Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Synthesis and Application of α-Carbonyl Nitrile Oxides

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1. General Information

All reagents were used without further purification, unless otherwise stated. Anhydrous solvents were obtained using standard drying techniques. Acetophenone and acetone were purchased from Sinopharm. 3-Methoxyacetophenone was purchased from Aladdin. 2-Acetonaphthone was purchased from Sigma-Aldrich. 4'-Methoxyacetophenone, 4'-phenoxyacetophenone and 1-adamantyl methyl ketone were purchased from TCI. *Tert*-butyl nitrite (TBN), 1,4-dioxane, ethyl propiolate, 3'-chloroacetophenone, 2'-methoxyacetophenone, 1'-acetonaphthone, 2-acetylbenzofuran and 2-acetylbenzo[b]thiophene were purchased from Energy-chemical. 4'-Methylacetophenone, 4-fluoroacetophenone, 4'-chloroacetophenone, 4'-bromoacetophenone, methyl 4-acetylbenzoate, 4-acetylbiphenyl, 2'-chloroacetophenone, 2-acetylfuran, 2-acetylthiophene and pinacolone were purchased from Mackin. The α-nitroketone **1z** was prepared according to the literature methods.[1]

Flash chromatography was performed on 200-300 mesh silica gel with the indicated solvent systems. ^{1}H NMR were recorded on a Bruker 400 (400 MHz) spectrometer and chemical shifts are reported in ppm down field from TMS, using TMS (0.00 ppm) or residual chloroform (7.26 ppm) as an internal standard. Data are reported as: (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, quint = quintuplet, hept = heptalet, m = multiplet; *J* = coupling constant in Hz, integration.). ^{13}C NMR spectra were recorded on a Bruker 400 (100 MHz) spectrometer, using proton decoupling unless otherwise noted. Chemical shifts are reported in ppm down field from TMS, using the central resonance of $CDCl_3$ (77.00 ppm) as the internal standard. HRMS were recorded by using Waters Xevo G2-XS QTof Benchtop Mass Spectrometer.

2. General Experimental Procedure

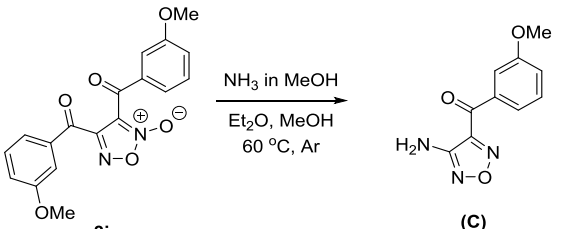
2.1 General Procedure for Synthesis of Isoxazoles

Ketones (1.0 equiv., 1.0 mmol) and ethyl propionate (1.5 equiv., 1.5 mmol) were dissolved in 1 mL 1,4-dioxane and then *t*-BuONO (4.0 equiv., 4.0 mmol, 528 μL) was added dropwise to the solution. The reaction mixtures were stirred at 60 ℃ in O_2. After certain time of the reaction, determined by TLC, the solution was concentrated in vacuo. The crude residues were purified by column chromatography using ethyl acetate/hexane mixture to obtain the corresponding products (**2a-2o**).

2.2 General Procedure for Synthesis of Furoxans

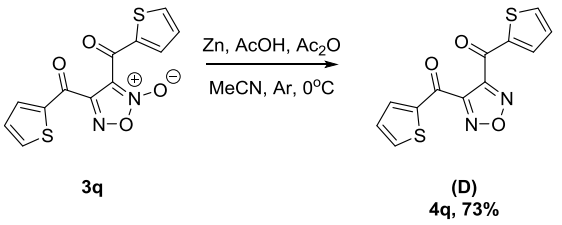
Ketones (1.0 equiv., 1.0 mmol) were dissolved in 1 mL 1,4-dioxane and then *t*-BuONO (4.0 equiv., 4.0 mmol, 528 μL) was added dropwise to the solution. The reaction mixtures were stirred at 60 ℃ in air. After certain time of the reaction, determined by TLC, the solution was concentrated in vacuo. The crude residues were purified by column chromatography using ethyl acetate/hexane mixture to obtain the corresponding products (**3a-3v**).

2.3 General Procedure for Synthesis of Inhibitor of hsolAC (4j)[2]



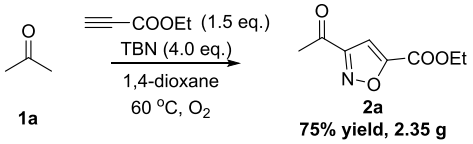
2.0 M NH_3 in MeOH (10 mL) was added to a solution of **3j** (1.0 equiv., 1.5 mmol, 531 mg) in Et_2O (5 mL) and MeOH (10 mL), and the mixture was stirred at r.t. for 30 min then heated to 60 ℃ for 2 hours. Upon cooling to r.t., the mixture was evaporated to dryness in vacuo, and the residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 0-30%) to give **4j** as an off-white solid (131 mg, 40%).

2.4 General Procedure for Synthesis of The Furazan (4q)[3]



In a 50 mL flask, **3q** (1.0 equiv., 3.47 mmol, 1062 mg) was dissolved in acetonitrile (28 mL). To this, metal zinc (1.0 equiv., 3.47 mmol, 416 mg), acetic acid (0.5 mL), and of acetic acid anhydride (1.4 mL) were added. The obtained solution was cooled in an ice water bath. The mixture was stirred for 16 hours to terminate the reaction. The reaction mixture was filtrated to remove insoluble matters. Acetonitrile was distilled off under reduced pressure to obtain a residue. The residue was recrystallized from chloroform to obtain the furazan **4q** as a yellow solid (735 mg, 73%).

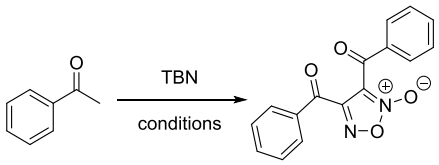
2.5 General Procedure Gram-Scale Reaction



Acetone **1a** (1.0 equiv., 17.2 mmol, 1.0 g) and ethyl propionate (1.5 equiv., 25.8 mmol) were dissolved in 1,4-dioxane (17 mL) and then *t*-BuONO (4.0 equiv., 68.8 mmol, 9.0 mL) was added dropwise to the solution. The reaction mixtures were stirred at 60 ℃ in O_2. After certain time of the reaction, determined by TLC, the solution was concentrated in vacuo. The crude residues were purified by column chromatography using ethyl acetate/hexane mixture to obtain the corresponding product (**2a**, 2.35 g, 75%).

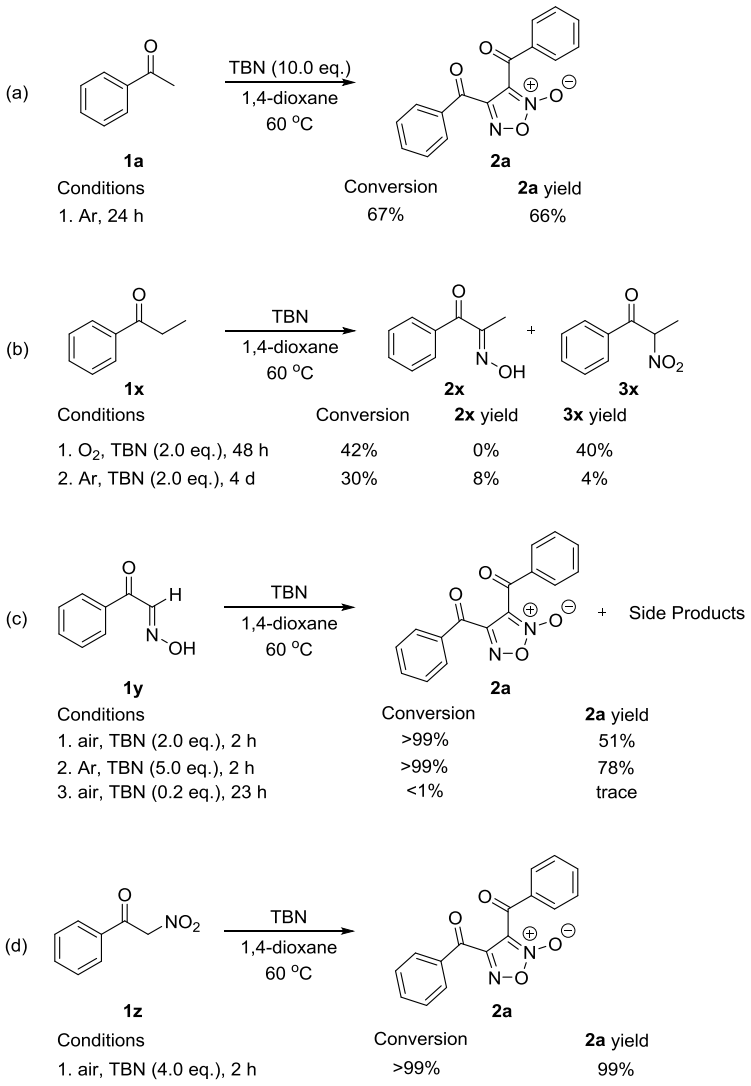
3. Supplementary Data

Table S1 Optimization of the reaction conditions

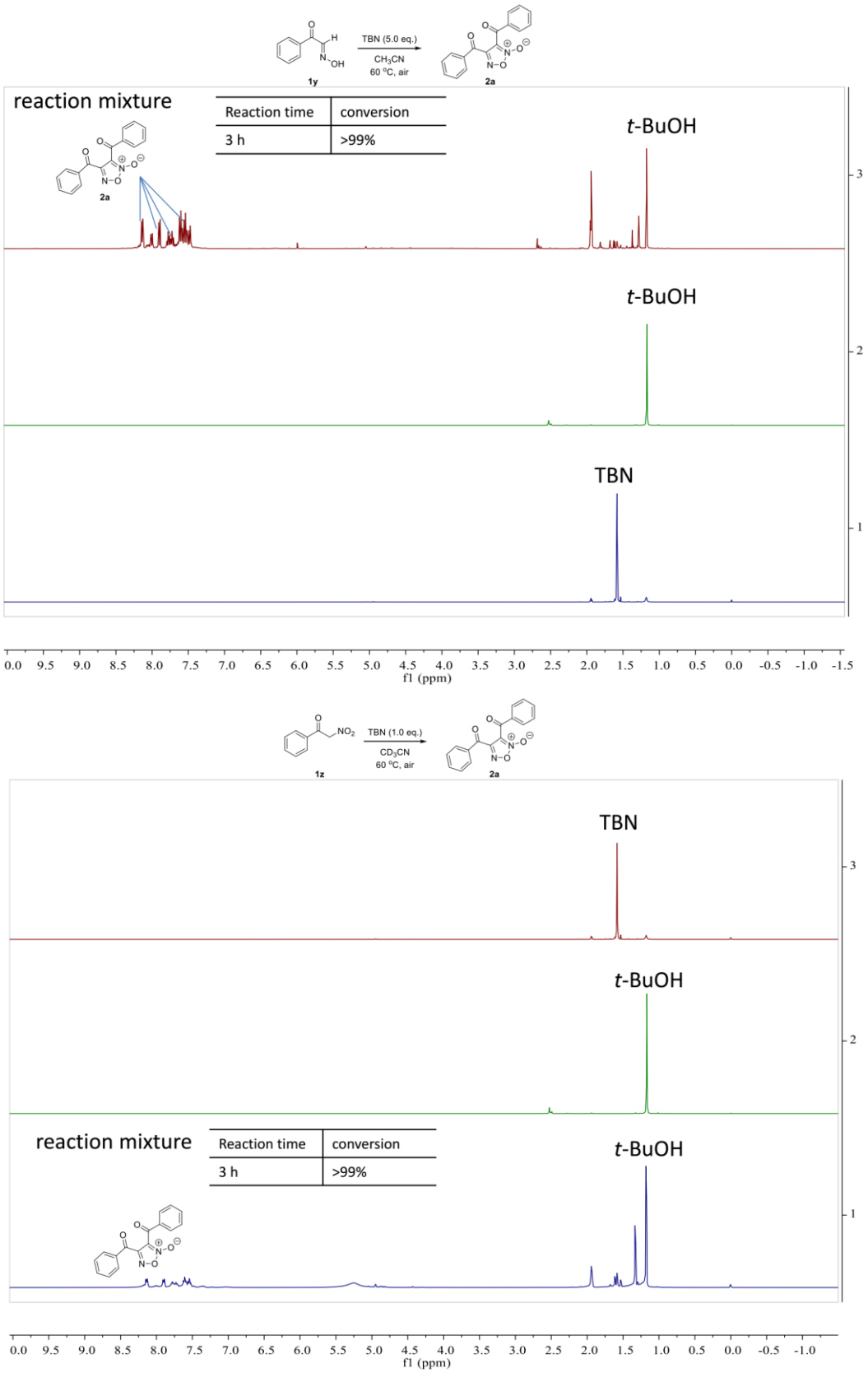


Entry	Atmosphere	TBN [equiv.]	Solvent	T [℃]	t [h]	Conversion [%][b]	Yield [%][b]
1	air	1.5	MeCN	r.t.	8.5	12	9
2	Ar	1.5	MeCN	r.t.	70	43	25
3	air	3.0	MeCN	50	35	73	68
4[c]	Ar	3.0	MeCN	50	60	25	5
5	air	4.0	MeCN	50	41	77	71
6	air	5.0	MeCN	50	41	80	64
7	air	4.0	MeCN	70	26	95	70
8	air	4.0	MeCN	70	49	>99	59
9	O_2	4.0	MeCN	50	45	88	68
10	air	4.0	toluene	80	18	>99	90
11	air	2.2	1,4-dioxane	60	4d	93	76
12	**air**	**4.0**	**1,4-dioxane**	**60**	**24**	**>99**	**95[d]**

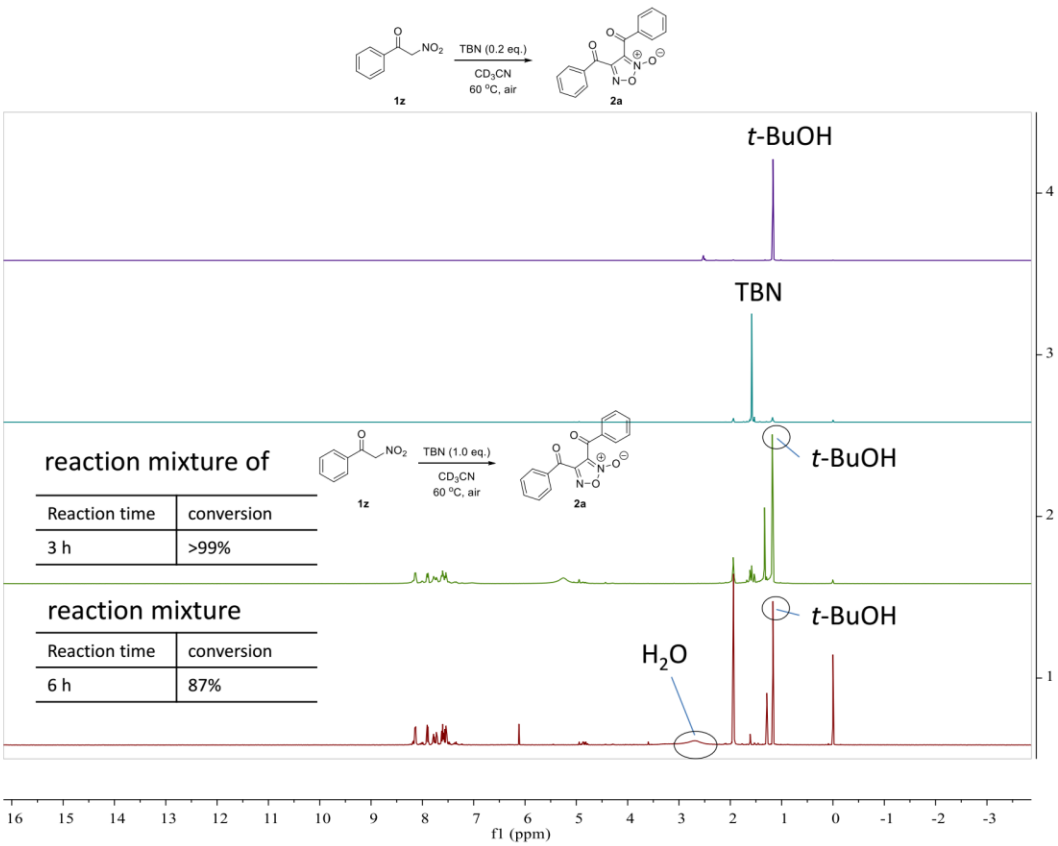
[a] If not otherwise noted, the reaction conditions are as follows:**1a** (1 mmol), Solvent (1.0 mL). [b] Determined by ^{1}H NMR. [c] Adding NHPI (30 mol%), [d] Isolated yield.



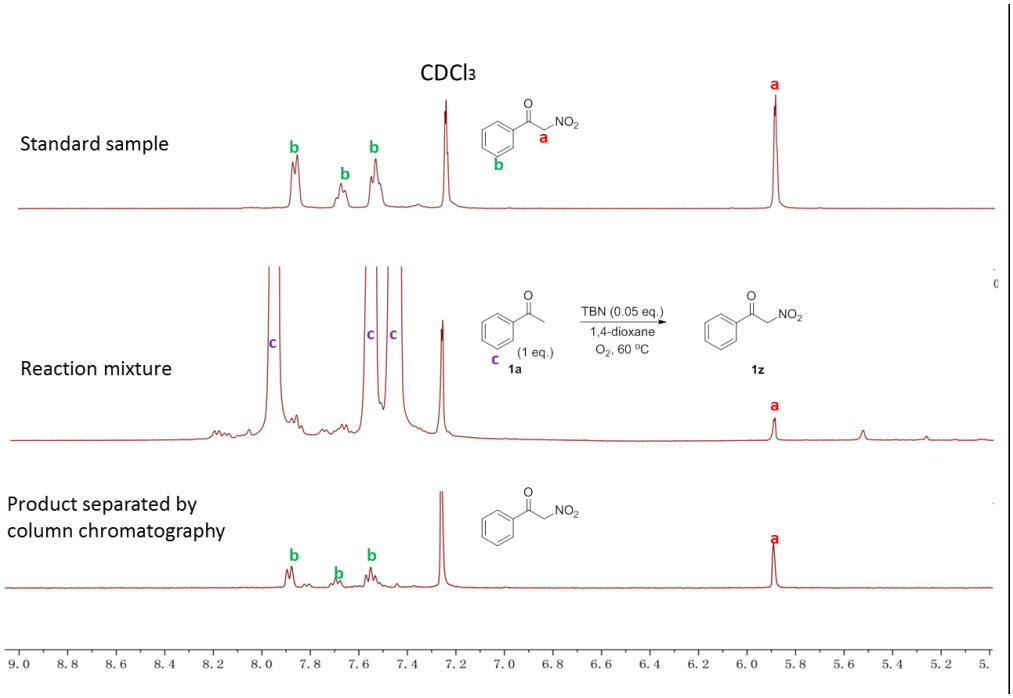
Scheme S1. Supplementary experiment data of control experiments.



Scheme S2. Formation of *tert*-butyl alcohol in the reactions of **1y** and **1z** detected by ^{1}H NMR.

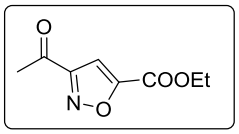


Scheme S3. Formation of H_2O in the reactions of **1z** with substoichiometric TBN detected by ^1H NMR.

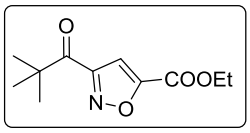


Scheme S4. Formation of **1z** in the reaction of **1a** with substoichiometric TBN detected by ^1H NMR.

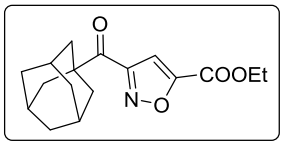
4. Analytical Data for Compounds



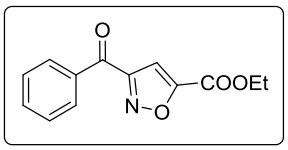
ethyl 3-acetylisoxazole-5-carboxylate (2a): Prepared according to the general procedure. 152 mg, 83% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.25 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 191.0, 162.3, 161.9, 156.2, 107.5, 62.7, 27.4, 14.1. **HRMS** (ESI): calcd for $C_8H_9NO_4H$ $(M+H)^+$: 184.0604. Found: 184.0608.



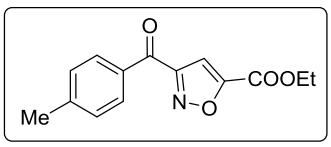
ethyl 3-pivaloylisoxazole-5-carboxylate (2b): Prepared according to the general procedure. 176 mg, 78% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.24 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.40 (s, 9H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 198.8, 160.8, 160.6, 156.3, 109.8, 62.5, 44.8, 26.5, 14.1. **HRMS** (ESI): calcd for $C_{11}H_{15}NO_4H$ $(M+H)^+$: 226.1074. Found: 226.1073.



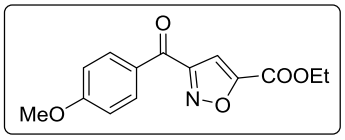
ethyl 3-((3S,5S)-adamantane-1-carbonyl)isoxazole-5-carboxylate (2c): Prepared according to the general procedure. 221 mg, 73% yield. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.19 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.10 - 2.08 (m, 9H), 1.79-1.76 (m, 6H), 1.40 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 198.5, 161.0, 160.5, 156.4, 110.0, 62.5, 47.4, 38.3, 38.0, 36.6, 36.51 28.0, 27.9, 14.1. **HRMS** (ESI): calcd for $C_{17}H_{21}NO_4H$ $(M+H)^+$: 304.1543. Found: 304.1544.



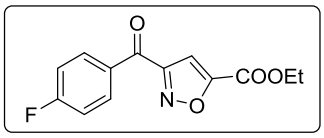
ethyl 3-benzoylisoxazole-5-carboxylate (2d): Prepared according to the general procedure. 232 mg, 95% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.30 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.67 (tt, *J* = 7.0, 1.2 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.42 (s, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 184.5, 162.2, 161.1, 156.3, 135.2, 134.4, 130.7, 128.7, 110.1, 62.7, 14.1. **HRMS** (ESI): calcd for $C_{13}H_{11}NO_4H$ $(M+H)^+$: 246.0761. Found: 246.0766.



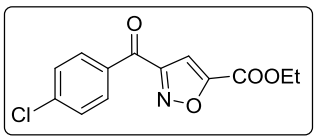
ethyl 3-(4-methylbenzoyl)isoxazole-5-carboxylate (2e): Prepared according to the general procedure. 210 mg, 81% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 2.46 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 184.0, 162.3, 161.0, 156.3, 145.7, 132.7, 130.9, 129.5, 110.2, 62.6, 21.9, 14.1. **HRMS** (ESI): calcd for $C_{14}H_{13}NO_4H$ $(M+H)^+$: 260.0927. Found: 260.0927.



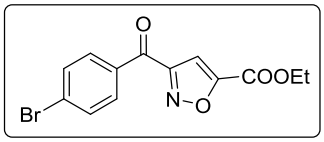
ethyl 3-(4-methoxybenzoyl)isoxazole-5-carboxylate (2f): Prepared according to the general procedure. 225 mg, 82% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 8.9 Hz, 2H), 7.40 (s, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 182.7, 164.8, 162.5, 160.9, 156.4, 133.3, 128.2, 114.1, 110.2, 62.6, 55.6, 14.1. **HRMS** (ESI): calcd for $C_{14}H_{13}NO_5H$ $(M+H)^+$: 276.0866. Found: 276.0863.



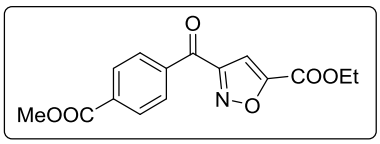
ethyl 3-(4-fluorobenzoyl)isoxazole-5-carboxylate (2g): Prepared according to the general procedure. 208 mg, 79% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.39 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.42 (s, 1H), 7.21 (t, *J* = 8.6 Hz, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 182.7, 167.9, 165.4, 162.1, 161.2, 156.2, 133.7, 133.6, 131.6, 131.5, 116.1, 115.9, 110.1, 62.7, 14.1. **HRMS** (ESI): calcd for $C_{13}H_{10}FNO_4H$ $(M+H)^+$: 264.0667. Found: 264.0670.



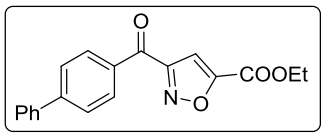
ethyl 3-(4-chlorobenzoyl)isoxazole-5-carboxylate (2h): Prepared according to the general procedure. 226 mg, 81% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.41 (s, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 183.1, 162.0, 161.3, 156.2, 141.2, 133.4, 132.1, 129.1, 110.0, 62.7, 14.1. **HRMS** (ESI): calcd for $C_{13}H_{10}ClNO_4H$ $(M+H)^+$: 280.0371. Found: 280.0371.



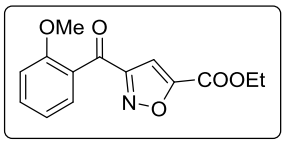
ethyl 3-(4-bromobenzoyl)isoxazole-5-carboxylate (2i): Prepared according to the general procedure. 230 mg, 71% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.41 (s, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 183.3, 162.0, 161.3, 156.2, 133.8, 132.2, 132.1, 130.1, 110.0, 62.7, 14.1. **HRMS** (ESI): calcd for $C_{13}H_{10}BrNO_4H$ $(M+H)^+$: 323.9866, 325.9846. Found: 323.9872, 325.9859.



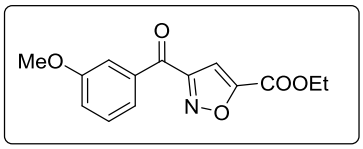
ethyl 3-(4-(methoxycarbonyl)benzoyl)isoxazole-5-carboxylate (2j): Prepared according to the general procedure. 231 mg, 75% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.38 (d, *J* = 8.7 Hz, 2H), 8.19 (d, *J* = 8.7 Hz, 2H), 7.45 (s, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 183.9, 166.0, 161.9, 161.3, 156.1, 138.2, 134.8, 130.5, 129.7, 109.9, 62.7, 52.5, 14.1. **HRMS** (ESI): calcd for $C_{15}H_{13}NO_6H$ $(M+H)^+$: 304.0816. Found: 304.0821.



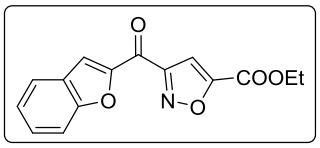
ethyl 3-([1,1'-biphenyl]-4-carbonyl)isoxazole-5-carboxylate (2k): Prepared according to the general procedure. 316 mg, 98% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.45 (s, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 184.0, 162.3, 161.1, 156.3, 147.1, 139.6, 133.9, 131.4, 129.0, 128.6, 127.4, 110.2, 62.7, 14.2. **HRMS** (ESI): calcd for $C_{19}H_{15}NO_4H$ $(M+H)^+$: 322.1074. Found: 322.1080.



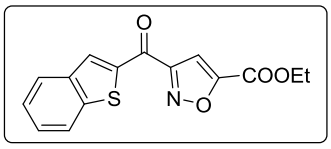
ethyl 3-(2-methylbenzoyl)isoxazole-5-carboxylate (2l): Prepared according to the general procedure. 272 mg, 99% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.64 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.54 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H), 7.32 (s, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 186.5, 163.0, 161.1, 158.9, 156.4, 134.4, 130.8, 126.7, 120.6, 112.7, 108.9, 62.6, 55.8, 14.1. **HRMS** (ESI): calcd for $C_{14}H_{13}NO_5H$ $(M+H)^+$: 276.0866. Found: 276.0863.



ethyl 3-(3-methoxybenzoyl)isoxazole-5-carboxylate (2m): Prepared according to the general procedure. 273 mg, 99% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.92 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.78 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.20 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 184.2, 162.2, 161.1, 159.8, 156.3, 136.3, 129.8, 123.7, 121.3, 114.3, 110.1, 62.7, 55.5, 14.1. **HRMS** (ESI): calcd for $C_{14}H_{13}NO_5H$ $(M+H)^+$: 276.0866. Found: 276.0869.

