) LC-MS/MS spectra in positive and negative mode from the Reaction Solution.

## LCMS of the reaction mixture after 5 min irradiation (RT = 2.3 min)



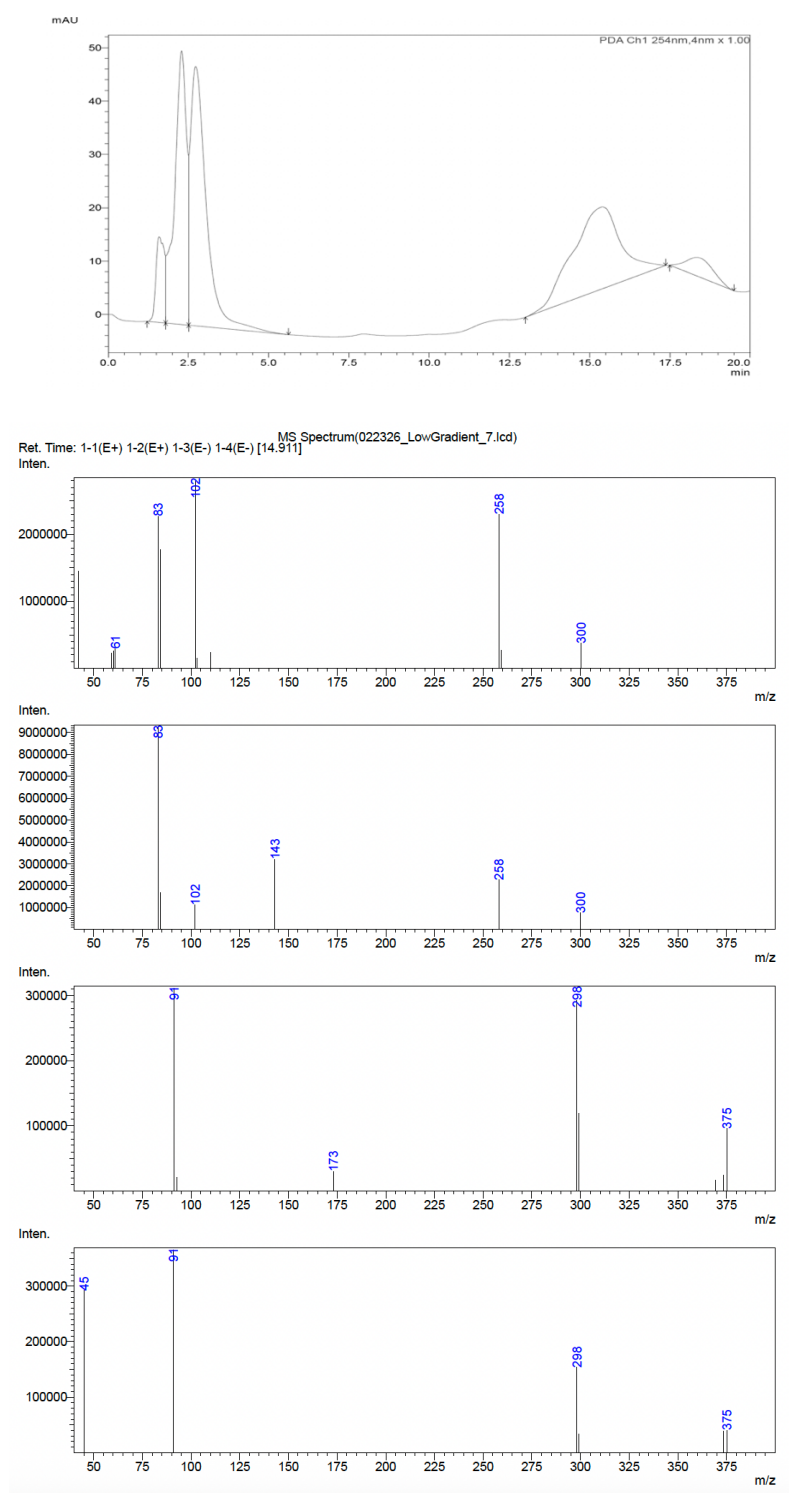
**Figure S2.** A) LC-UV spectra of the reaction mixture before irradiation. B) LC-MS/MS spectra in positive and negative mode from the Reaction Solution.

# LCMS of the reaction mixture after 10 min irradiation (RT = 15 min)

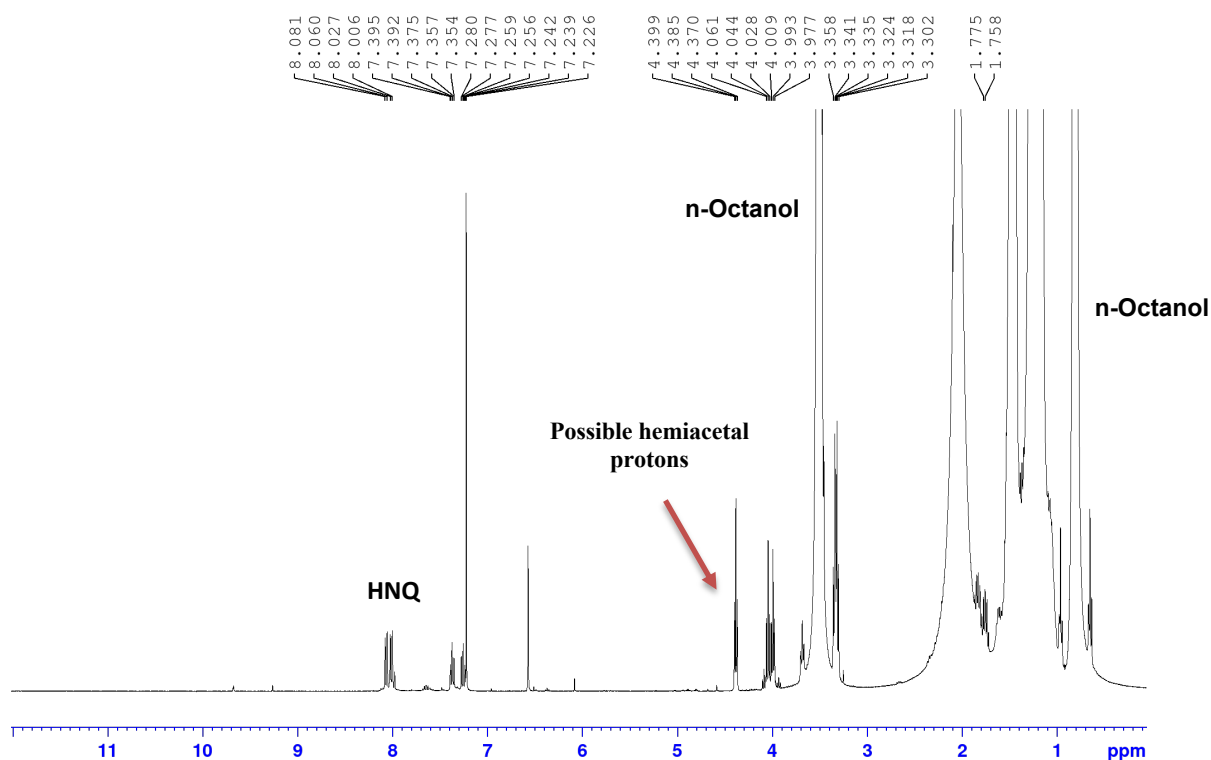


**Figure S3. A)** LC-UV spectra of the reaction mixture before irradiation. **B)** LC-MS/MS spectra in positive and negative mode from the Reaction Solution.

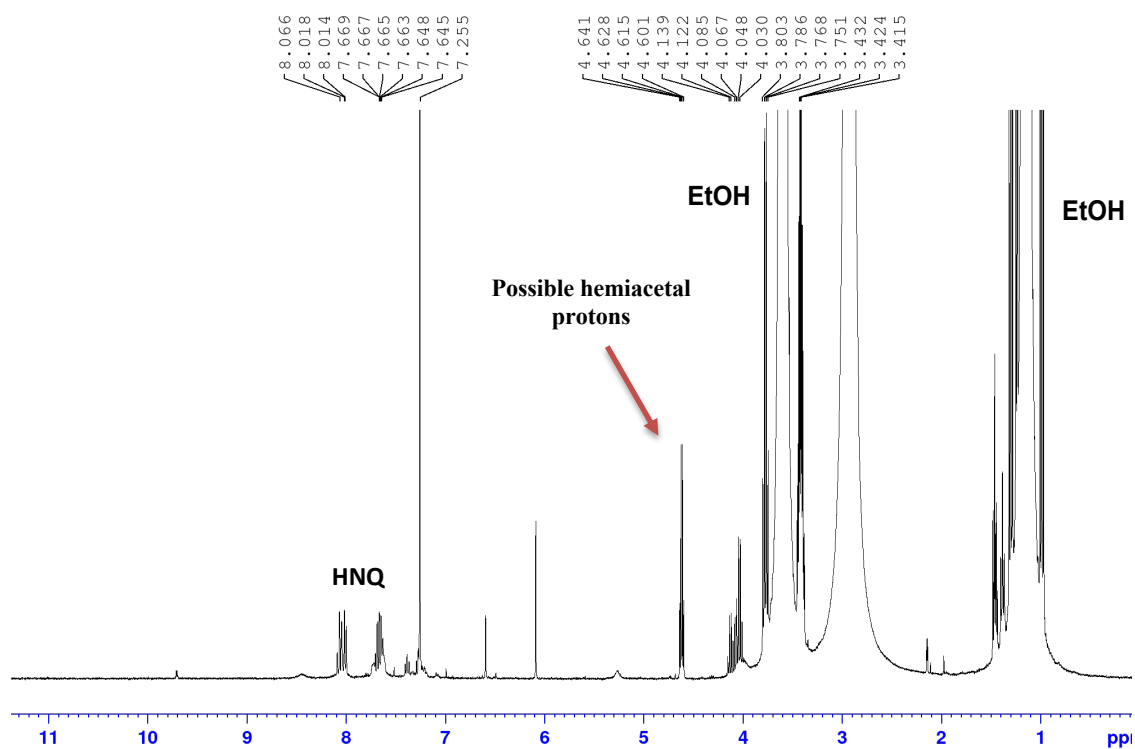
LCMS of the reaction mixture after 20 min irradiation (RT = 15 min).



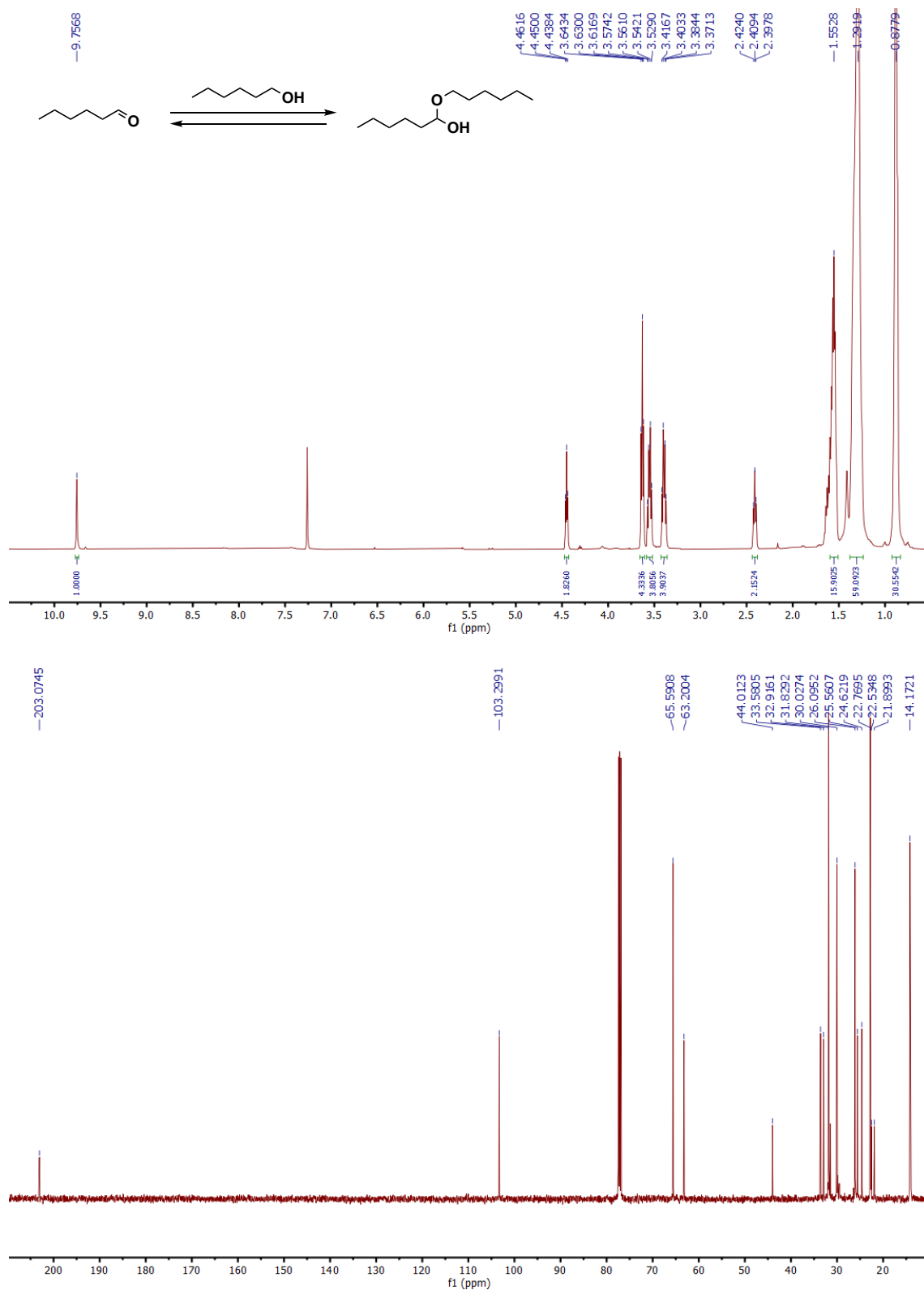
**Figure S4. A)** LC-UV spectra of the reaction mixture before irradiation. **B)** LC-MS/MS spectra in positive and negative mode from the Reaction Solution.



**Figure S5.** Crude  $^1\text{H}$  NMR of HNQ +  $\text{Yb}(\text{OTf})_3$  in 1-octanol after  $150^\circ\text{C}$ , 30 min



**Figure S6.** Crude  $^1\text{H}$  NMR of HNQ +  $\text{Yb}(\text{OTf})_3$  in EtOH after  $150^\circ\text{C}$ , 30 min



**Figure S7.** <sup>1</sup>H NMR and <sup>13</sup>C NMR of the isolate possible hemiacetal product formation from the reaction of NQ + Yb(OTf)<sub>3</sub> in 1-hexanol after 150°C, 30 min

### Synthesis of 2-ethoxy-1,4-naphthoquinone

A solution of 2-hydroxy-1,4-naphthoquinone (50 mg, 0.29 mmol) in EtOH (4 mL) was treated with a 5% HCl solution (0.1 mL), and the reaction mixture was refluxed for 24 h. Then the solvent was removed under reduced pressure, and the residue was purified by preparative-TLC (DCM/MeOH, 97:3) to afford 2-ethoxy-1,4-naphthoquinone (49.9 mg, 86%). <sup>1</sup>H NMR (δ, CDCl<sub>3</sub>, 500 MHz): 8.12 (d, *J*= 7.7 Hz, 1H), 7.89 (d, *J*= 7.7 Hz, 1H), 7.69 (t, *J*= 7.7 Hz, 1H), 7.57 (t, *J*= 7.7 Hz, 1H), 5.97 (s, 1H), 4.24 (q, *J*= 7.1 Hz, 2H), 1.57 (t, *J*= 7.1 Hz, 3H); <sup>13</sup>C NMR (δ, CDCl<sub>3</sub>, 125 MHz): 185.1 (C), 180.3 (C), 159.8 (C), 134.3 (CH), 133.4 (CH), 132.1 (C), 131.2 (C), 126.8 (CH), 126.2 (CH), 110.3 (CH), 65.4 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>).

