Supporting information

Discovery of 4-nitro-3-phenylisoxazole derivatives as potent antibacterial agents derived from the studies of [3+2] cycloaddition

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Reagents and instrument

All reagents were commercially available in Sigma-Aldrich with analytical purity. Melting points were tested in digital melting point analyzer with micro-display window (uncorrected, Shanghai Microelectronics Technology Co., Ltd.). The ^{1}H and ^{13}C NMR spectra were recorded on Bruker (Avance) 400 MHz and JEOL (Japan) 500 MHz NMR instrument with chemical reported as δ in $CDCl_3$ and DMSO-d_6, tetramethylsilane (TMS) as the internal standard. The high-resolution mass spectrometer (HRMS) was tested in TSQ 8000 high-resolution mass spectrometer and AB SCIEX X500R QTOF.

***In vitro* antibacterial bioassay**

The antibacterial activities of all compounds were evaluated by turbidimeter test in NB medium followed reported methods. NB medium was prepared by 5.0 g glucose, 2.5 g peptone, 0.5 g yeast powder, 1.5 g beef extract and 500 mL pure water, pH = 7.0~7.2. Dimethylsulfoxide (DMSO) was used as a blank control, and bismerthiazol, fluopyram were positive controls.

Xanthomonas oryzae (*Xoo*), *Pseudomonas syringae* (*Psa*) and *Xanthomonas axonopodis* (*Xac*) were obtained from State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Center for R&D of Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China.[1,2] *Xoo*, *Psa*, and *Xac* were incubated in NB medium at 28 ± 1 ℃ and continuously shaken at 180 rpm until the logarithmic growth phase to get seed liquid. A 40 μL seed liquid of *Xoo*, *Psa* or *Xac* was added in 5 mL medicated NB medium containing various concentrations of compounds or positive control. The incubated test tubes were incubated at 28 ± 1 ℃ and continuously shaken at 180 rpm for 24 - 48 h until the bacteria were incubated on the logarithmic growth phase.

The growth of the cultures was monitored by measuring the optical density at 595 nm (OD_{595}) and calculated by the equation: turbidity corrected values = $OD_{\text{bacterial well}}$

– $OD_{\text{no bacterial well}}$, and the inhibition rate (I) was calculated by the equation: $I = (C - T) \div C \times 100\%$. C is the turbidity corrected value of blank control; T is the turbidity corrected value of treated NB medium. Inhibitions of all the compounds at 100, 50 μg/mL were calculated by the equation. EC_{50} values of compounds **5o-5w**, bismerthiazol, and fluopyram against *Xoo*, *Psa* and *Xac* were calculated by GraphPad Prism 8 software, which were tested from 200 μg/mL, 100 μg/mL, 50 μg/mL, 25 μg/mL, 12.5 μg/mL, 6.25 μg/mL, 3.125 μg/mL, and 1.5625 μg/mL.

Procedure for preparation of compound 3

Compound **1** (1 mmol) and compound **2** (1.2 mmol) were dissolved in a solution in DMF (6 mL). The mixture was added with NCS (2 mmol) and TEA (1 mmol), and then stirred for 6 h at 25 ℃. The solution was extracted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL). The organic layer was dried over by magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude compound. The residue was purified by silica-gel column using PE/EtOAc = 10/1 to give compound 3.

3,5-Diphenyl-isoxazole (3a) Light yellow solid; 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 4H), 7.52 – 7.44 (m, 6H), 6.84 (s, 1H); Spectral properties were in accordance with the literature.[3]

3-phenyl-5-(p-tolyl)isoxazole (3b) White solid; 74% yield; mp: 129.8-131.2℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.6, 2.0 Hz,2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.44 (m, 3H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.78 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 163.0, 140.6, 130.0, 129.7, 129.2, 128.9, 126.8, 125.8, 124.8, 96.9, 21.6; ESI-HRMS $C_{16}H_{13}NO$ ($[M+H]^+$): calcd 236.1069, found 236.1066.

5-(2-fluorophenyl)-3-phenylisoxazole (3c) White solid; 76% yield; mp: 66.2-68.6℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 1H), 7.92 – 7.88 (m, 2H), 7.51 – 7.47 (m, 3H), 7.46 – 7.41 (m, 1H), 7.30 (m, 1H), 7.22 (m, 1H), 7.04 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 150.7, 148.2, 146.6, 125.4 (d, *J* = 6.4 Hz), 124.1, 123.2 (d, *J* = 4.2 Hz), 122.2, 121.6, 119.9 (d, *J* = 2.8 Hz), 113.1 (d, *J* = 13.6 Hz), 112.8 (d, *J* =

8.4 Hz), 101.4 (d, J = 7.0 Hz); ESI-HRMS $C_{15}H_{10}FNO$ ($[M+H]^+$): calcd 240.0819, found 240.0815.

5-(3-fluorophenyl)-3-phenylisoxazole (3d) Light yellow solid; 86% yield; mp: 69.3-71.2℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 2H), 7.63 (dd, J = 7.6, 1.2 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.49 (dd, J = 5.2, 2.0 Hz, 3H), 7.47 – 7.44 (m, 1H), 7.20 – 7.13 (m, 1H), 6.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 164.1 (d, J = 14.4 Hz), 163.2, 162.1 (d, J = 9.2 Hz), 130.9 (d, J = 8.4 Hz), 130.3, 129.4 (d, J = 9.3 Hz), 129.1, 126.9, 121.7, 117.3 (d, J = 22.5 Hz), 112.9 (d, J = 23.4 Hz), 98.4; ESI-HRMS $C_{15}H_{10}FNO$ ($[M+H]^+$): calcd 240.0819, found 240.0815.

5-(4-fluorophenyl)-3-phenylisoxazole (3e) Light yellow solid; 86% yield; mp: 138.2-140.9 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 4H), 7.51 – 7.45 (m, 3H), 7.23 – 7.14 (m, 2H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 164.9, 163.0 (d, J = 36.4 Hz), 130.2, 128.9 (d, J = 33.2 Hz), 128.4, 128.0 (d, J = 9.4 Hz), 126.9, 123.9, 116.3 (d, J = 22.6 Hz), 97.4; ESI-HRMS $C_{15}H_{10}FNO$ ($[M+H]^+$): calcd 240.0819, found 240.0815.

5-(4-methoxyphenyl)-3-phenylisoxazole (3f) Light yellow solid; 65% yield; mp: 106.1-108.2℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.6, 2.0 Hz, 2H), 7.81 – 7.75 (m, 2H), 7.52 – 7.44 (m, 3H), 7.05 – 6.97 (m, 2H), 6.71 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 150.4, 149.0, 124.0, 123.5, 123.2, 122.0, 121.5, 116.3, 111.6, 97.0, 64.4; ESI-HRMS $C_{16}H_{13}NO_2$ ($[M+H]^+$): calcd 252.1019, found 252.1016.

3-phenyl-5-(4-(trifluoromethyl)phenyl)isoxazole (3g) Light yellow solid; 88% yield; mp: 166.1-167.9℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 2H), 7.90 – 7.85 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.54 – 7.47 (m, 3H), 6.94 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 168.8, 163.2, 132.1, 131.8, 130.6, 130.3, 129.0, 128.7, 126.9, 126.1 (q, J = 4.2 Hz), 125.1, 99.0; ESI-HRMS $C_{16}H_{10}F_3NO$ ($[M+H]^+$): calcd 290.0787, found 290.0784.

5-phenyl-3-(m-tolyl)isoxazole (3h) White solid; 71% yield; mp: 69.3-71.2℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 2H), 7.71 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.54 – 7.43 (m, 3H), 7.38 (t, J = 7.6 Hz, 1H), 7.29 (s, 1H), 6.83 (s, 1H), 2.44 (s, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 170.3, 163.1, 138.7, 130.8, 130.2, 129.0, 129.0, 128.9, 127.5, 127.5, 125.9, 124.0, 97.6, 21.5; ESI-HRMS $C_{16}H_{13}NO$ ($[M+H]^+$): calcd 236.1069, found 236.1066.

5-phenyl-3-(p-tolyl)isoxazole (3i) White solid; 71% yield; mp: 115.5-116.4℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.54 – 7.41 (m, 3H), 7.29 (d, J = 8.0 Hz, 2H), 6.81 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.0, 140.2, 130.2, 129.7, 129.0, 127.5, 126.7, 126.3, 125.9, 97.5, 21.5; ESI-HRMS $C_{16}H_{13}NO$ ($[M+H]^+$): calcd 236.1069, found 236.1066.

3-(4-methoxyphenyl)-5-phenylisoxazole (3j) White solid; 76% yield; mp: 109.0-112.4 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 4H), 7.54 – 7.41 (m, 3H), 7.06 – 6.97 (m, 2H), 6.78 (s, 1H), 3.87 (d, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 162.6, 161.0, 130.2, 129.0, 128.2, 127.5, 125.8, 121.6, 114.3, 97.3, 55.4; ESI-HRMS $C_{16}H_{13}NO_2$ ($[M+H]^+$): calcd 252.1019, found 252.1019.

3-(3-chlorophenyl)-5-phenylisoxazole (3k) White solid; 65% yield; mp: 113.2-114.5 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 3H), 7.80 – 7.74 (m, 1H), 7.54 – 7.41 (m, 5H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 161.9, 135.0, 130.9, 130.5, 130.3, 130.1, 129.1, 127.2, 127.0, 125.9, 124.9, 97.4; ESI-HRMS $C_{15}H_{10}ClNO$ ($[M+H]^+$): calcd 256.0523, found 256.0519.

3-(m-tolyl)-5-(p-tolyl)isoxazole (3l) Light yellow solid; 68% yield; mp: 65.4-166.7℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.70 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 3H), 6.77 (s, 1H), 2.43 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 163.1, 140.5, 138.7, 130.8, 129.7, 129.1, 128.8, 127.5, 125.8, 124.8, 124.0, 97.0, 21.6, 21.5; ESI-HRMS $C_{17}H_{15}NO$ ($[M+H]^+$): calcd 250.1226, found 250.1222.

Procedure for preparation of compound 5

Compound **1** (1 mmol) and compound **4** (1.2 mmol) were dissolved in a solution of DMF (6 mL). The mixture was added NCS (2 mmol) and TEA (1 mmol), then stirred for 6 h at 25 ℃. The solution was extracted with EtOAc (50 mL) and washed with

saturated $NaHCO_3$ (2 × 50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude compound. The residue was purified by silica-gel column using PE/EtOAc = 5/1 to give the product.

1-(3-phenylisoxazol-4-yl)ethan-1-one (5a) Light yellow solid; 61% yield; mp: 70.6~72.7℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.73 – 7.64 (m, 2H), 7.53 – 7.43 (m, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 163.5, 160.8, 130.3, 129.4, 128.4, 127.4, 120.9, 29.8; ESI-HRMS $C_{11}H_9NO_2$ ($[M+H]^+$): calcd 188.0706, found 188.0704.

1-(3-(m-tolyl)isoxazol-4-yl)ethan-1-one (5b) Light yellow solid; 57% yield; mp: 96.0~97.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.51 – 7.44 (m, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 2.44 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 150.8, 148.8, 130.6, 124.9, 124.0, 122.7, 121.8, 121.3, 116.8, 43.9, 37.2; ESI-HRMS $C_{12}H_{11}NO_2$ ($[M+H]^+$): calcd 202.0862, found 202.0860.

1-(3-(4-methoxyphenyl)isoxazol-4-yl)ethan-1-one (5c) White solid; 53% yield; mp: 95.1~96.6℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.73 – 7.62 (m, 2H), 7.04 – 6.92 (m, 2H), 3.86 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 163.6, 161.2, 160.4, 130.9, 120.7, 119.5, 113.8, 55.4, 29.8; ESI-HRMS $C_{12}H_{11}NO_3$ ($[M+H]^+$): calcd 218.0811, found 218.0809.