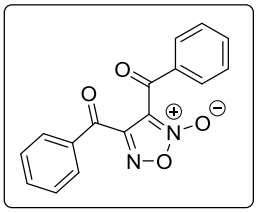


ethyl 3-(benzofuran-2-carbonyl)isoxazole-5-carboxylate (2n): Prepared according to the general procedure. 228 mg, 80% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.34 (s, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.50 (s, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.5, 161.5, 161.5, 156.6, 156.1, 150.1, 129.7, 127.0, 124.4, 124.2, 120.3, 112.7, 109.4, 62.8, 14.1. **HRMS** (ESI): calcd for $C_{15}H_{11}NO_5H$ $(M+H)^+$: 286.0710. Found: 286.0714.

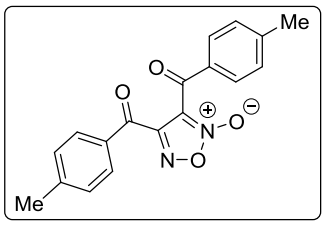


ethyl 3-(benzo[b]thiophene-2-carbonyl)isoxazole-5-carboxylate (2o): Prepared according to the general procedure. 253 mg, 84% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.45 (s, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 4.49 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR**

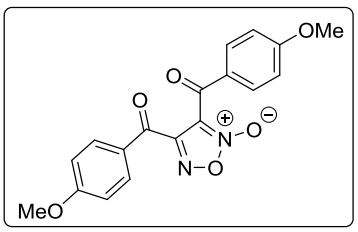
(100 MHz, Chloroform-*d*) δ 177.4, 161.8, 161.3, 156.2, 143.4, 140.7, 139.2, 135.0, 128.4, 127.0, 125.3, 122.9, 109.6, 62.7, 14.1. **HRMS** (ESI): calcd for $C_{15}H_{11}NO_4SH$ $(M+H^+)$: 302.0482. Found: 302.0485.



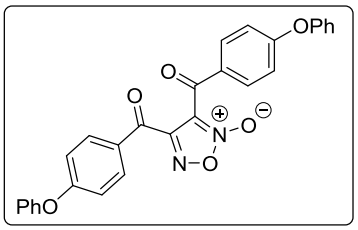
3,4-dibenzoyl-1,2,5-oxadiazole 2-oxide (3a): Prepared according to the general procedure. 139 mg, 95% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.20 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.86 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.70 (dt, *J* = 13.7, 7.5 Hz, 2H), 7.54 (dt, *J* = 13.8, 7.9 Hz, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 181.8, 180.5, 154.3, 135.5, 135.3, 133.87, 133.85, 130.6, 129.7, 129.3, 129.0, 111.6. **HRMS** (ESI): calcd for $C_{16}H_{10}N_2O_4Na$ $(M+Na)^+$: 317.0533. Found: 317.0529.



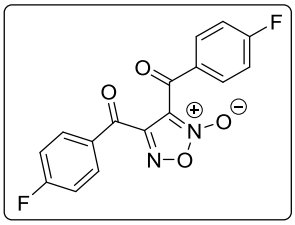
3,4-bis(4-methylbenzoyl)-1,2,5-oxadiazole 2-oxide (3b): Prepared according to the general procedure. 155.5 mg, 97% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 2.46 (s, 3H), 2.44 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 181.3, 180.0, 154.6, 147.0, 146.8, 131.49, 131.46, 130.7, 130.0, 129.84, 129.76, 111.9, 22.01, 21.97. **HRMS** (ESI): calcd for $C_{18}H_{14}N_2O_4Na$ $(M+Na)^+$: 345.0846. Found: 345.0839.



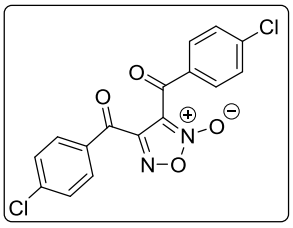
3,4-bis(4-methoxybenzoyl)-1,2,5-oxadiazole 2-oxide (3c): Prepared according to the general procedure. 150.5 mg, 85% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 9.0 Hz, 2H), 7.85 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.91 (d, *J* = 8.7 Hz, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 179.9, 178.7, 165.5, 165.4, 154.8, 133.2, 132.4, 127.0, 126.9, 114.6, 114.4, 112.2, 55.8, 55.7. **HRMS** (ESI): calcd for $C_{18}H_{14}N_2O_6H$ $(M+H)^+$: 355.0925. Found: 355.0913.



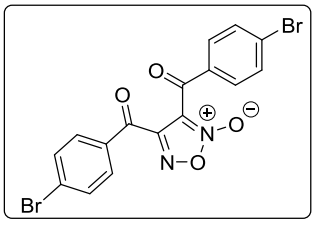
3,4-bis(4-methoxybenzoyl)-1,2,5-oxadiazole 2-oxide (3d): Prepared according to the general procedure. 219.5 mg, 92% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 9.0 Hz, 2H), 7.84 (d, *J* = 8.9 Hz, 2H), 7.47 – 7.39 (m, 4H), 7.29 – 7.22 (m, 2H), 7.14 – 7.00 (m, 8H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 180.0, 178.7, 164.3, 164.2, 154.7, 154.62, 154.61, 133.2, 132.4, 130.3, 128.2, 128.1, 125.4, 125.3, 120.71, 120.68, 117.5, 117.3, 112.0. **HRMS** (ESI): calcd for $C_{28}H_{18}N_2O_6H$ $(M+H)^+$: 479.1238. Found: 479.1236.



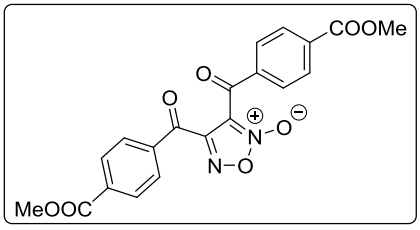
3,4-bis(4-fluorobenzoyl)-1,2,5-oxadiazole 2-oxide (3e): Prepared according to the general procedure. 156.8 mg, 95% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.28 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.91 (dd, *J* = 8.9, 5.2 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.23 – 7.18 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 180.1, 178.8, 168.47, 168.45, 165.89, 165.87, 154.2, 133.6, 133.5, 132.7, 132.6, 130.23, 130.20, 130.17, 130.14, 116.9, 116.64, 116.60, 116.4, 111.5. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -99.6 (m, 1F), -100.1 (m, 1F). **HRMS** (ESI): calcd for $C_{16}H_8F_2N_2O_4Na$ $(M+Na)^+$: 353.0344. Found: 353.0347.



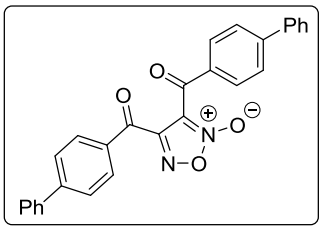
3,4-bis(4-chlorobenzoyl)-1,2,5-oxadiazole 2-oxide (3f): Prepared according to the general procedure. 128 mg, 70% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.18 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 180.5, 179.2, 154.0, 142.40, 142.38, 132.1, 131.9, 131.0, 129.7, 129.5, 111.3. **HRMS** (ESI): calcd for $C_{16}H_8Cl_2N_2O_4Na$ $(M+Na)^+$: 384.9753. Found: 384.9752.



3,4-bis(4-bromobenzoyl)-1,2,5-oxadiazole 2-oxide (3g): Prepared according to the general procedure. 195.2 mg, 86% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 4H), 7.68 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 180.7, 179.4, 154.0, 132.7, 132.5, 132.4, 131.9, 131.33, 131.32, 131.0, 111.3. **HRMS** (ESI): calcd for $C_{16}H_8Br_2N_2O_4Na$ $(M+Na)^+$: 474.8723. Found: 474.8722.

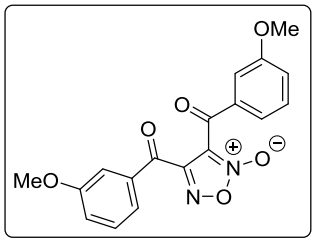


3,4-bis(4-(methoxycarbonyl)benzoyl)-1,2,5-oxadiazole 2-oxide (3h): Prepared according to the general procedure. 168 mg, 82% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.27 (d, *J* = 8.5 Hz, 2H), 8.21 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 2H), 3.98 (s, 3H), 3.96 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 181.3, 180.0, 165.8, 165.7, 153.9, 136.8, 136.7, 135.9, 135.8, 130.5, 130.4, 130.2, 130.1, 129.7, 129.5, 111.2, 52.8. **HRMS** (ESI): calcd for $C_{20}H_{14}N_2O_8Na$ $(M+Na)^+$: 433.0642. Found: 433.0646.

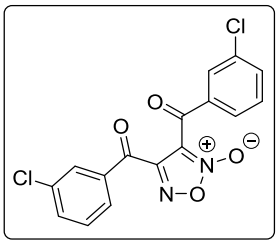


3,4-di([1,1'-biphenyl]-4-carbonyl)-1,2,5-oxadiazole 2-oxide (3i): Prepared according to the general procedure. 215 mg, 96% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 8.6 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.77 (dd, *J* = 14.4, 8.4 Hz, 4H), 7.69 – 7.60 (m, 4H), 7.55 – 7.40 (m, 6H). **^{13}C NMR** (100 MHz,

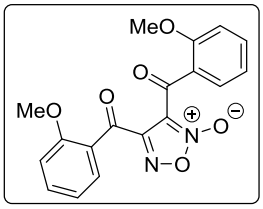
Chloroform-*d*) δ 181.3, 180.0, 154.6, 148.3, 148.1, 139.3, 132.6, 132.5, 131.3, 130.4, 129.14, 129.11, 128.8, 127.9, 127.7, 127.44, 127.43, 111.9. **HRMS** (ESI): calcd for $C_{28}H_{18}N_2O_4H$ $(M+H)^+$: 447.1339. Found: 447.1348.



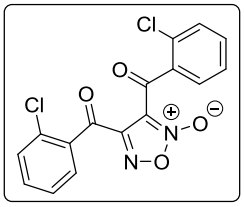
3,4-bis(3-methoxybenzoyl)-1,2,5-oxadiazole 2-oxide (3j): Prepared according to the general procedure. 153.3 mg, 86% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.43 – 7.33 (m, 3H), 7.27 – 7.19 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) 181.6, 180.3, 160.3, 160.0, 154.3, 135.2, 135.1, 130.2, 130.1, 123.6, 122.5, 122.4, 122.3, 113.9, 112.9, 111.6, 55.58, 55.56. **HRMS** (ESI): calcd for $C_{18}H_{14}N_2O_6Na$ $(M+Na)^+$: 377.0744. Found: 377.0747.



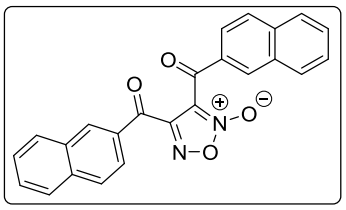
3,4-bis(3-chlorobenzoyl)-1,2,5-oxadiazole 2-oxide (3k): Prepared according to the general procedure. 126.9 mg, 70% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.17 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.83 (s, 1H), 7.69 (dt, *J* = 14.1, 7.6 Hz, 3H), 7.50 (dt, *J* = 15.7, 7.9 Hz, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 180.6, 179.2, 153.8, 135.8, 135.52, 135.45, 135.3, 135.2, 135.1, 130.6, 130.40, 130.3, 129.4, 128.7, 127.8, 111.1. **HRMS** (ESI): calcd for $C_{16}H_8Cl_2N_2O_4Na$ $(M+Na)^+$: 384.9753. Found: 384.9751.



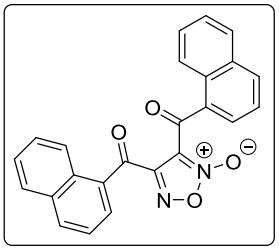
3,4-bis(2-methoxybenzoyl)-1,2,5-oxadiazole 2-oxide (3l): Prepared according to the general procedure. 176.9 mg, 99.9% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 – 7.68 (m, 1H), 7.55 – 7.47 (m, 3H), 7.01 – 6.87 (m, 4H), 3.80 (s, 3H), 3.77 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 182.0, 180.0, 159.5, 159.1, 156.2, 136.0, 135.8, 131.3, 131.0, 124.7, 124.6, 121.2, 121.1, 114.0, 112.0, 111.4, 56.1, 55.9. **HRMS** (ESI): calcd for $C_{18}H_{14}N_2O_6Na$ $(M+Na)^+$: 377.0744. Found: 377.0746.



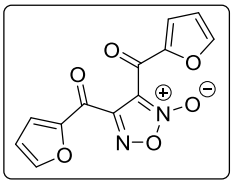
3,4-bis(2-chlorobenzoyl)-1,2,5-oxadiazole 2-oxide (3m): Prepared according to the general procedure. 180.3 mg, 99% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.74 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.65 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.58 – 7.48 (m, 3H), 7.44 (d, *J* = 8.3 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 182.5, 180.0, 154.0, 134.34, 134.30, 134.26, 134.2, 133.5, 132.7, 131.7, 131.2, 131.1, 130.6, 127.6, 127.1, 112.3. **HRMS** (ESI): calcd for $C_{16}H_8Cl_2N_2O_4Na$ $(M+Na)^+$: 384.9753. Found: 384.9760.



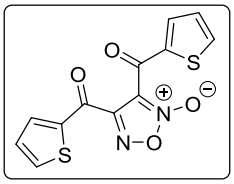
3,4-di(2-naphthoyl)-1,2,5-oxadiazole 2-oxide (3n): Prepared according to the general procedure. 194.4 mg, 95% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 8.36 (s, 1H), 8.11 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.98 – 7.87 (m, 6H), 7.73 – 7.52 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 181.6, 180.3, 154.7, 136.7, 136.5, 134.2, 132.9, 132.4, 132.3, 131.33, 131.30, 130.27, 129.99, 129.91, 129.87, 129.4, 129.1, 128.0, 127.9, 127.38, 127.35, 124.4, 123.8, 112.0. **HRMS** (ESI): calcd for $C_{24}H_{14}N_2O_4Na$ $(M+Na)^+$: 417.0846. Found: 417.0852.



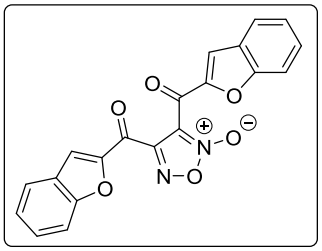
3,4-di(1-naphthoyl)-1,2,5-oxadiazole 2-oxide (3o): Prepared according to the general procedure. 195.9 mg, 99% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 8.6 Hz, 1H), 8.59 (d, *J* = 7.9 Hz, 1H), 8.14 (d, *J* = 7.3 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.88 – 7.76 (m, 3H), 7.63 – 7.48 (m, 5H), 7.45 (t, *J* = 7.7 Hz, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 183.6, 181.3, 155.9, 135.9, 133.9, 133.8, 133.4, 131.8, 130.8, 130.7, 130.6, 130.4, 129.3, 129.1, 128.7, 127.2, 127.1, 125.3, 125.0, 124.4, 124.2, 113.1. **HRMS** (ESI): calcd for $C_{24}H_{14}N_2O_4Na$ $(M+Na)^+$: 417.0846. Found: 417.0850.



3,4-di(furan-2-carbonyl)-1,2,5-oxadiazole 2-oxide (3p): Prepared according to the general procedure. 43.2 mg, 32% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.81 (s, 1H), 7.78 (d, *J* = 3.7 Hz, 1H), 7.61 (s, 1H), 7.47 (d, *J* = 3.7 Hz, 1H), 6.70 (dd, *J* = 3.6, 1.5 Hz, 1H), 6.66 (dd, *J* = 3.6, 1.4 Hz, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 168.2, 166.5, 153.0, 150.4, 149.9, 149.5, 148.7, 124.4, 121.8, 113.8, 113.4, 110.5. **HRMS** (ESI): calcd for $C_{12}H_6N_2O_6Na$ $(M+Na)^+$: 297.0124. Found: 297.0126.

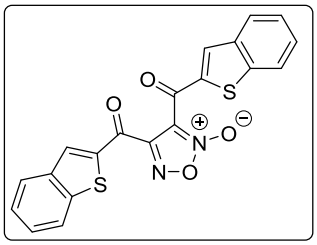


3,4-di(thiophene-2-carbonyl)-1,2,5-oxadiazole 2-oxide (3q): Prepared according to the general procedure. 127.2 mg, 83% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 3.5 Hz, 1H), 7.96 – 7.85 (m, 2H), 7.74 (d, *J* = 3.5 Hz, 1H), 7.28 (d, *J* = 4.5 Hz, 1H), 7.21 (t, *J* = 4.4 Hz, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.2, 171.5, 153.6, 140.5, 140.0, 138.01, 137.99, 137.3, 136.2, 129.1, 129.0, 111.3. **HRMS** (ESI): calcd for $C_{12}H_6N_2O_4S_2Na$ $(M+Na)^+$: 328.9661. Found: 328.9665.

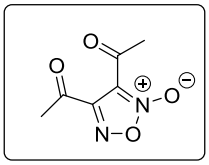


3,4-di(benzofuran-2-carbonyl)-1,2,5-oxadiazole 2-oxide (3r): Prepared according to the general procedure. 159.6 mg, 85% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.78 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.59 (s, 2H), 7.49 –

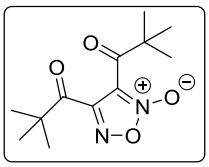
7.28 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 170.3, 168.5, 156.8, 156.1, 153.1, 150.0, 149.4, 130.3, 130.0, 126.8, 126.7, 124.7, 124.3, 124.0, 120.4, 117.4, 112.8, 112.4, 110.5. **HRMS** (ESI): calcd for $C_{20}H_{10}N_2O_6Na$ $(M+Na)^+$: 397.0431. Found: 397.0442.



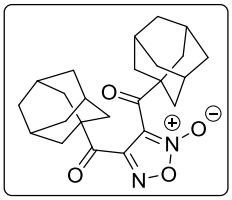
3,4-bis(benzo[b]thiophene-2-carbonyl)-1,2,5-oxadiazole 2-oxide (3s): Prepared according to the general procedure. 141.2 mg, 70% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 8.02 – 8.00 (m, 2H), 7.93 – 7.90 (m, 3H), 7.59 – 7.51 (m, 2H), 7.50 – 7.41 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 174.7, 173.0, 153.5, 144.0, 143.9, 139.7, 139.4, 139.0, 138.6, 135.3, 134.1, 129.1, 129.0, 127.2, 127.0, 125.66, 125.65, 123.1, 123.0, 111.1. **HRMS** (ESI): calcd for $C_{20}H_{10}N_2O_4S_2H$ $(M+H)^+$: 407.0160. Found: 407.0168.



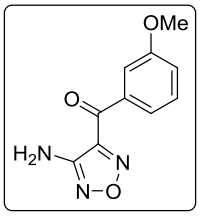
3,4-diacetyl-1,2,5-oxadiazole 2-oxide (3t): *t*-BuONO (4.0 equiv., 528 μL) was dissolved in 0.6 mL 1,4-dioxane, and stirred for 1 min under O_2. Then acetone (1.0 equiv., 1.0 mmol) dissolved in 0.4 mL 1,4-dioxane was added dropwise to the solution. The reaction mixtures were stirred at 60 ℃. After 7 hours of the reaction, the solution was concentrated in vacuo. The crude residues were purified by column chromatography using ethyl acetate/hexane mixture to obtain corresponding products (**3t**). 82.5 mg, 97% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 2.69 (s, 3H), 2.61 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 188.6, 185.2, 153.4, 111.5, 29.2, 28.2. **HRMS** (ESI): calcd for $C_6H_6N_2O_4H$ $(M+H)^+$: 171.0400. Found: 171.0403.



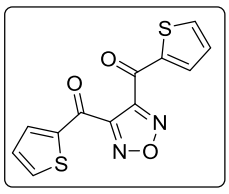
3,4-dipivaloyl-1,2,5-oxadiazole 2-oxide (3u): Prepared according to the general procedure. 82 mg, 65% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 1.39 (s, 9H), 1.28 (s, 9H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 197.2, 196.5, 153.2, 112.2, 45.8, 44.7, 26.1, 25.8. **HRMS** (ESI): calcd for $C_{12}H_{18}N_2O_4Na$ $(M+Na)^+$: 277.1159. Found: 277.1161.



3-((3R,5R)-adamantane-1-carbonyl)-4-((3R,5R,7R)-adamantane-1-carbonyl)-1,2,5-oxadiazole 2-oxide (3v): Prepared according to the general procedure. 159 mg, 78% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 2.20 – 2.02 (m, 12H), 1.99 – 1.87 (m, 6H), 1.83 – 1.69 (m, 12H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 196.7, 195.9, 153.2, 112.1, 48.4, 47.4, 37.6, 37.3, 36.3, 36.12, 27.70, 27.66. **HRMS** (ESI): calcd for $C_{24}H_{30}N_2O_4Na$ $(M+Na)^+$: 433.2098. Found: 433.2101.



(4-amino-1,2,5-oxadiazol-3-yl)(3-methoxyphenyl)methanone (4j): Prepared according to the general procedure. 131.4 mg, 40% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.25 – 7.21 (m, 1H), 5.32 (s, 2H), 3.90 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 185.36, 159.83, 156.84, 142.85, 136.59, 129.85, 123.39, 121.42, 114.34, 55.55. **HRMS** (ESI): calcd for $C_{10}H_9N_3O_3H$ $(M+H)^+$: 220.0717. Found: 220.0716.



(1,2,5-oxadiazole-3,4-diyl)bis(thiophen-2-ylmethanone) (4q): Prepared according to the general procedure. 735 mg, 73% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.05 (dd, *J* = 4.0, 1.2 Hz, 2H), 7.90 (dd, *J* = 5.0, 1.2 Hz, 2H), 7.24 (dd, *J* = 4.9, 3.9 Hz, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.93, 151.93, 141.48, 137.86, 137.30, 128.99. **HRMS** (ESI): calcd for $C_{12}H_6N_2O_3S_2Na$ $(M+Na)^+$: 312.9717 Found: 312.9724.

5. References

[1] a) W. Ai, R. Shi, L. Zhu, D. Jiang, X. Ma, J. Yuan, Z. Wang, Z, *RSC Adv.* **2015**, *5*, 24044-24048; b) C. Zhao, X. Zhang, Z. Xu, Y Chen, *Chin. J. Synth. Chem.* **2009**, *17*, 125-127.

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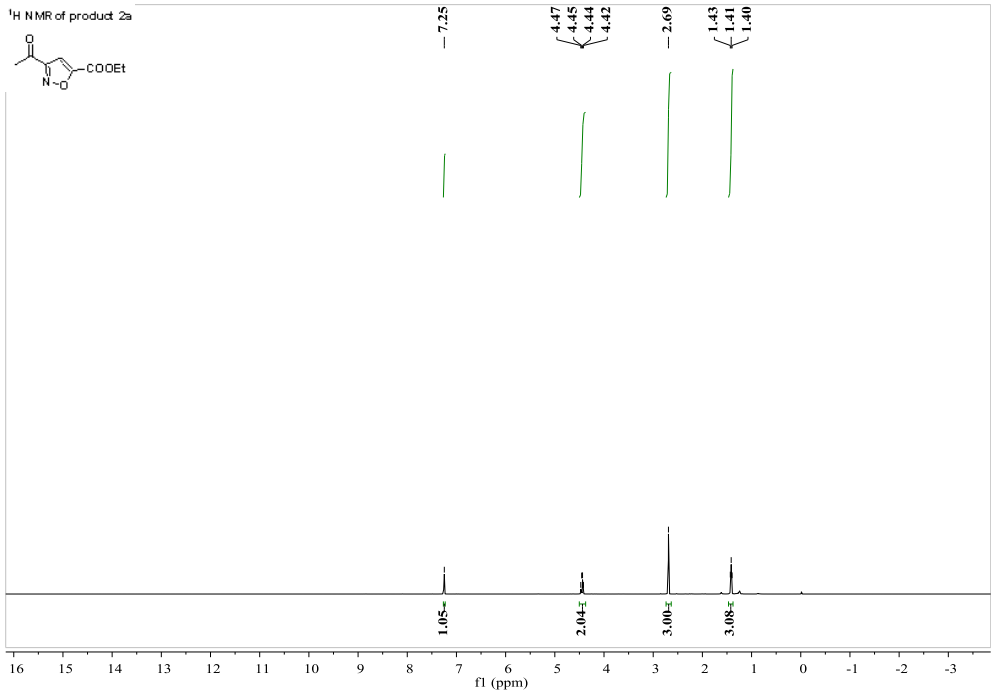
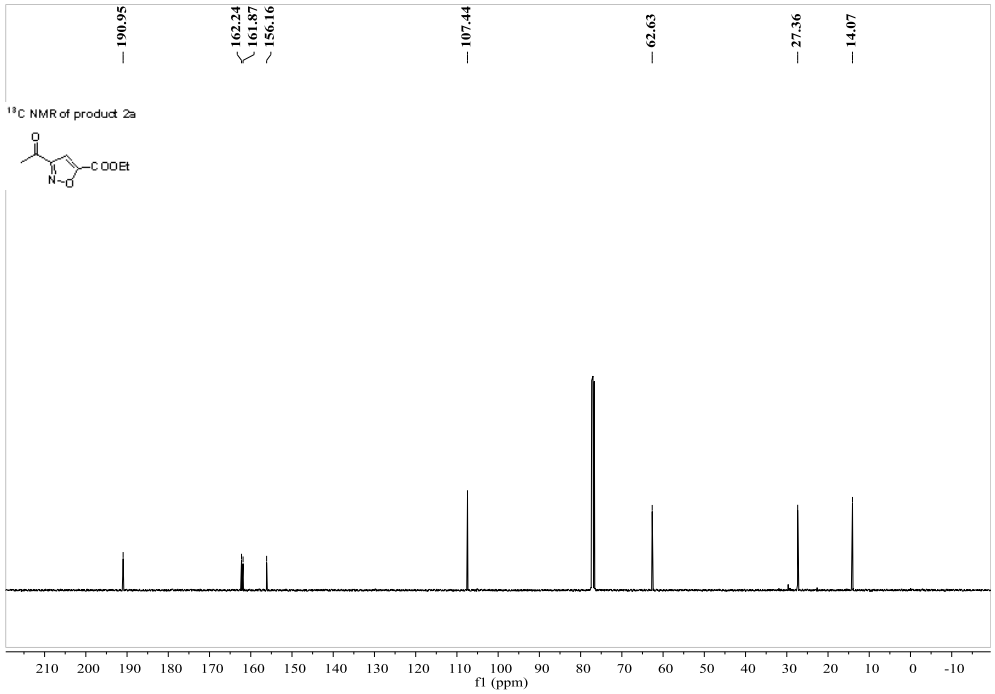
[3] a) T. Koga, A. Takase, S. Yasuda, S. Yamashita, H. Gorohmaru, T. Thiemann, S. Mataka, K. Takahashi, *Chem. Phys. Lett.* **2002**, *354*, 173-178; b) H. Gorohmaru, T. Thiemann, T. Sawada, K. Takahashi, K. Nishi-i, N. Ochi, Y. Kosugi, S. Mataka, *Heterocycles* **2002**, *56*, 421-431.