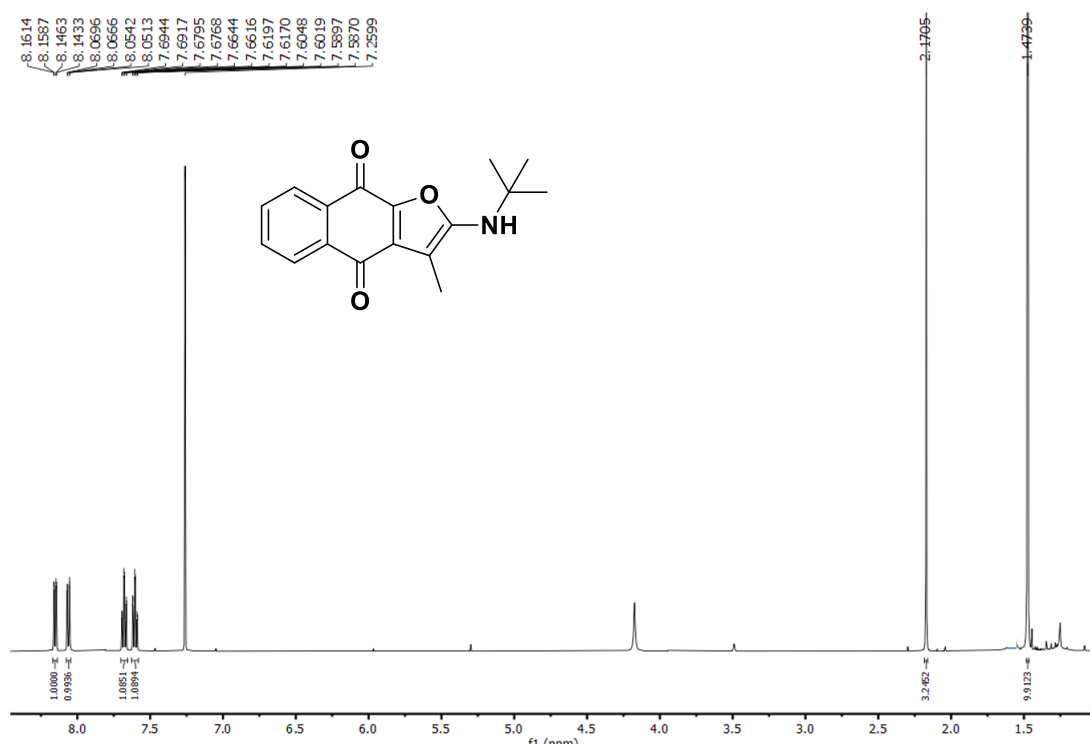
### Synthesis of 2-ethoxy-3-hydroxy-1,4-naphthoquinone (10)

A solution of 2,3-epoxy-2,3-dihydronaphthoquinone (80 mg, 0.46 mmol) in EtOH (5 mL) was refluxed for 24 h. Then, the solvent was removed under reduced pressure, and the residue was purified by preparative-TLC to yield 2-ethoxy-3-hydroxy-1,4-naphthoquinone (22.1 mg, 22%). <sup>1</sup>H NMR (δ, CDCl<sub>3</sub>, 500 MHz): 8.09 (d, *J*= 7.5 Hz, 1H), 8.05 (d, *J*= 7.5 Hz, 1H), 7.70 (m, 2H), 4.50 (q, *J*= 7.0 Hz, 2H), 1.43 (t, *J*= 7.0 Hz, 3H); <sup>13</sup>C NMR (δ, CDCl<sub>3</sub>, 125 MHz): 182.3 (C), 181.4 (C), 143.2 (C), 139.8 (C), 134.7 (CH), 133.5 (CH), 131.6 (C), 129.3 (C), 126.9 (CH), 126.2 (CH), 69.08 (CH<sub>2</sub>), 15.9 (CH<sub>3</sub>).

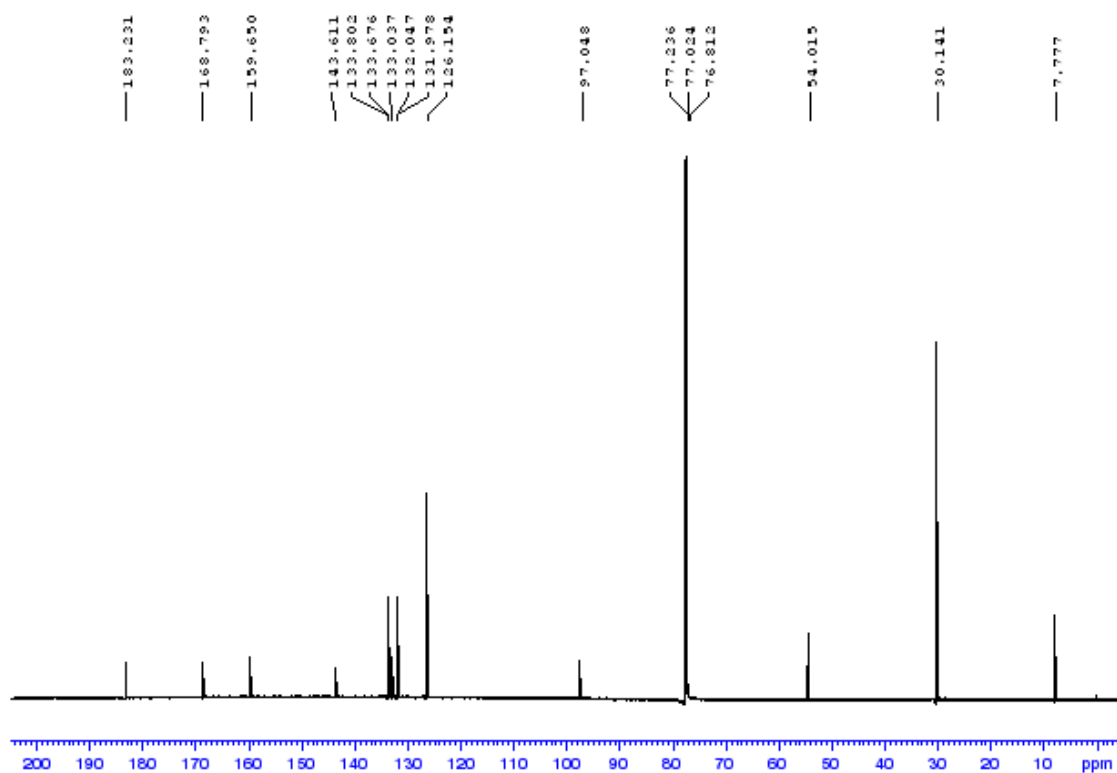
### Obtention of compound 4a from 2-ethoxy-3-hydroxy-1,4-naphthoquinone (11)

A solution of 2-ethoxy-3-hydroxy-1,4-naphthoquinone (18.0 mg, 0.08 mmol), *t*-butyl isocyanide (30.0 μL, 0.24 mmol) and Yb(OTf)<sub>3</sub> (2.0 mg, 10 mol %) in 2 mL of EtOH, was irradiated for 30 min at 150° C. The reaction mixture was then cooled to room temperature, and the alcohol was removed under reduced pressure. The crude was purified by preparative-TLC using hexanes/EtOAc (7:3) to yield 3.8 mg (16%) of **4a** as an amorphous blue solid.

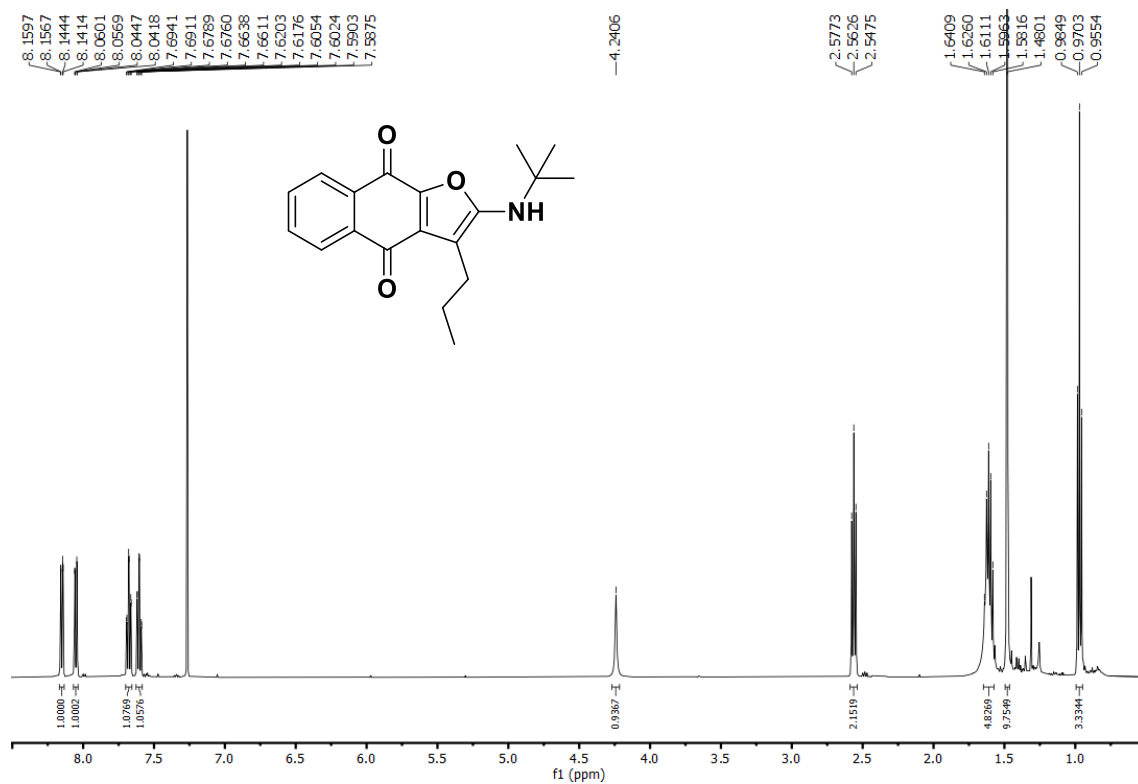
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 600 MHz) of compound 4a**



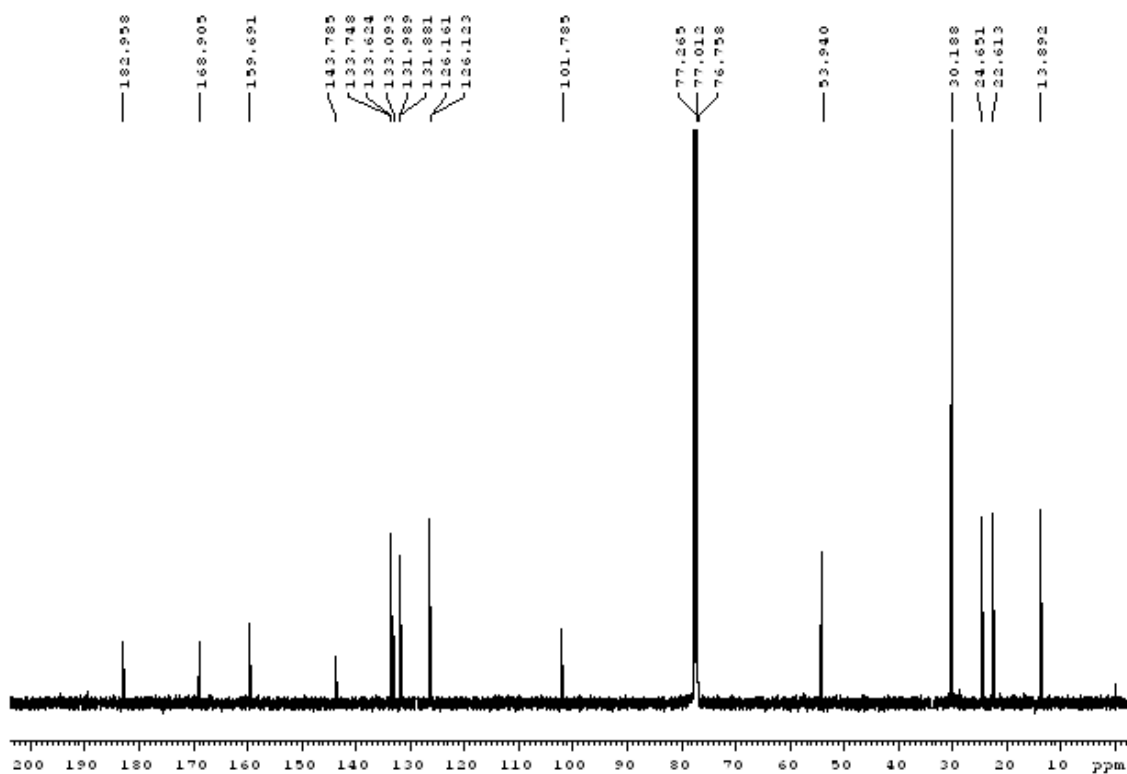
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz) of compound 4a**



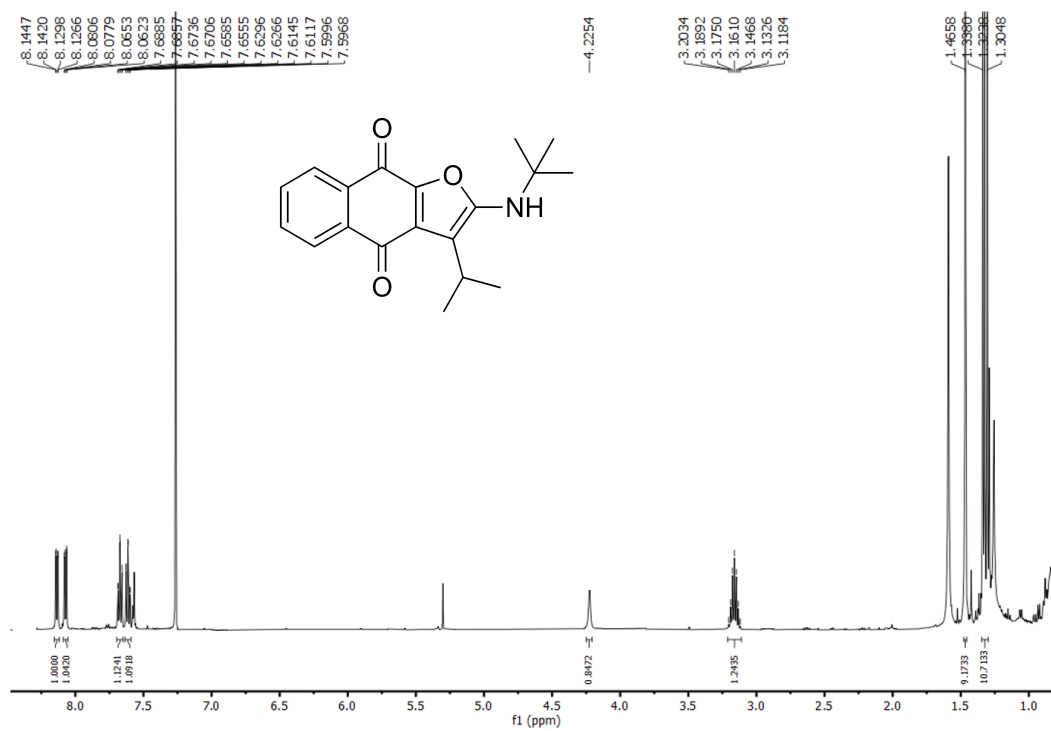
### $^1\text{H-NMR}$ ( $\text{CDCl}_3$ , 500 MHz) of compound 4b



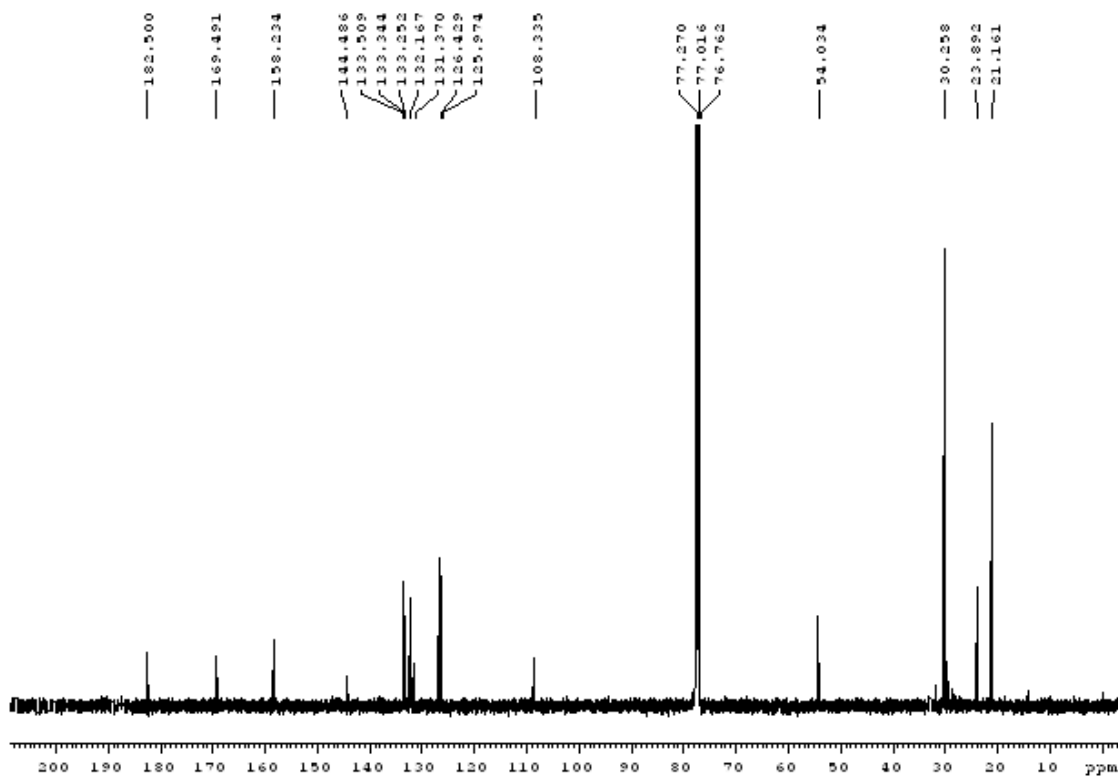
### $^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ , 125 MHz) of compound 4b