1-(3-(3-chlorophenyl)isoxazol-4-yl)ethan-1-one (5d) Light yellow solid; 58% yield; mp: 114.1~115.7℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.73 (t, *J* = 1.6 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.48 (m, 1H), 7.40 (t, *J* = 8.0 Hz, 1H),2.49(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 151.0, 147.9, 127.5, 123.7, 123.7, 123.3, 123.3, 122.2, 116.5, 43.8; ESI-HRMS $C_{11}H_8ClNO_2$ ($[M+H]^+$): calcd 222.0316, found 222.0316.

1-(3-(4-(trifluoromethyl)phenyl)isoxazol-4-yl)ethan-1-one (5e) White solid; 62% yield; mp: 100.2~102.8℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 151.0, 147.9, 125.9, 125.7, 124.8, 124.0, 120.3(d, *J* = 3.8 Hz), 116.5, 43.8; ESI-HRMS $C_{12}H_8F_3NO_2$ ($[M+H]^+$): calcd 256.0579, found 256.0565.

1-(3-(2-nitrophenyl)isoxazol-4-yl)ethan-1-one (5f) Yellow solid; 43% yield; mp:133.3~135.6 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.28 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.54 (dd, *J* = 7.2, 1.6 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 162.1, 159.3, 148.5, 133.5, 132.2, 131.1, 124.9, 123.8, 120.7, 28.9; ESI-HRMS $C_{11}H_8N_2O_4$ ($[M+Na]^+$): calcd 255.0376, found 255.0376.

1-(3-(3-nitrophenyl)isoxazol-4-yl)ethan-1-one (5g) Light yellow solid; 48% yield; mp: 114.9~116.1℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.65 (t, *J* = 2.0 Hz, 1H), 8.36 (m, 1H), 8.14 – 8.05 (m, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 164.0, 159.2, 148.1, 135.5, 129.3, 129.1, 125.0, 124.8, 120.4, 29.6; ESI-HRMS $C_{11}H_8N_2O_4$ ($[M+Na]^+$): calcd 255.0376, found 255.0369.

1-(3-(4-nitrophenyl)isoxazol-4-yl)ethan-1-one (5h) Yellow solid; 48% yield; mp: 159.9~161.2℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.32 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 164.0, 159.3, 148.9, 133.7, 130.7, 123.4, 120.5, 29.7; ESI-HRMS $C_{11}H_8N_2O_4$ ($[M+Na]^+$): calcd 255.0376, found 255.0376.

Ethyl 3-phenylisoxazole-4-carboxylate (5i) Colorless oil; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.79 – 7.75 (m, 2H), 7.50 – 7.45 (m, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.3, 160.9, 130.2, 129.5, 128.2, 127.3, 113.1, 61.1, 14.1; ESI-HRMS $C_{12}H_{11}NO_3$ ($[M+H]^+$): calcd 218.0811, found 218.0810.

Ethyl 3-(3-chlorophenyl)isoxazole-4-carboxylate (5j) White solid; 63% yield; mp:41.1~42.8℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.80 (t, *J* = 1.6 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.47 (m, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 160.7, 160.1, 134.2, 130.3, 129.6, 129.5, 129.0, 127.7, 113.1, 61.3, 14.1; ESI-HRMS $C_{12}H_{10}ClNO_3$ ($[M+H]^+$): calcd 252.0422, found 252.0418.

Ethyl 3-(4-methoxyphenyl)isoxazole-4-carboxylate (5k) White solid; 60% yield; mp: 46.3~48.1℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 164.2, 161.2, 160.9, 160.4, 131.0, 119.4, 113.7, 112.8, 61.1, 55.4, 14.2; ESI-HRMS $C_{13}H_{13}NO_4$ ($[M+Na]^+$): calcd 270.0737, found 270.0737.

Ethyl 3-(3-(trifluoromethyl)phenyl)isoxazole-4-carboxylate (5l) Colorless oil; 44% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.09 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 161.0, 160.2, 132.9, 130.8 (q, J = 33.2 Hz), 128.8, 128.2, 127.9, 125.2, 122.5, 113.2, 61.4, 14.1; ESI-HRMS $C_{13}H_{10}F_3NO_3$ ($[M+H]^+$): calcd 286.0685, found 286.0675.

Ethyl 3-(4-(trifluoromethyl)phenyl)isoxazole-4-carboxylate (5m) White solid; 63% yield; mp:35.3~37.1°C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.6, 164.5, 160.8, 160.4, 132.3, 131.0, 130.0, 125.3 (d, J = 2.4 Hz), 113.15, 61.43, 14.18.; ESI-HRMS $C_{13}H_{10}F_3NO_3$ ($[M+H]^+$): calcd 286.0685, found 286.0676.

Ethyl 3-(4-nitrophenyl)isoxazole-4-carboxylate (5n) White solid; 52% yield; mp: 95.4~97.5°C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.33 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.8 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 160.5, 159.7, 148.9, 133.6, 130.7, 123.4, 113.1, 61.5, 14.2; ESI-HRMS $C_{12}H_{10}N_2O_5$ ($[M+H]^+$): calcd 263.0662, found 263.0648.

4-nitro-3-phenylisoxazole (5o) Light yellow solid; 61% yield; mp: 87.1~89.5°C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.73 – 7.65 (m, 2H), 7.58 – 7.51 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 156.6, 134.2, 131.3, 129.9, 129.0, 125.6; Spectral properties were in accordance with the literature.[4]

3-(2-fluorophenyl)-4-nitroisoxazole (5p) White solid; 57% yield; mp: 84.7~85.8°C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.62 – 7.54 (m, 2H), 7.32 (m, 1H), 7.25 – 7.21 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 161.1, 159.1, 152.3, 134.1 (d, J = 8.2 Hz), 131.8, 125.5, 116.5 (d, J = 20.6 Hz), 113.9 (d, J = 14.4 Hz).

3-(3-fluorophenyl)-4-nitroisoxazole (5q) White solid; 59% yield; mp: 69.7~72.5°C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.80 – 7.66 (m, 2H), 7.21 (m, 2H); ^{13}C NMR

(100 MHz, DMSO-d_6) δ 165.3, 164.0, 162.8, 155.8, 134.3, 132.6 (d, J = 9.2 Hz), 122.0 (d, J = 3.6 Hz), 116.2, 116.0.

3-(4-Fluoro-phenyl)-4-nitro-isoxazole (5r) White solid; 63% yield; mp:85.5~86.6℃;^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.55 – 7.47 (m, 2H), 7.46 – 7.40 (m, 1H), 7.31 – 7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 161.2, 160.8, 155.5 (d, J = 2.6 Hz), 130.4 (d, J = 8.3 Hz), 126.6 (d, J = 8.6 Hz), 125.4 (d, J = 3.2 Hz), 118.2 (d, J = 20.8 Hz), 116.8 (d, J = 23.9 Hz).

3-(2-bromophenyl)-4-nitroisoxazole (5s) White solid; 53% yield; mp: 53.5~55.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.73 (m, 1H), 7.52 – 7.39 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.8, 145.1, 127.6, 126.6, 126.5, 125.8, 122.8, 121.8, 118.5.

3-(3-bromophenyl)-4-nitroisoxazole (5t) White solid; 55% yield; mp: 90.0~92.4℃;^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.85 (t, J = 2.0 Hz, 1H), 7.71 (m, 1H), 7.67 – 7.59 (m, 1H), 7.40 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.2, 144.4, 127.6, 127.3, 126.1, 124.9, 123.3, 122.3, 117.6.

4-nitro-3-(p-tolyl)isoxazole (5u) White solid; 56% yield; mp: 48.3~49.7℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.9, 132.9, 120.6, 115.0, 111.5, 111.3, 105.7, 24.9.

4-(4-nitroisoxazol-3-yl)benzonitrile (5v) White solid; 42% yield; mp: 131.2~132.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, J = 6.4 Hz, 1H), 7.87 – 7.81 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 155.7, 133.7, 132.8, 131.0, 130.3, 118.7, 113.9.

4-nitro-3-(3-nitrophenyl)isoxazole (5w) White solid; 36% yield; White solid; mp: 100.0~101.0℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.62 (t, J = 2.0 Hz, 1H), 8.45 (m,1H), 8.09 – 8.02 (m, 1H), 7.75 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 155.2,148.1, 136.5, 134.6, 130.7, 127.3, 126.0, 125.1

Procedure for preparation of compound 6

Compound **1** (1 mmol) was dissolved in a solution of DMF (6 mL). The mixture was added NCS (2 mmol), then stirred for 6 h at 25 ℃. The solution was extracted with

EtOAc (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude compound. The residue was purified by silica-gel column using PE/EtOAc = 10/1 to give the product. Yellow oil; 85% yield; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.50 (m, 3H), 7.85 (dd, J = 8.0, 1.6 Hz, 2H), 8.43 (s, 1H). Spectral properties were in accordance with the literature.[5]

References

[1] J. Shi, M. Ding, N. Luo, S. Wan, P. Li, J. Li, X. Bao, *J Agric Food Chem*. **2020**, *68*, 9613-9623.

[2] J. Chen, C. Yi, S. Wang, S. Wu, S. Li, D. Hu, B. Song, *Bioorg Med Chem Lett*. **2019**, *29*, 1203-1210.

[3] S. Mohammed, R.A. Vishwakarma, S.B. Bharate, *RSC Adv*. **2015**, *5*, 3470-3473.

[4] R. Nesi, S. Turchi, D. Giomi, *J Org Chem*. **1996**, *61*, 7933-7936.

[5] T. Chau, H. Dhondt, M. Flipo, B. Déprez, N. Willand, *Tetrahedron Lett.* **2015**, *56*, 4119-4123.