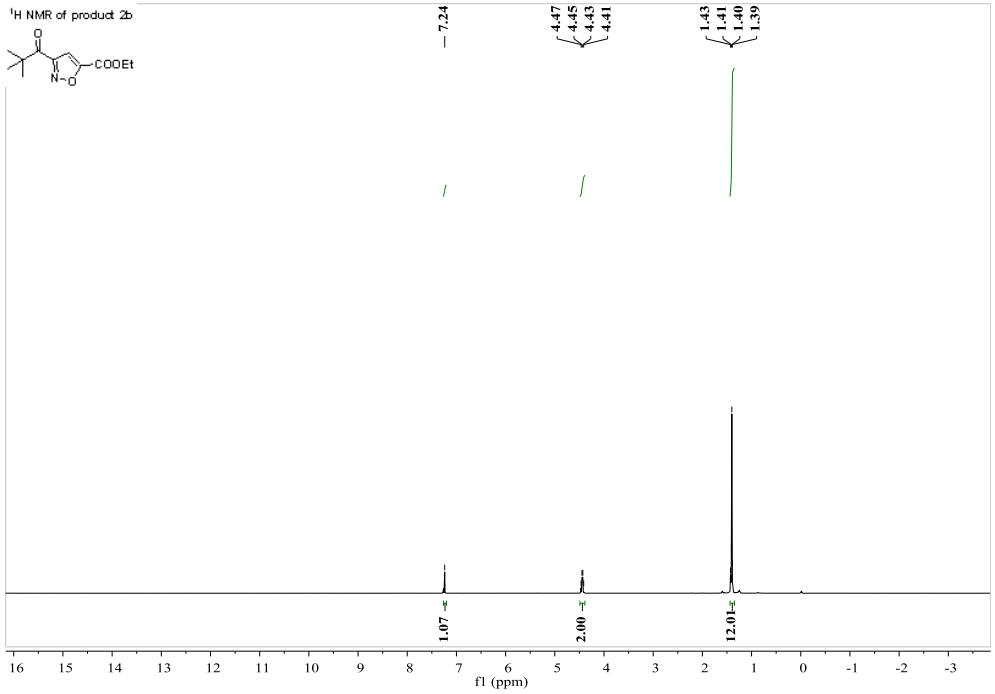
6. Spectral Data

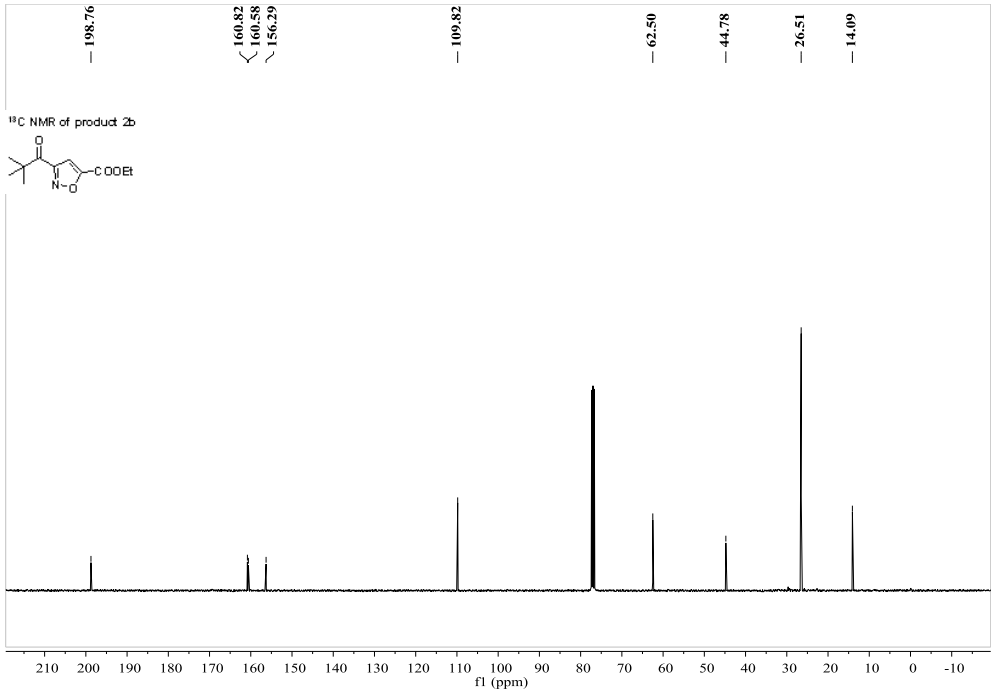
NMR data of **2a**



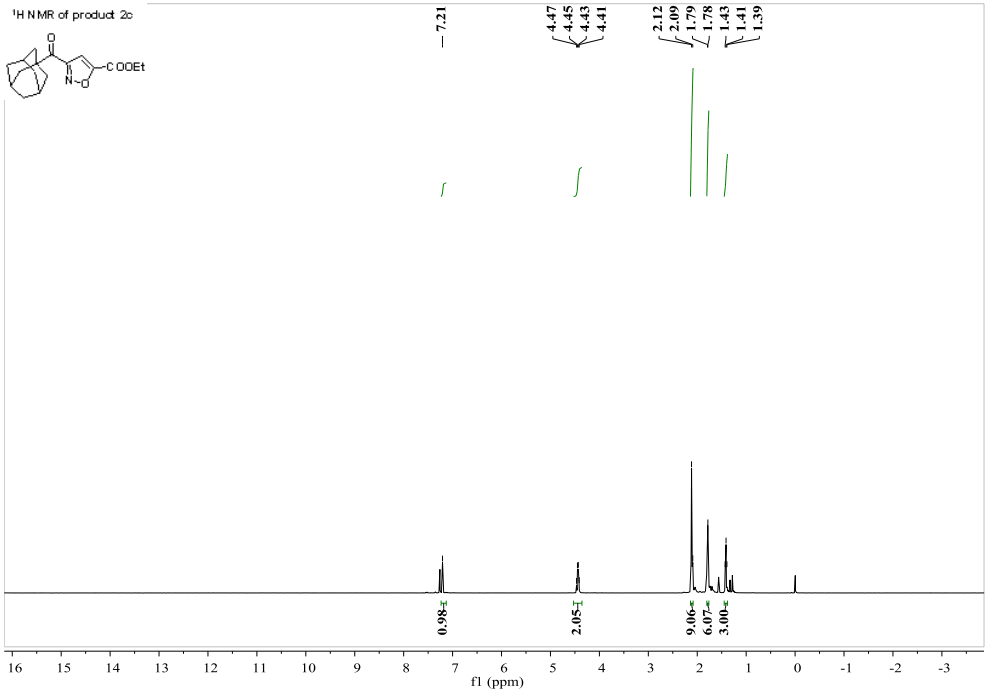


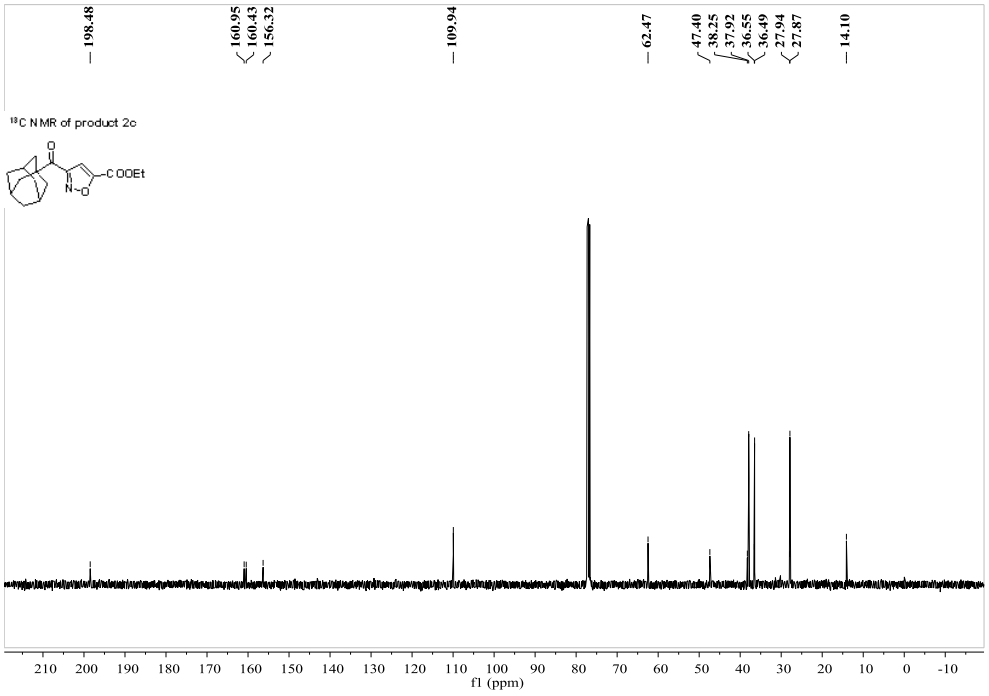
NMR data of **2b**



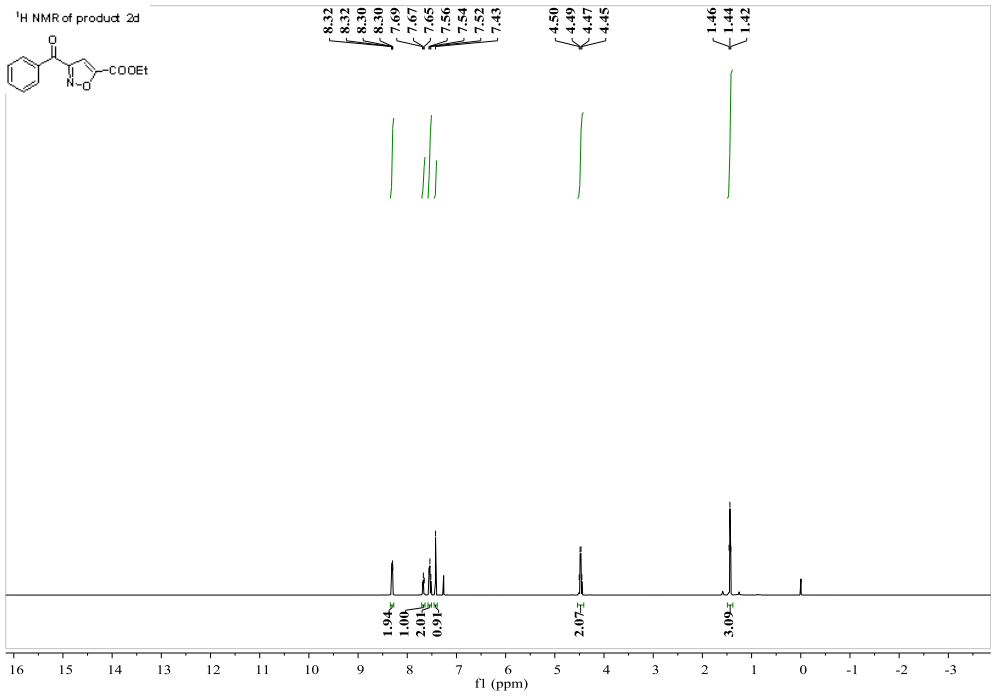


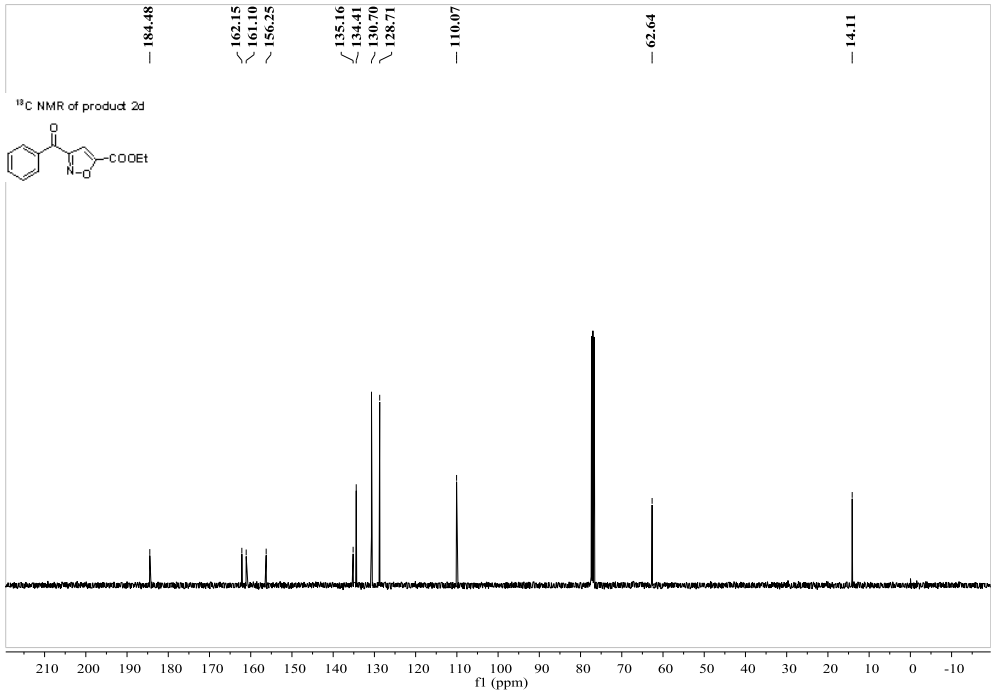
NMR data of **2c**



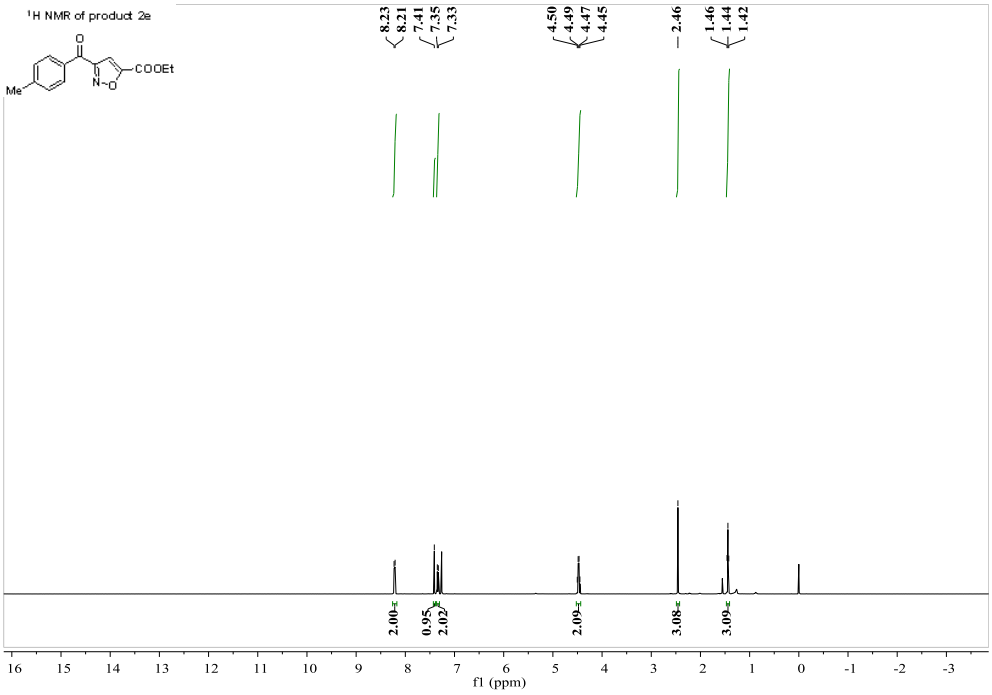


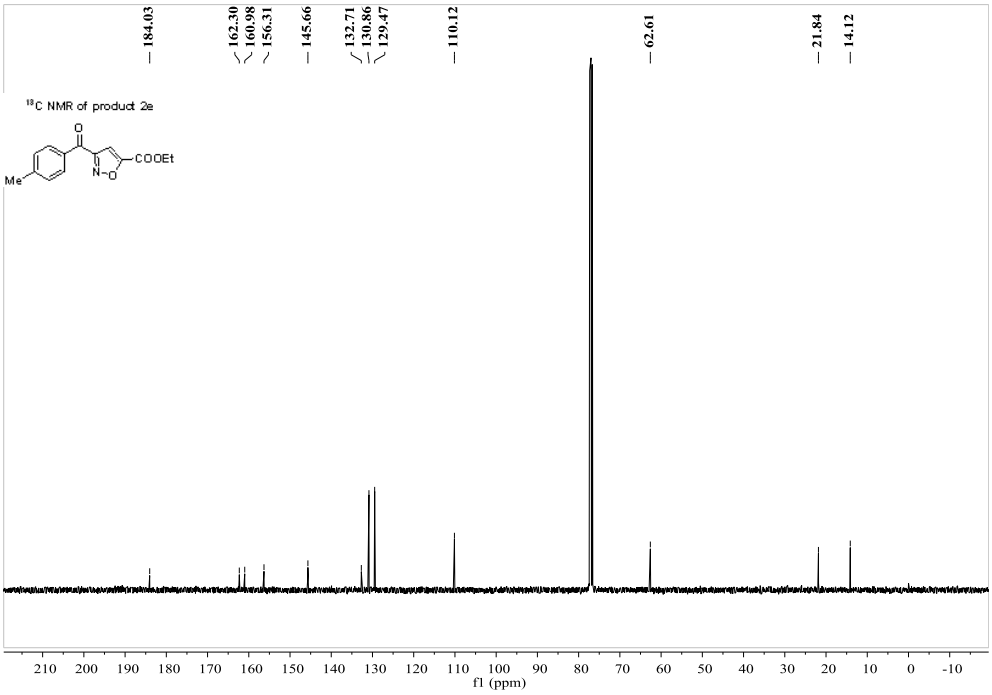
NMR data of **2d**



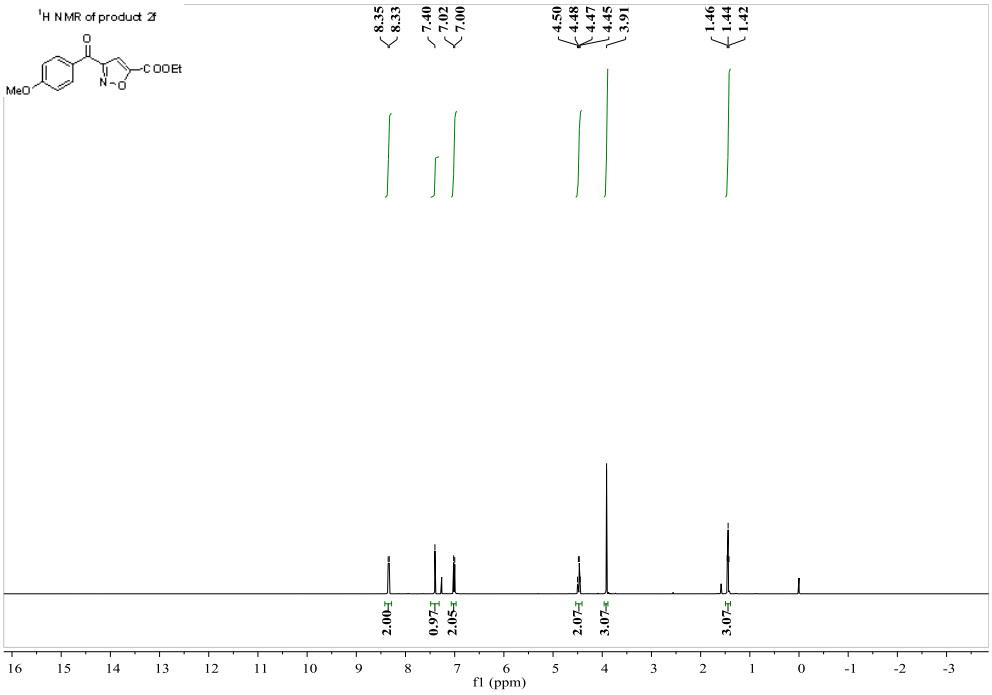


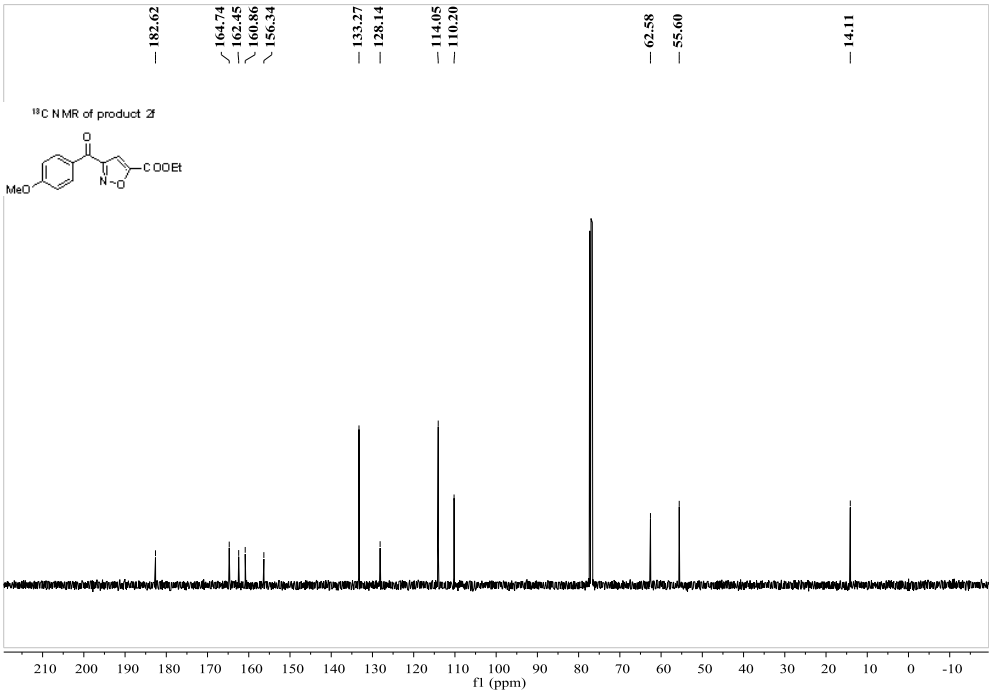
NMR data of **2e**



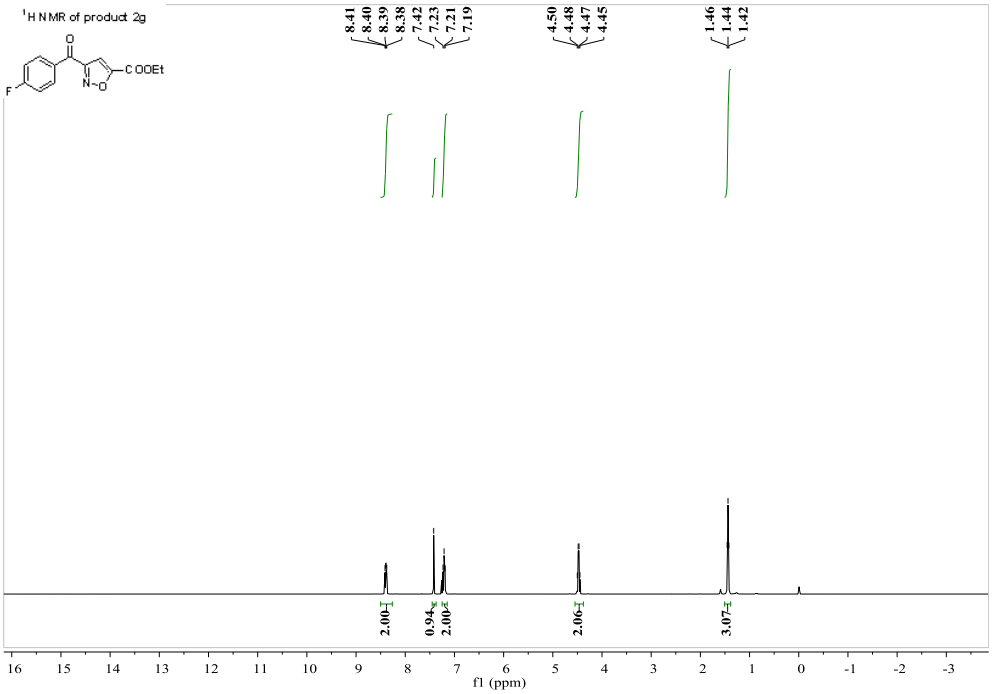


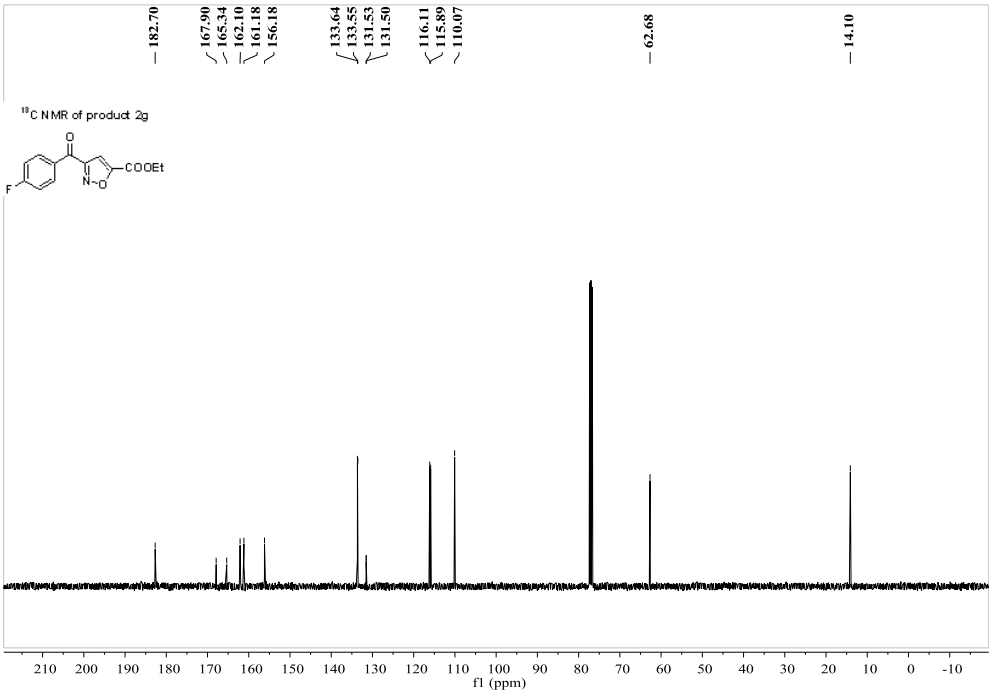
NMR data of **2f**



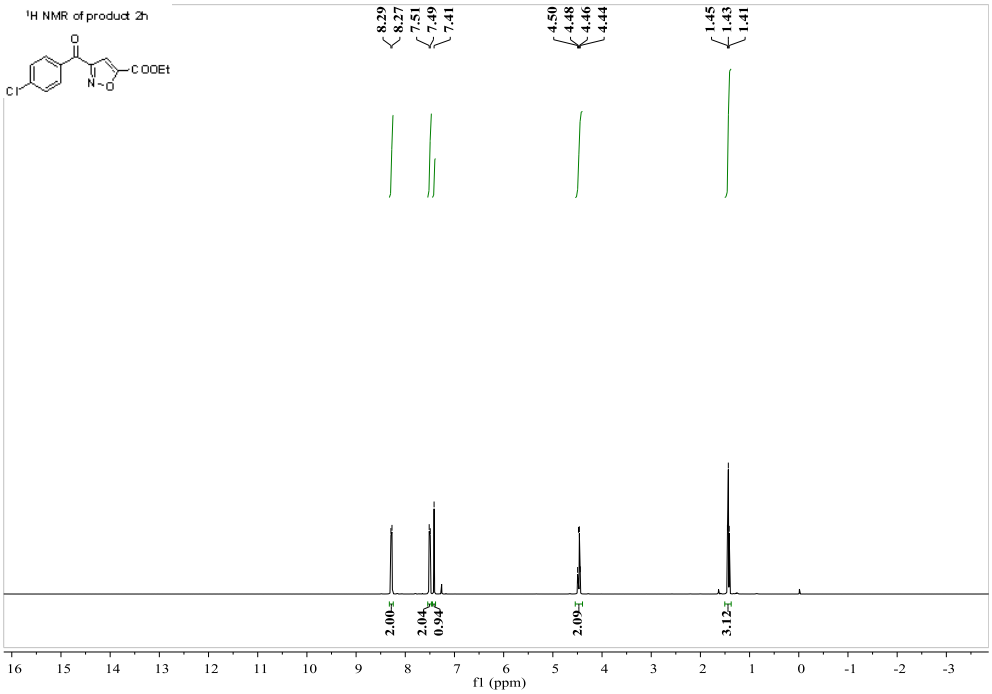


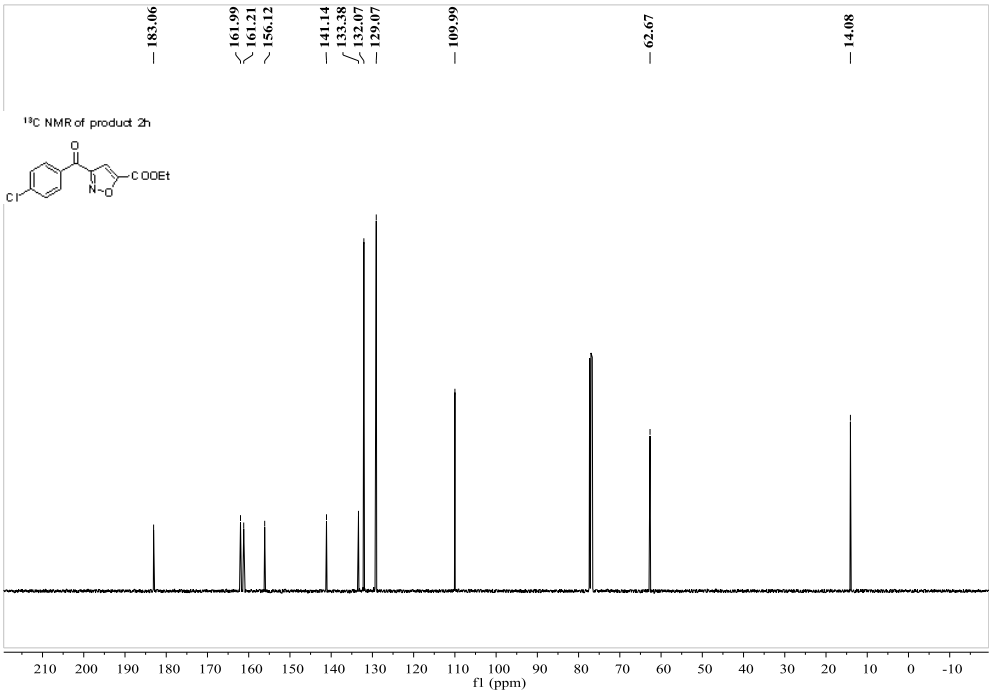
NMR data of **2g**



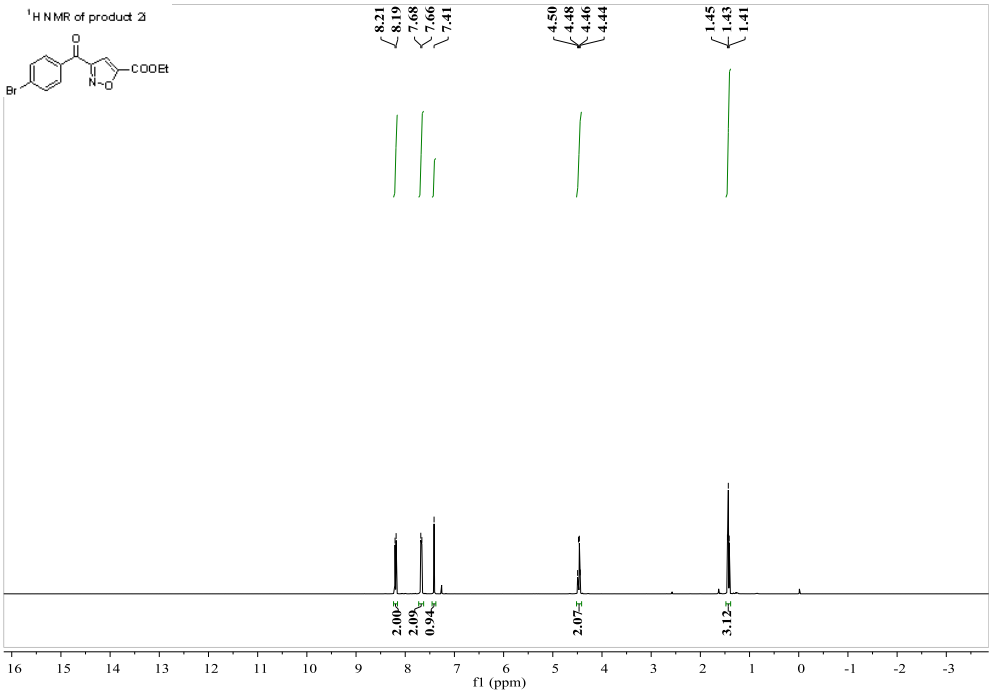


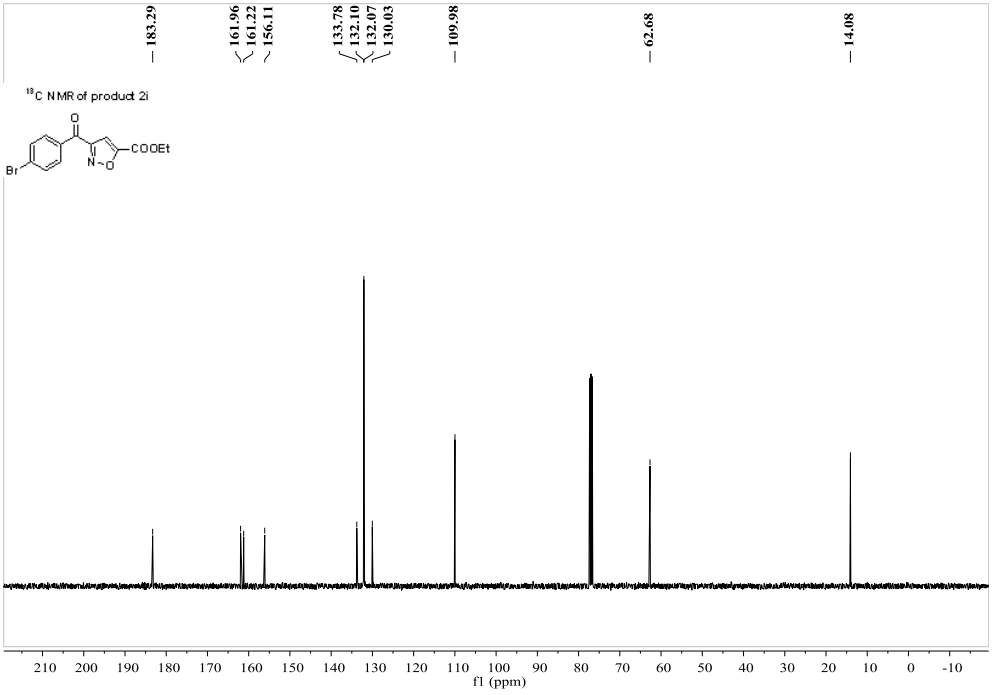