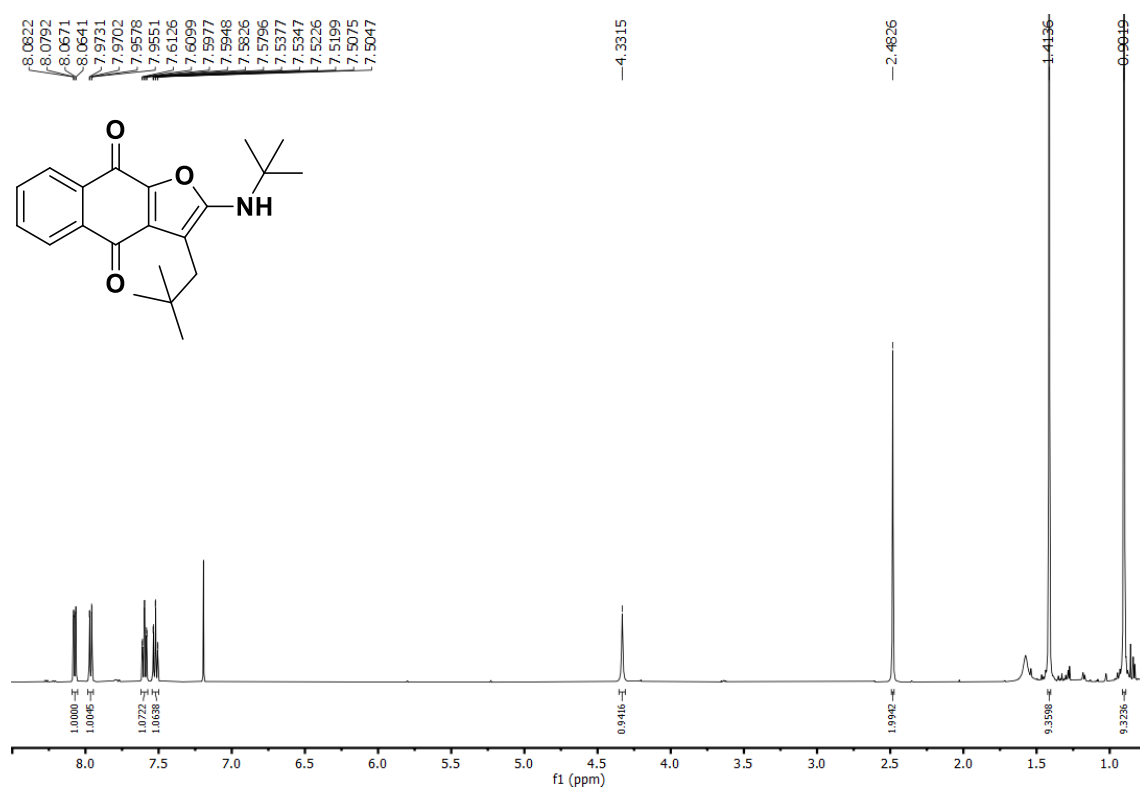
### $^1\text{H-NMR}$ ( $\text{CDCl}_3$ , 500 MHz) of compound 4c



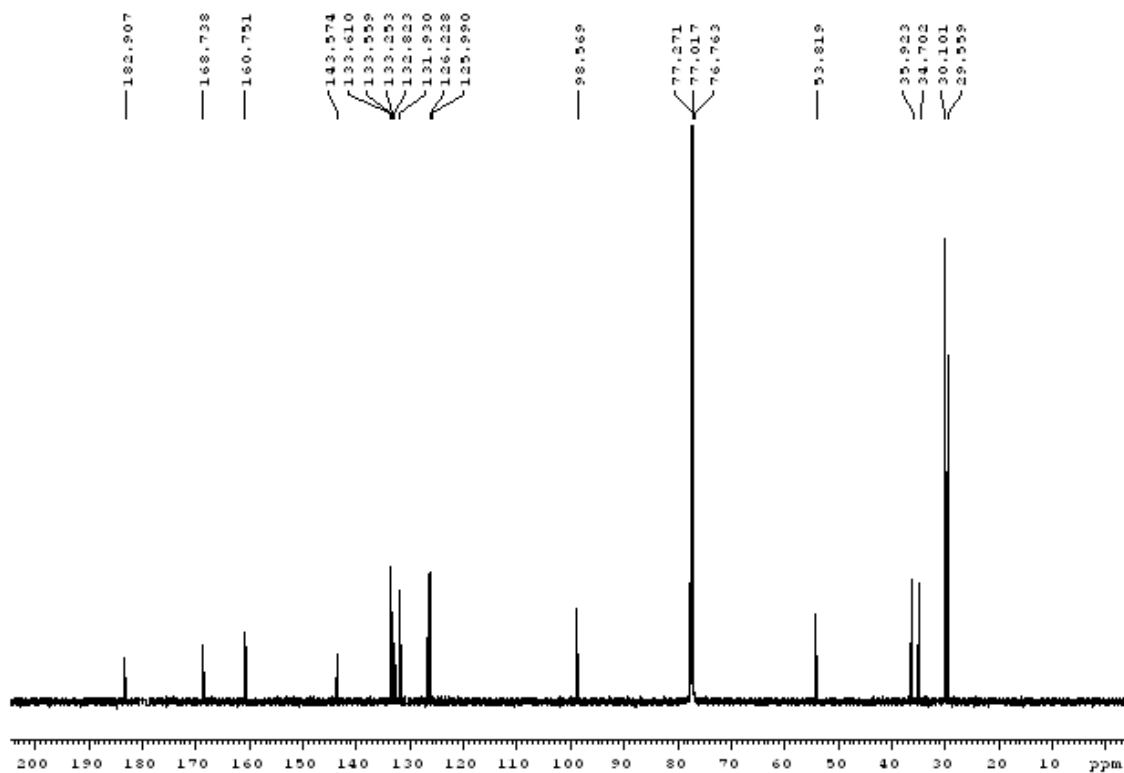
### $^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ , 150 MHz) of compound 4c



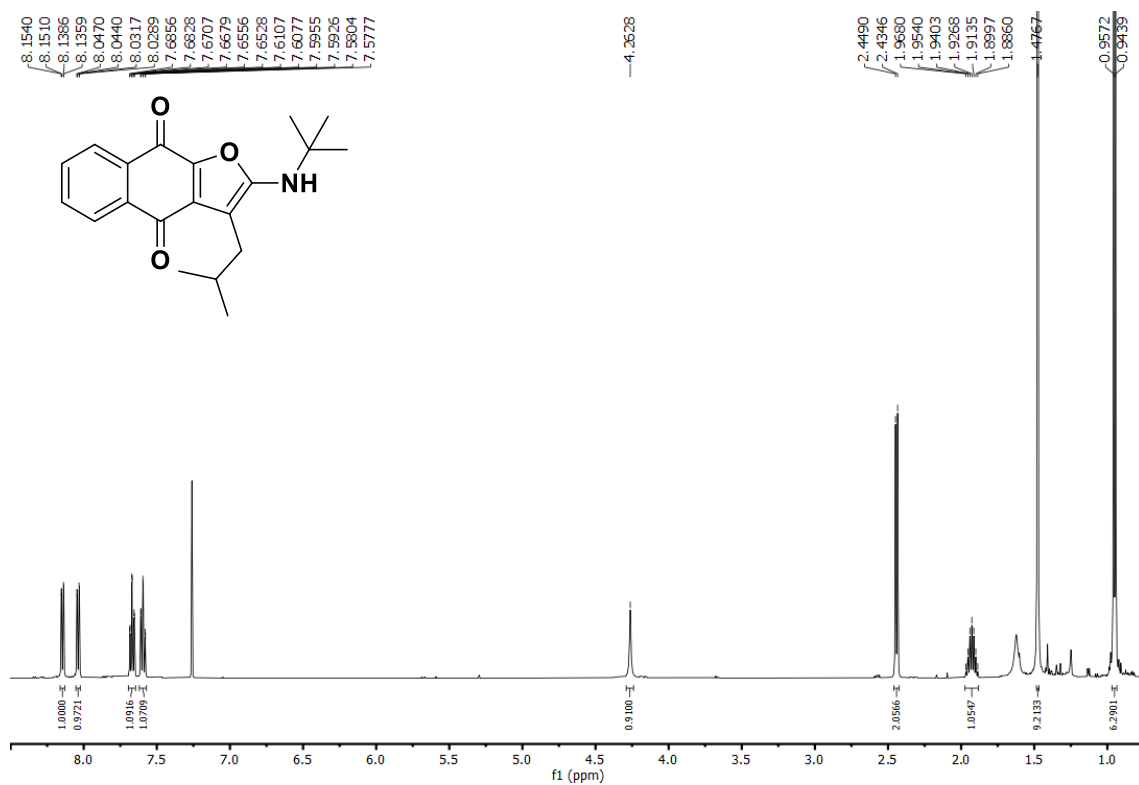
### <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 600 MHz) of compound 4d



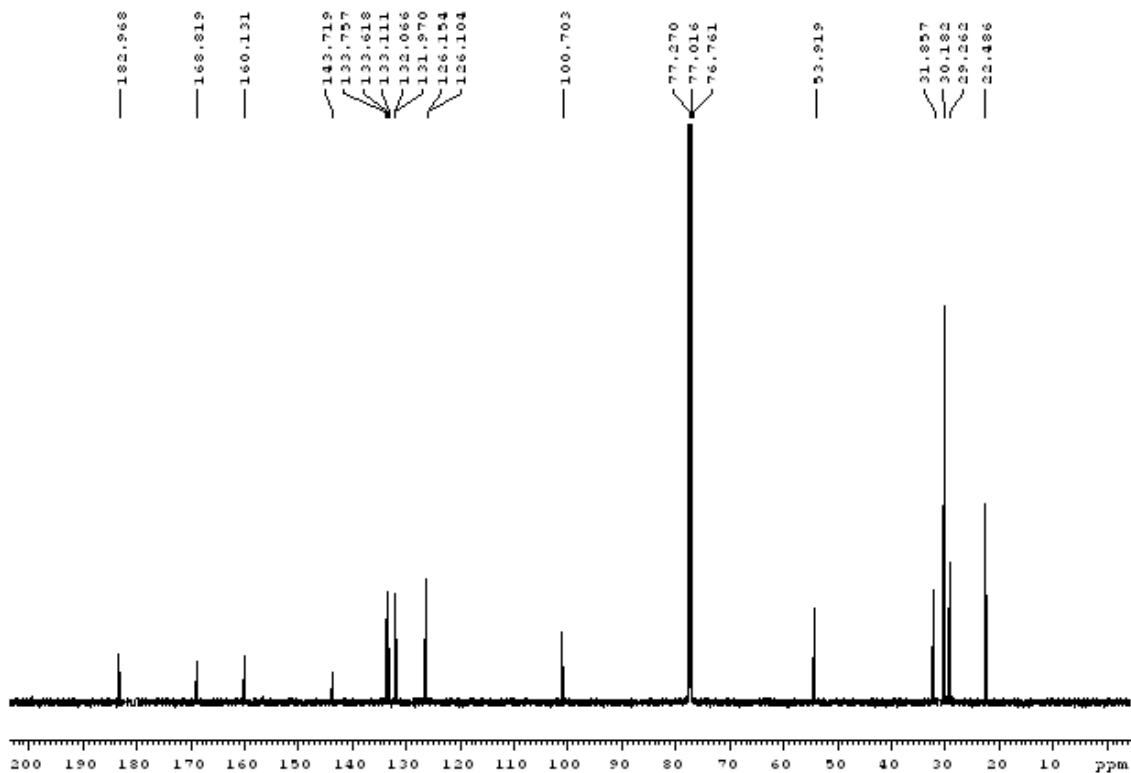
### <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz) of compound 4d



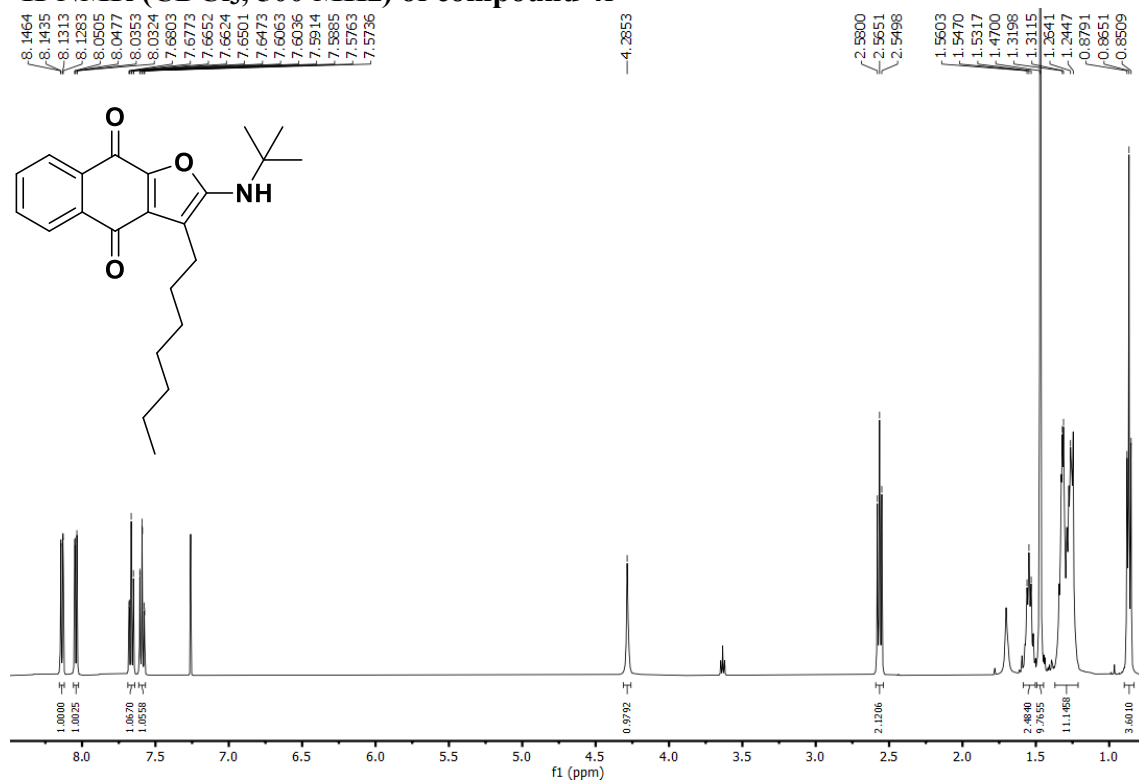
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 4e**



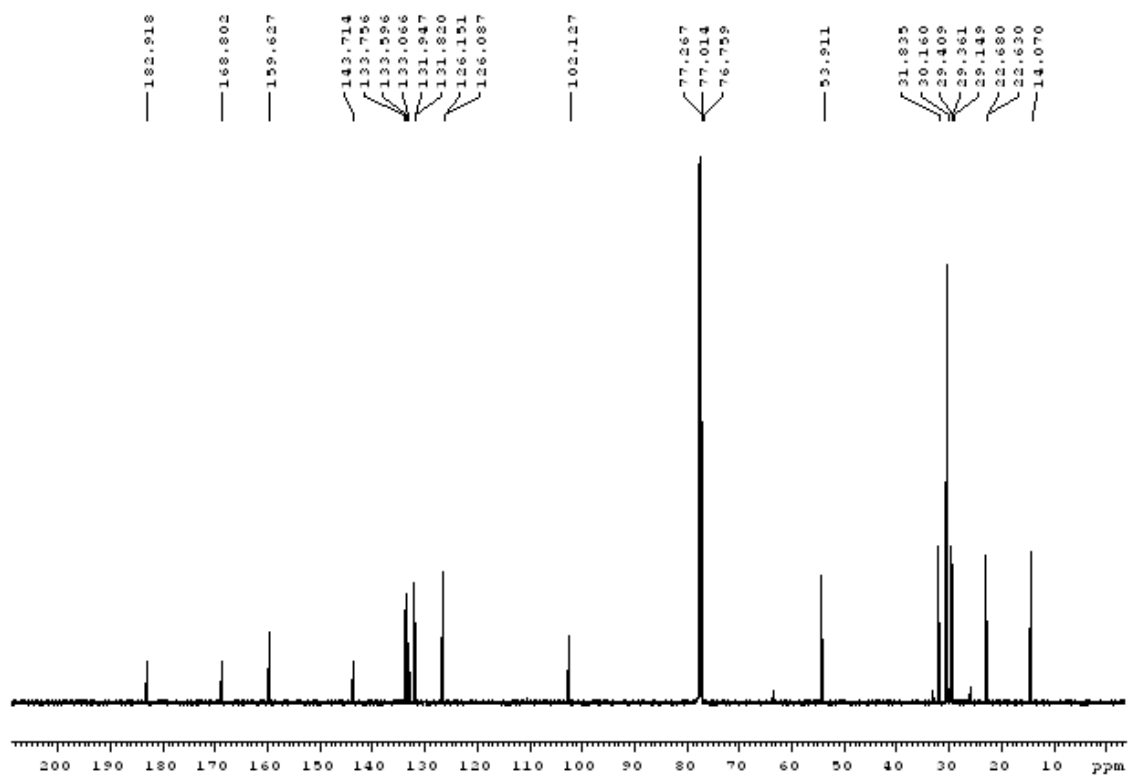
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz) of compound 4e**