Spectrum of Compound 3, 5 and 6

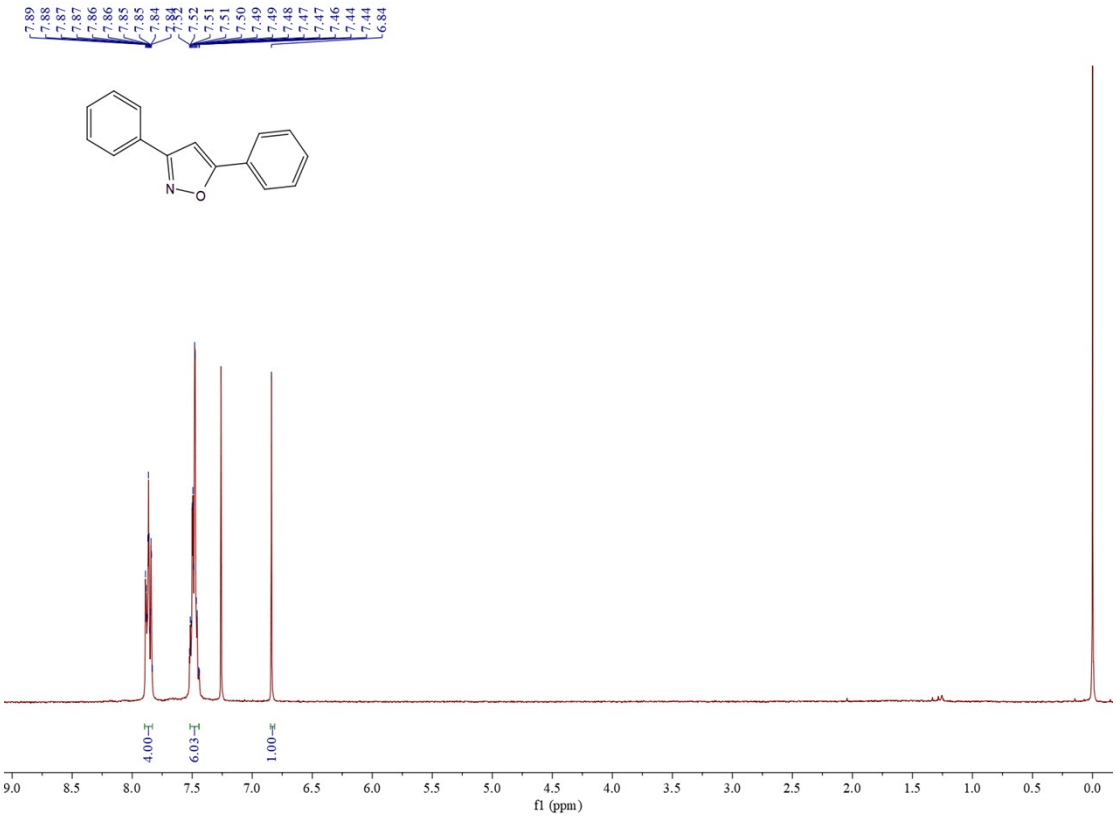

Fig. S1. [1]H NMR spectrum of compound **3a**

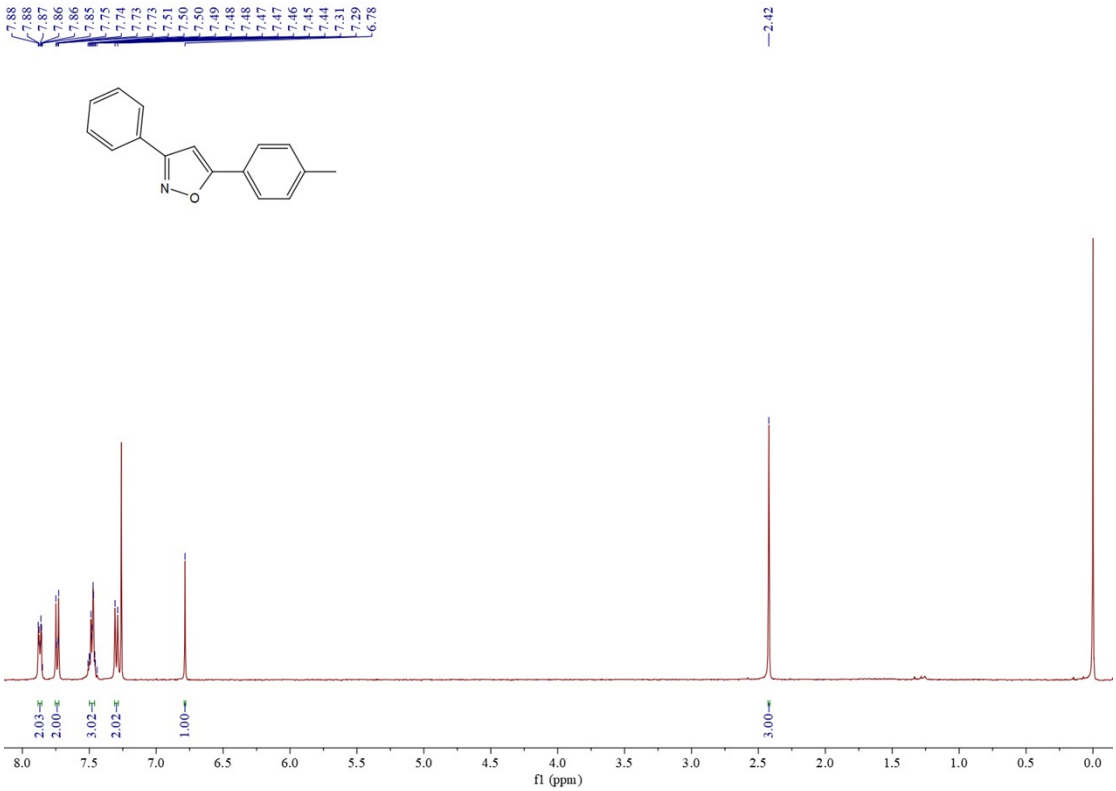

Fig. S2. [1]H NMR spectrum of compound **3b**

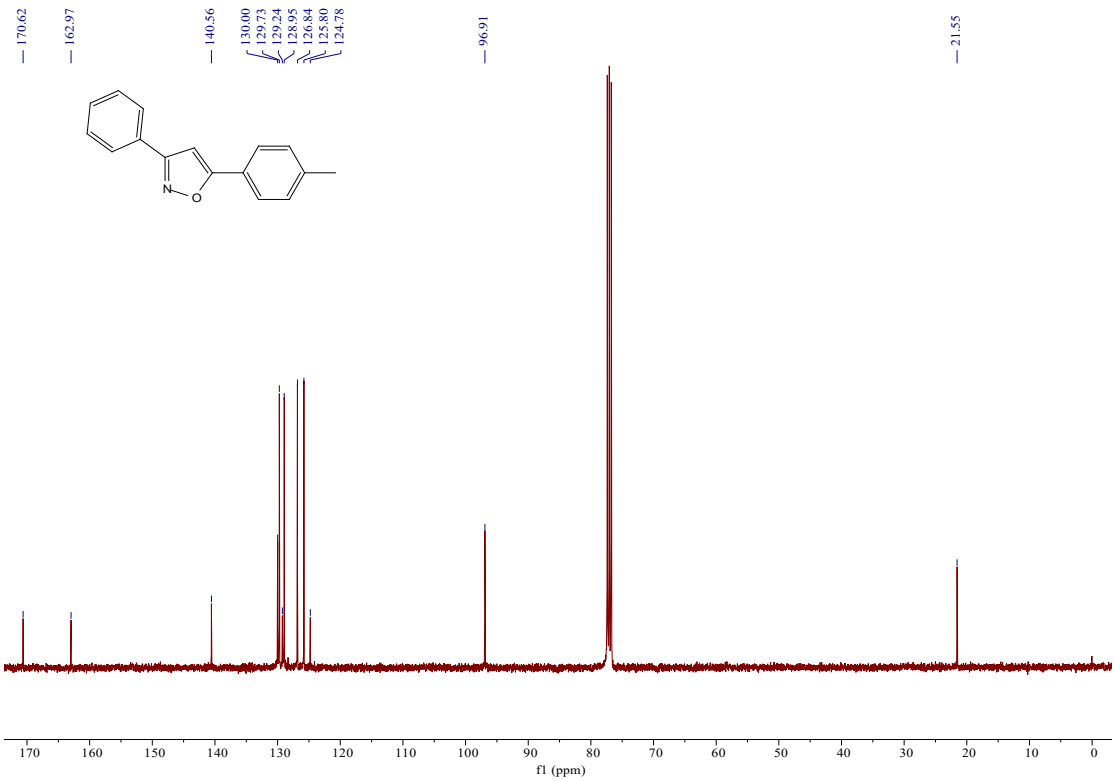

Fig. S3. ^{13}C NMR spectrum of compound **3b**

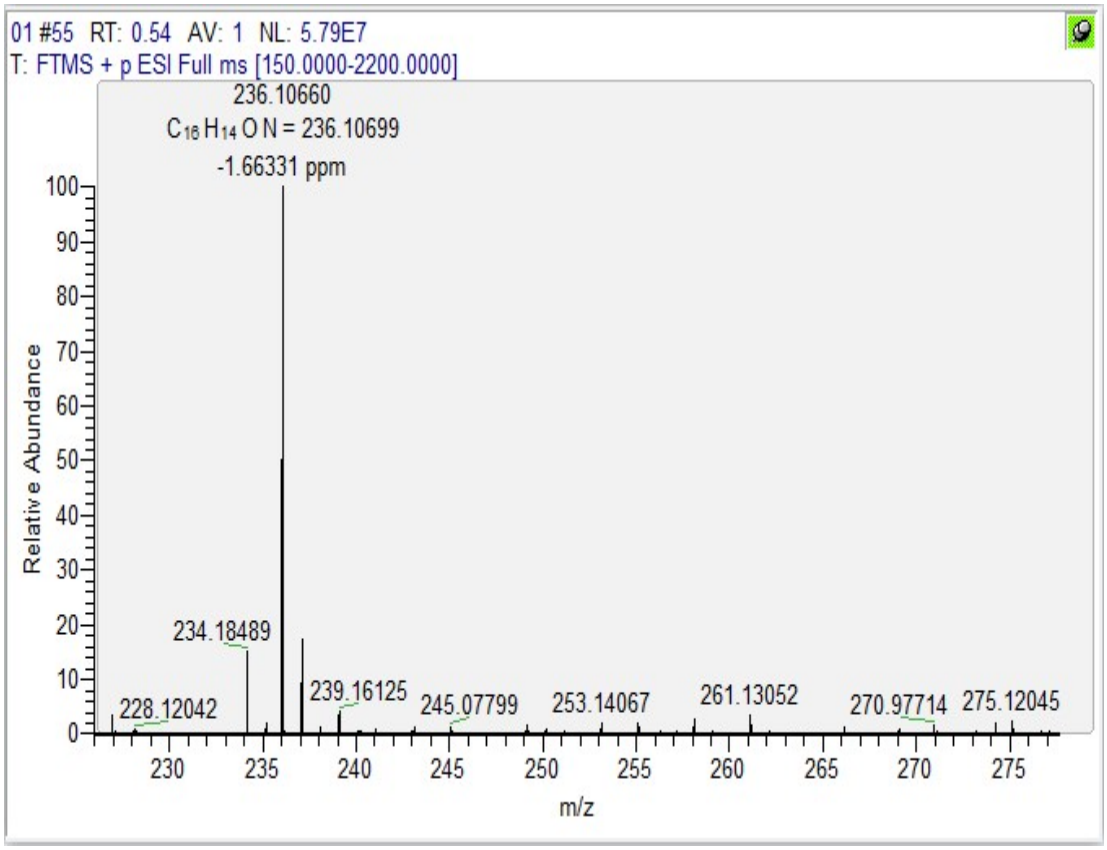