NMR data of **2h**



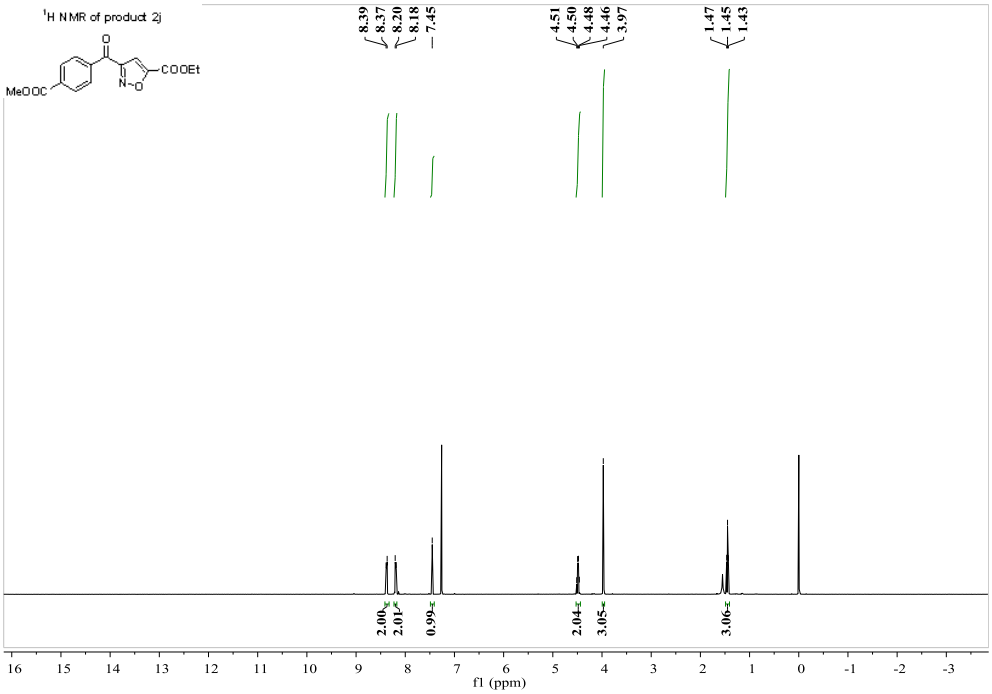


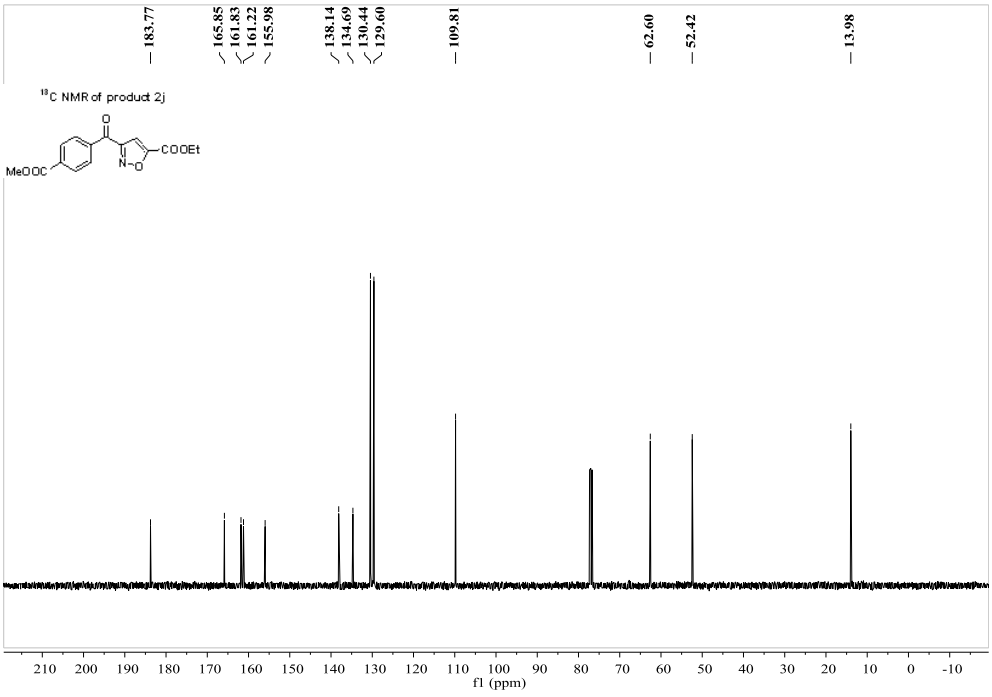
NMR data of **2i**



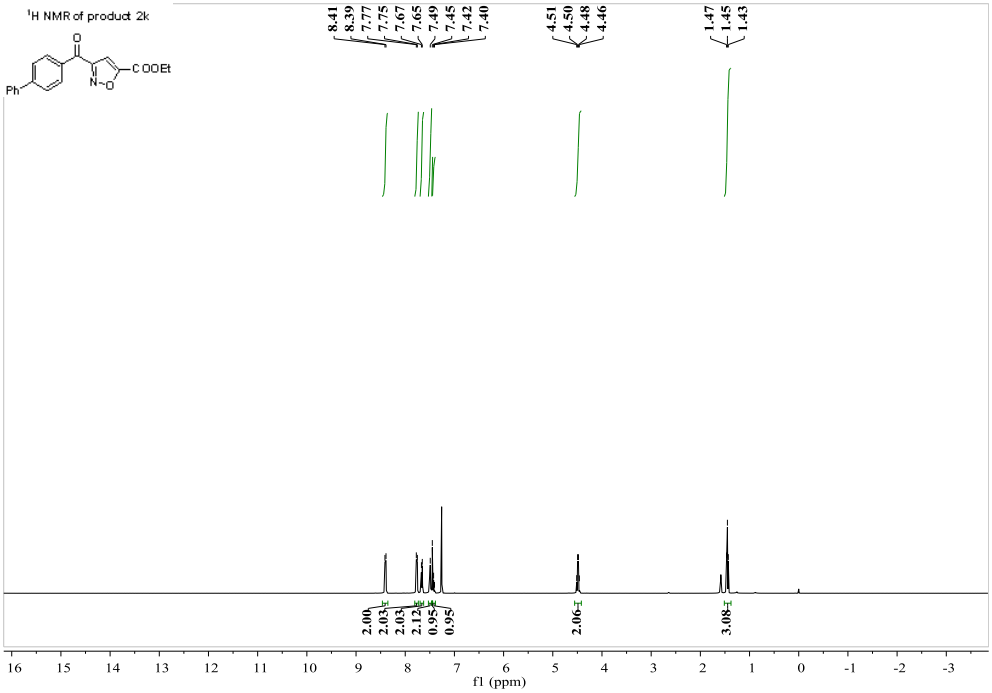


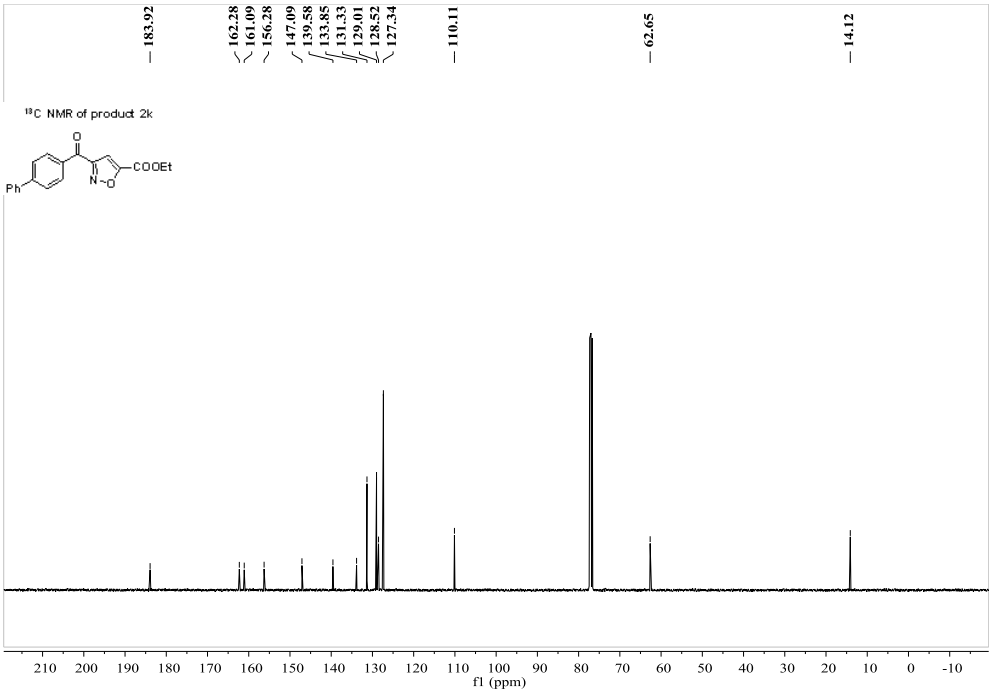
NMR data of **2j**



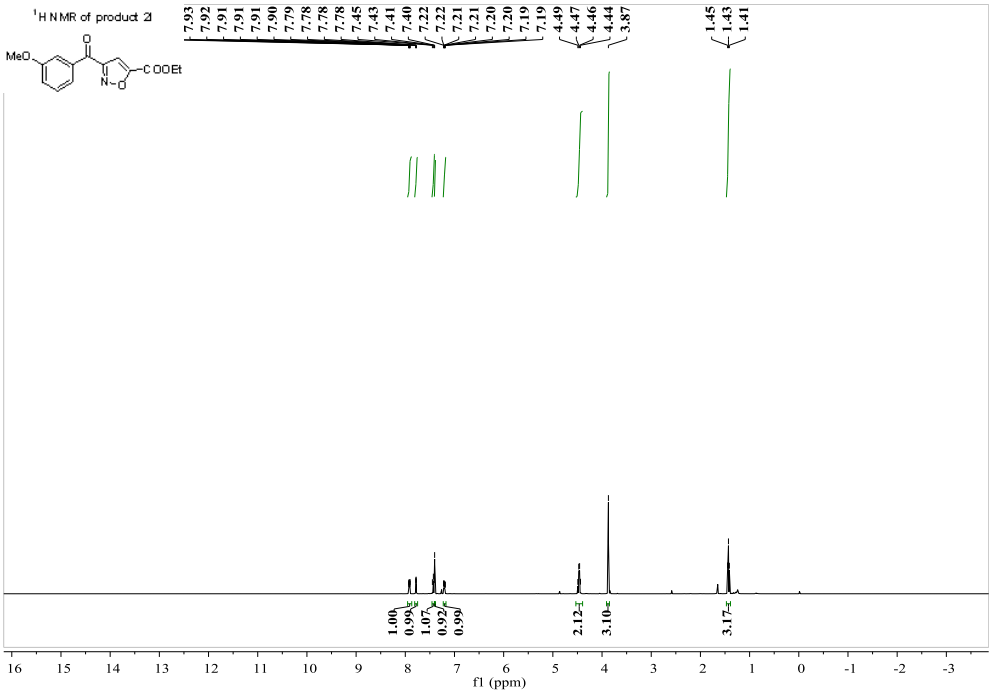


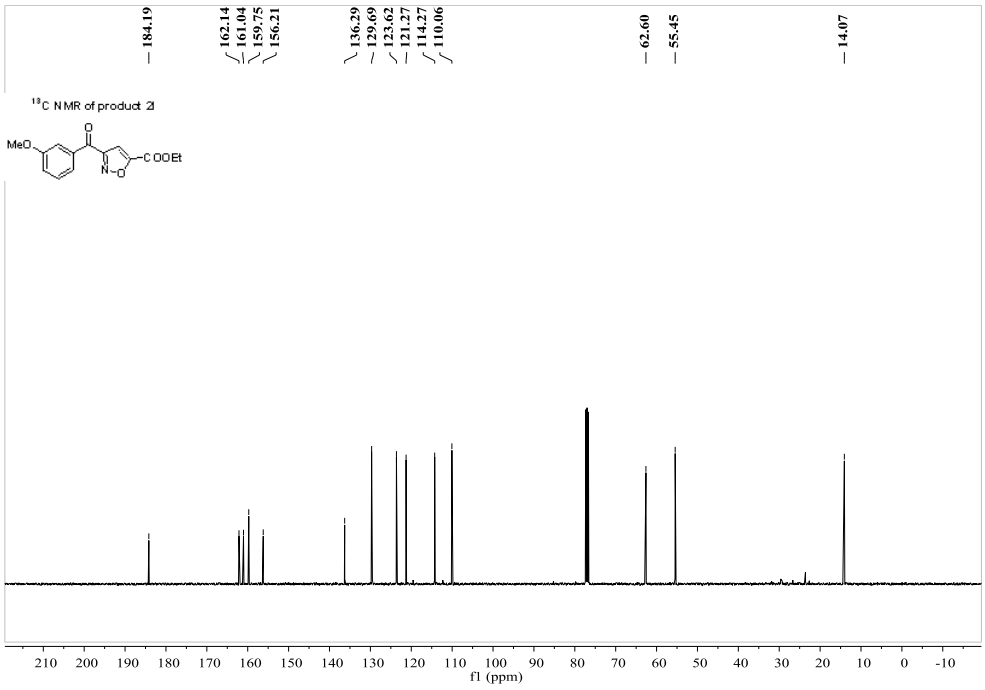
NMR data of **2k**



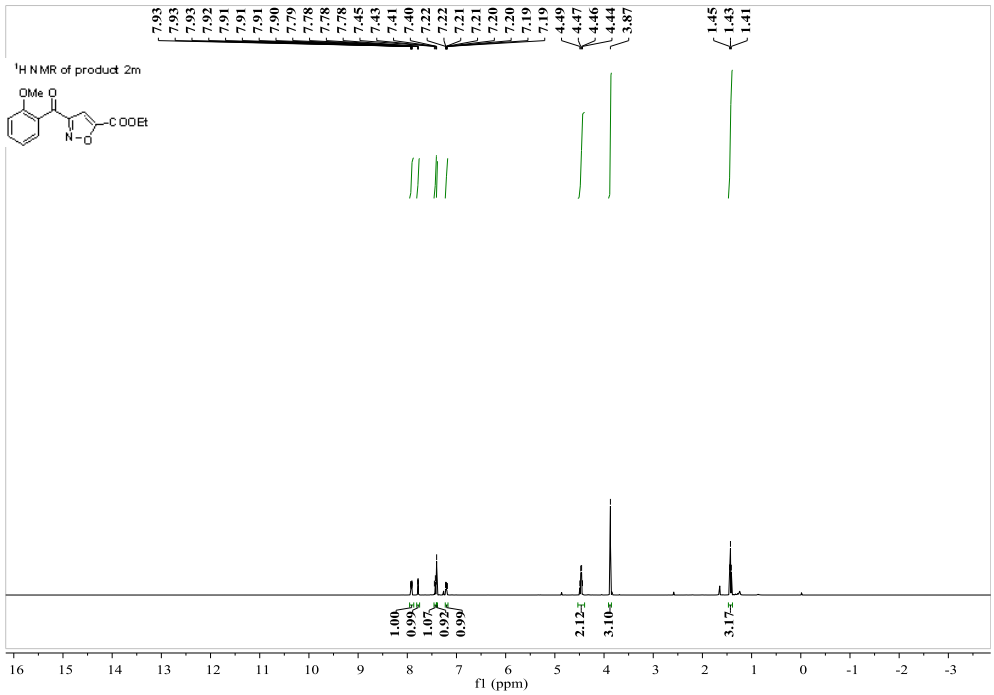


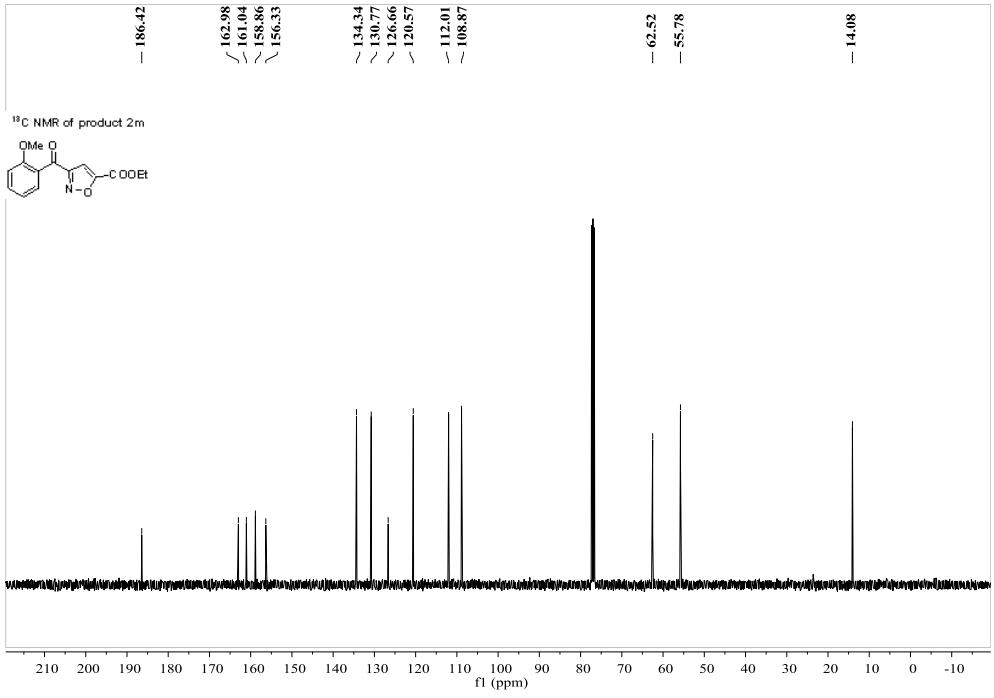
NMR data of **2l**



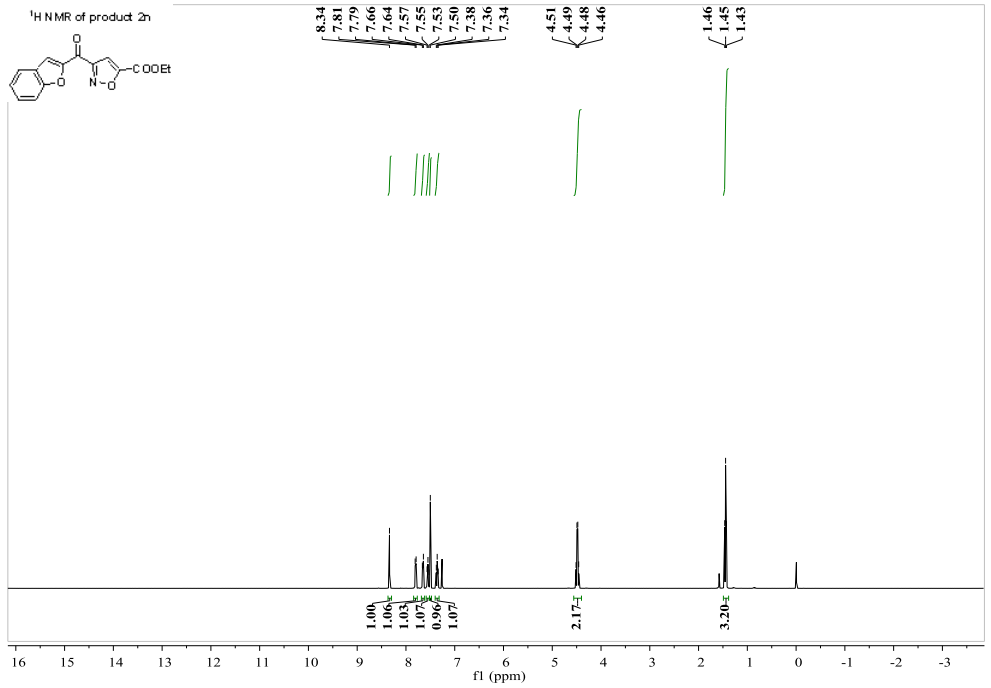


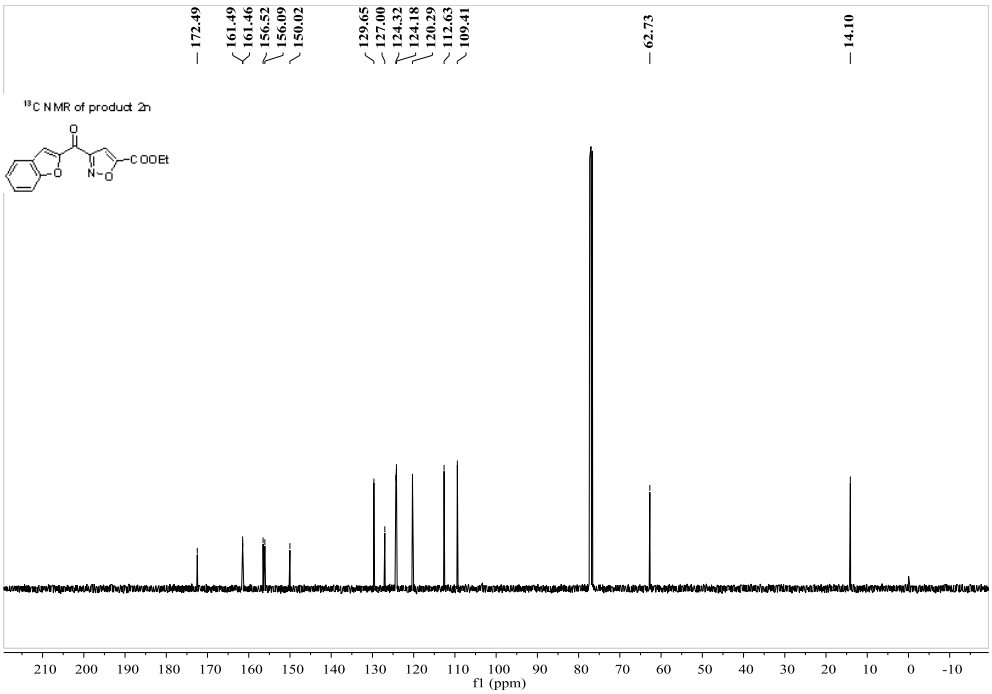
NMR data of **2m**



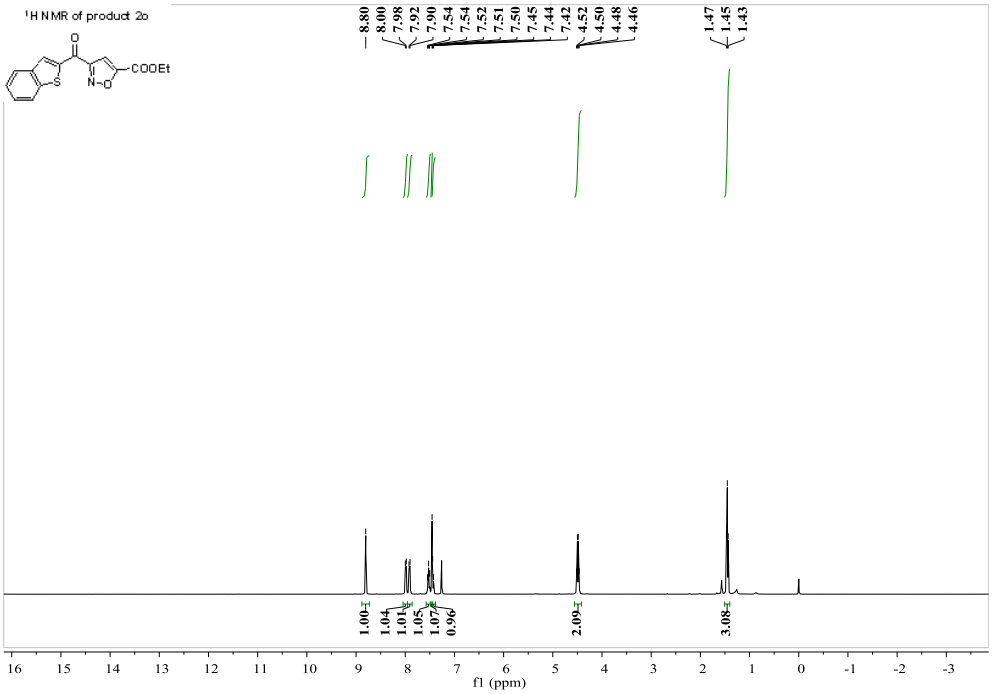


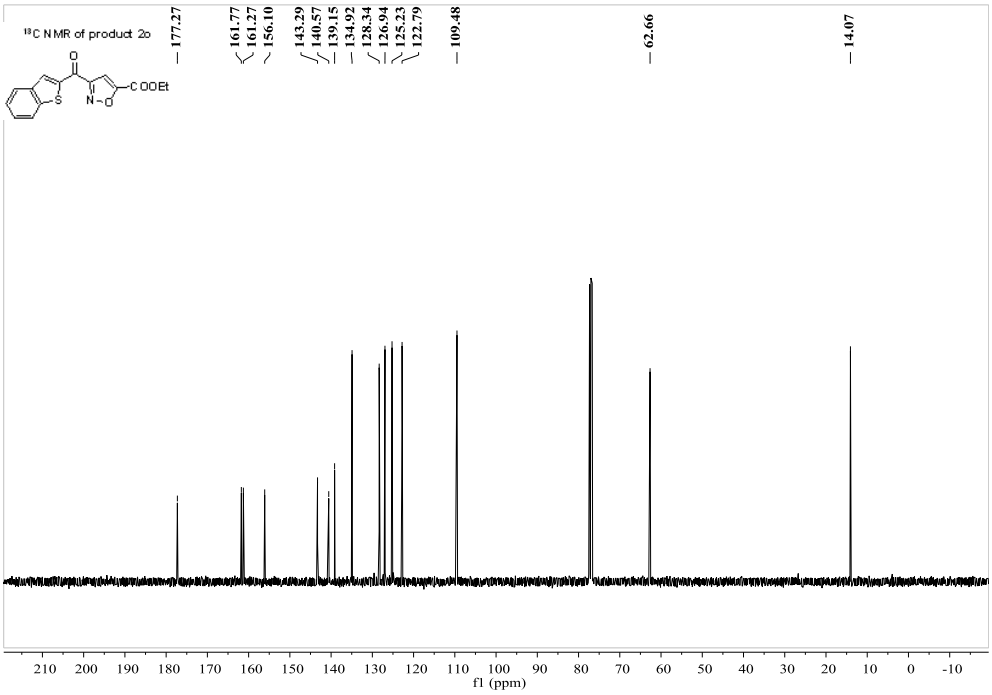
NMR data of **2n**



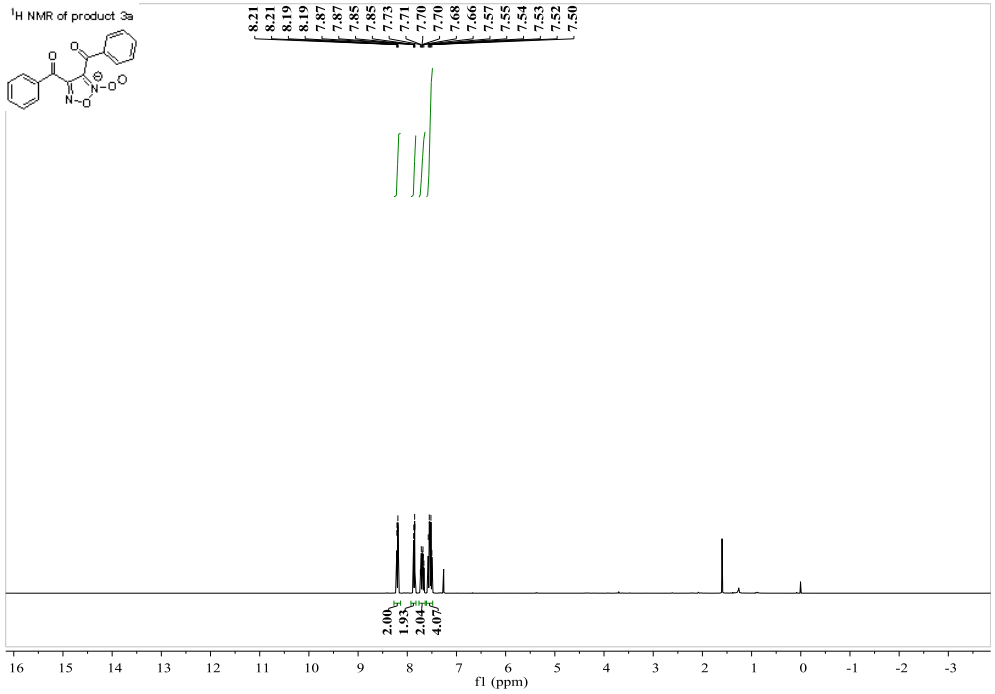


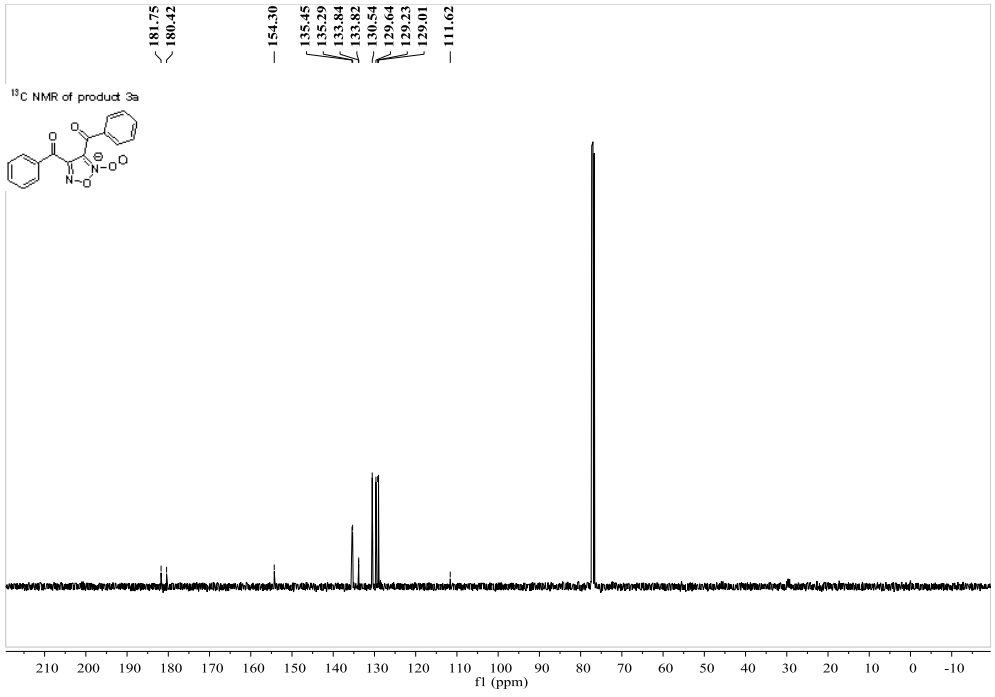
NMR data of **2o**



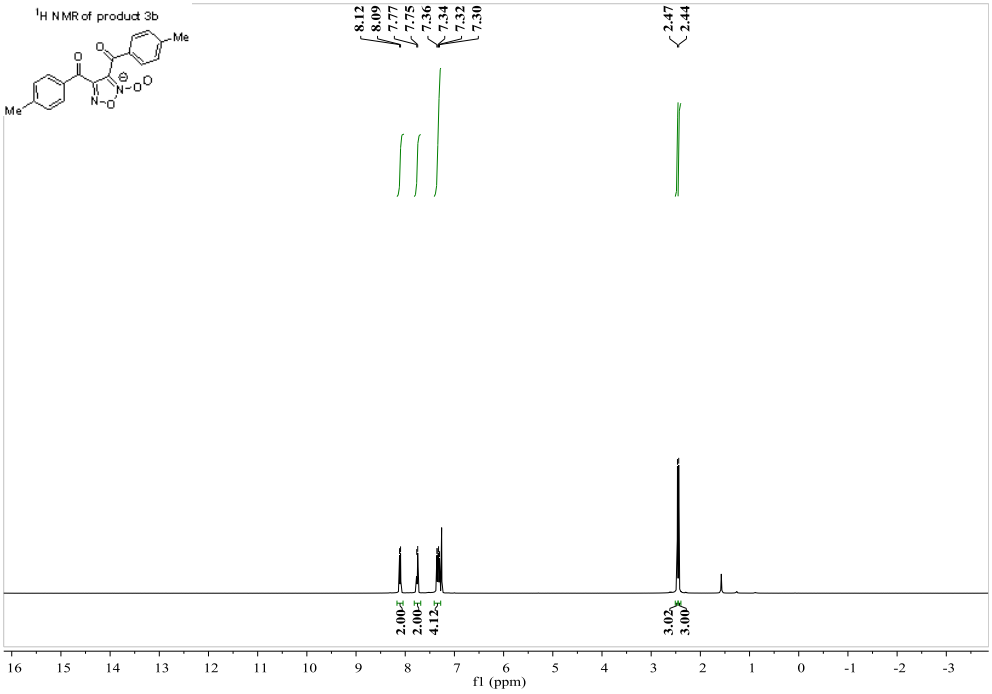