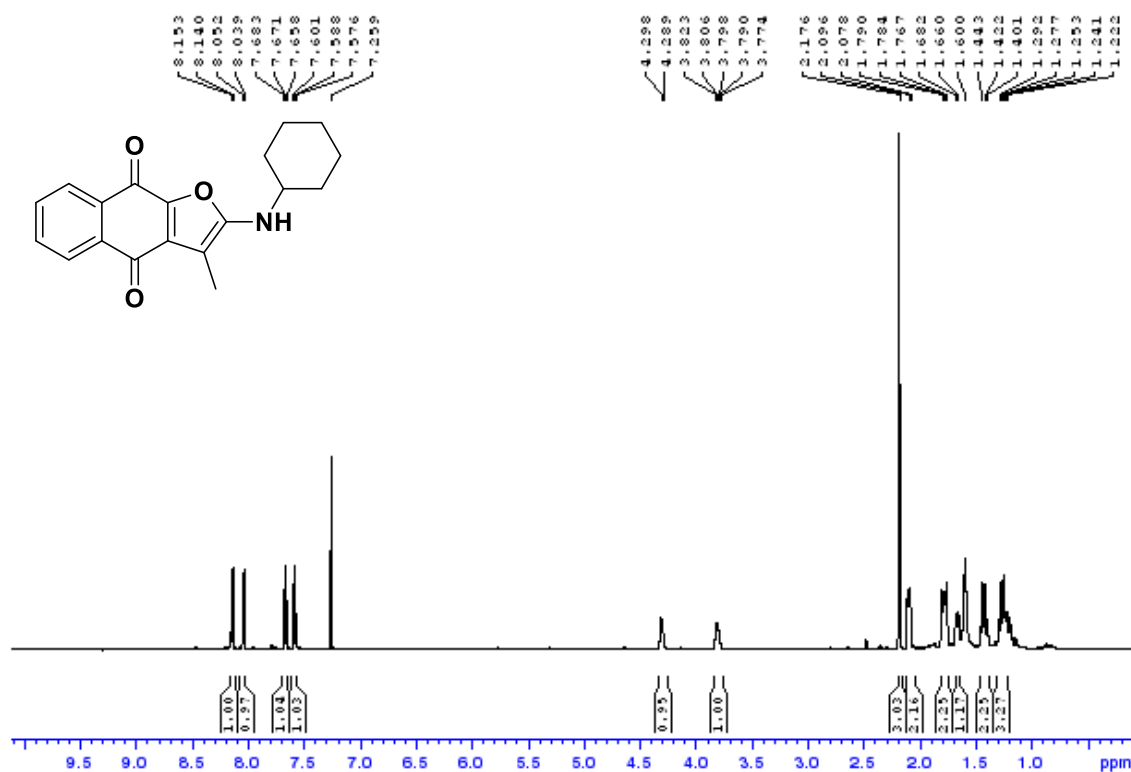
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 4f**



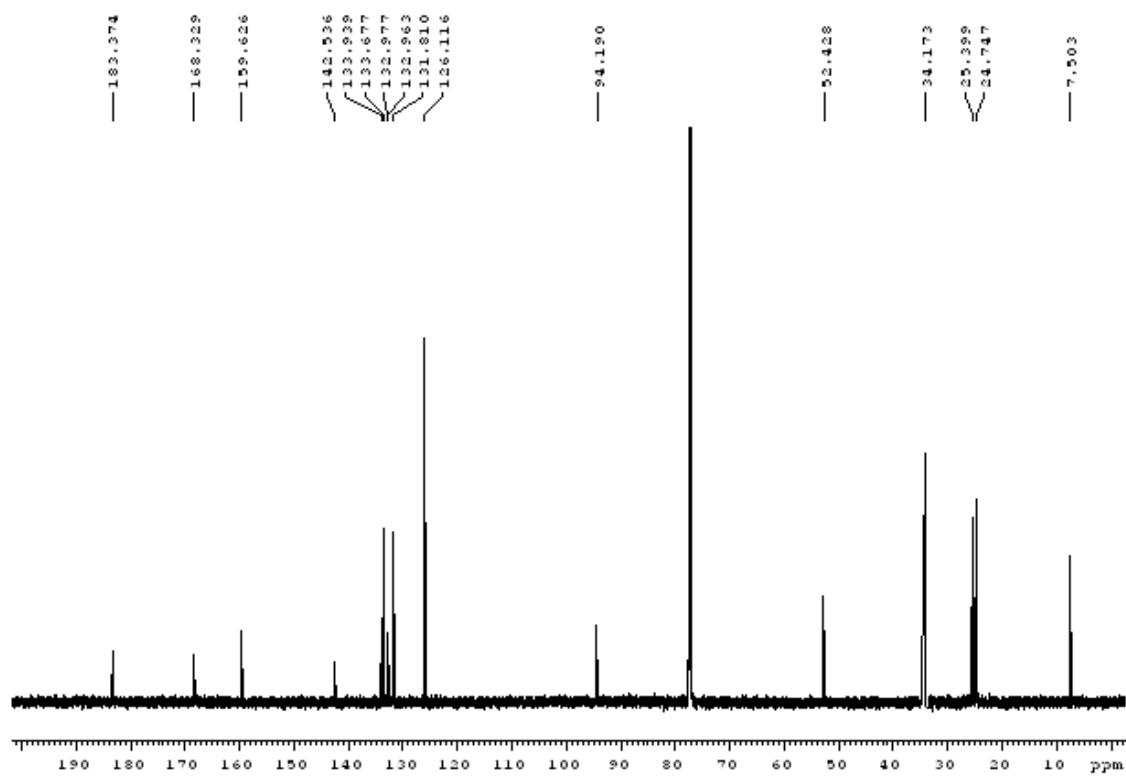
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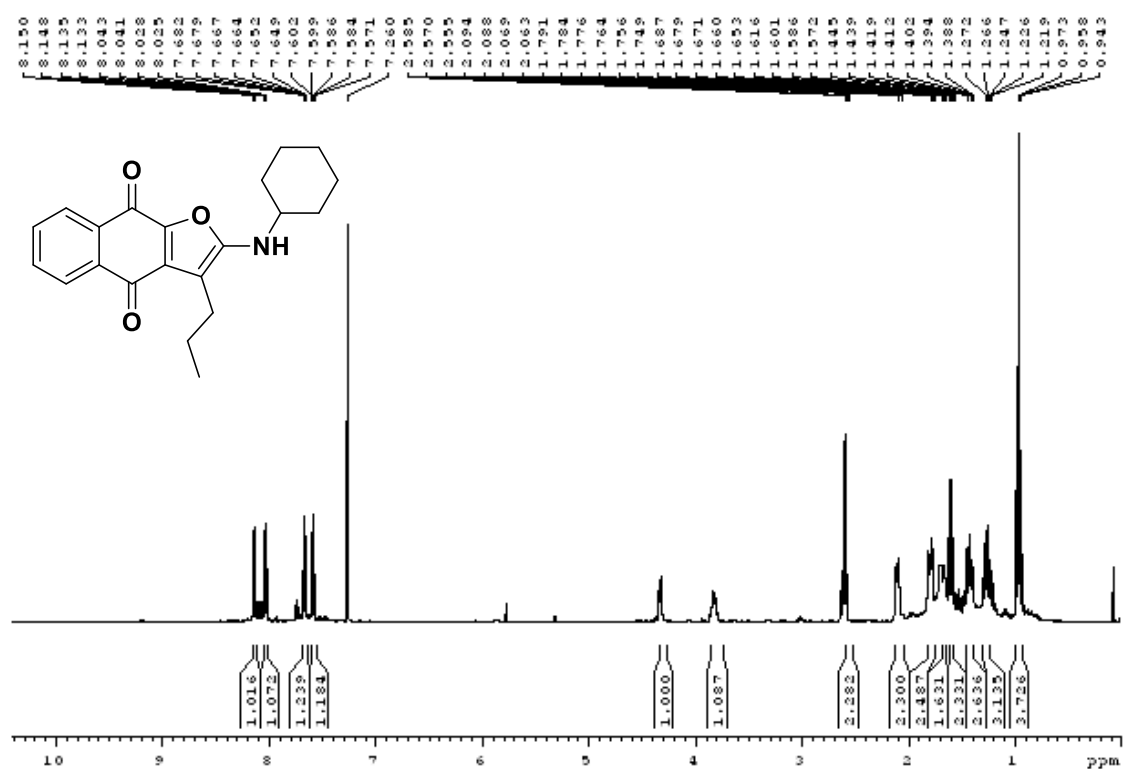
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 600 MHz) of compound 5a**



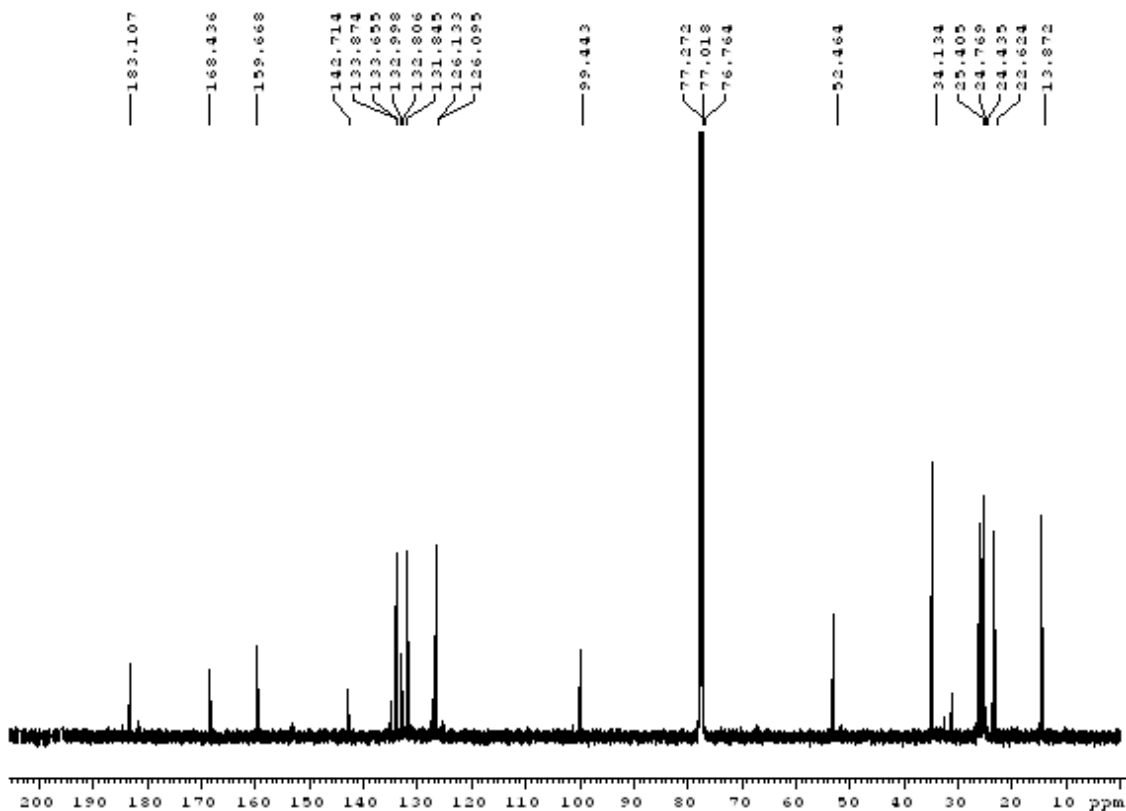
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz) of compound 5a**



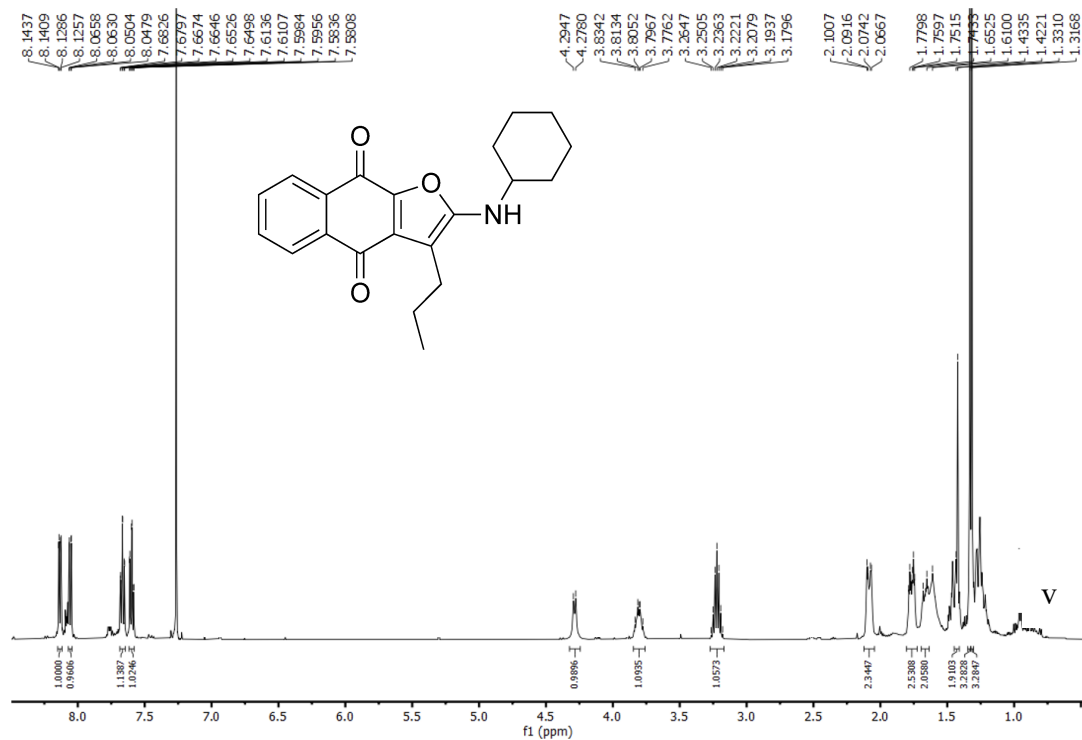
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 600 MHz) of compound 5b**



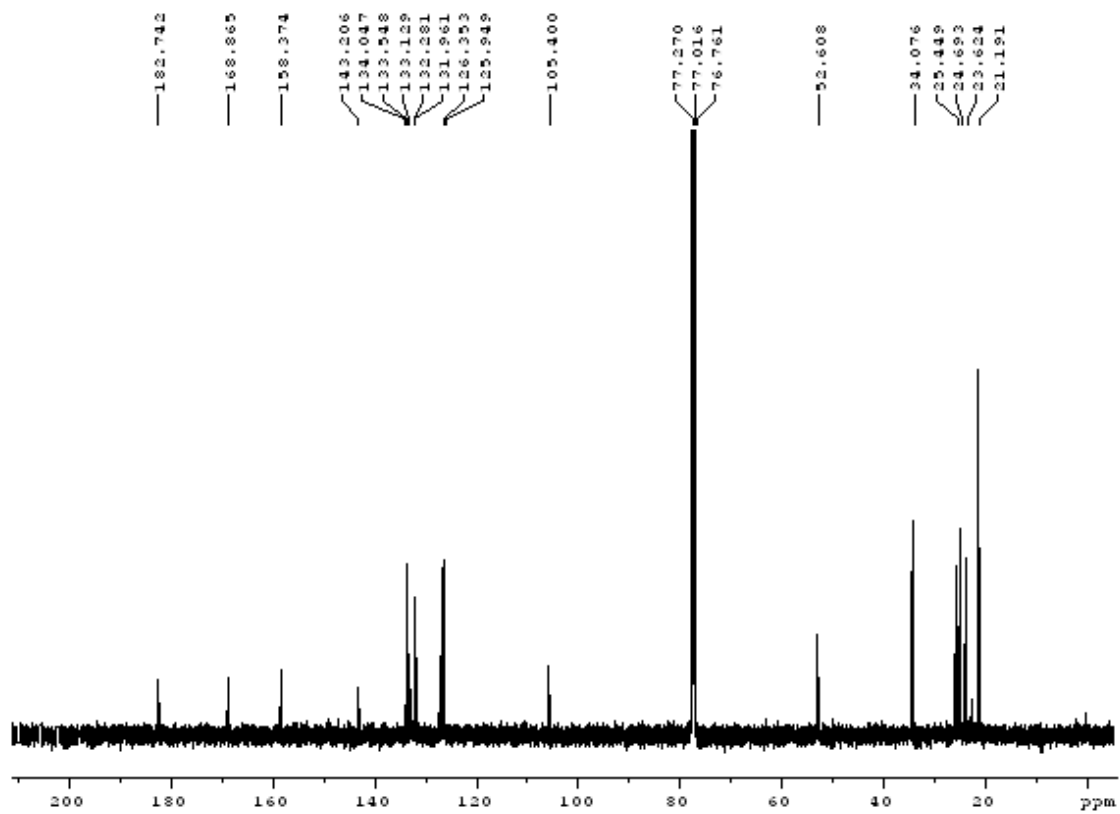
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz) of compound 5b**