Fig. S4. HRMS spectrum of compound **3b**

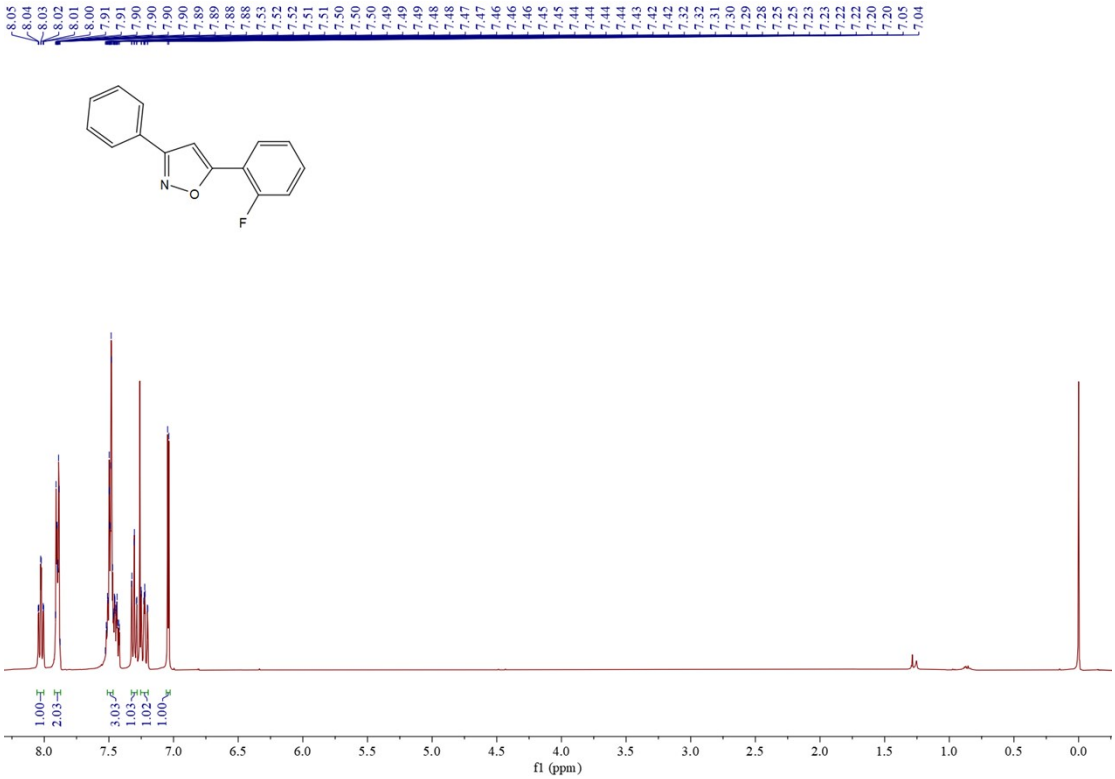

Fig. S5. ^{1}H NMR spectrum of compound **3c**

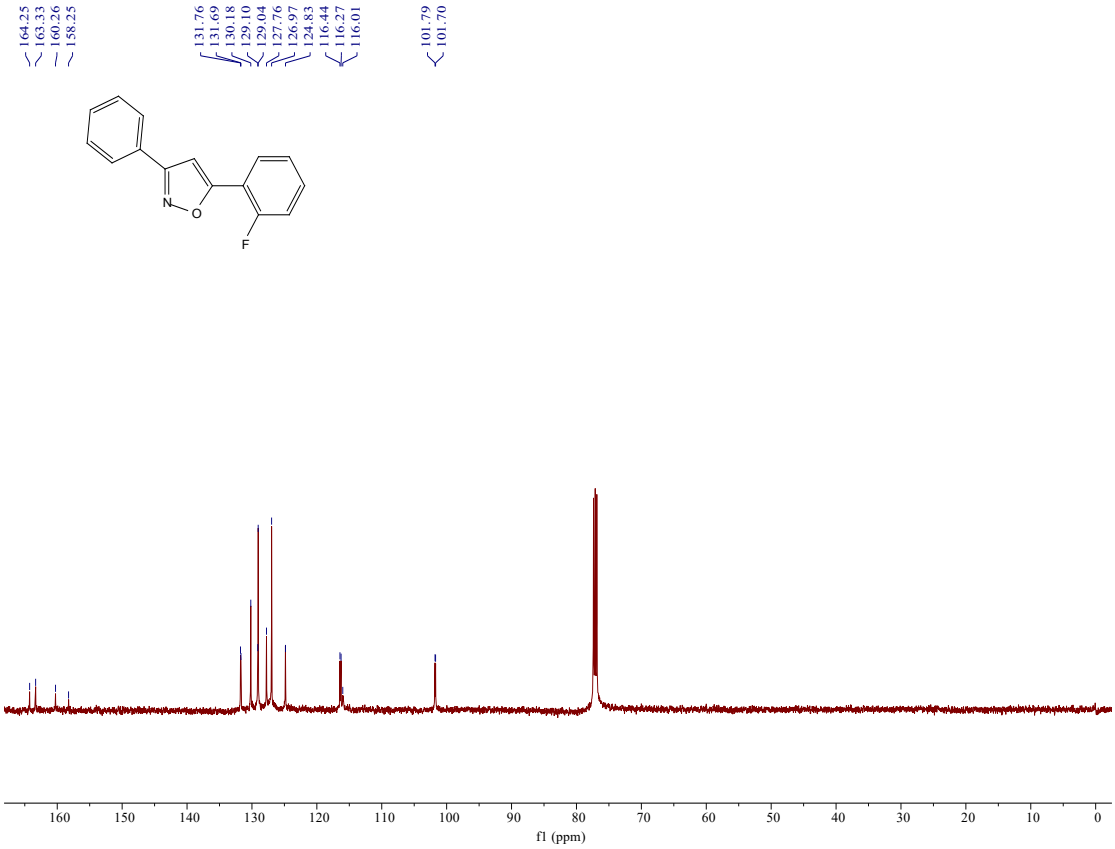

Fig. S6. ^{13}C NMR spectrum of compound **3c**

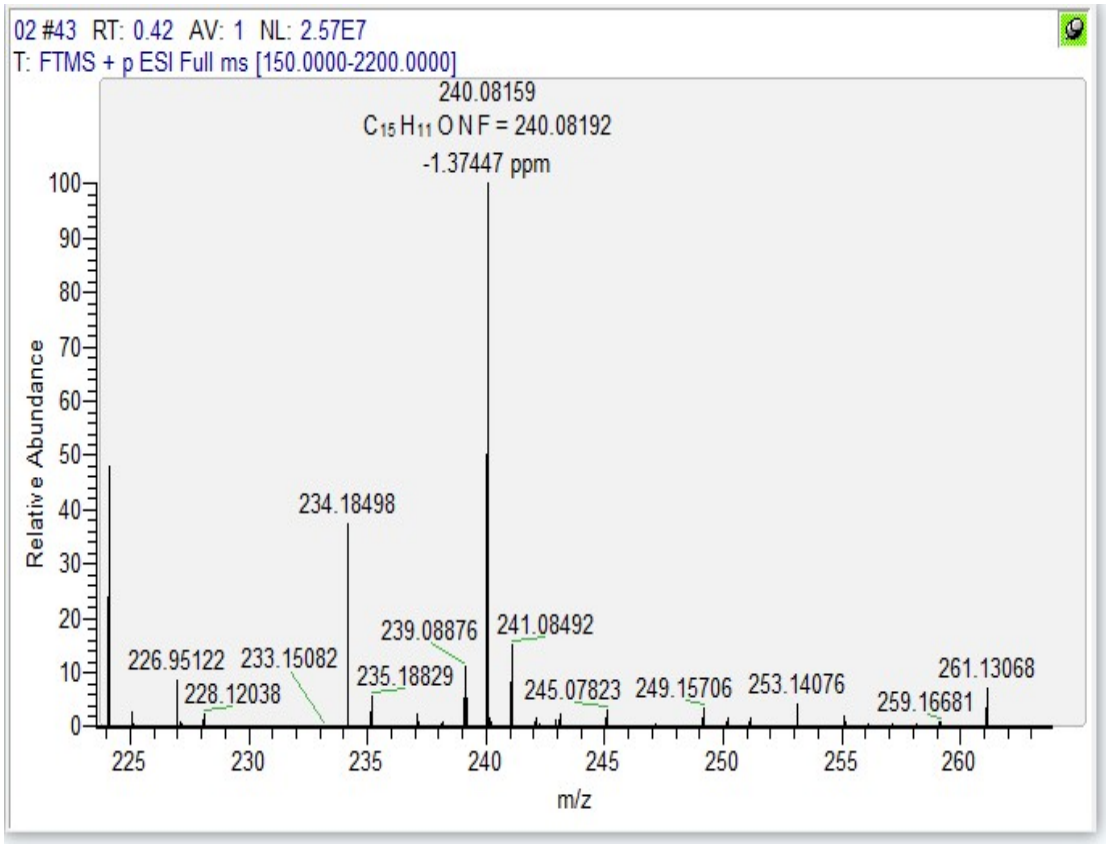

Fig. S7. HRMS spectrum of compound **3c**

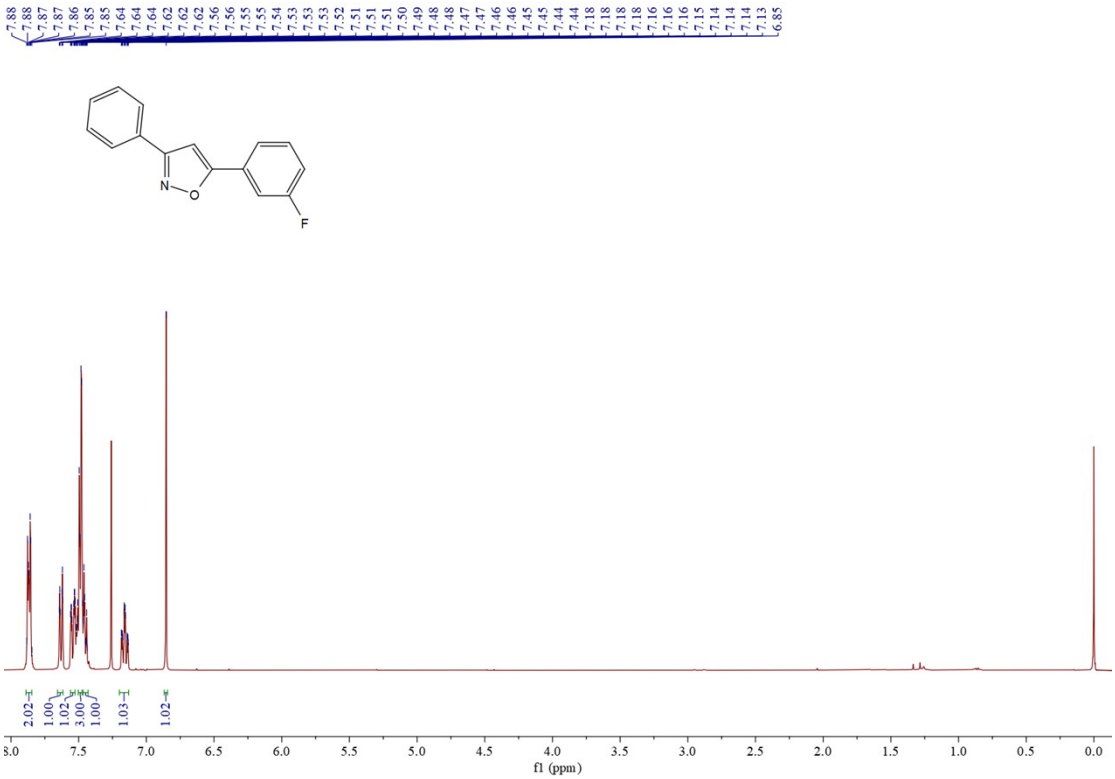

Fig. S8. ^{1}H NMR spectrum of compound **3d**