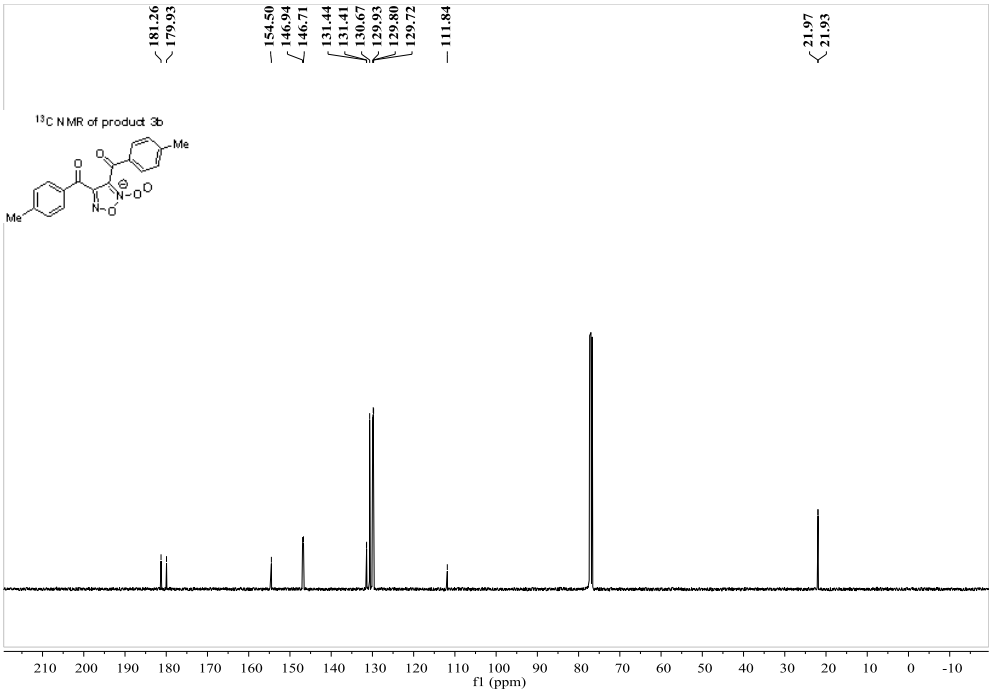
NMR data of **3a**



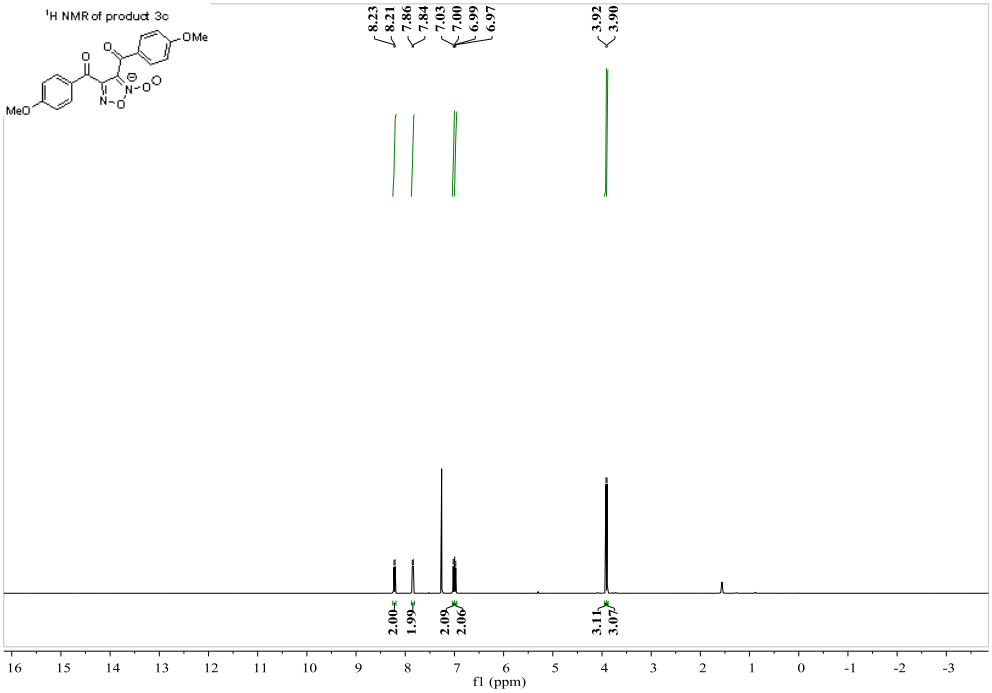


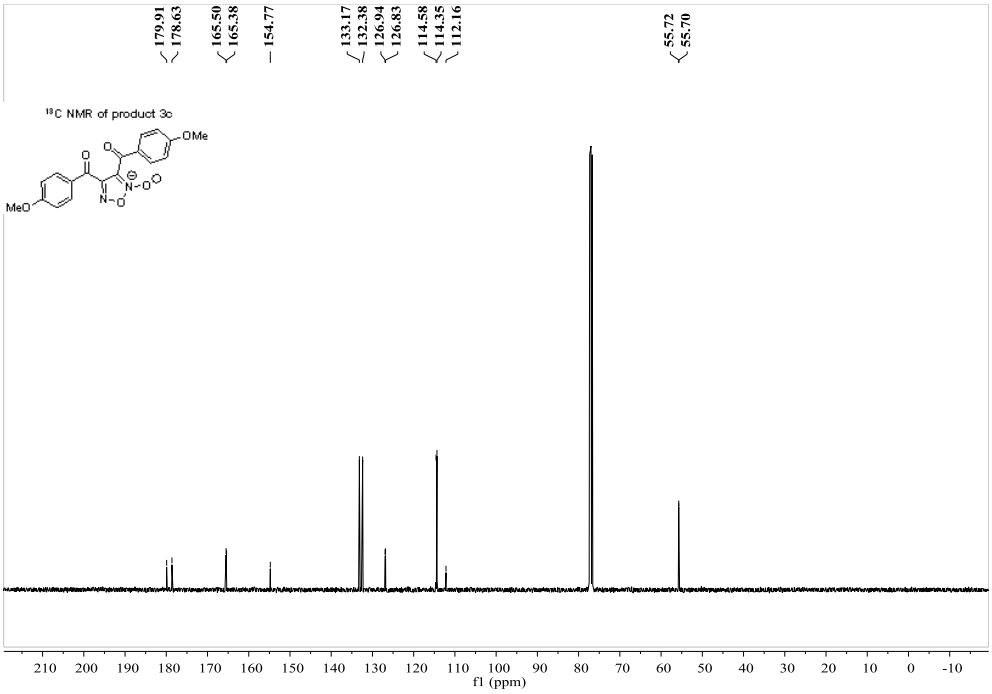
NMR data of **3b**



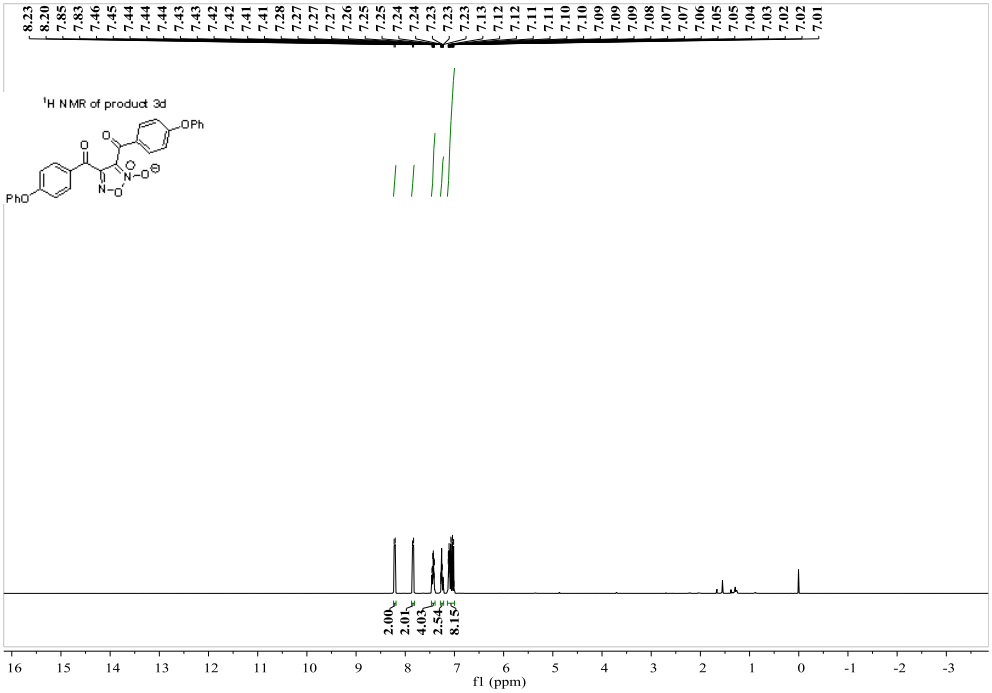


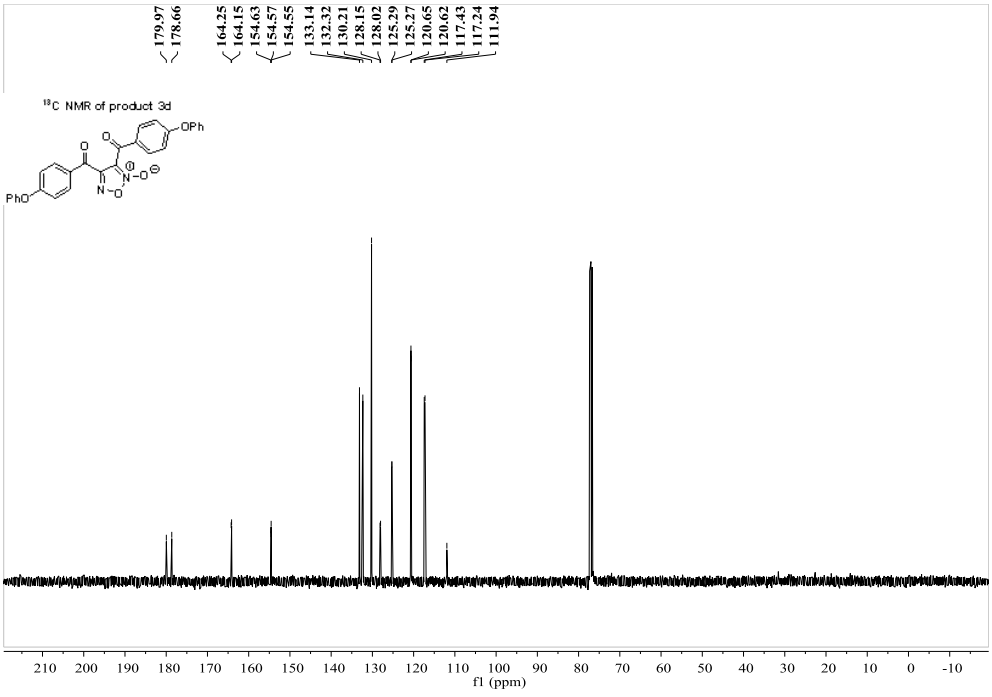
NMR data of **3c**



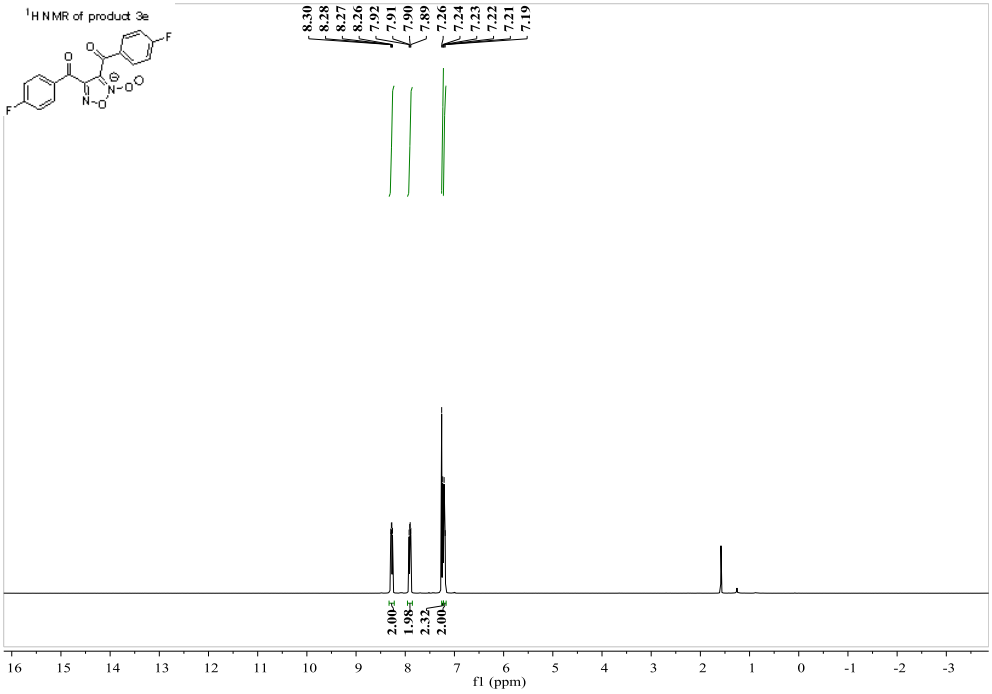


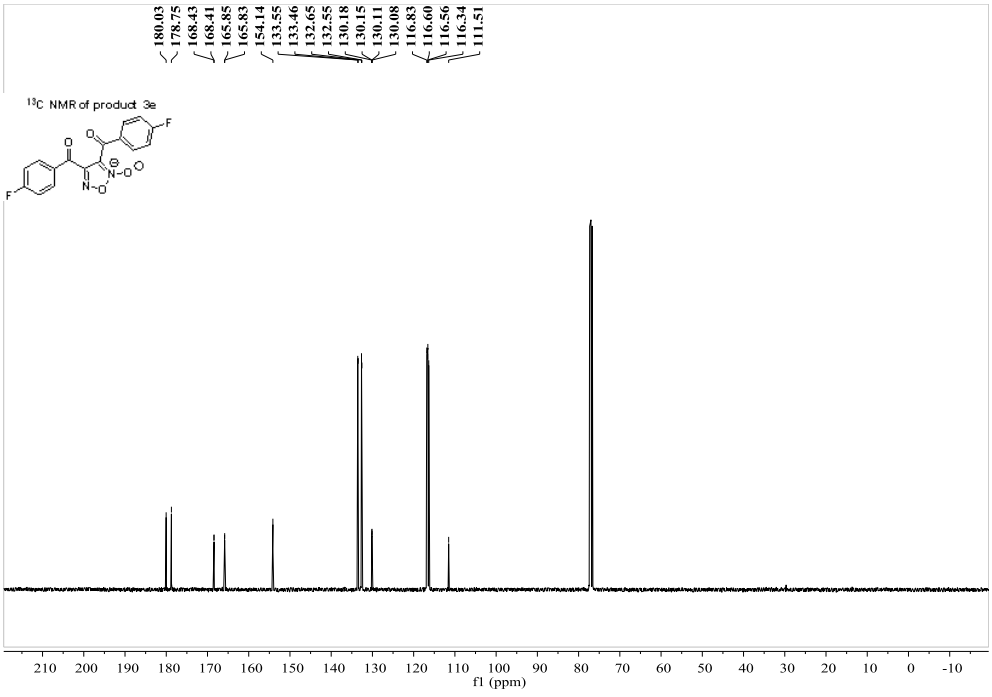
NMR data of **3d**

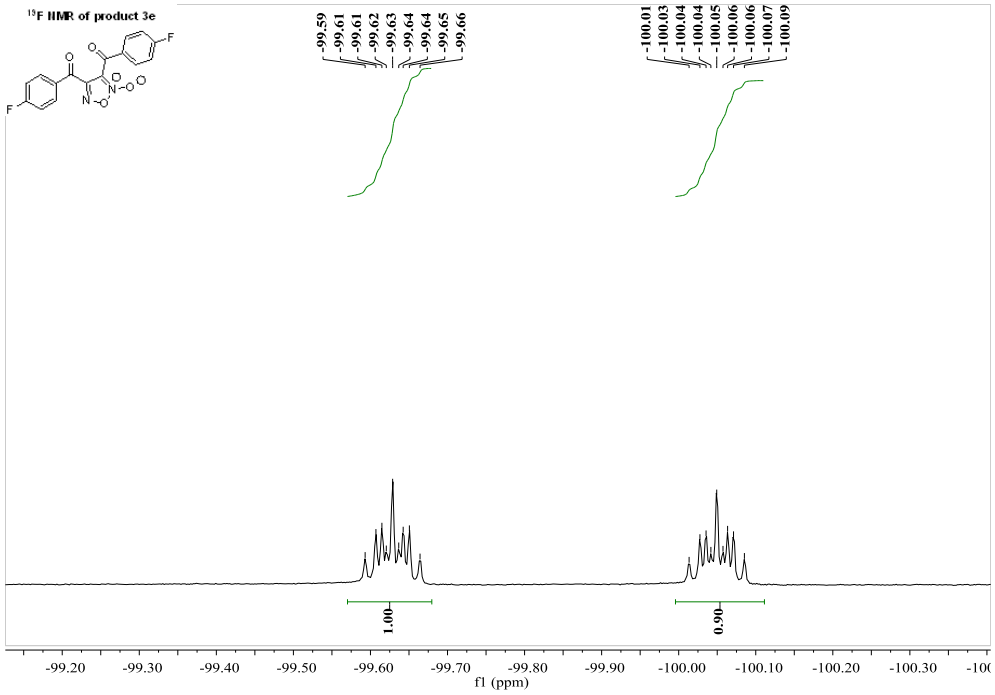




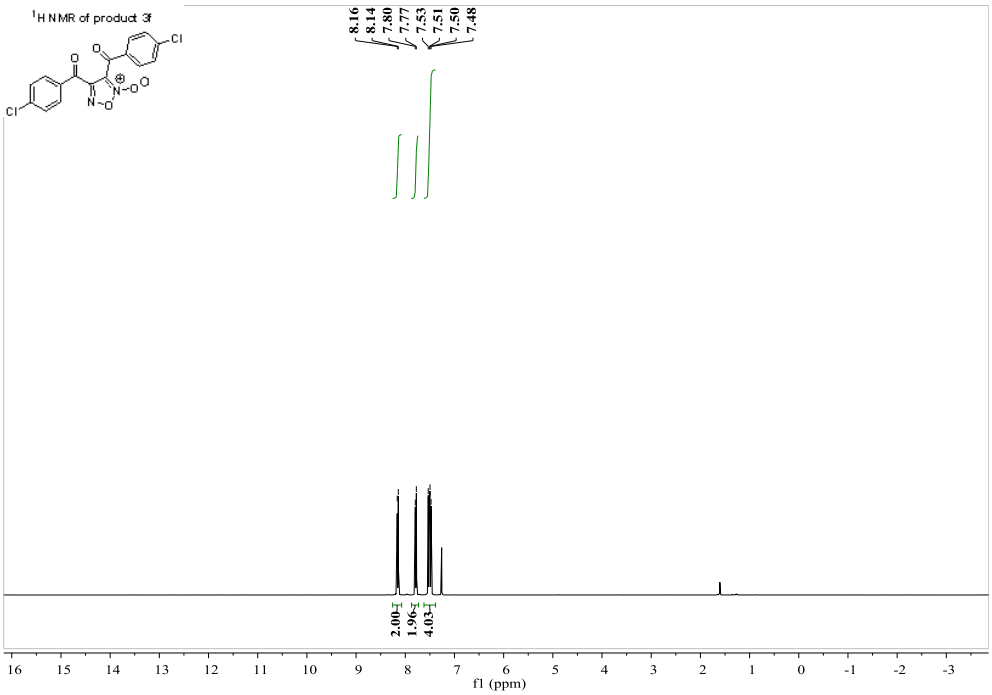
NMR data of **3e**

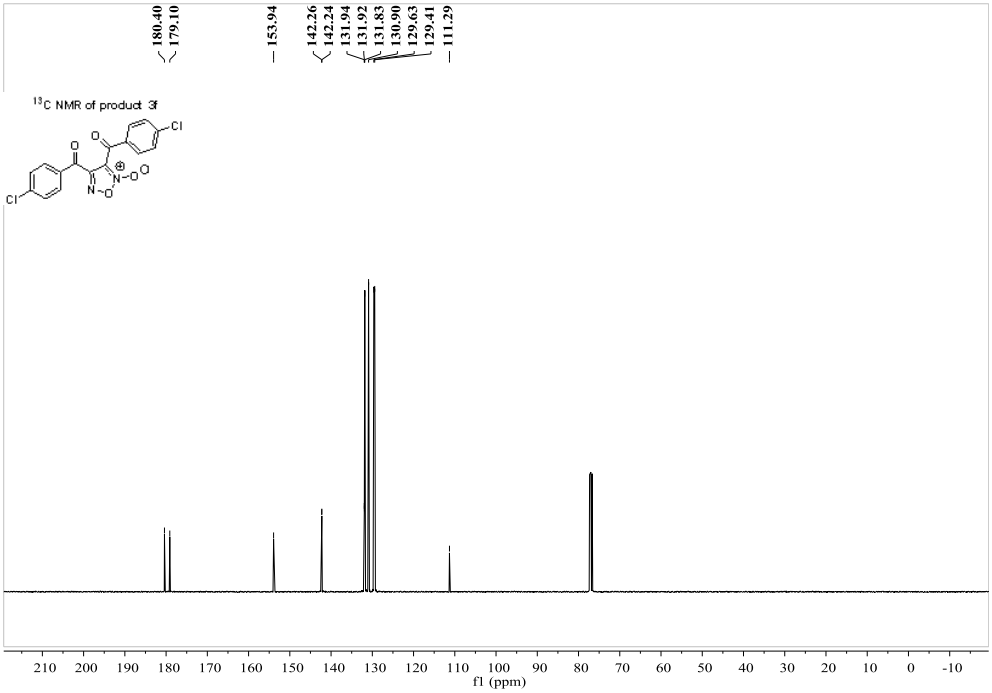




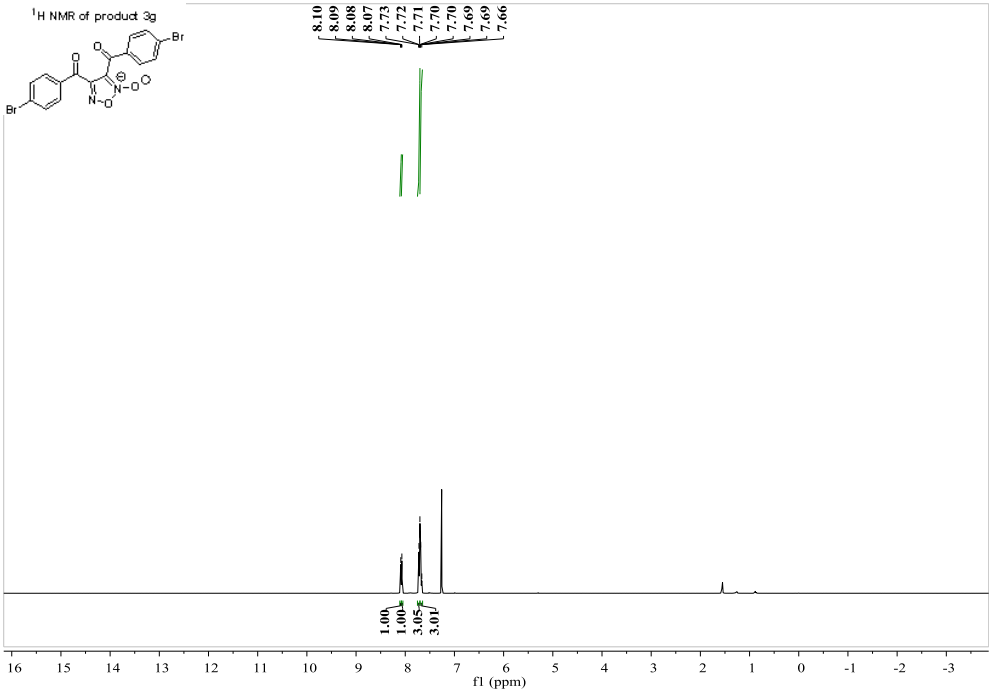

^{19}F NMR of product 3e
-99.59
-99.61
-99.61
-99.62
-99.63
-99.64
-99.64
-99.65
-99.66
-100.01
-100.03
-100.04
-100.04
-100.05
-100.06
-100.06
-100.07
-100.09
1.00
0.90
-99.20
-99.30
-99.40
-99.50
-99.60
-99.70
-99.80
-99.90
-100.00
-100.10
-100.20
-100.30
f1 (ppm)