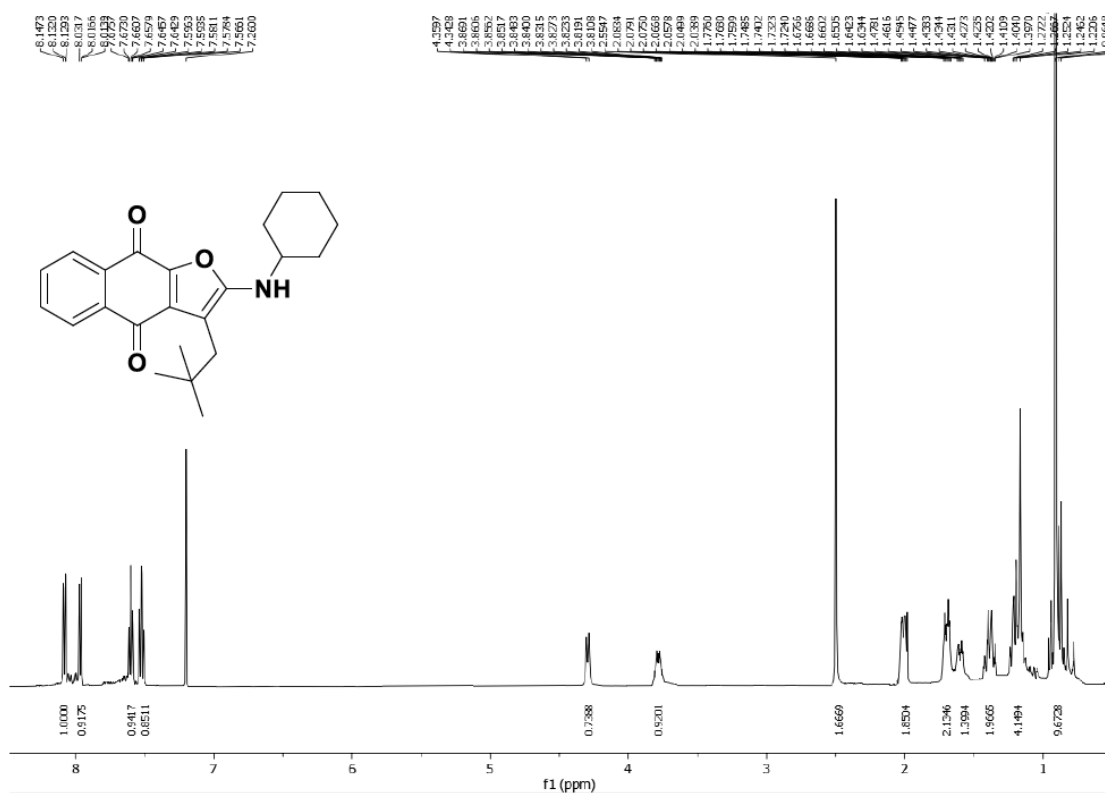
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 5c**



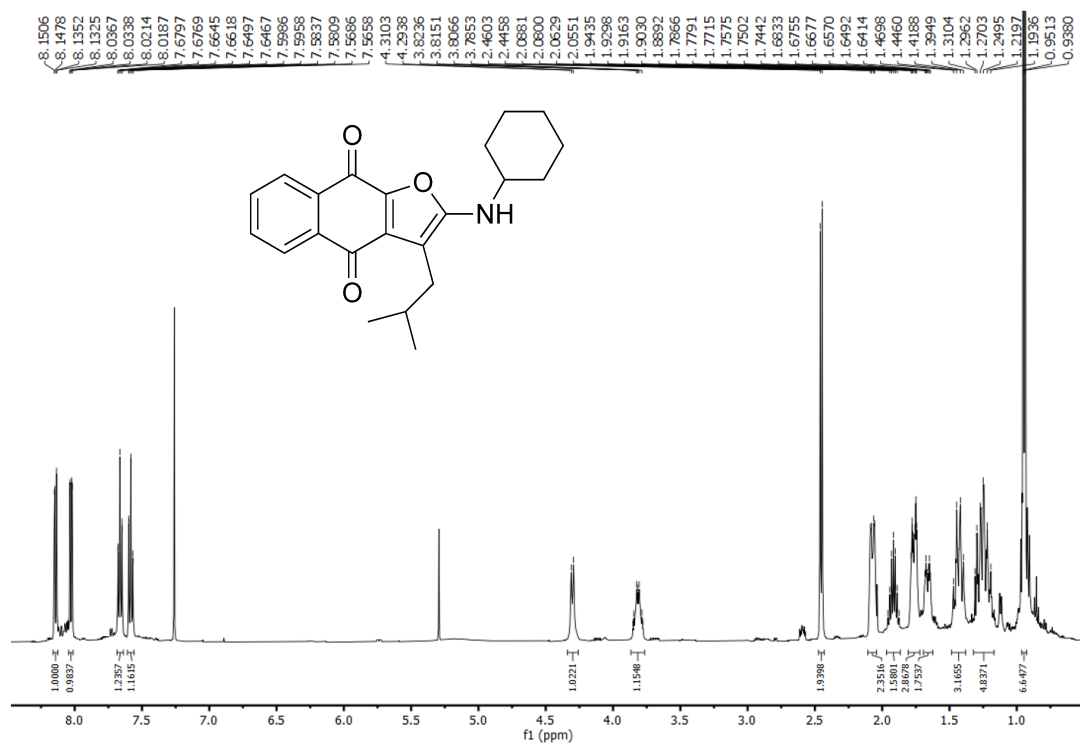
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz) of compound 5c**



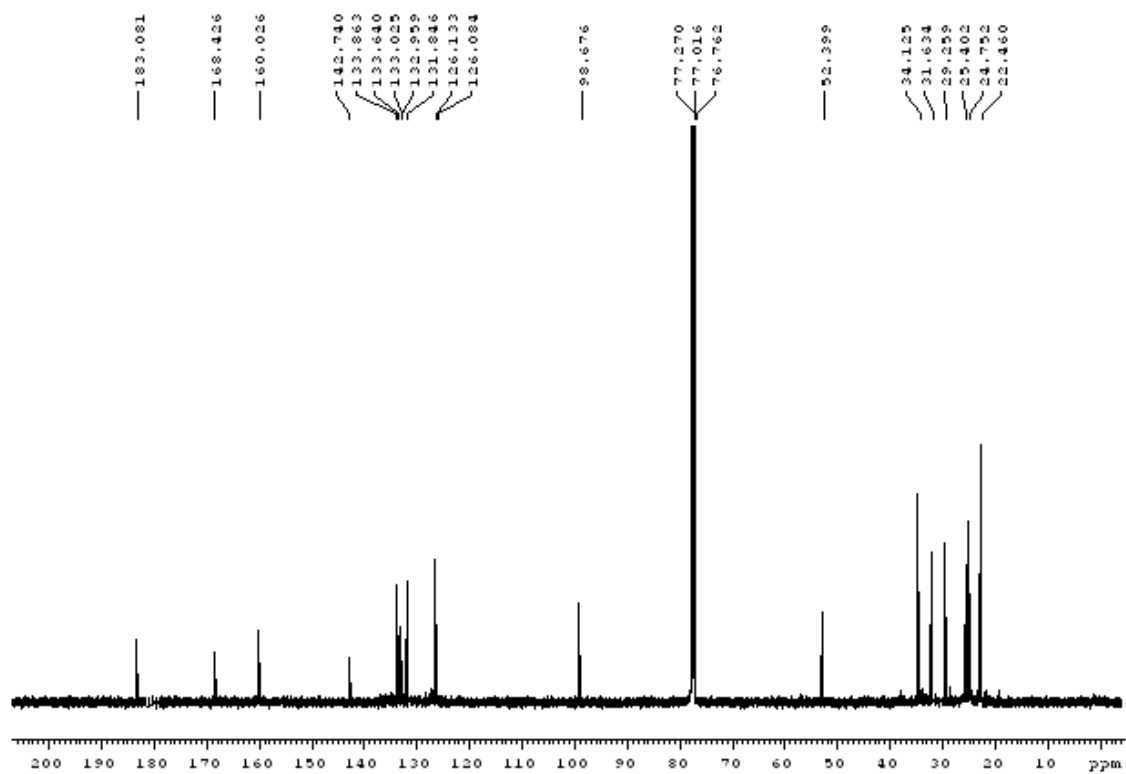
# <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 5d



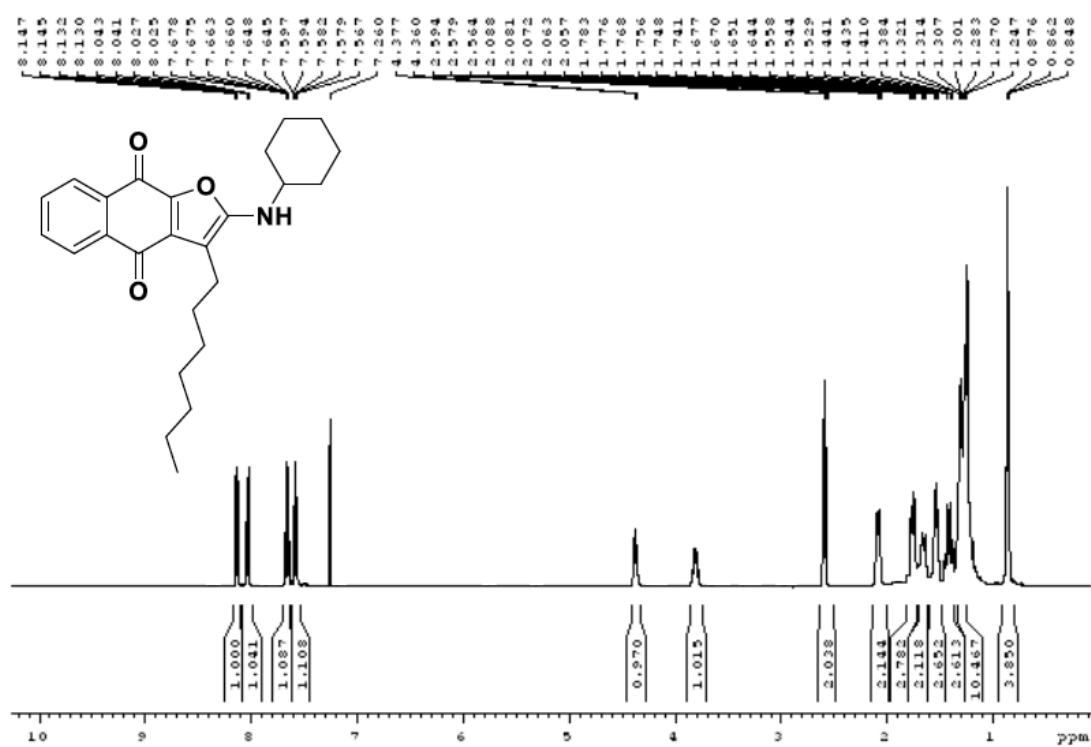
### <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 5e



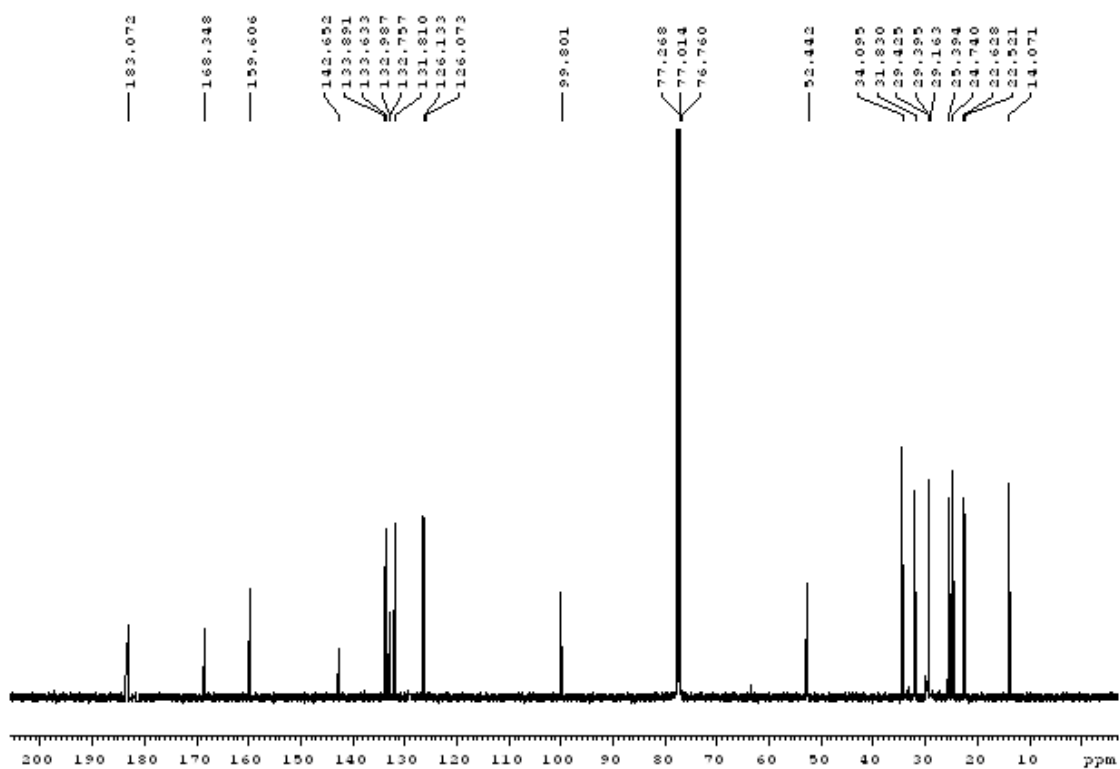
### <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz) of compound 5e



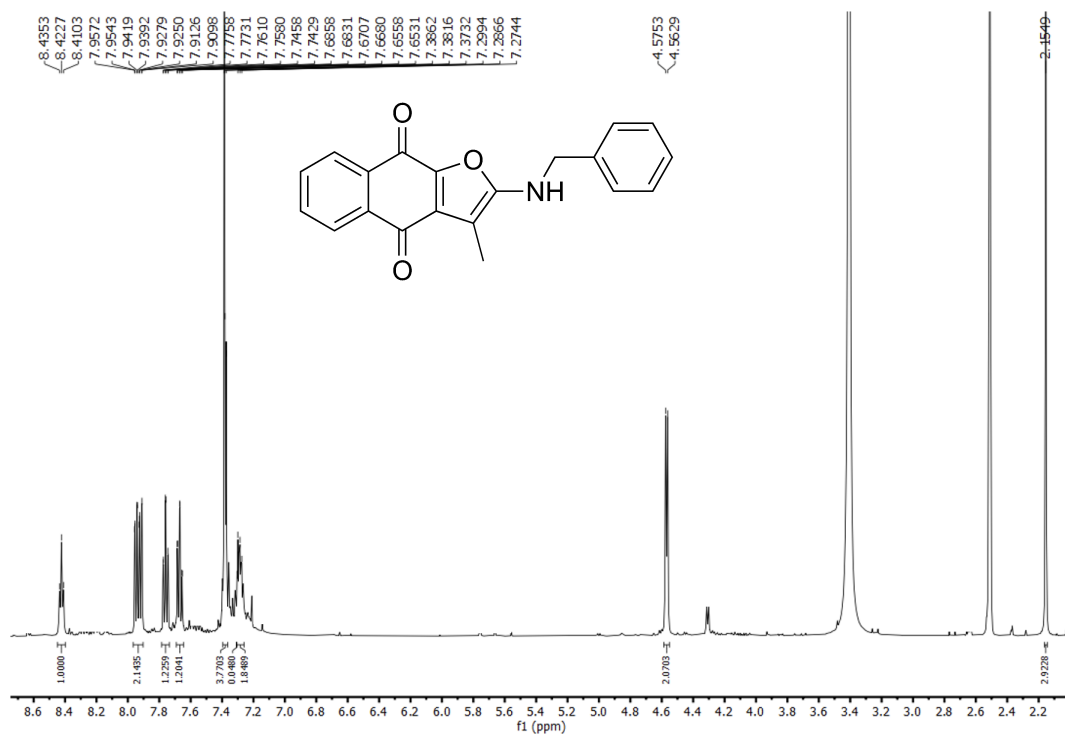
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 5f**



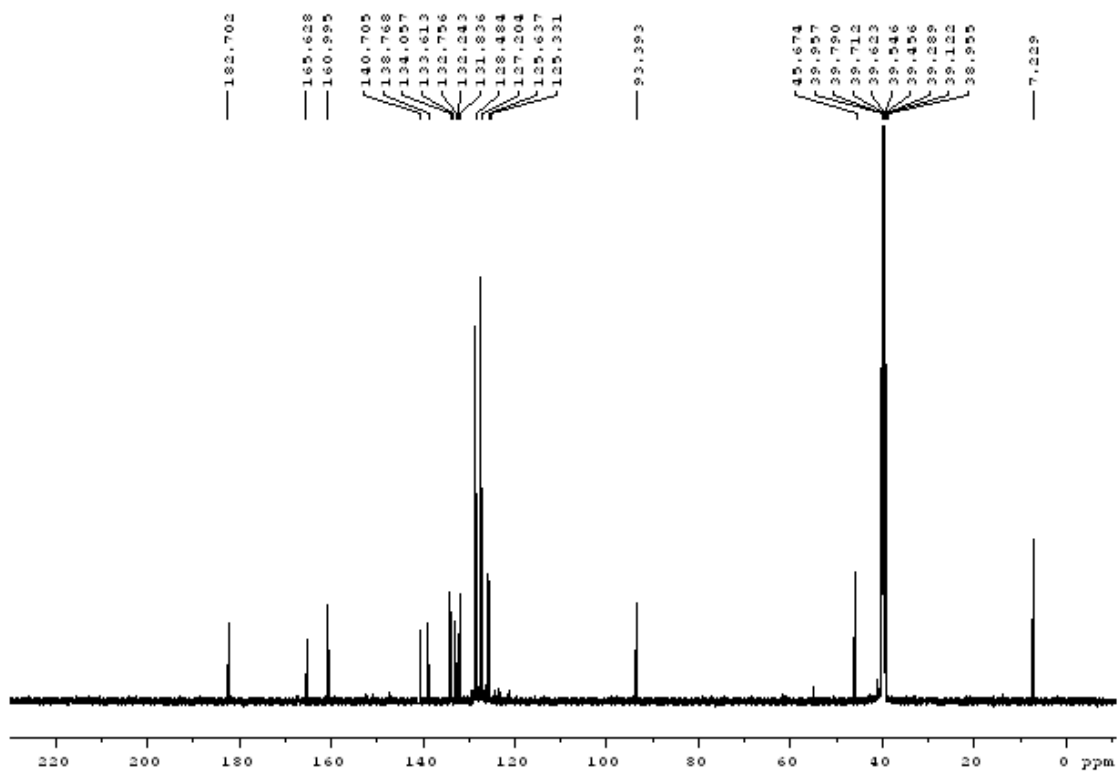
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz) of compound 5f**