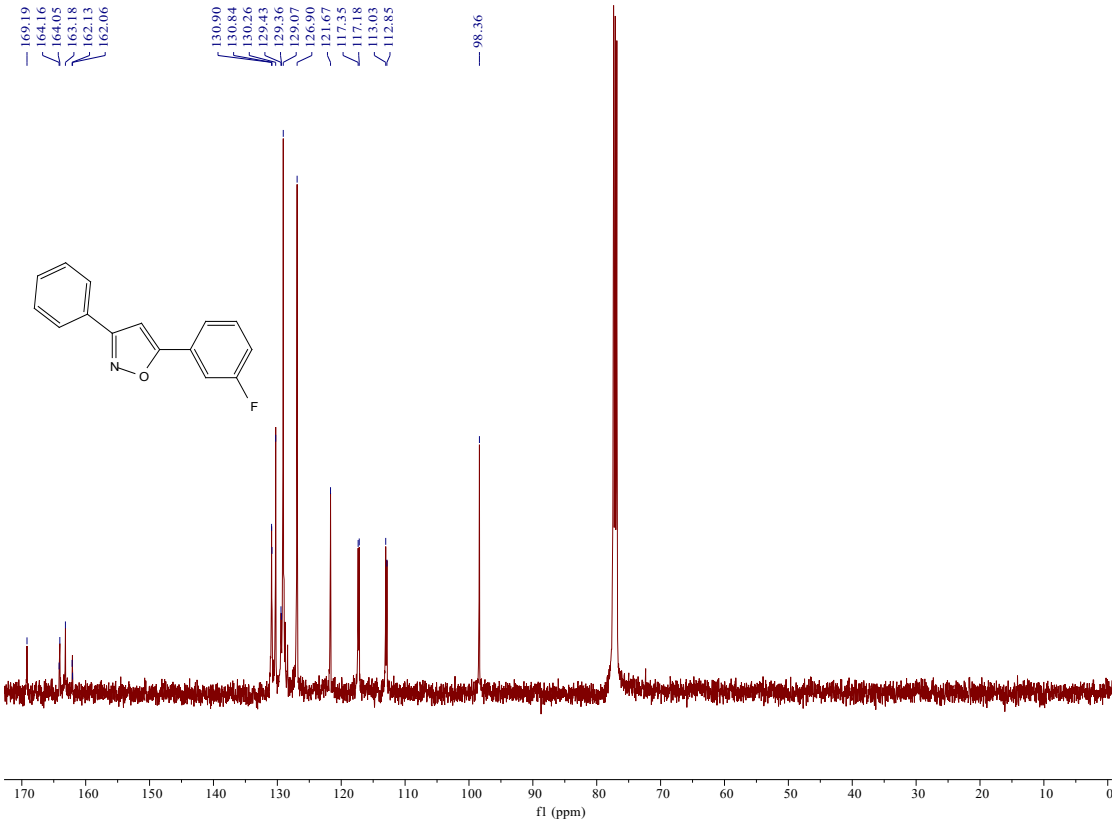

Fig. S9. ^{13}C NMR spectrum of compound **3d**

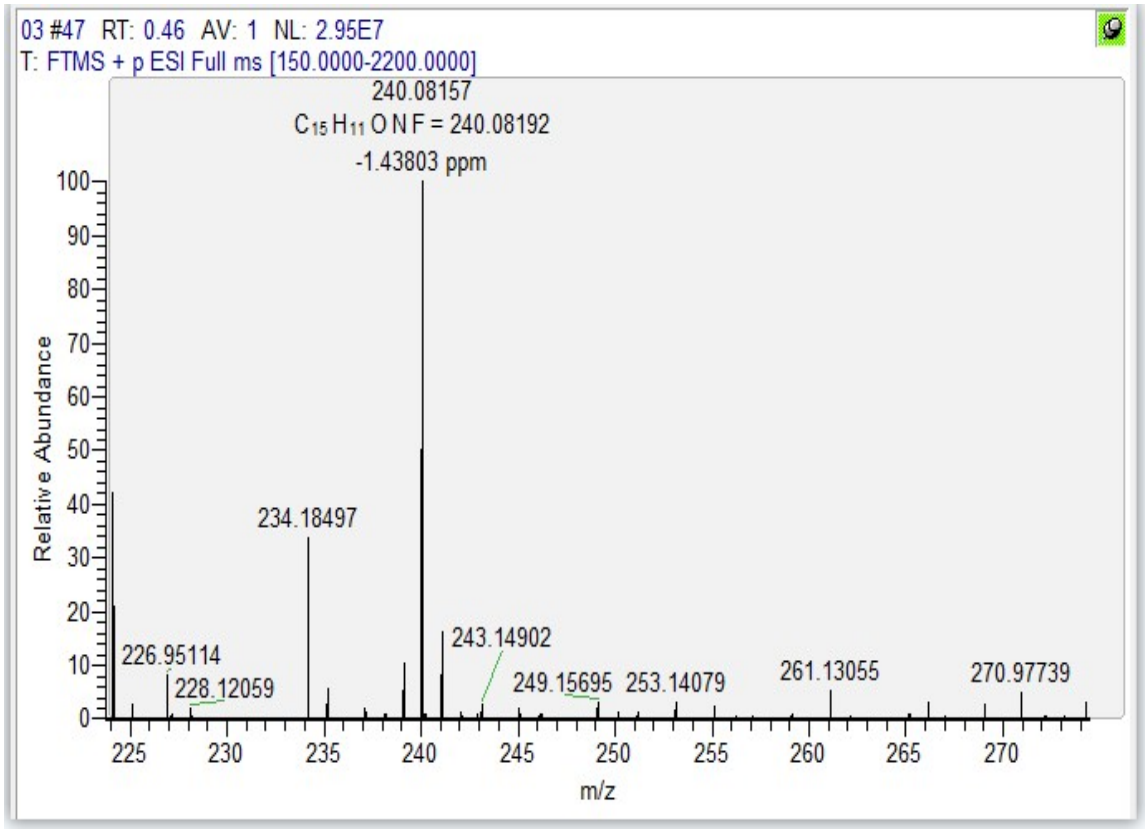

Fig. S10. HRMS spectrum of compound **3d**

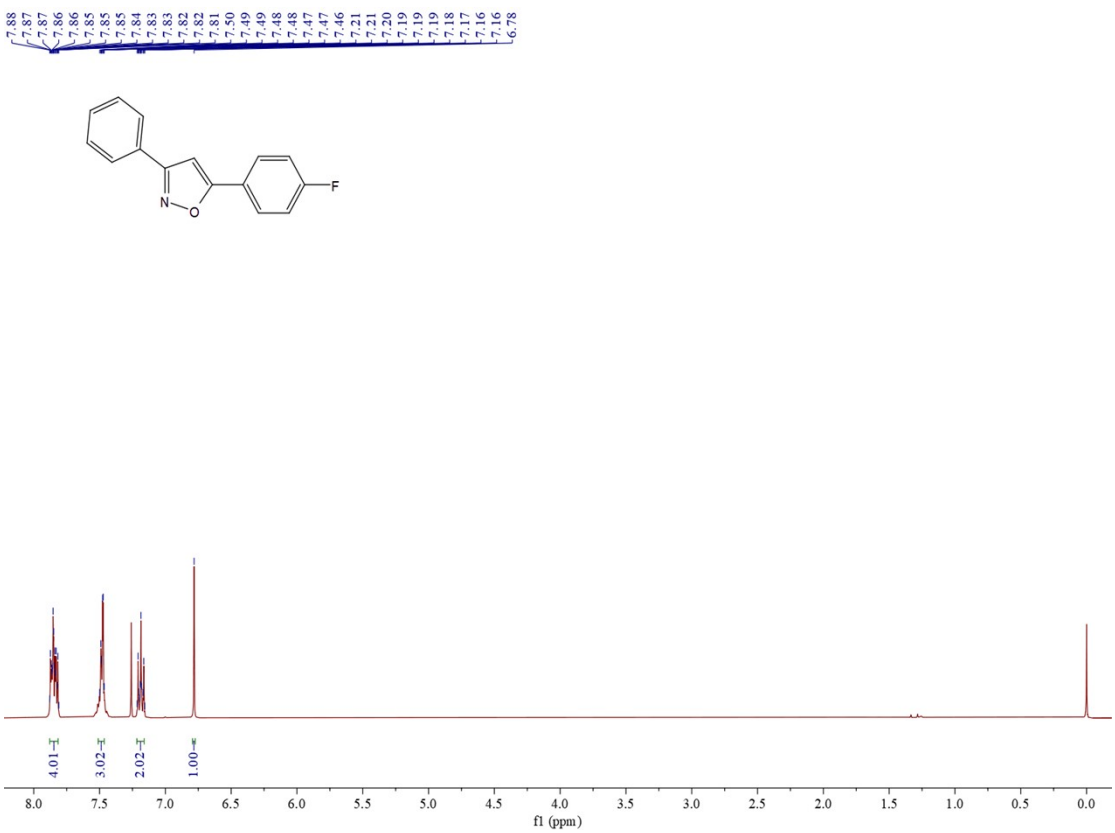

Fig. S11. [1]H NMR spectrum of compound **3e**

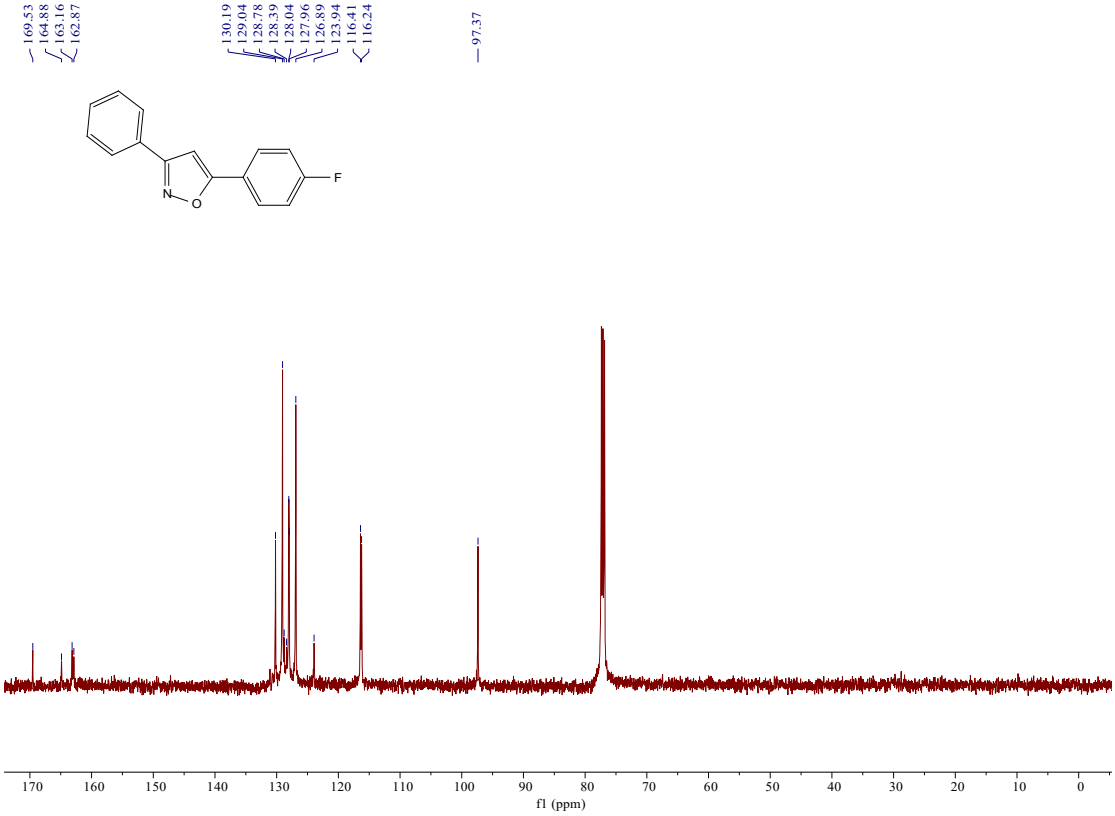

Fig. S12. [13]C NMR spectrum of compound **3e**