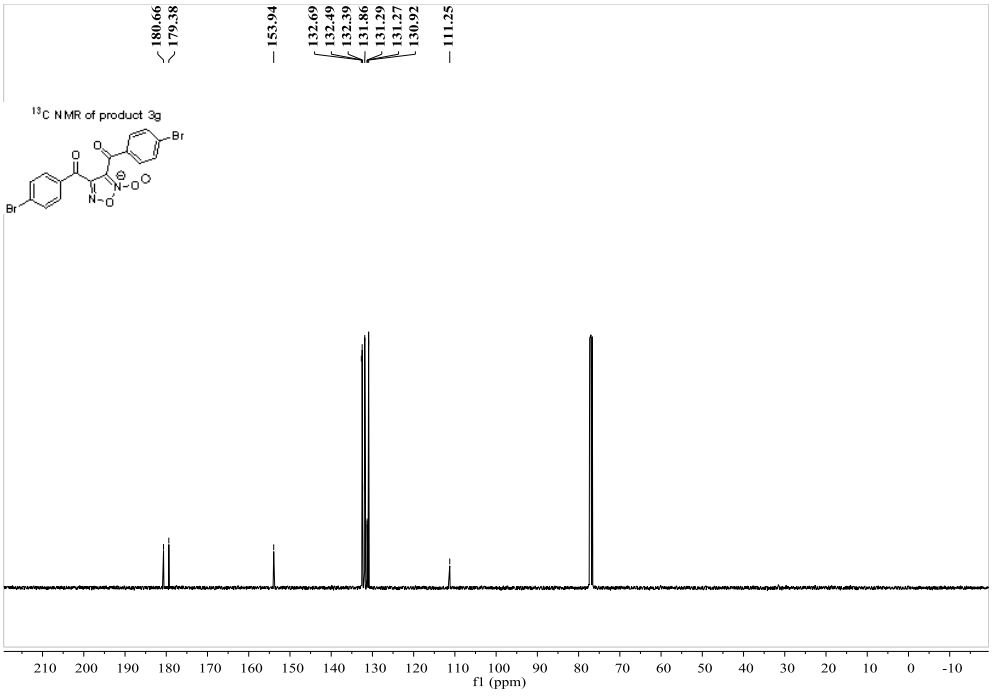
NMR data of **3f**



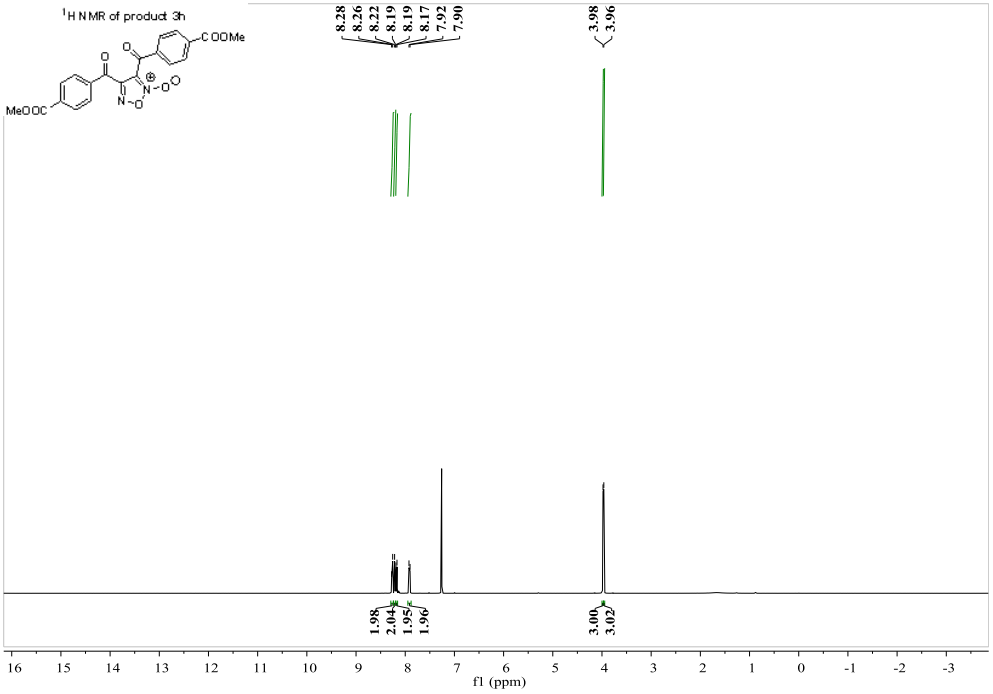


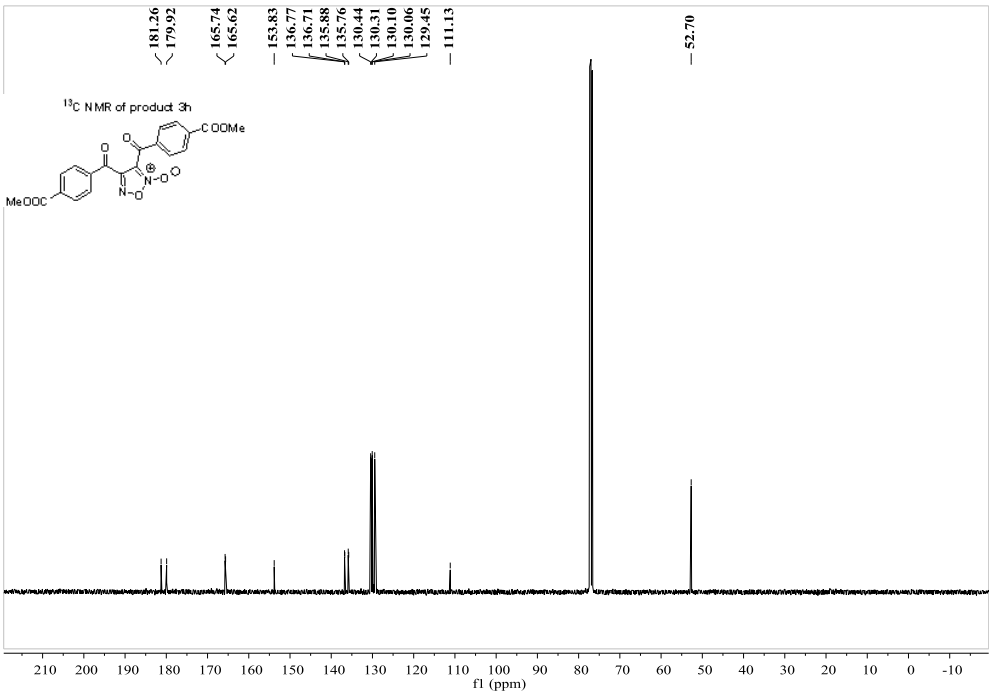
NMR data of **3g**



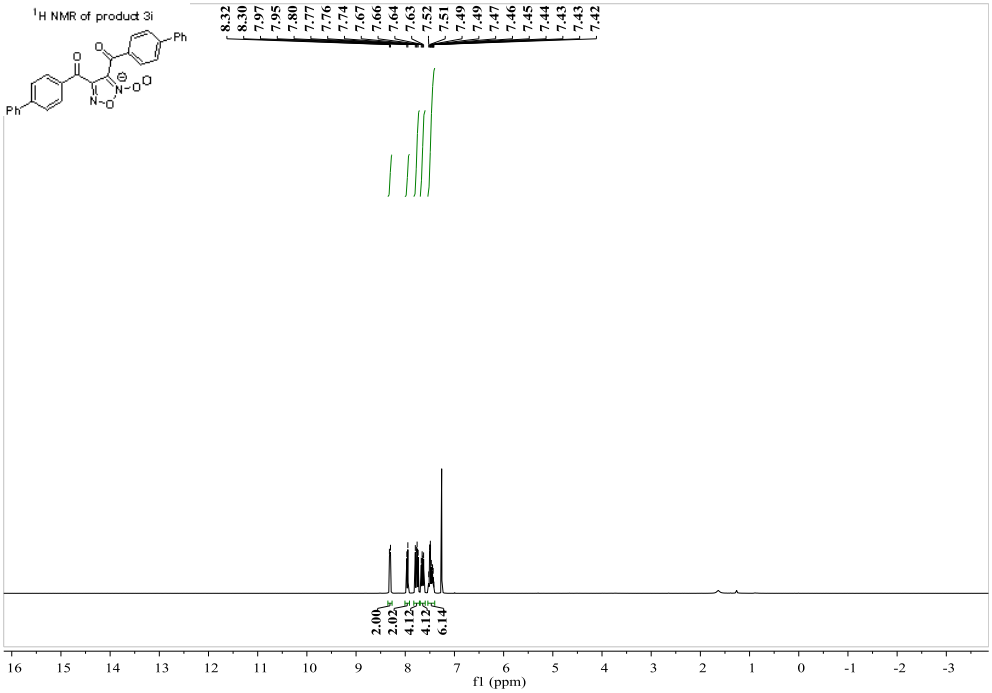


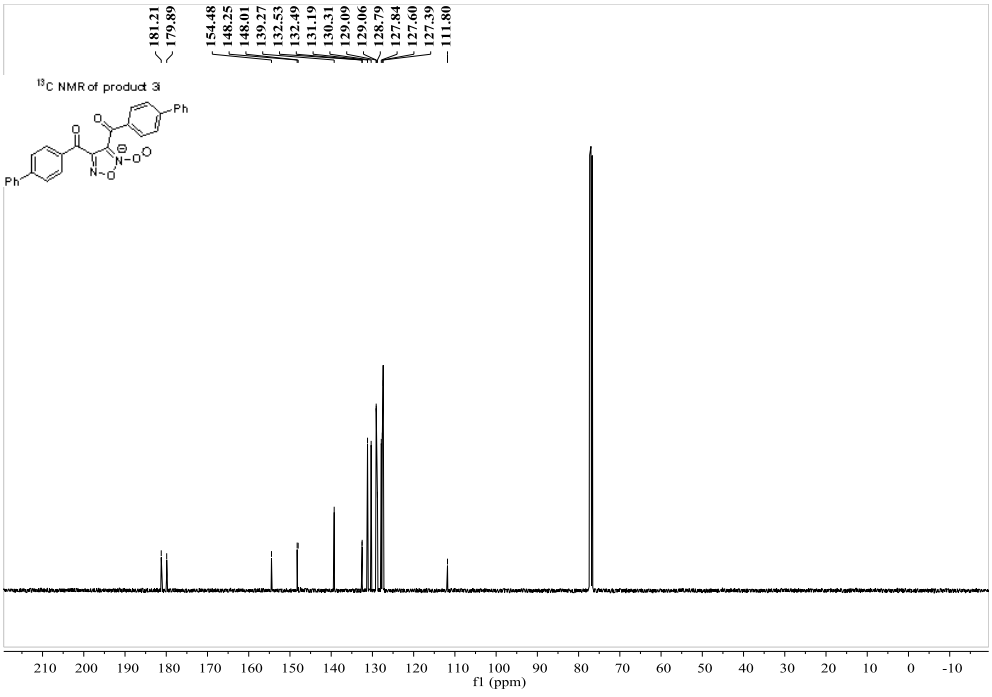
NMR data of **3h**



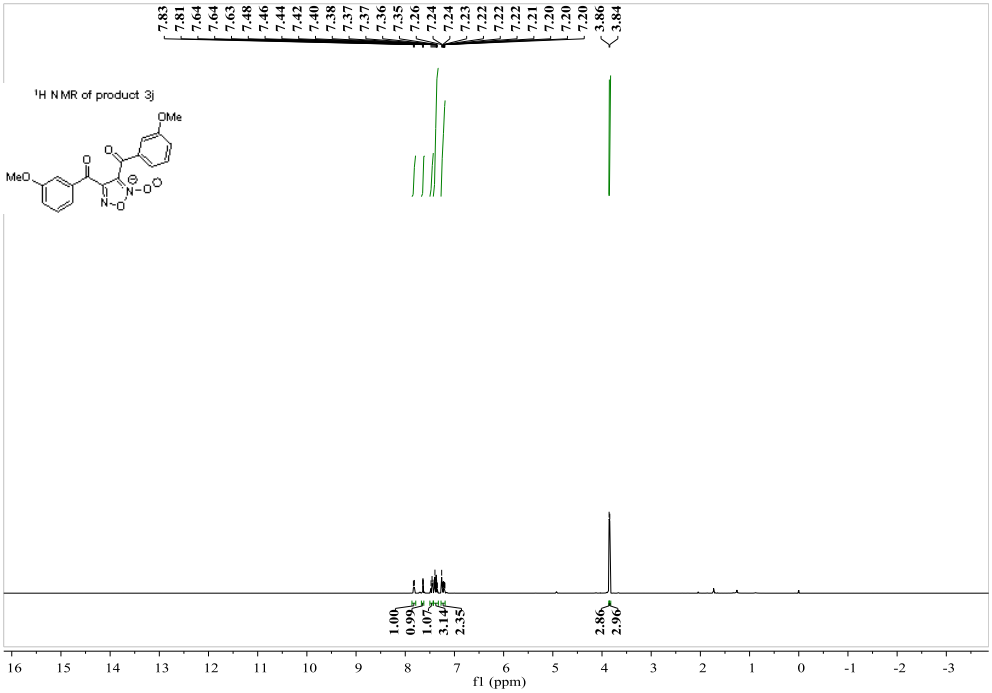


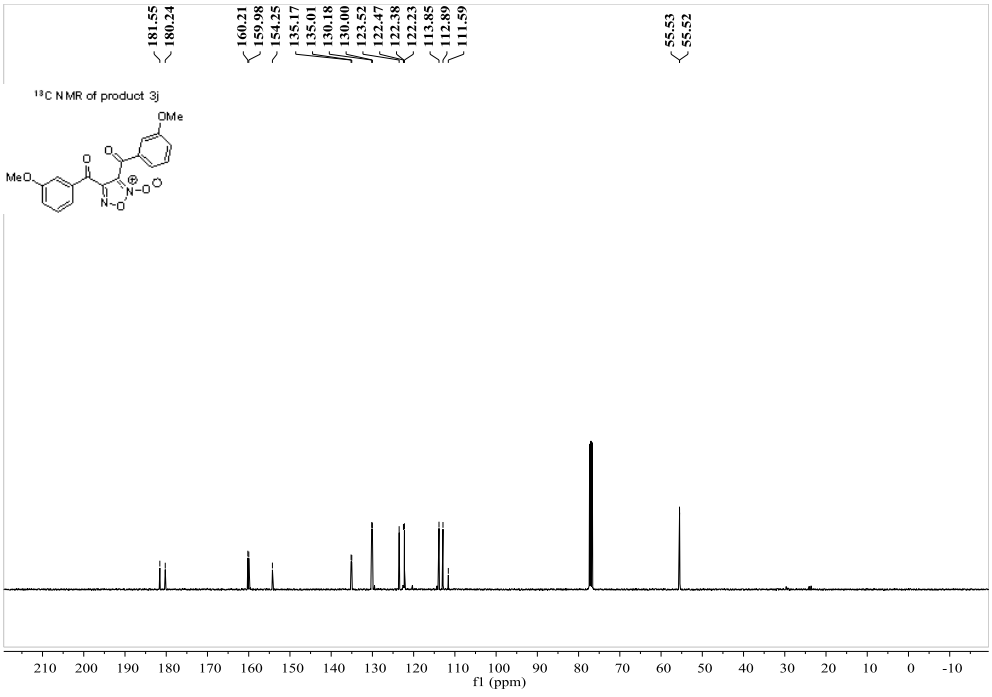
NMR data of **3i**



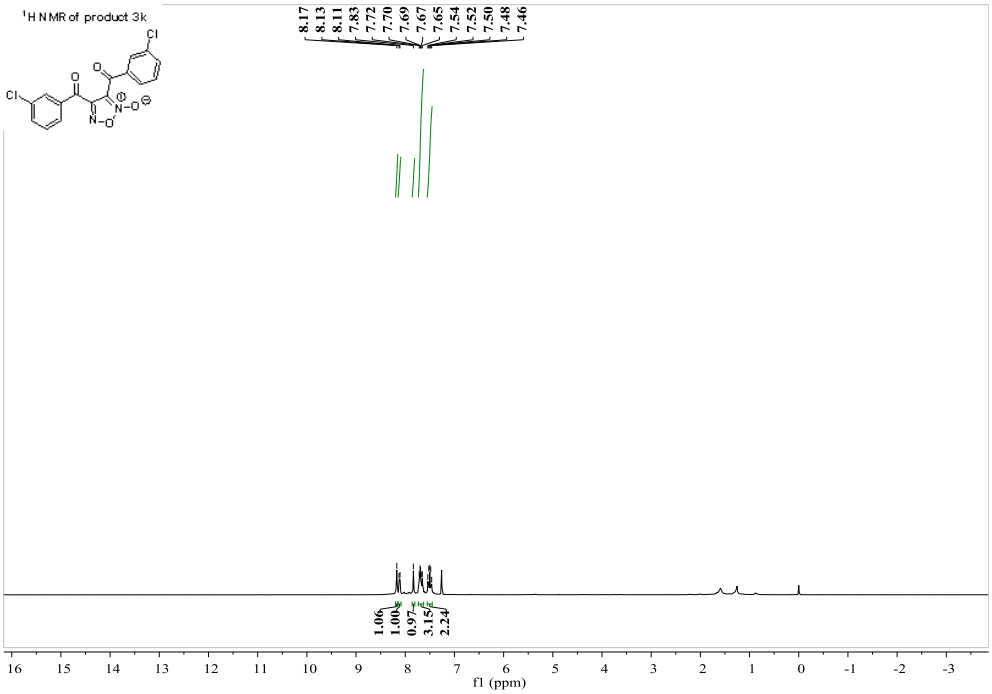


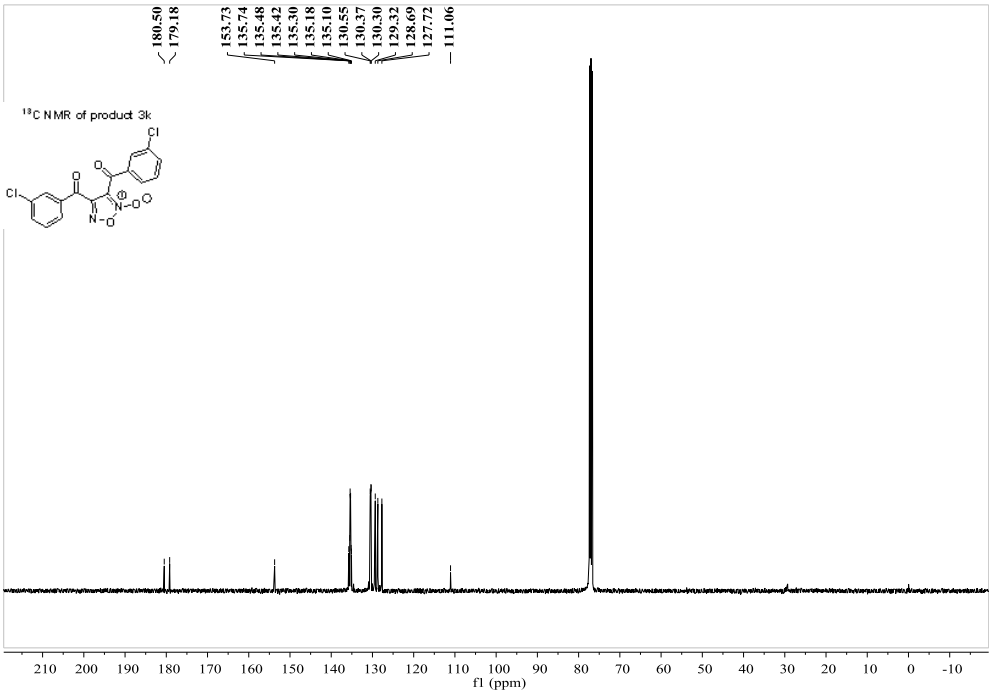
NMR data of **3j**



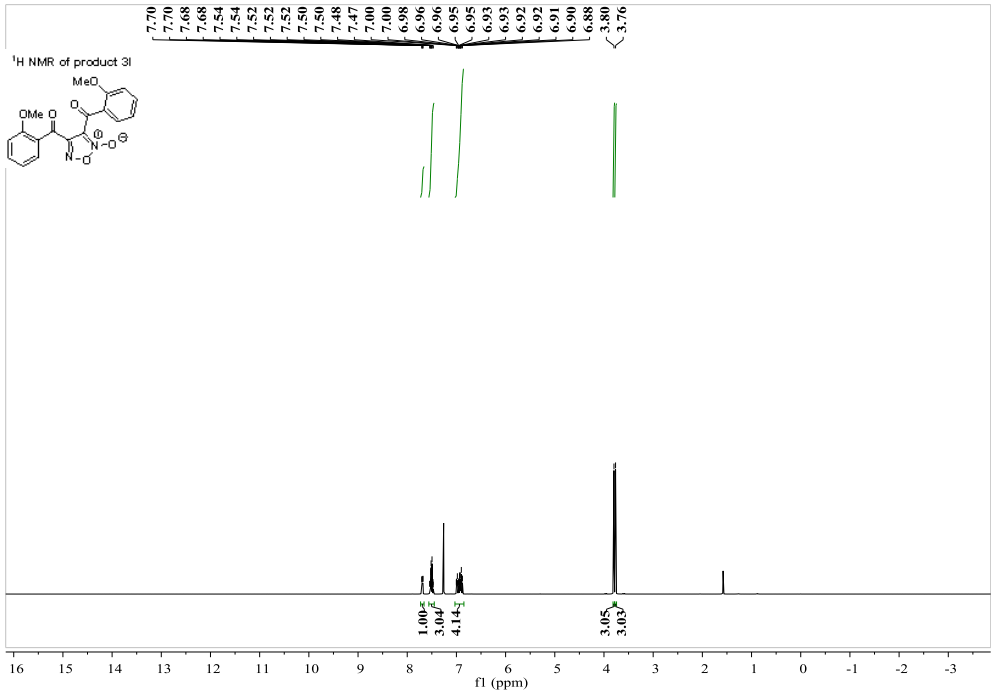


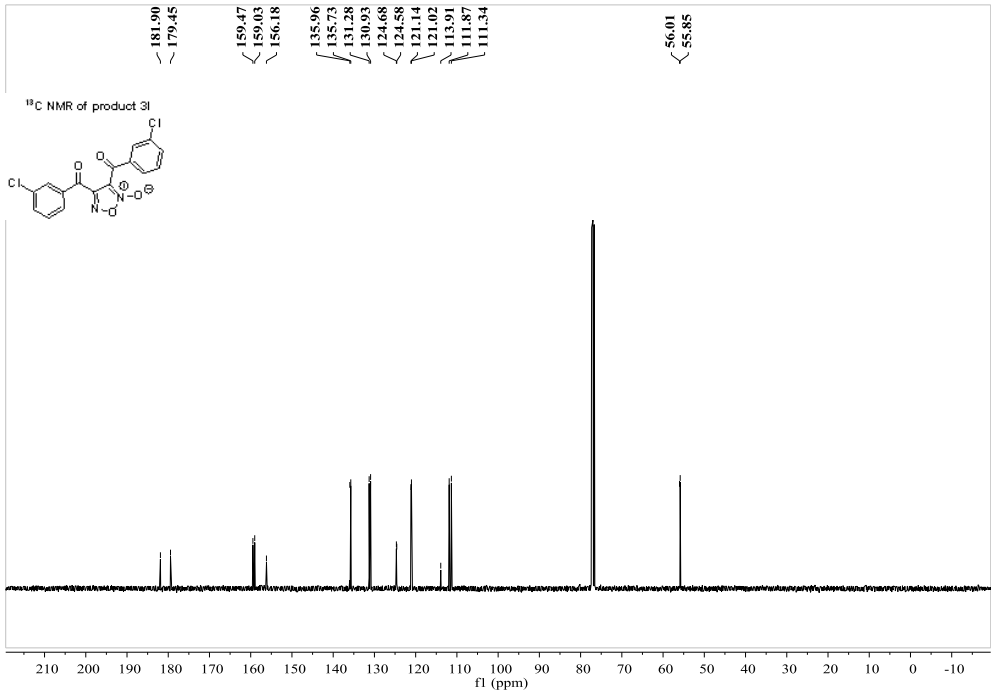
NMR data of **3k**