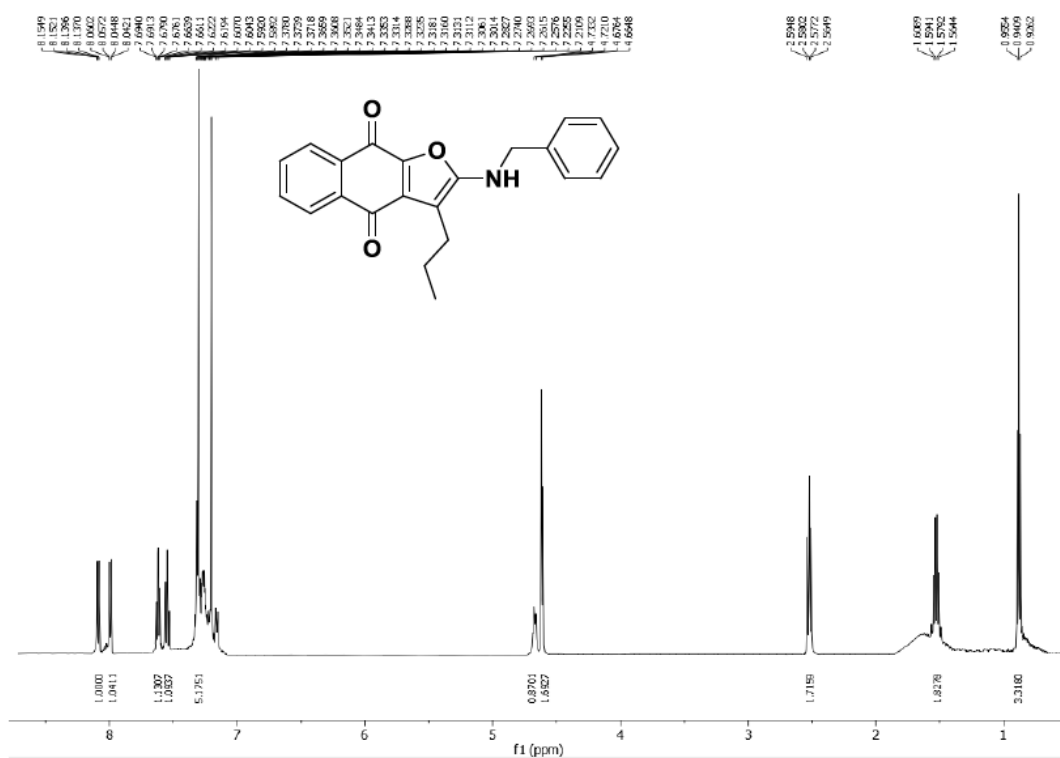
**<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 600 MHz) of compound 6a**



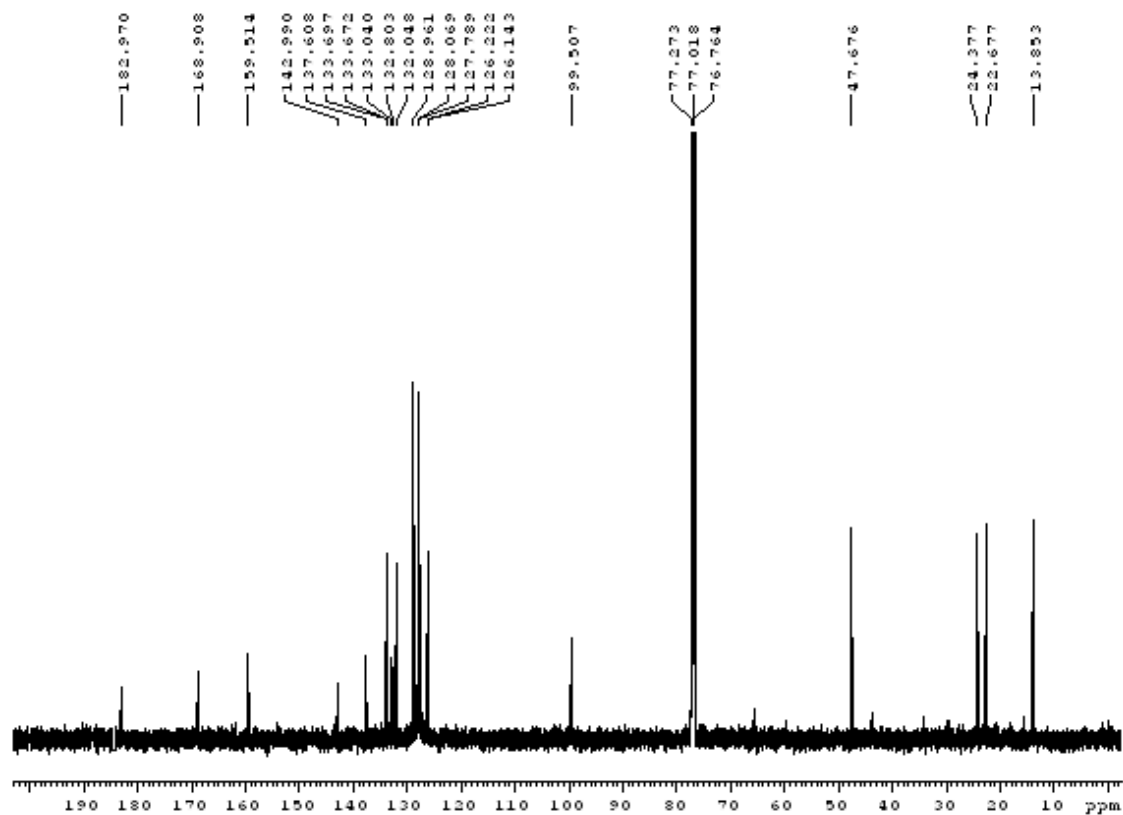
**<sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 150 MHz) of compound 6a**



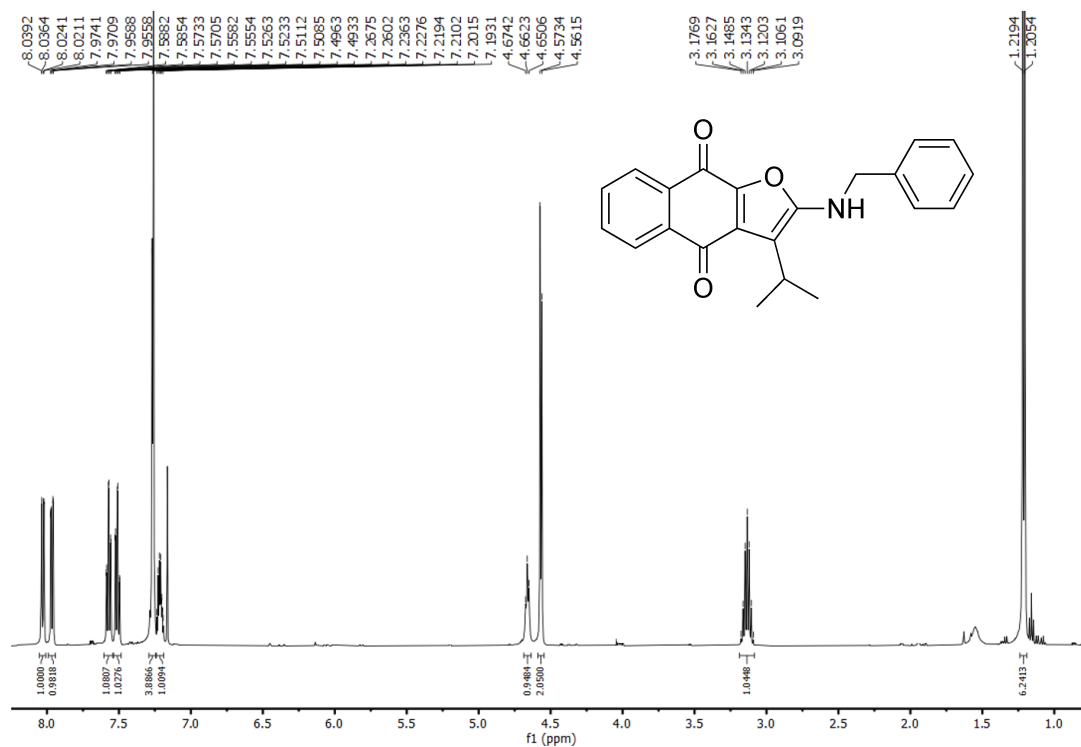
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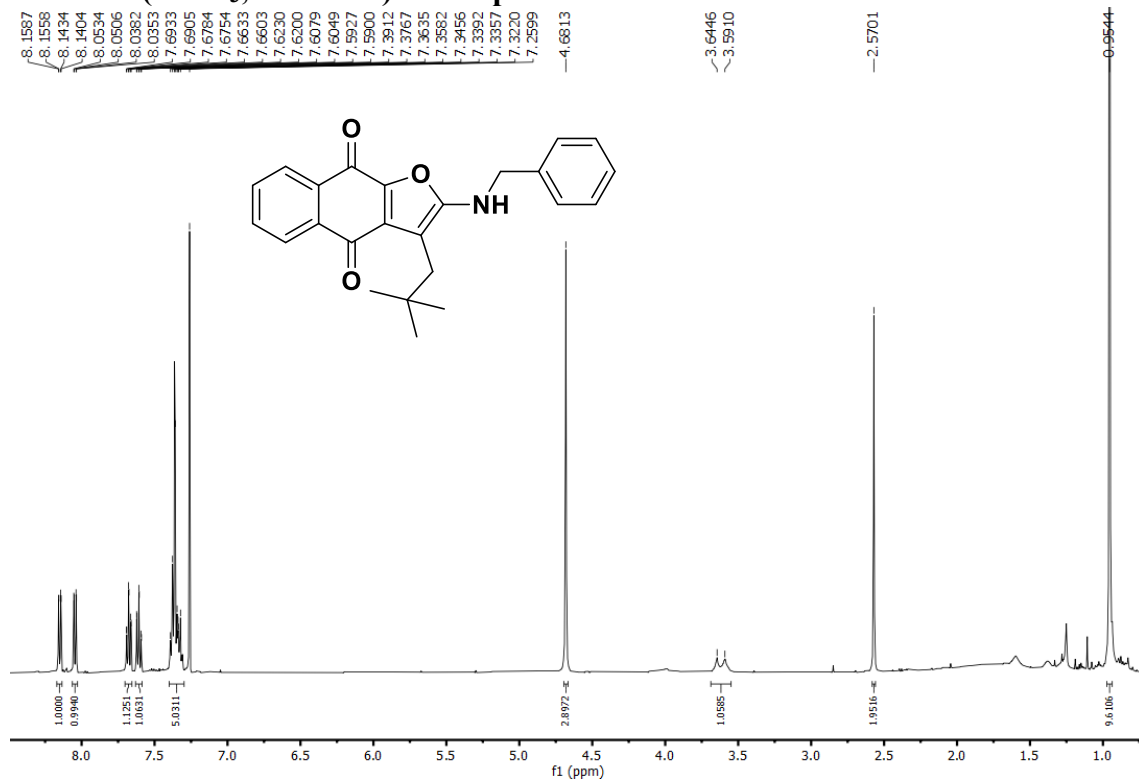
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz) of compound 6b**



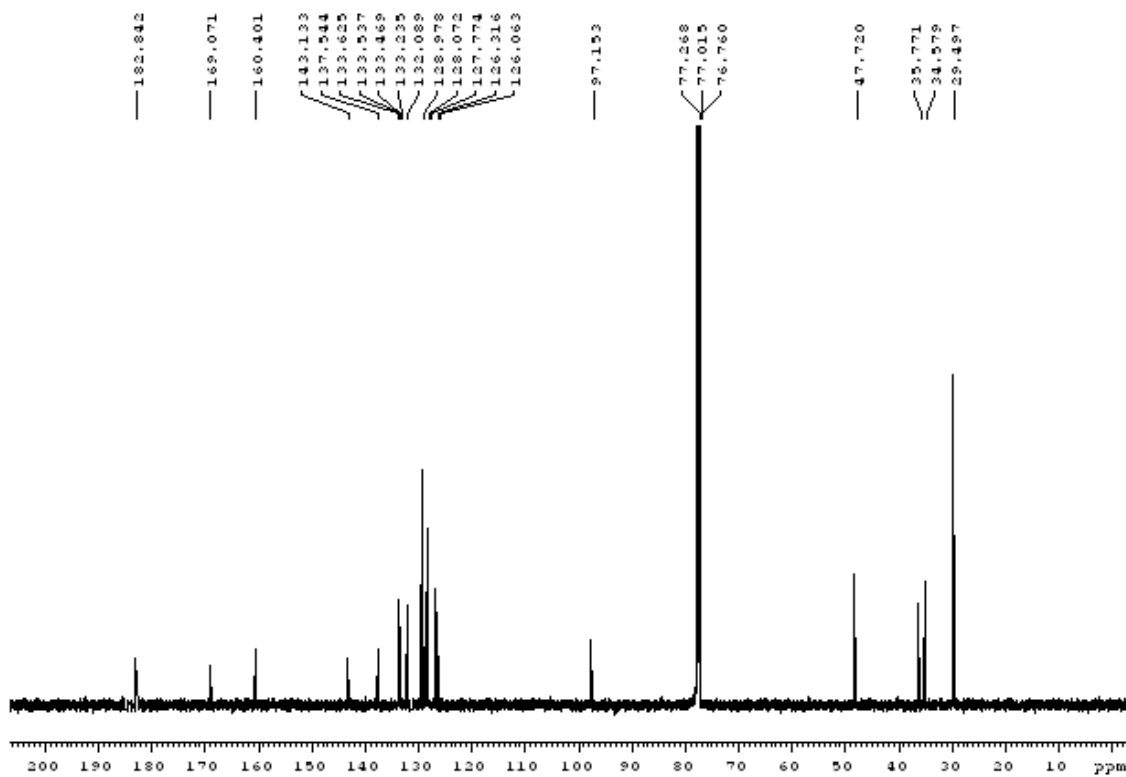
### <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 6c



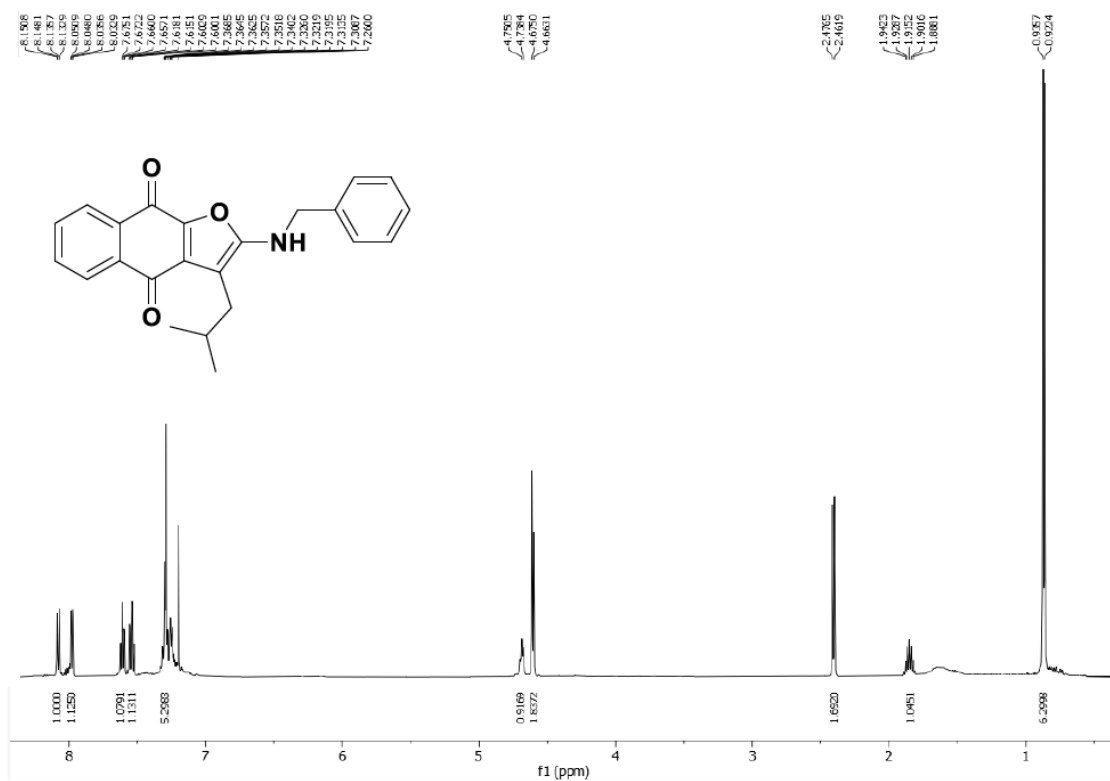
### <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 600 MHz) of compound 6d