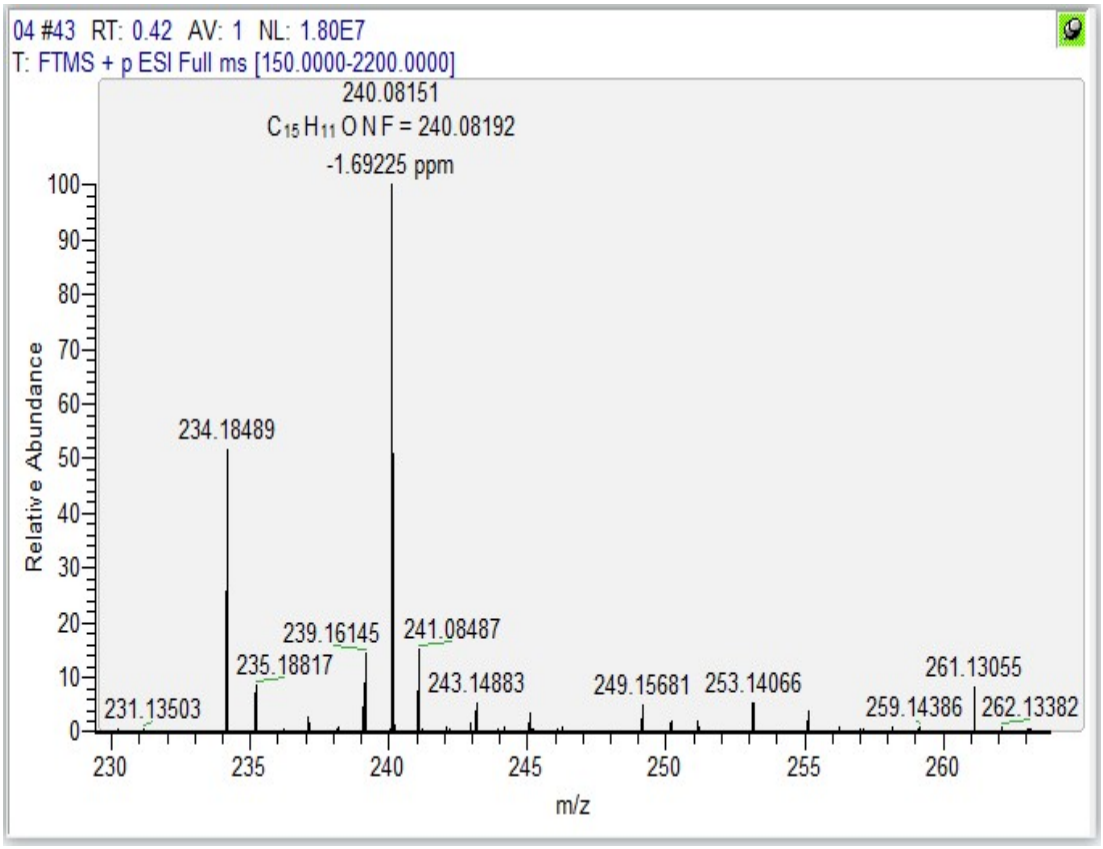

Fig. S13. HRMS spectrum of compound **3e**

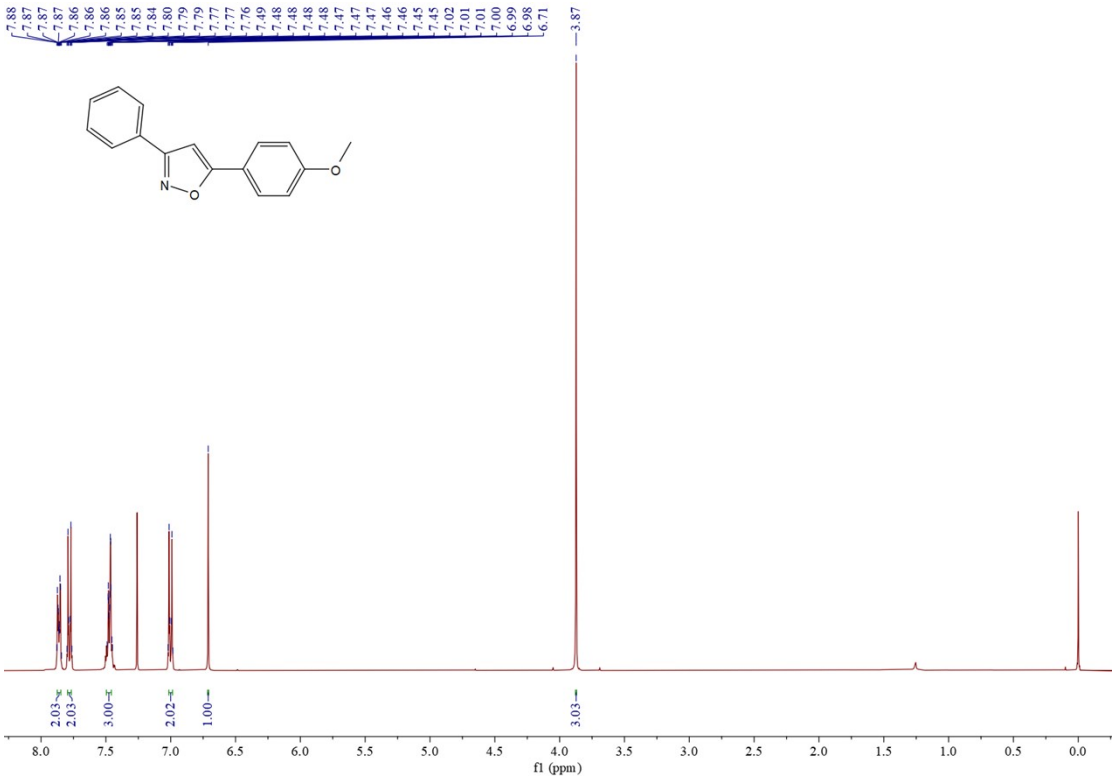

Fig. S14. ^{1}H NMR spectrum of compound **3f**

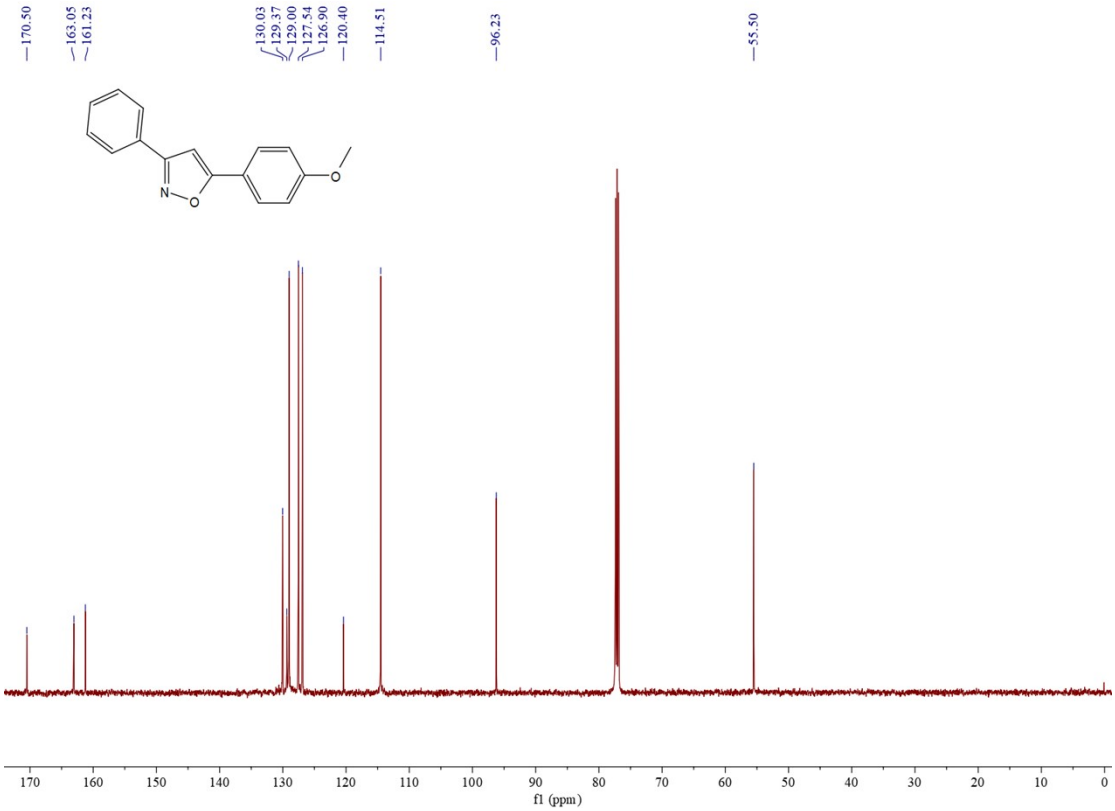

Fig. S15. ^{13}C NMR spectrum of compound **3f**

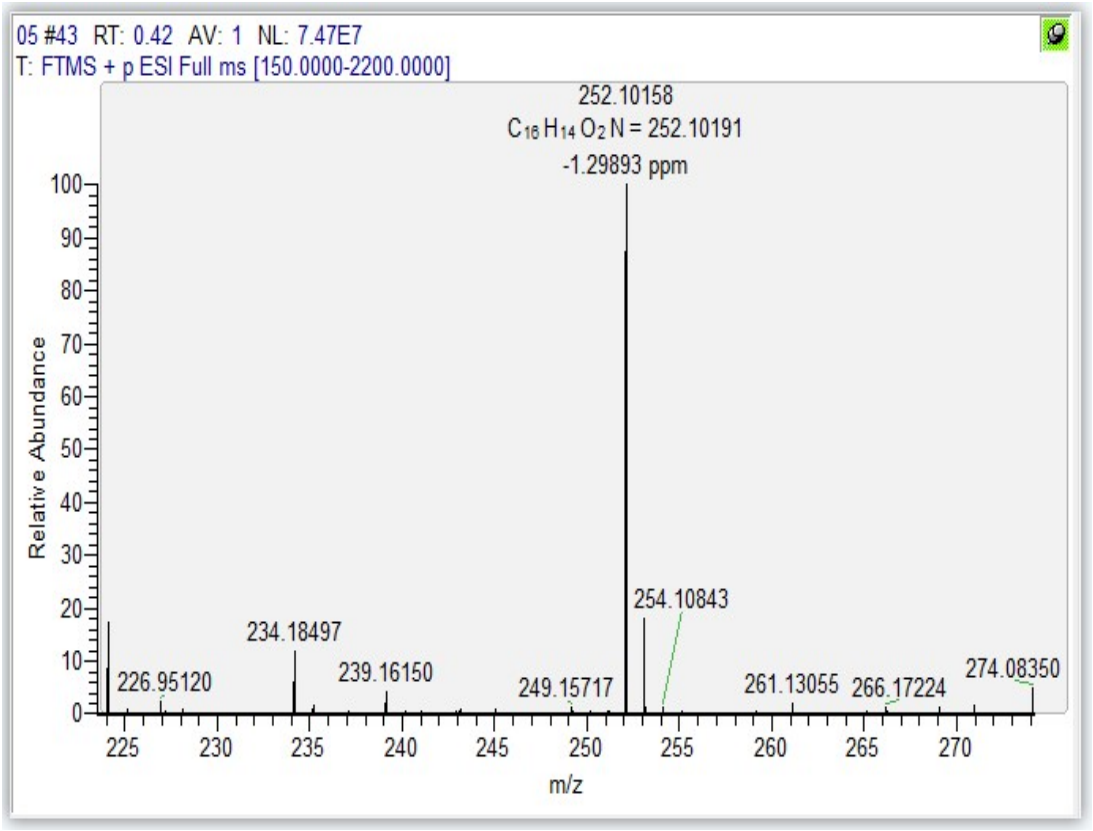

Fig. S16. HRMS spectrum of compound **3f**