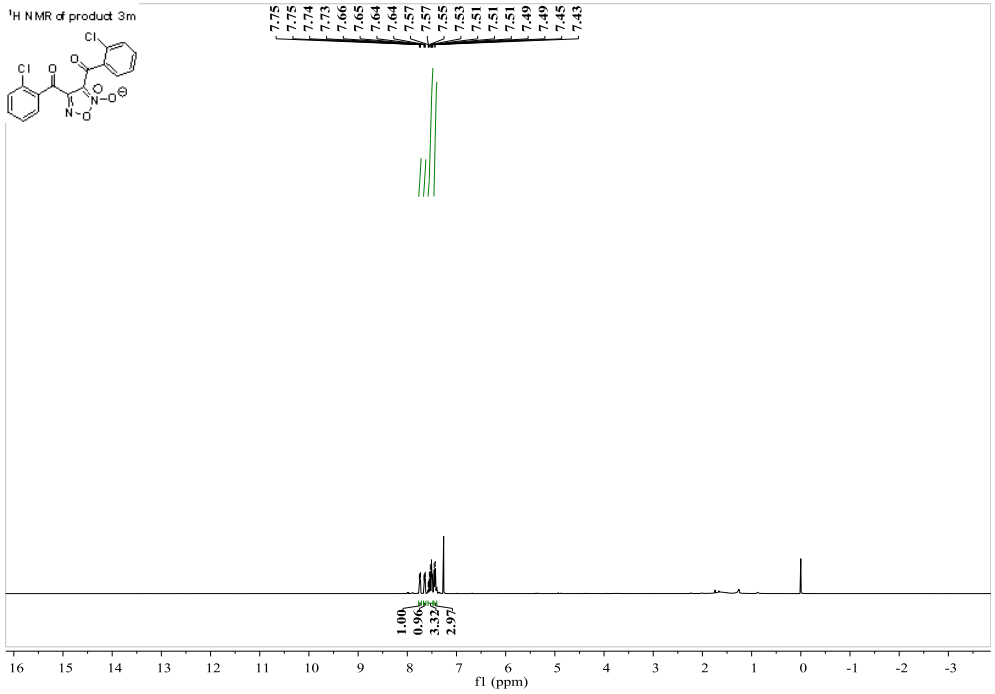


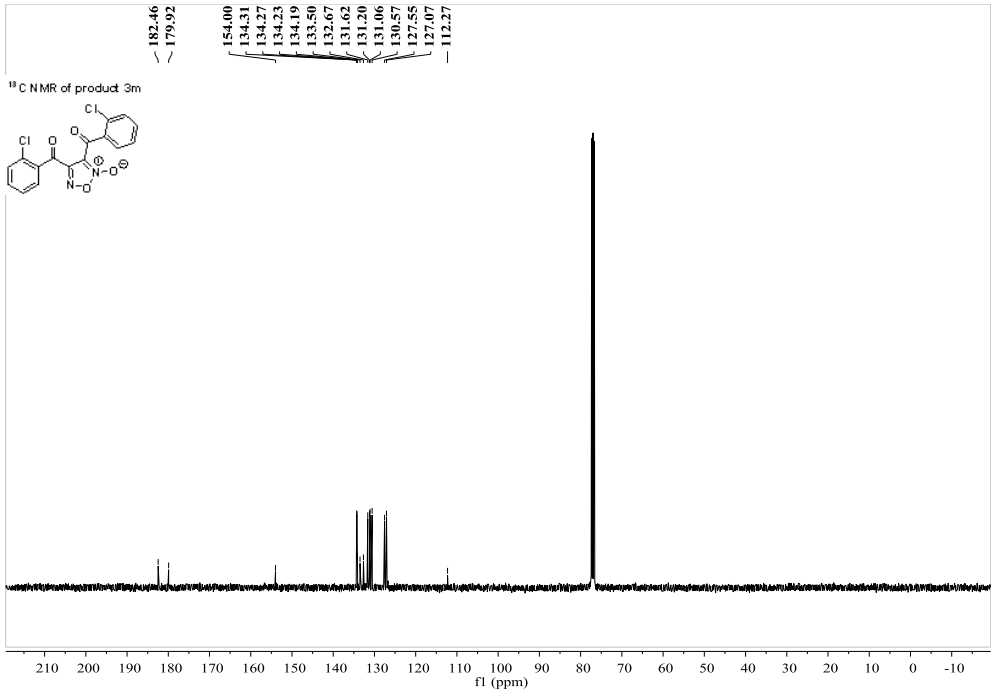
NMR data of **3l**



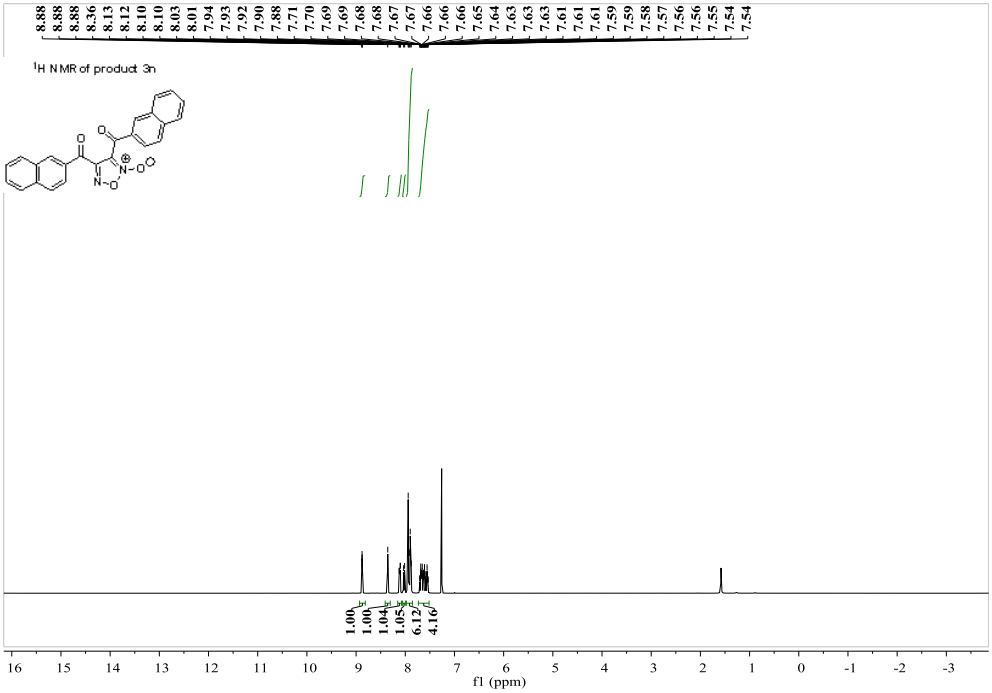


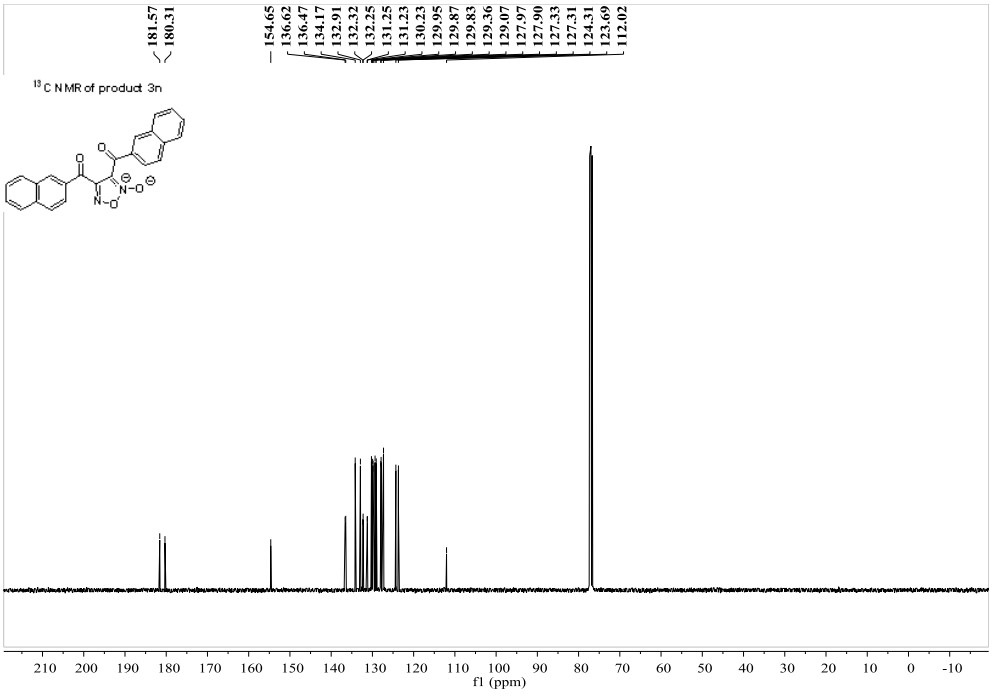
NMR data of **3m**



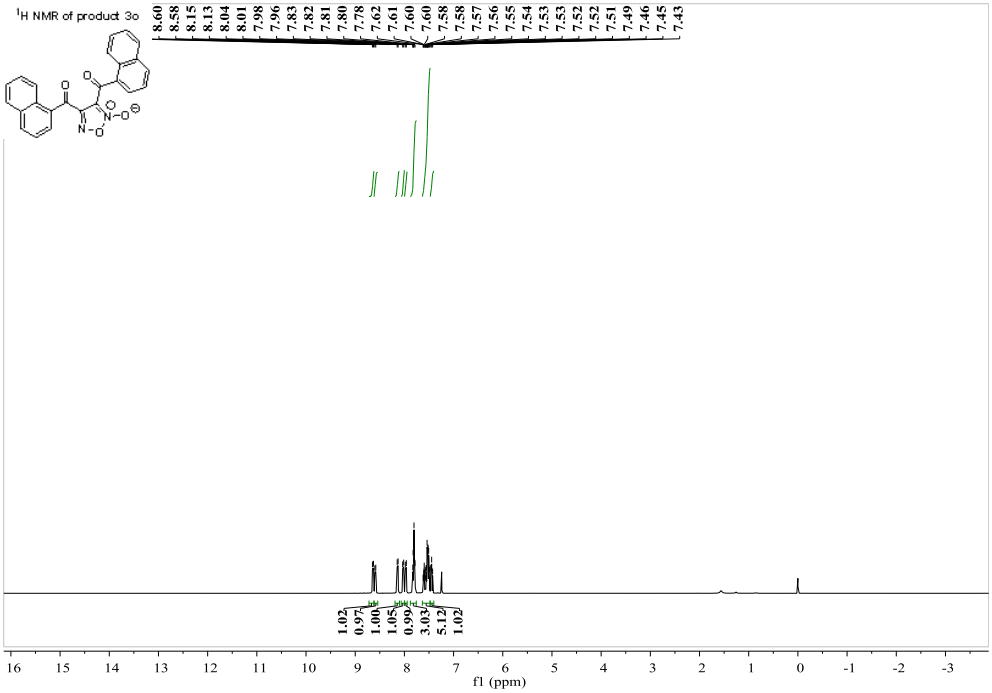


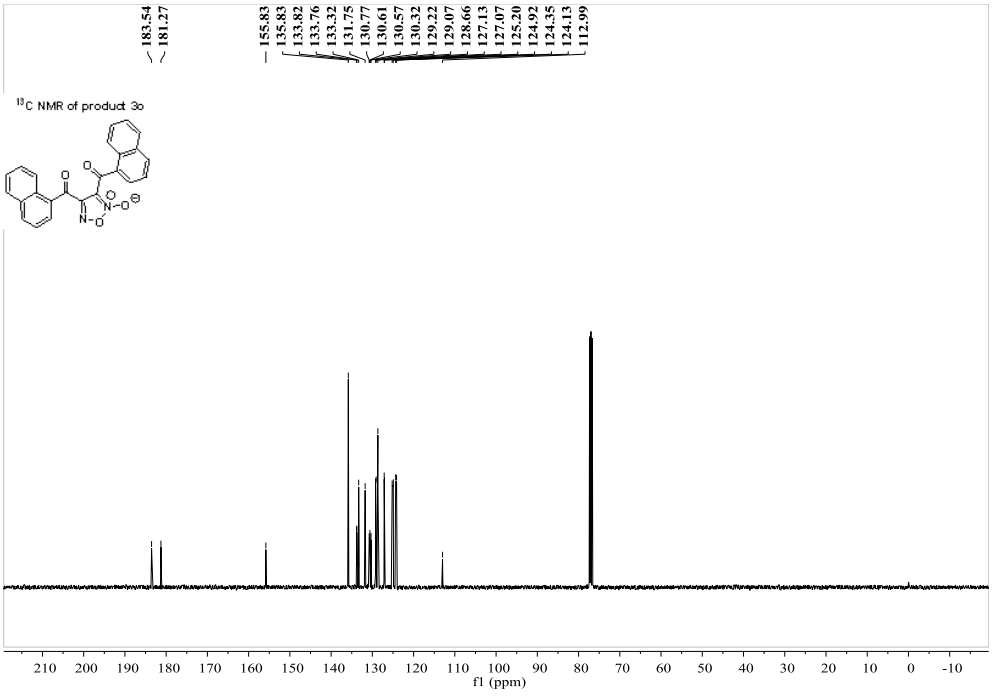
NMR data of **3n**



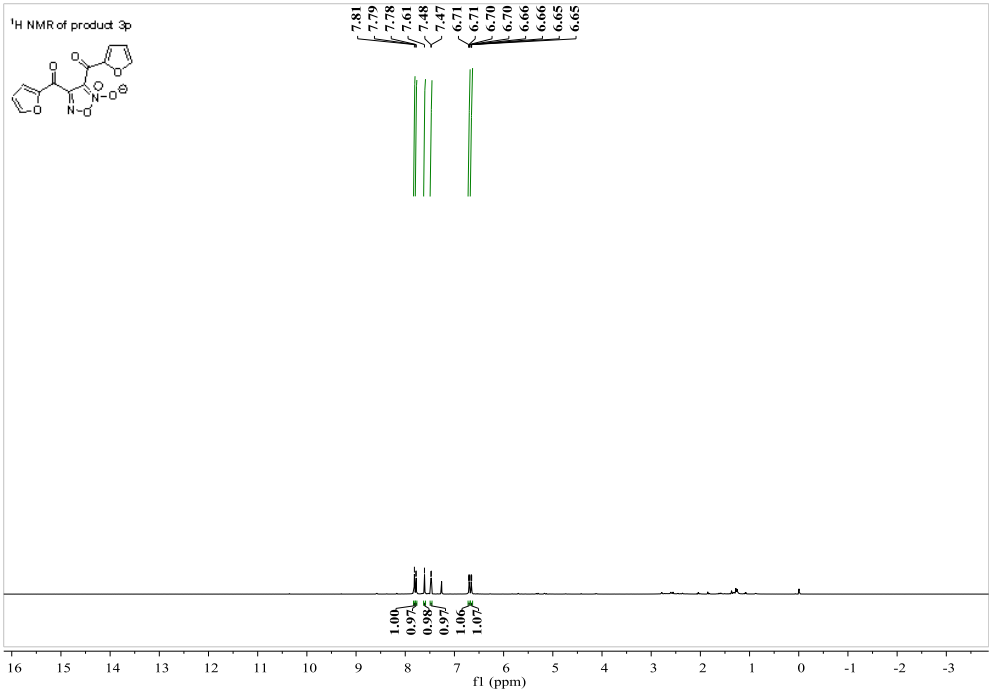


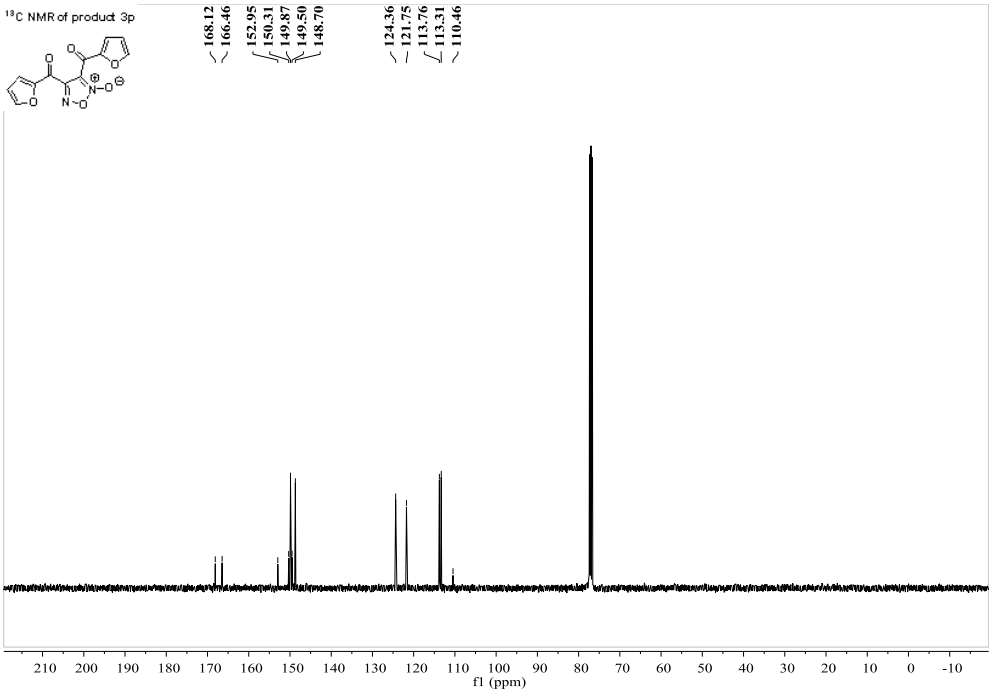
NMR data of **3o**



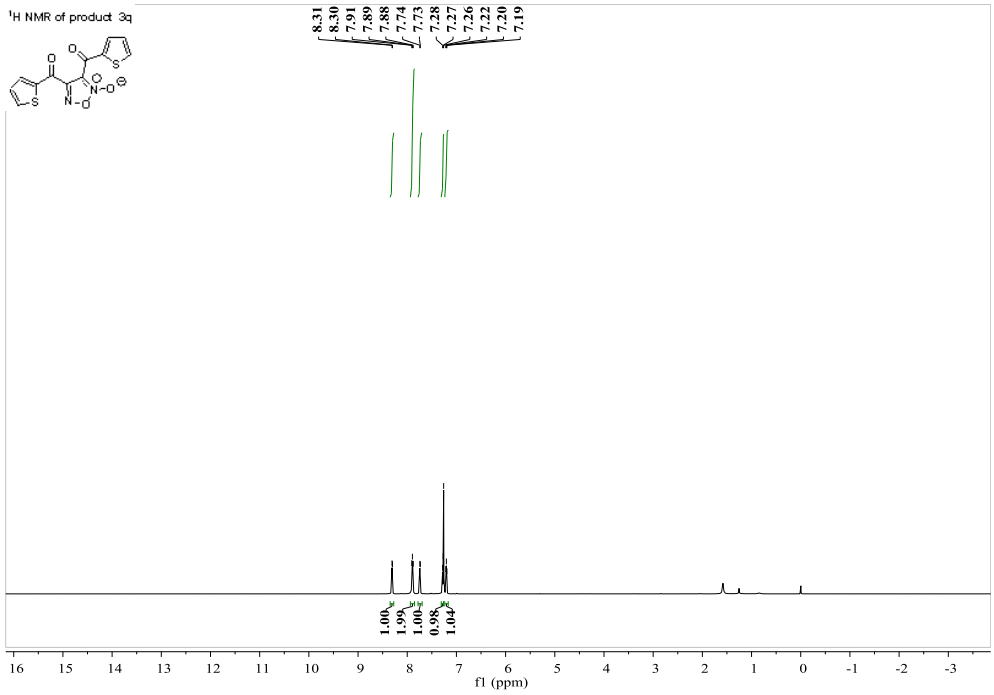


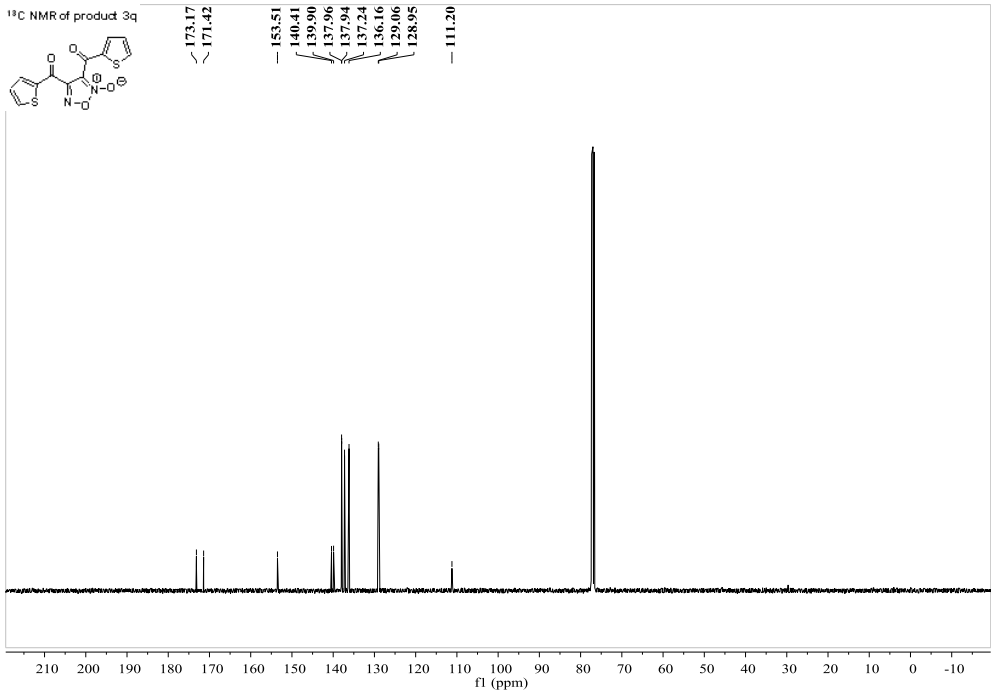
NMR data of **3p**



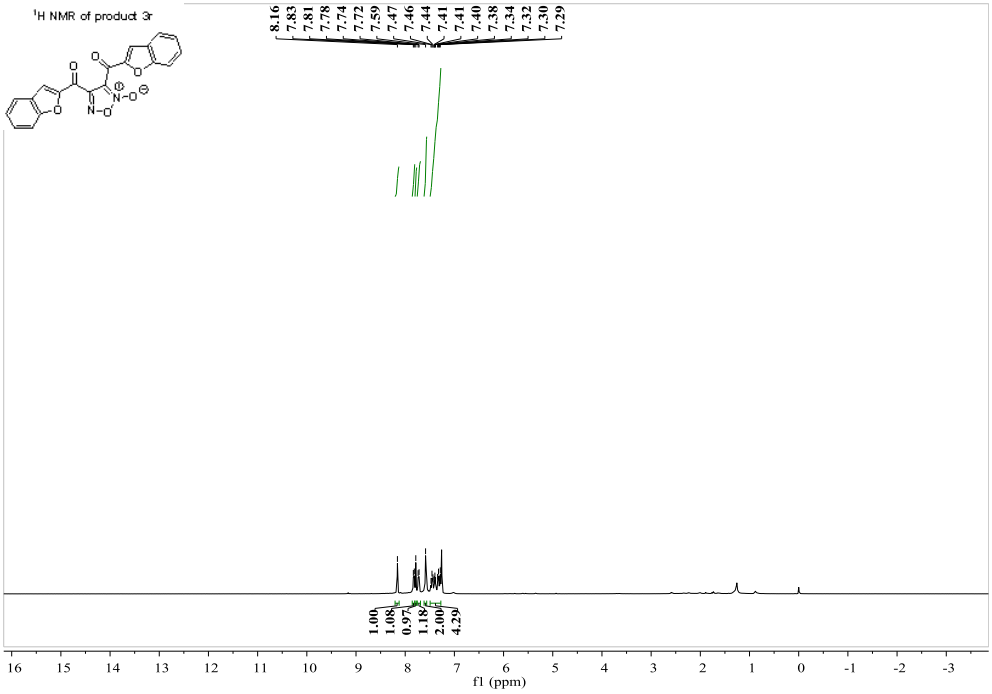


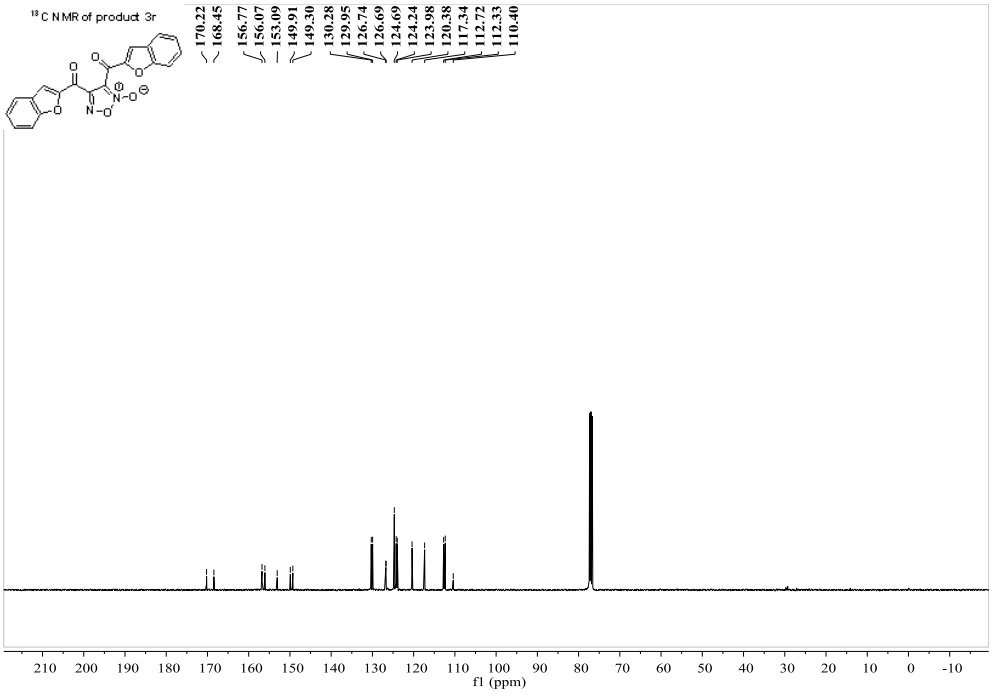