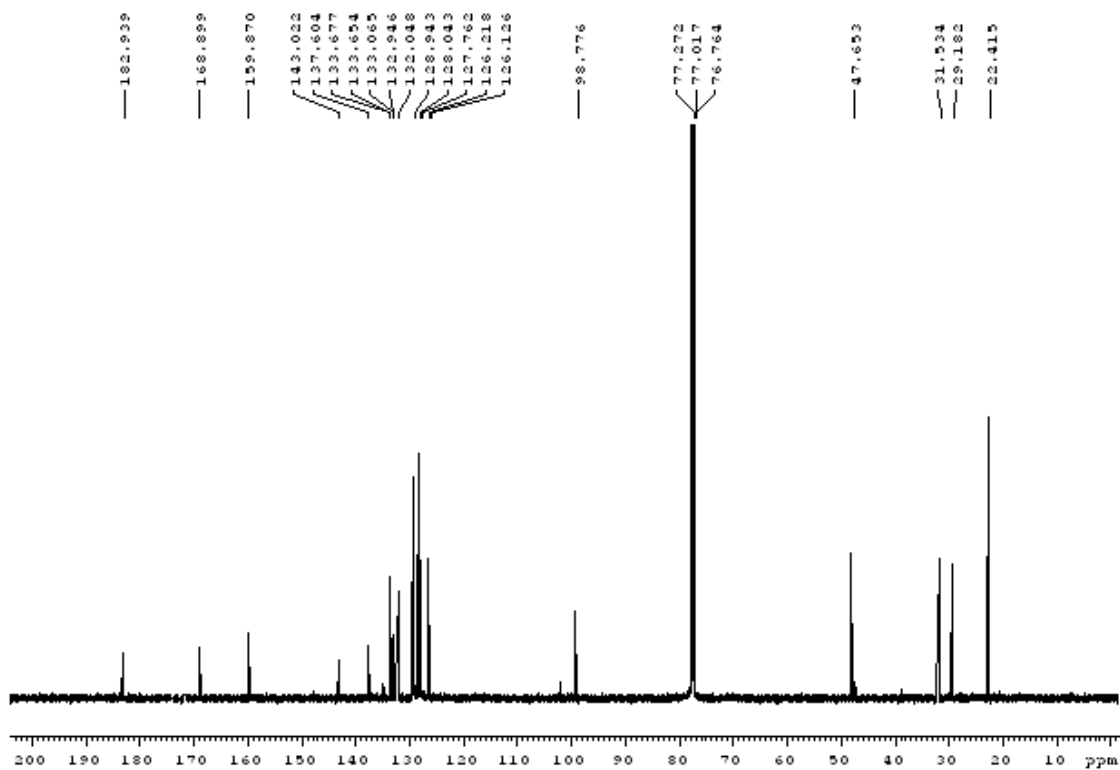
### <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz) of compound 6d



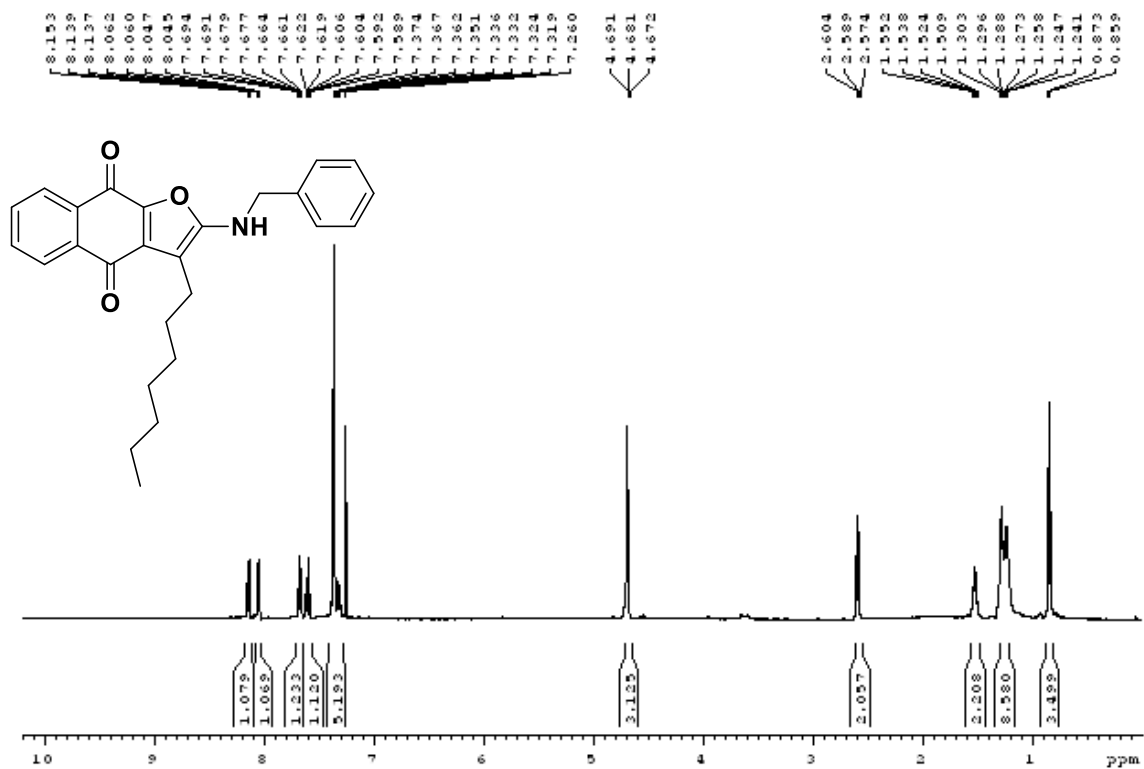
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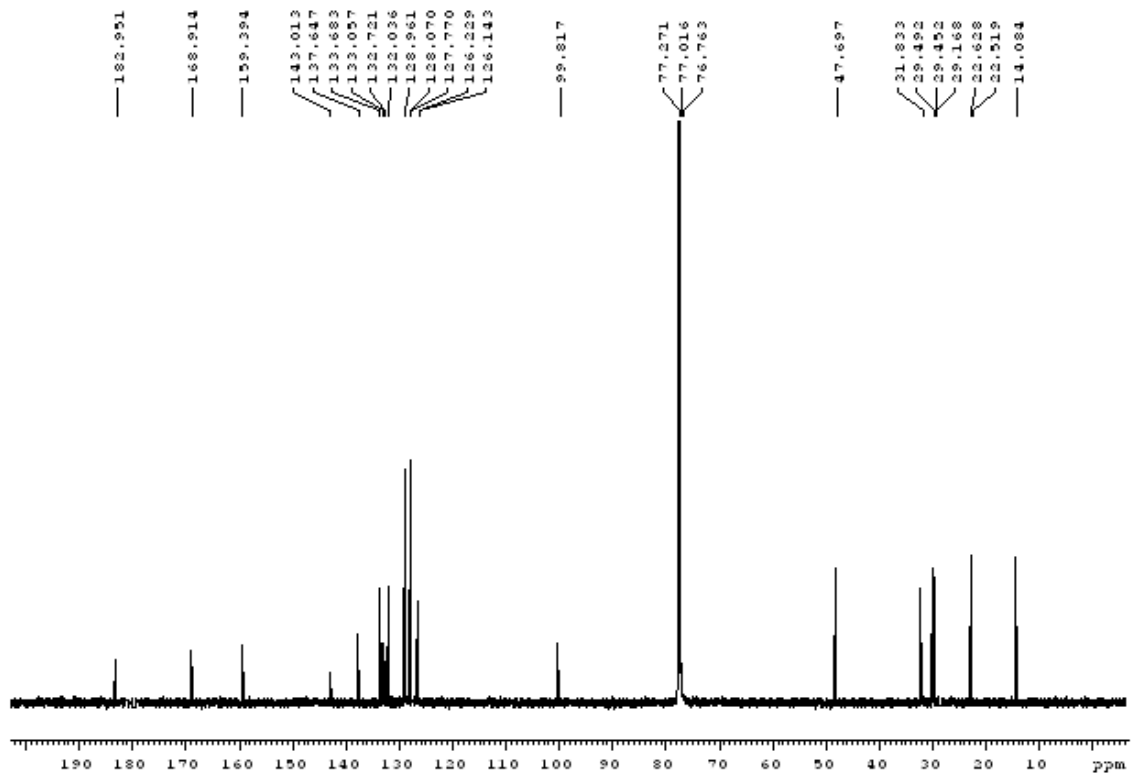
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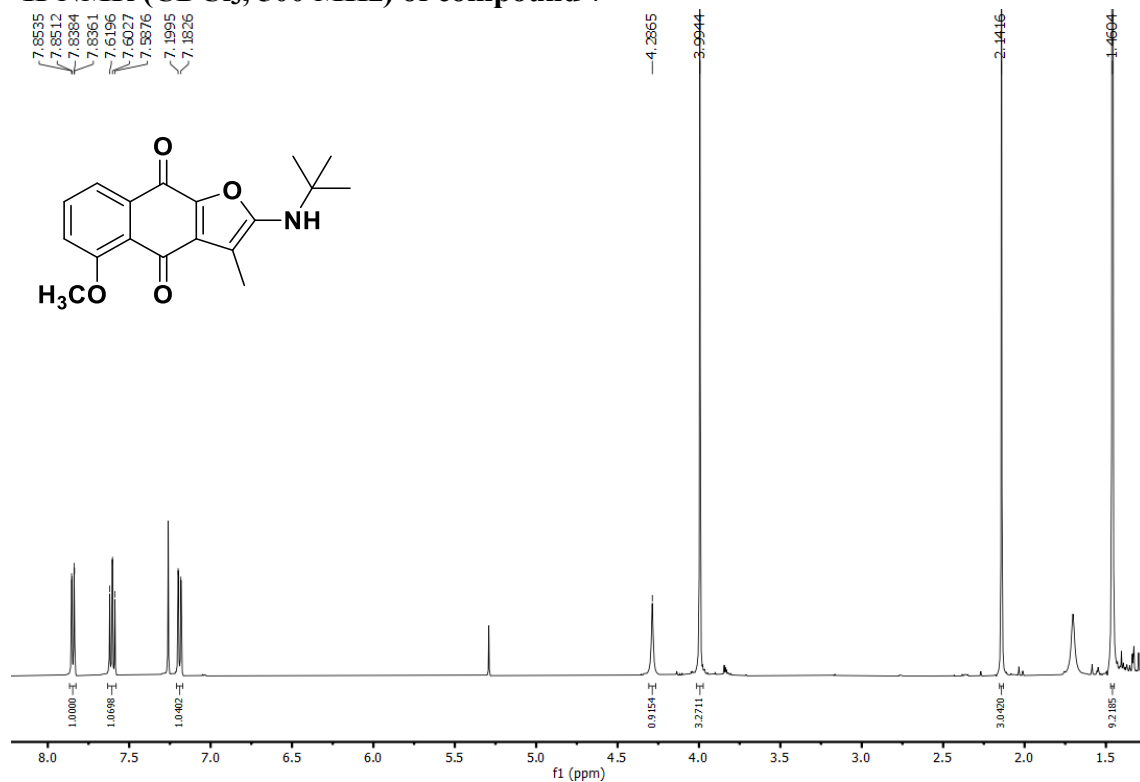
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 6f**



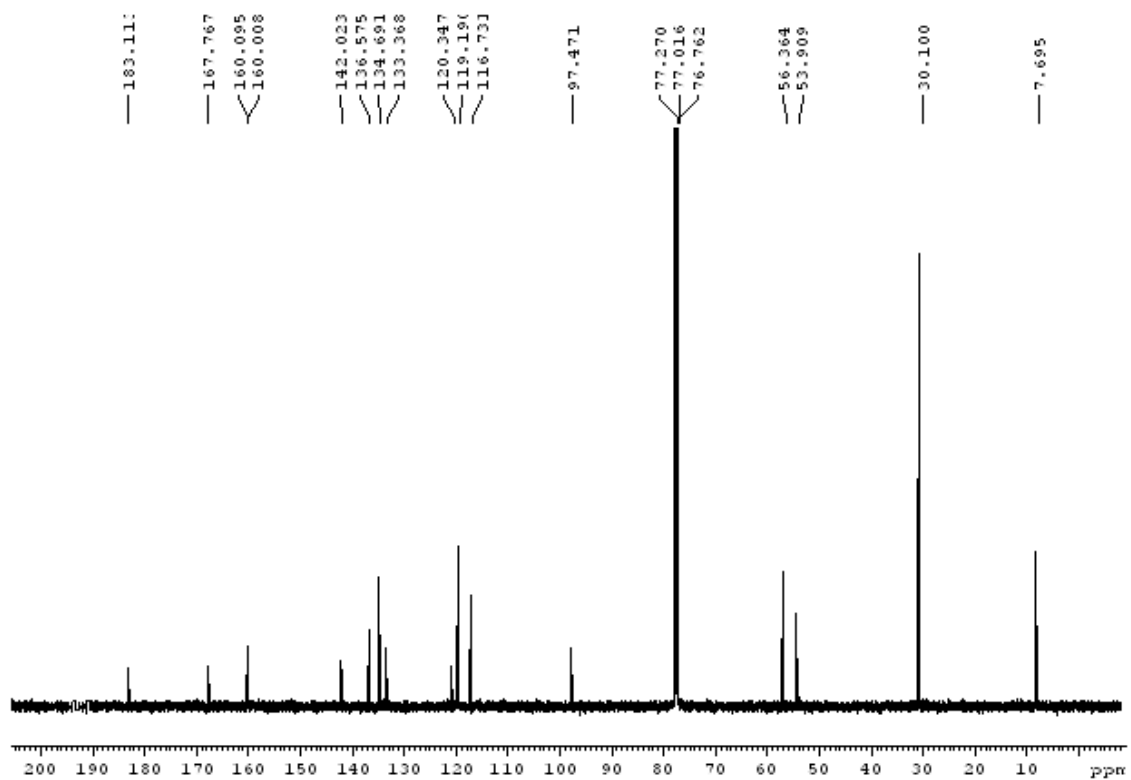
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125 MHz) of compound 6f**



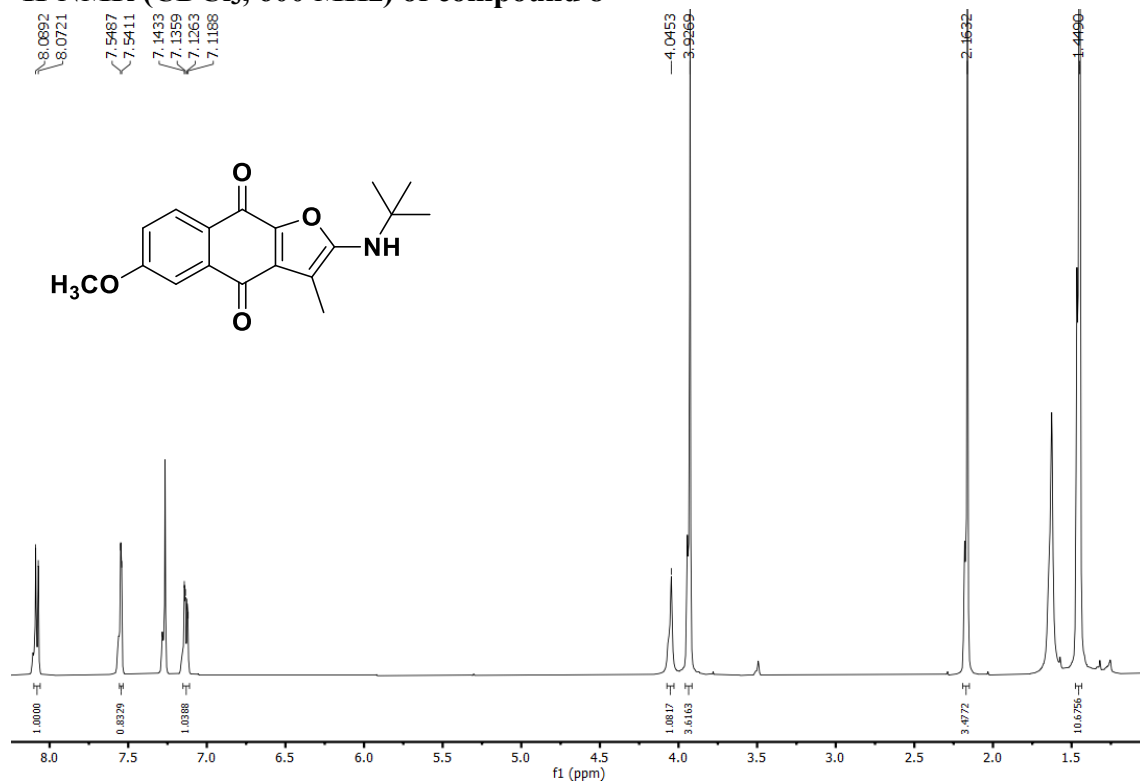
**<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz) of compound 7**