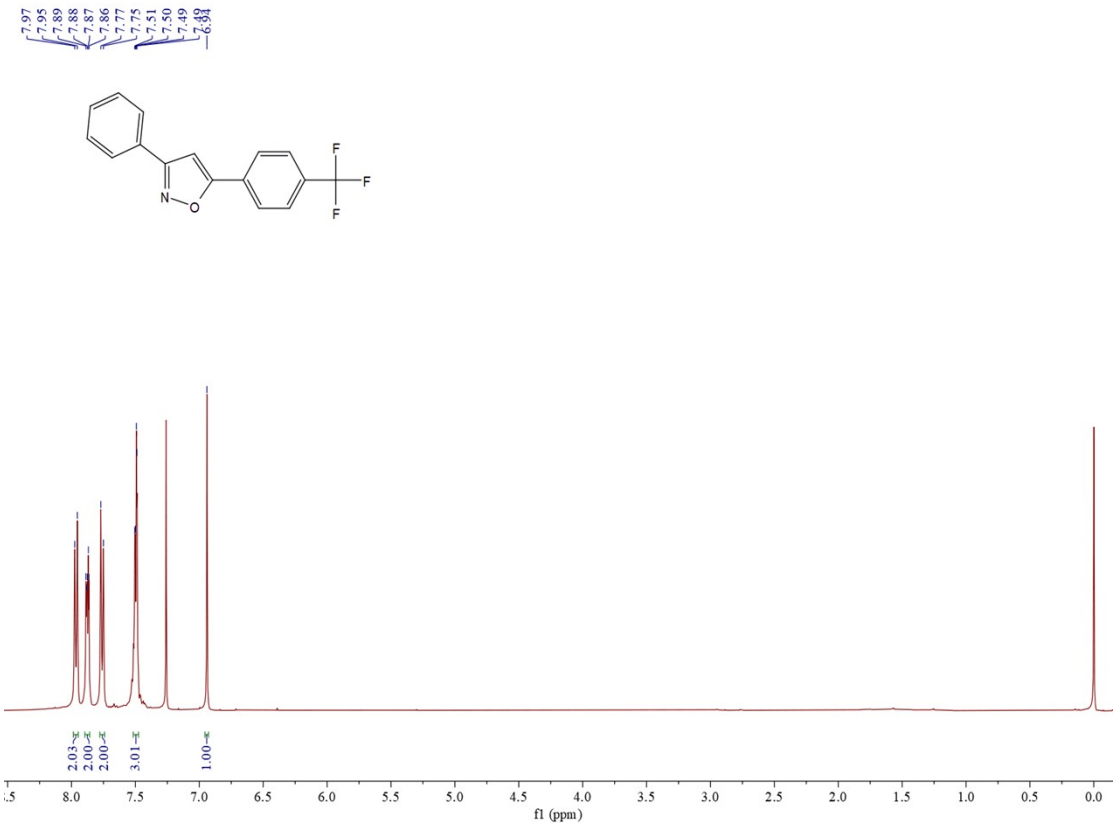

Fig. S17. ^{1}H NMR spectrum of compound **3g**

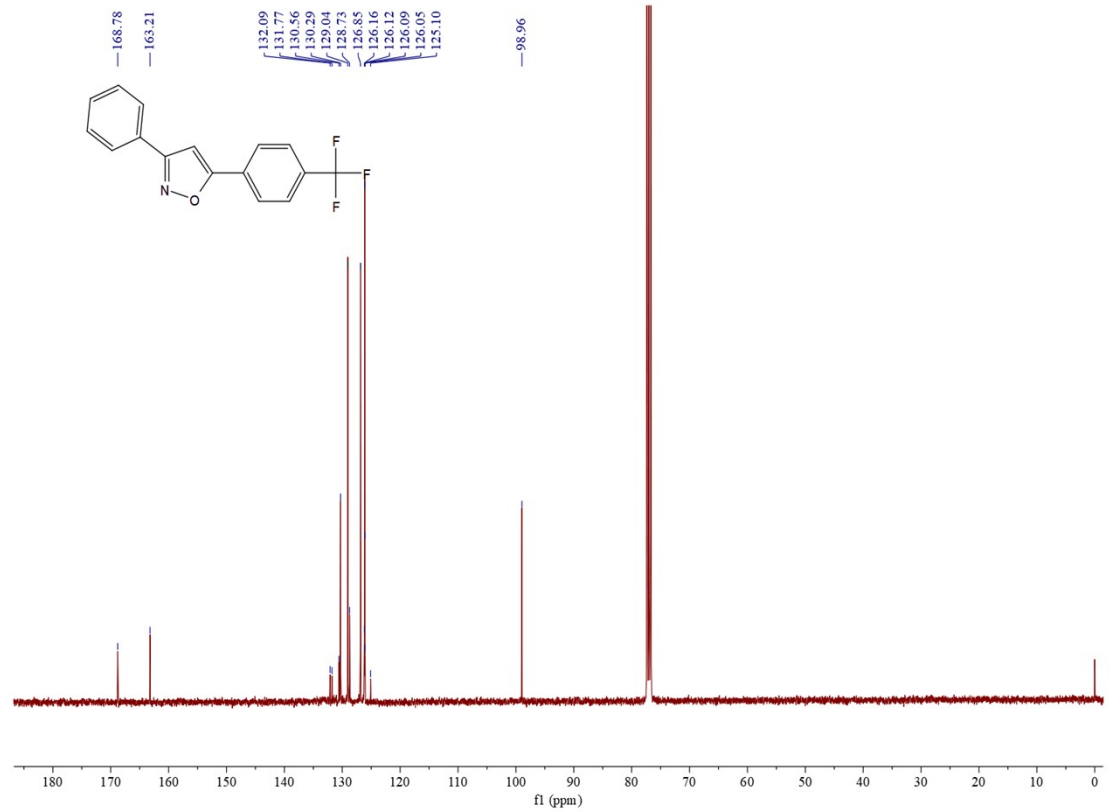

Fig. S18. ^{13}C NMR spectrum of compound **3g**

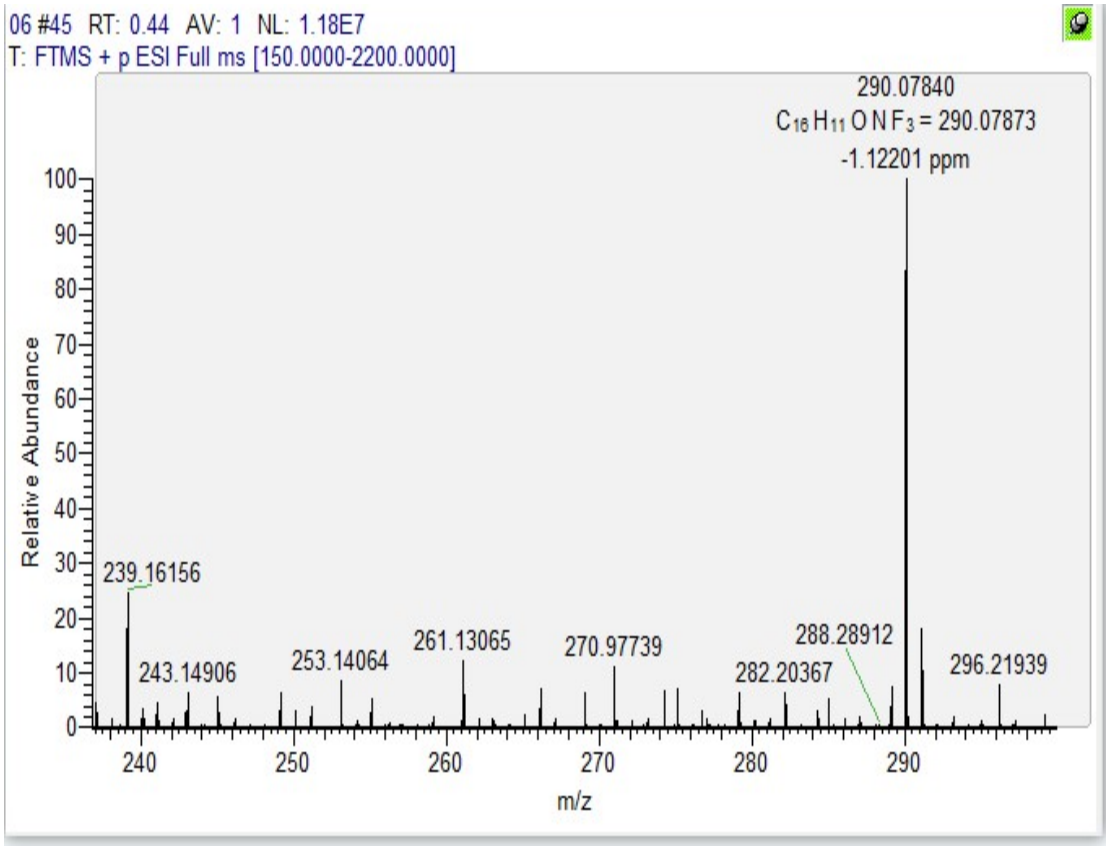

Fig. S19. HRMS spectrum of compound **3g**

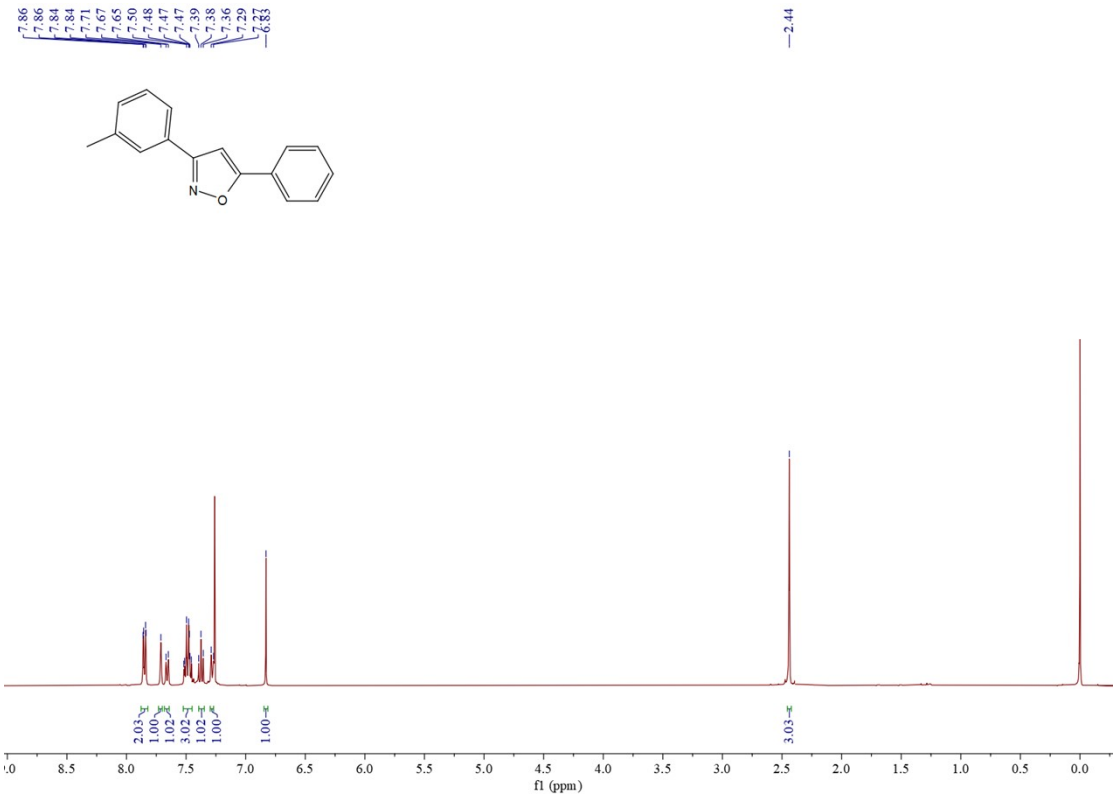

Fig. S20. [1]H NMR spectrum of compound **3h**