NMR data of **3q**



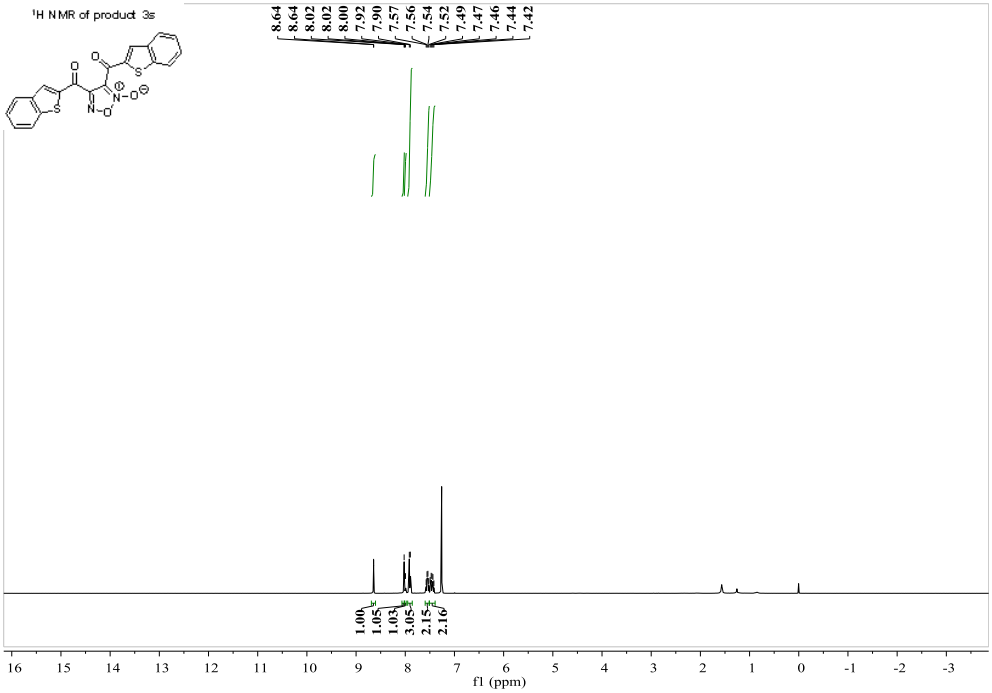


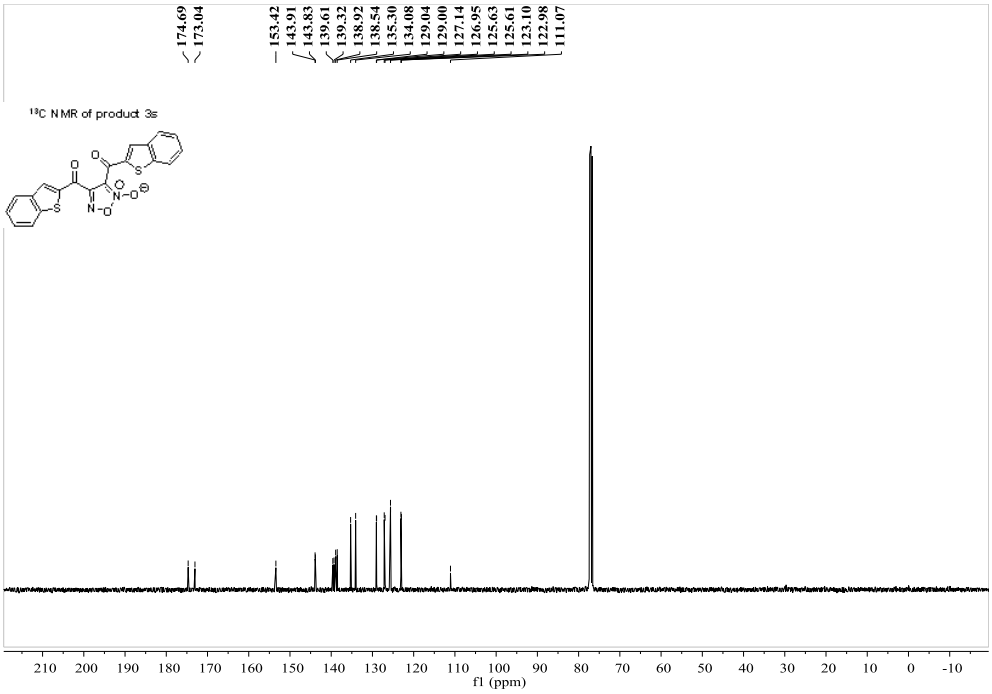
NMR data of **3r**



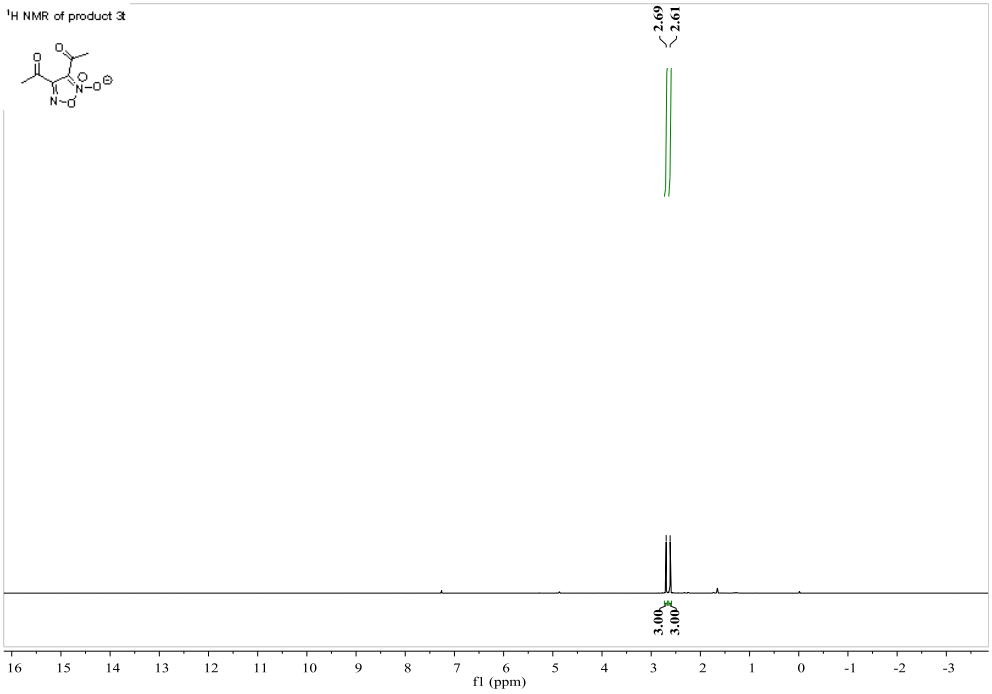


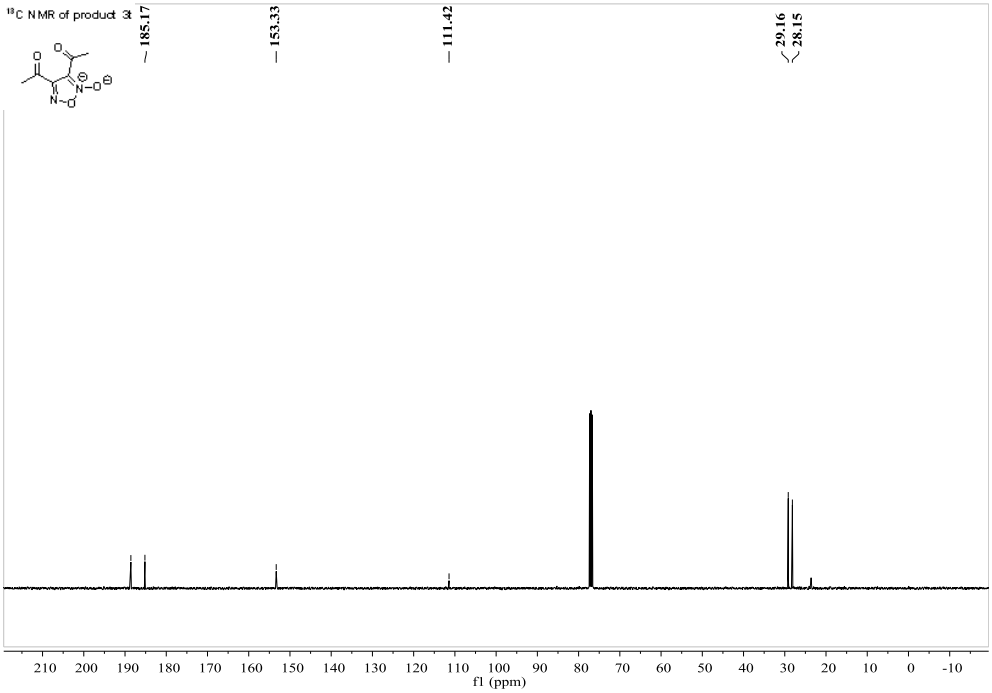
NMR data of **3s**



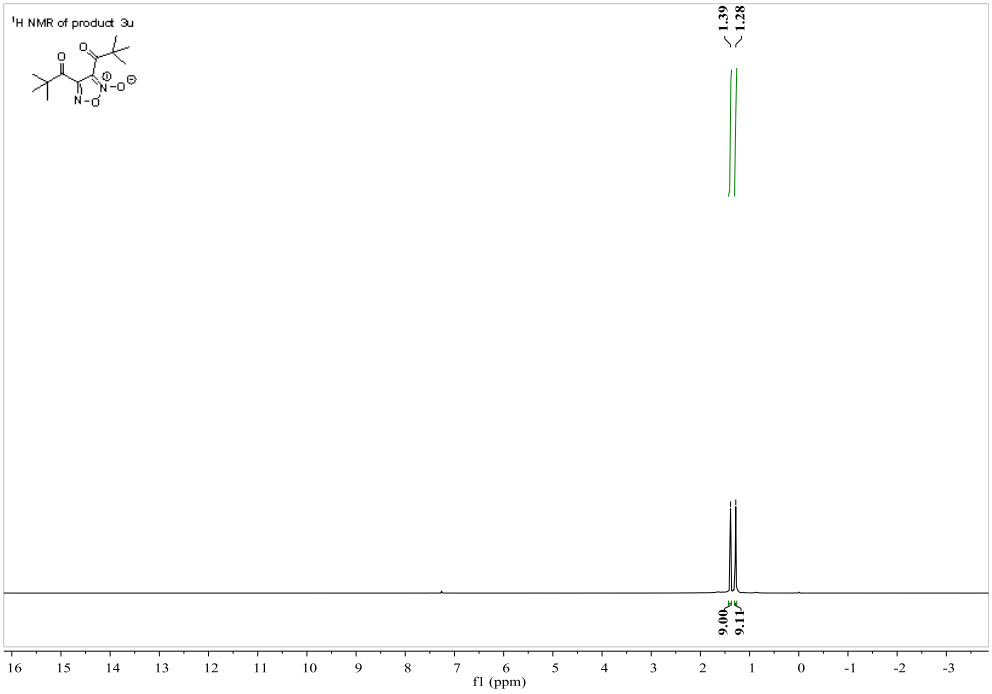


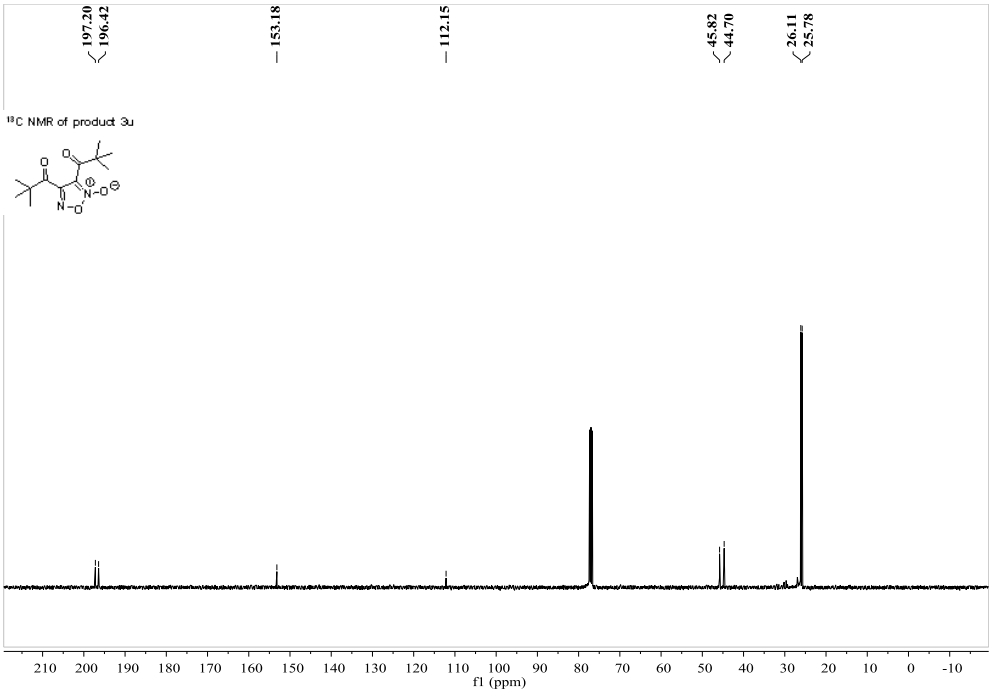
NMR data of **3t**



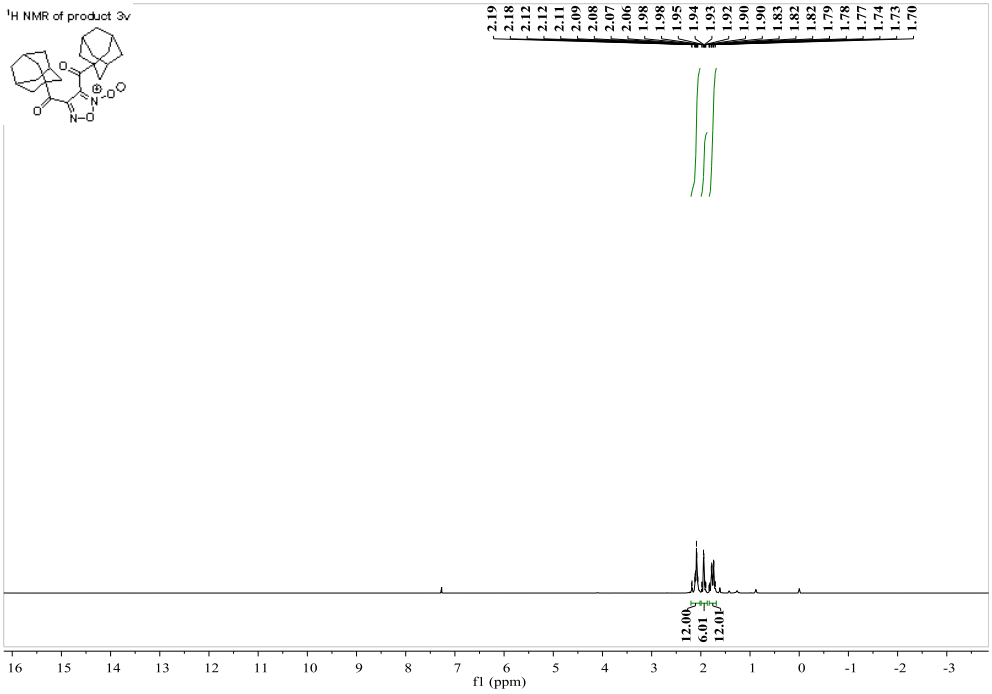


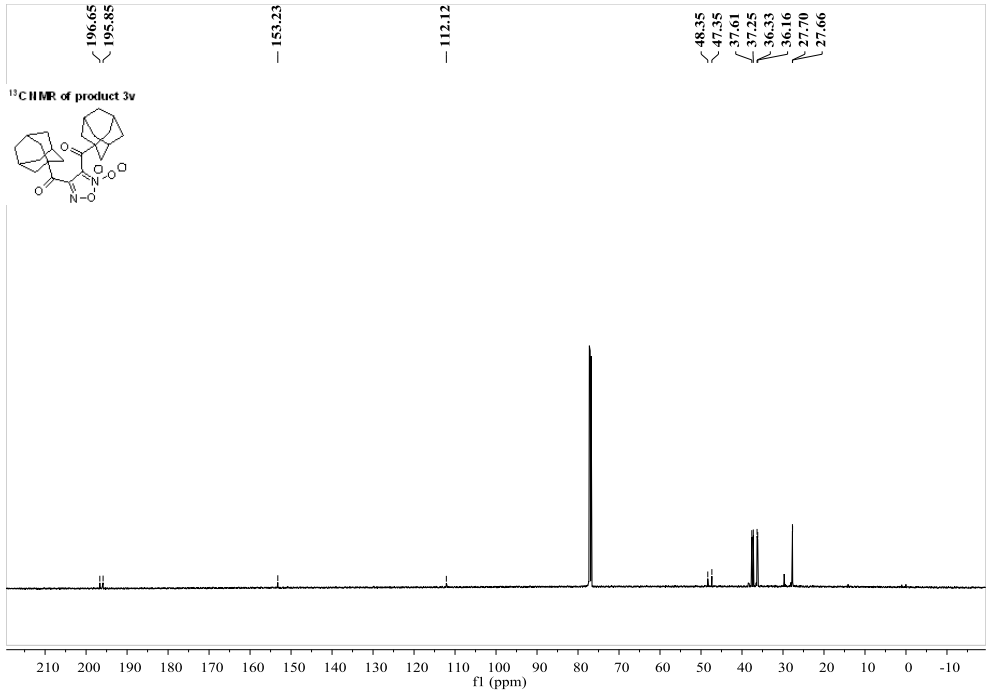
NMR data of **3u**



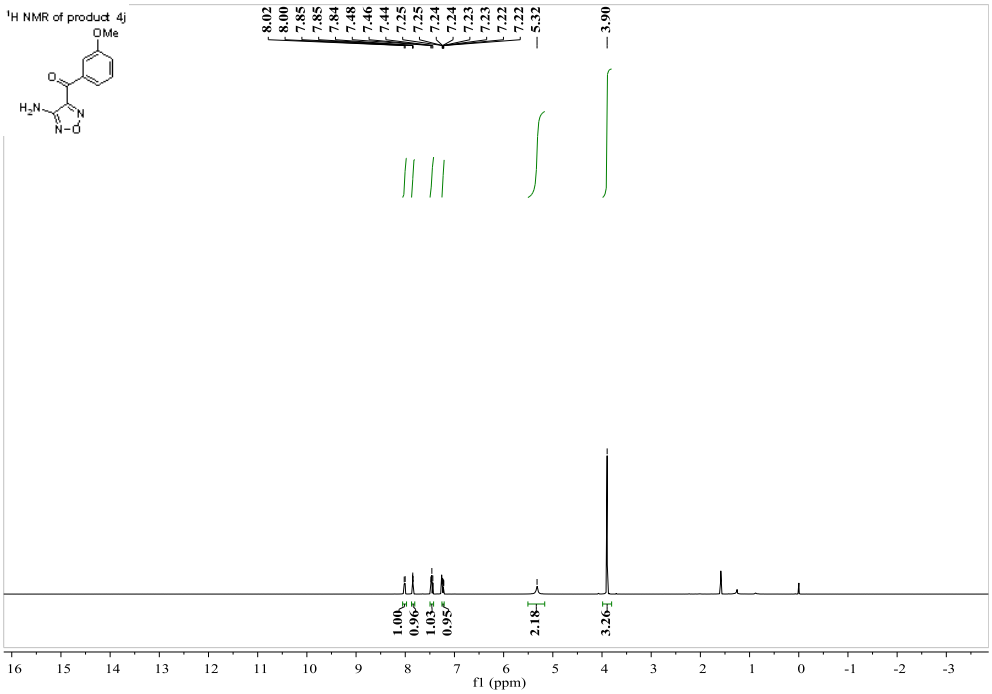


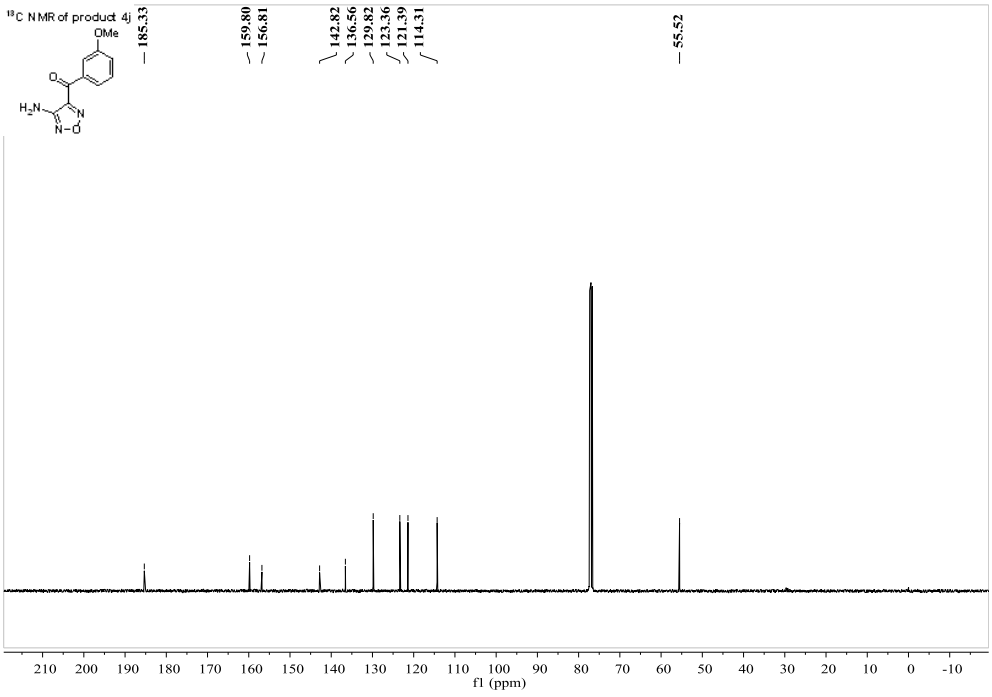
NMR data of **3v**





NMR data of **4j**





NMR data of **4q**