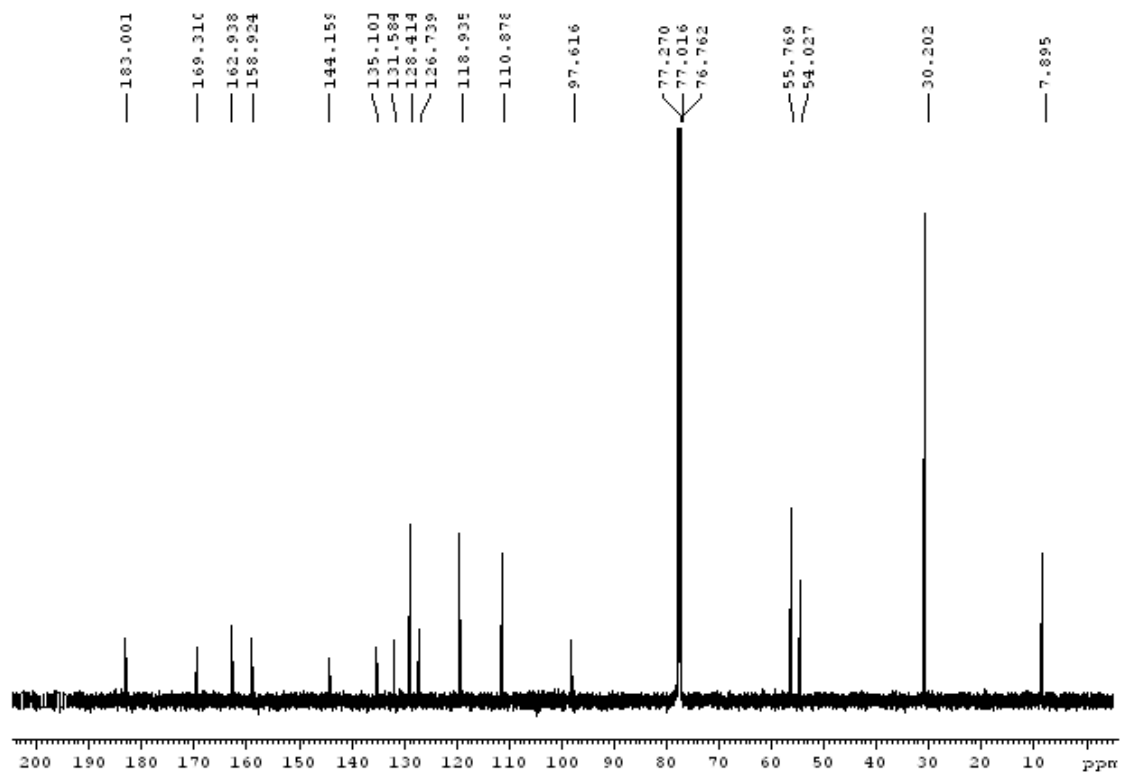
**<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz) of compound 7**



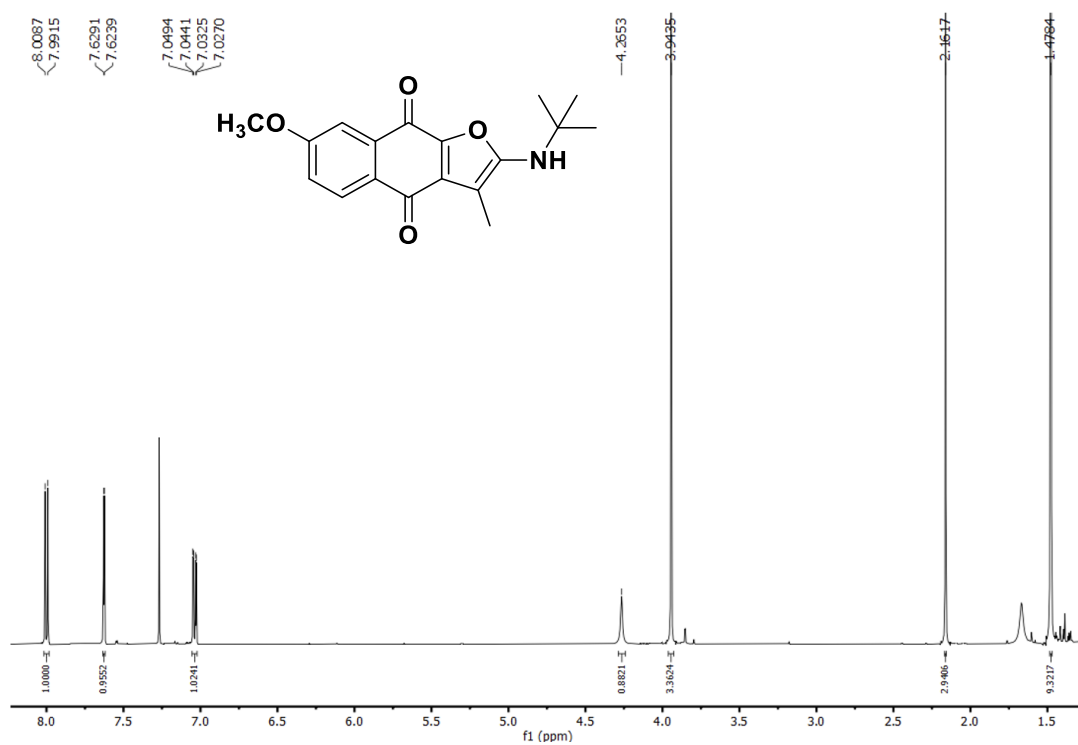
### <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 600 MHz) of compound 8



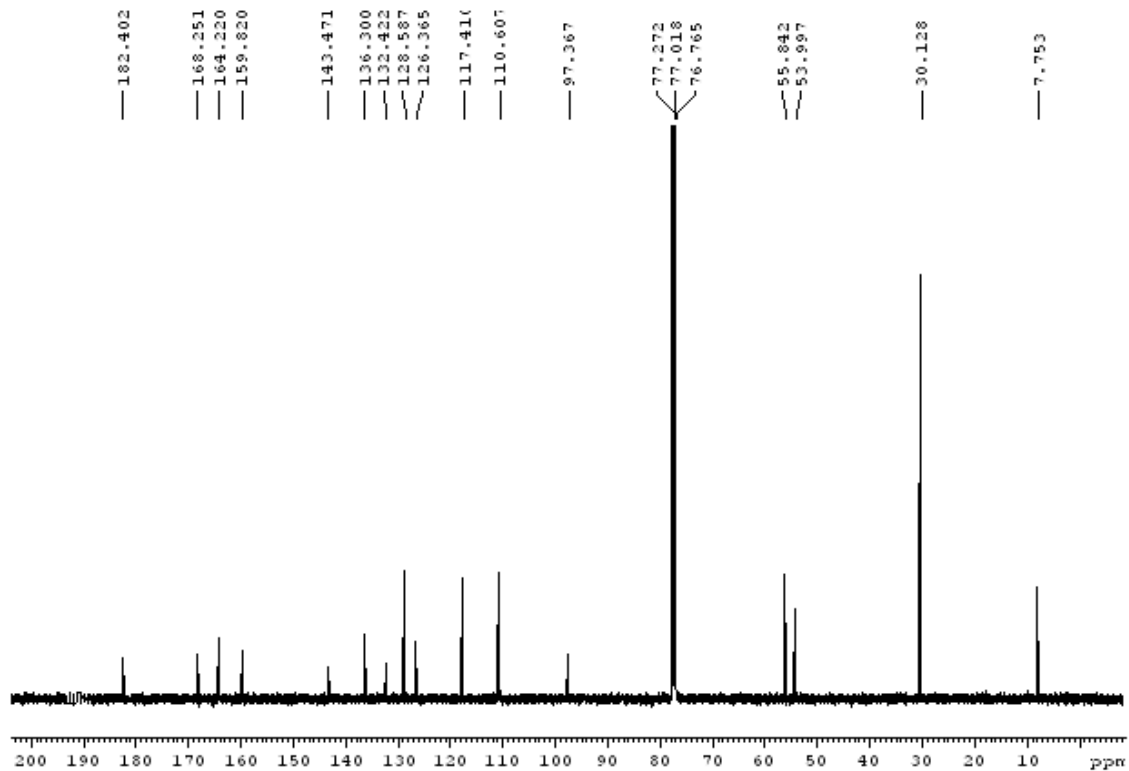
### <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz) of compound 8



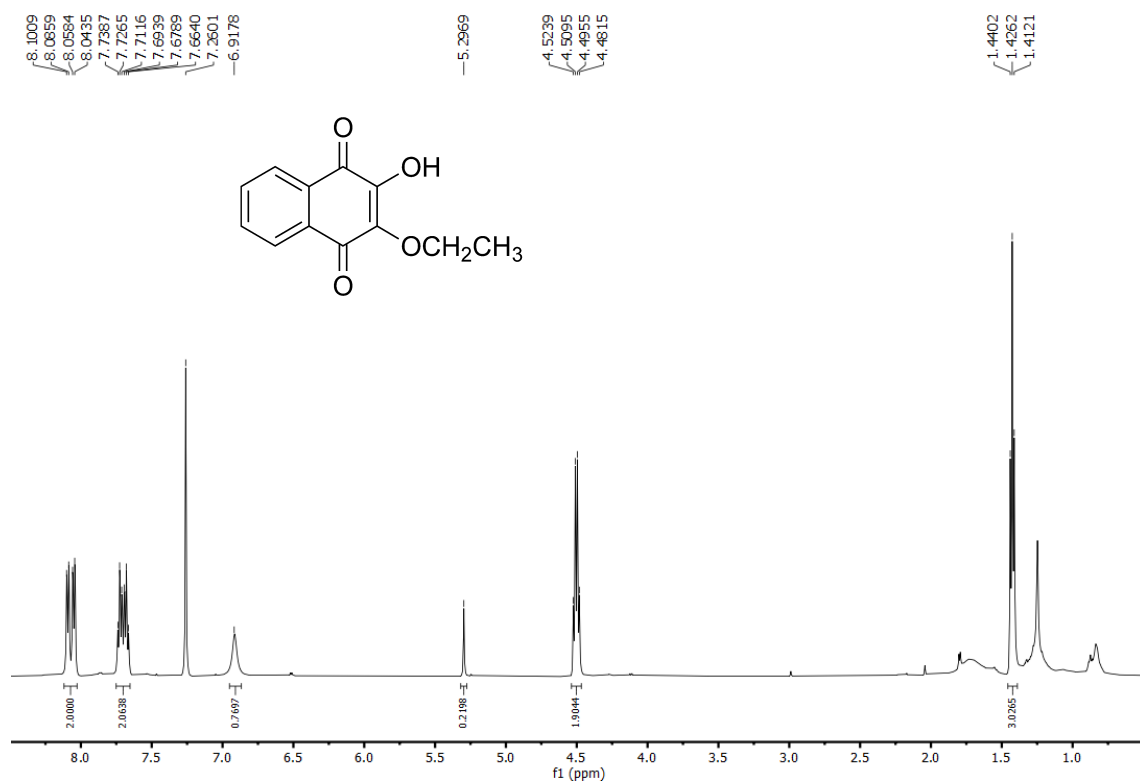
### $^1\text{H-NMR}$ ( $\text{CDCl}_3$ , 600 MHz) of compound 9



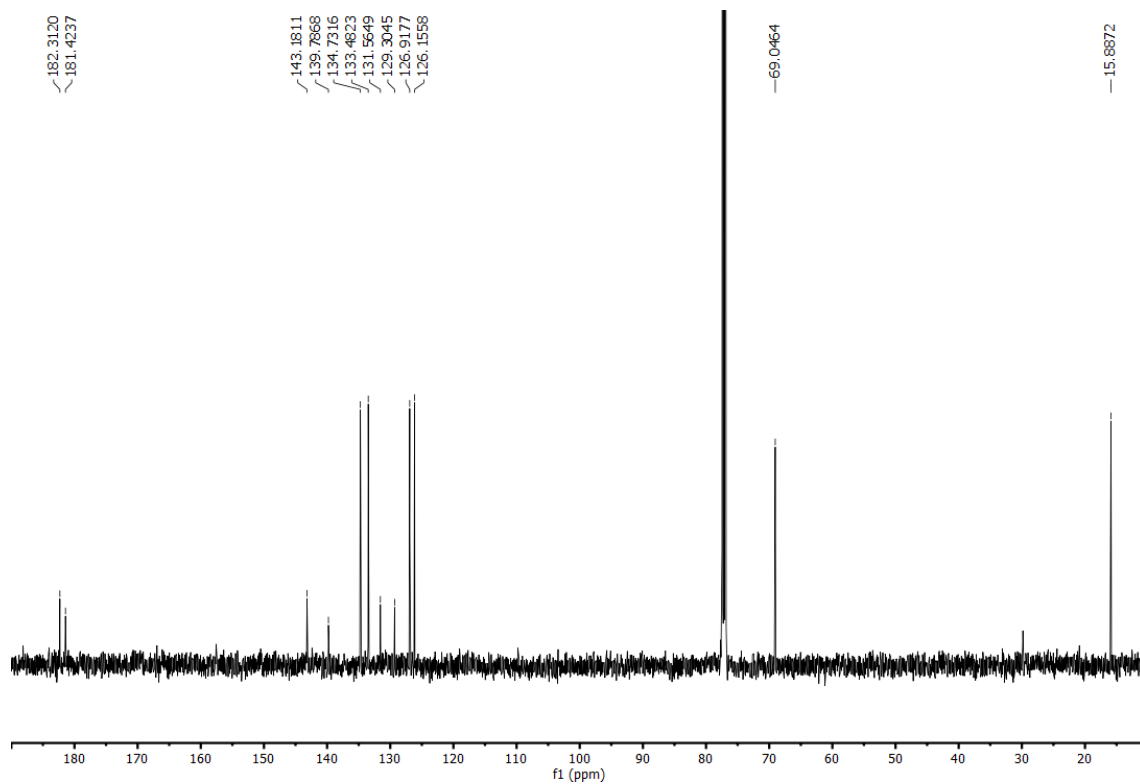
### $^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ , 150 MHz) of compound 9



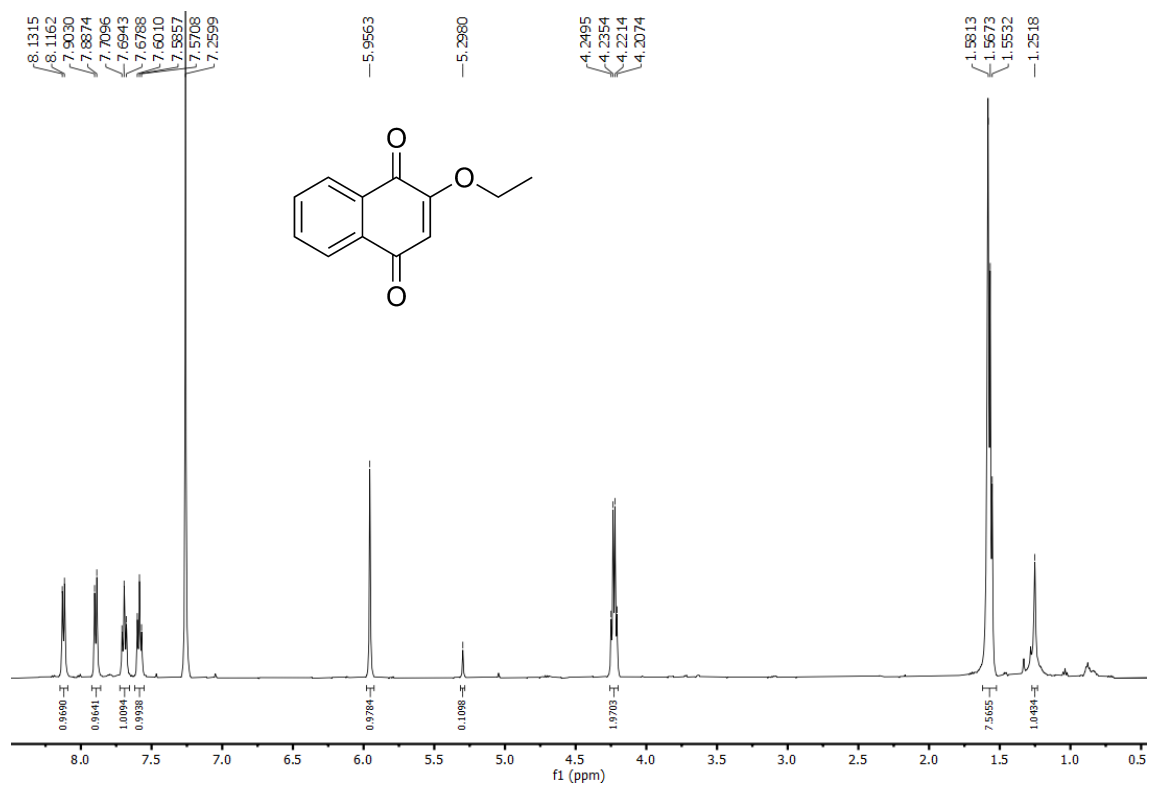
**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) of 3-ethoxy-2-hydroxy-1,4-naphthoquinone (10)**



**<sup>13</sup>CNMR (CDCl<sub>3</sub>, 125 MHz) of 3-ethoxy-2-hydroxy-1,4-naphthoquinone (10)**



**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) of 2-ethoxy-1,4-naphthoquinone (11)**



**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) of 2-ethoxy-1,4-naphthoquinone (11)**