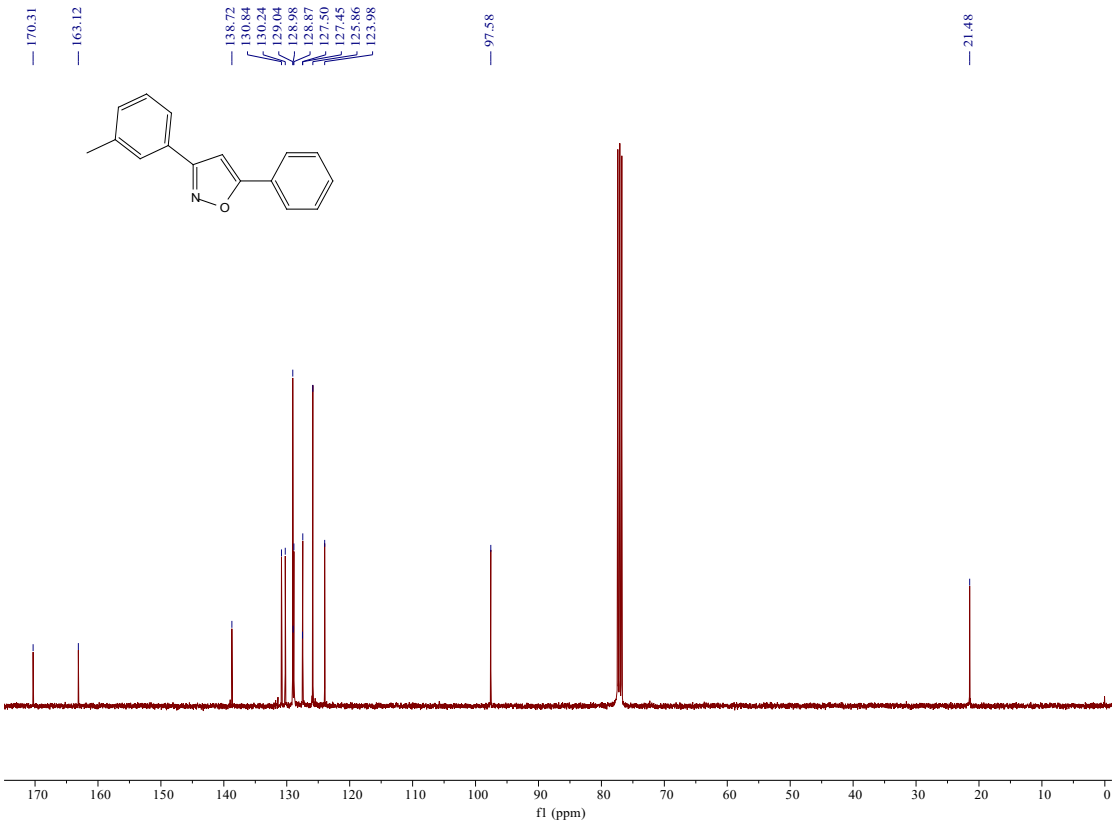

Fig. S21. ^{13}C NMR spectrum of compound **3h**

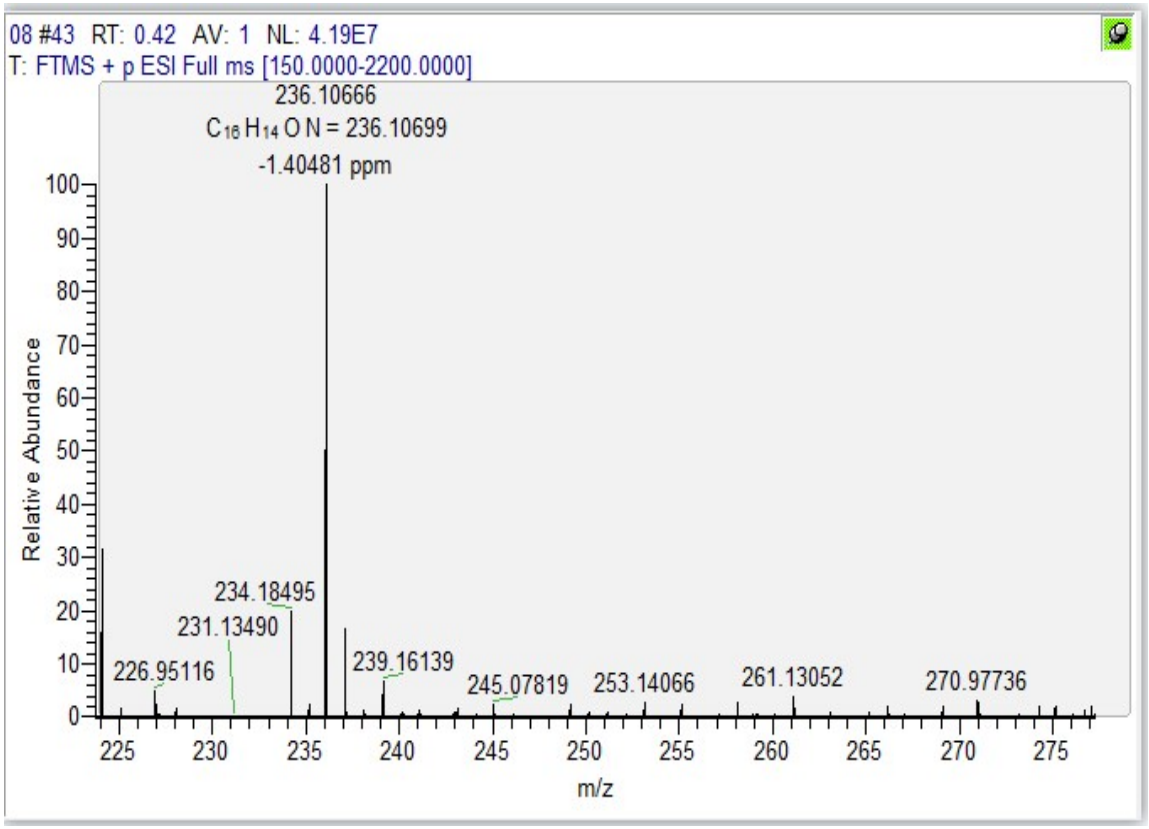

Fig. S22. HRMS spectrum of compound **3h**

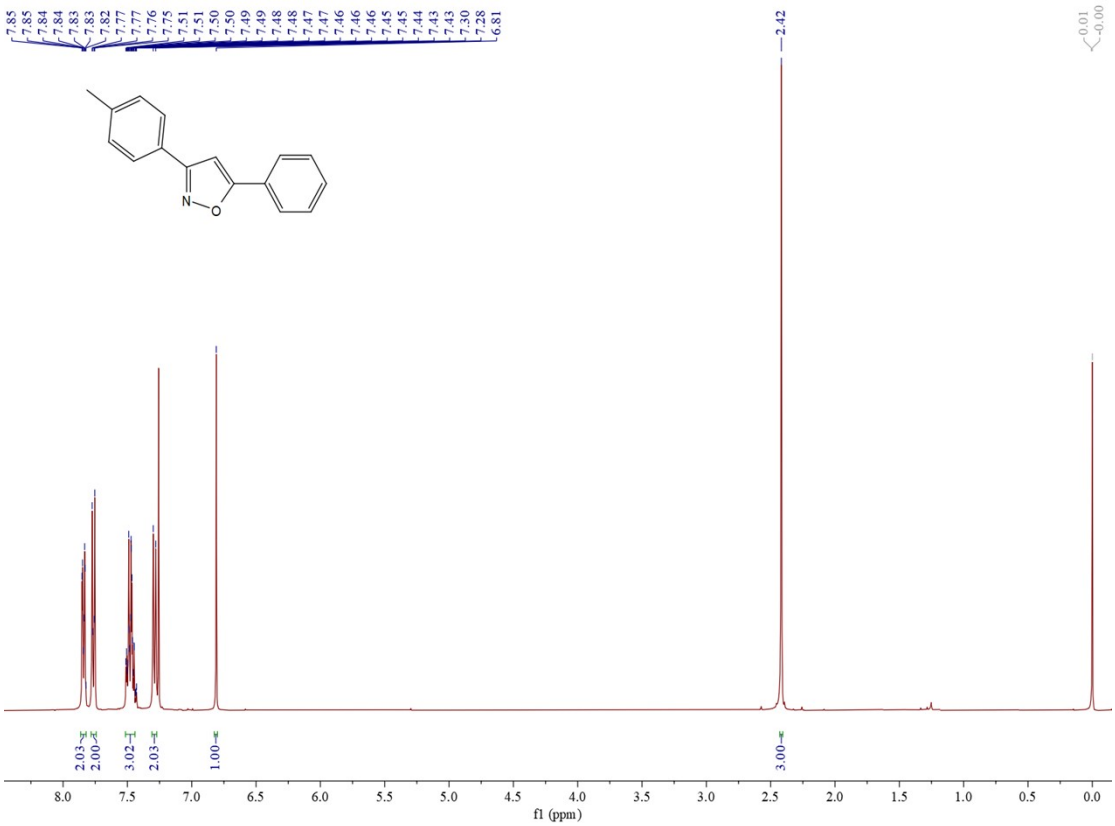

Fig. S23. ^{1}H NMR spectrum of compound **3i**

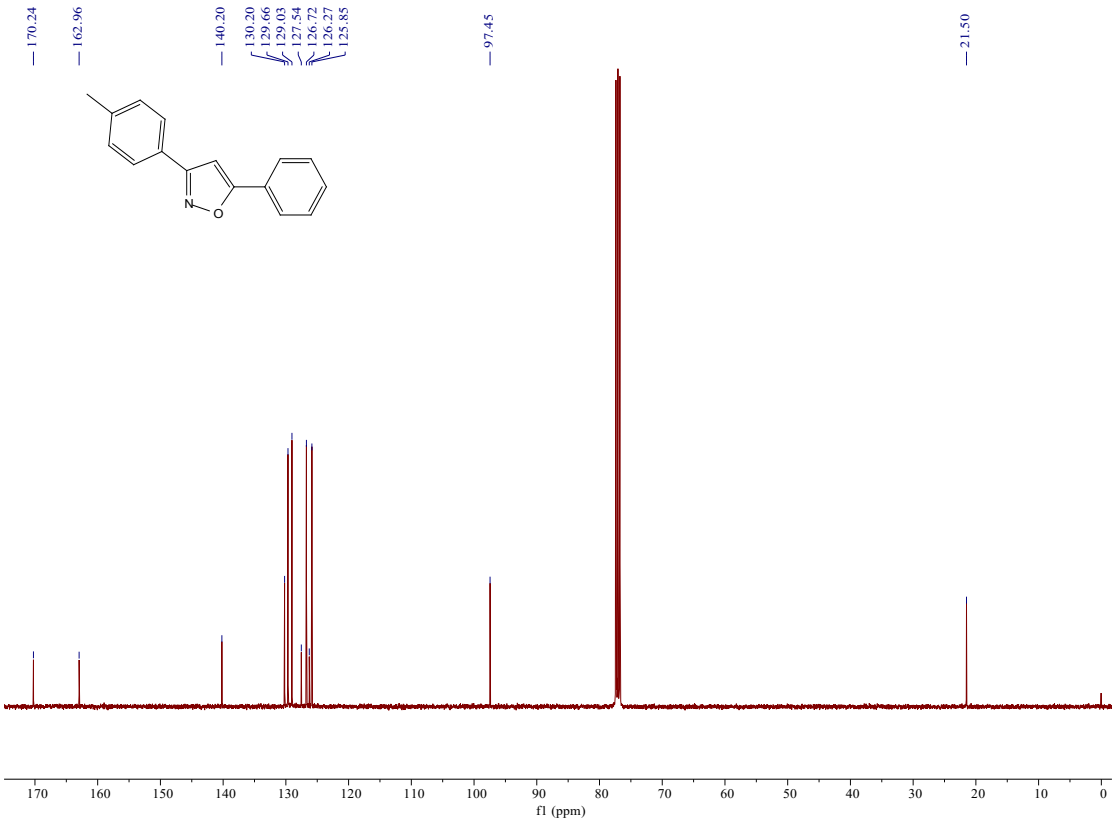

Fig. S24. ^{13}C NMR spectrum of compound **3i**

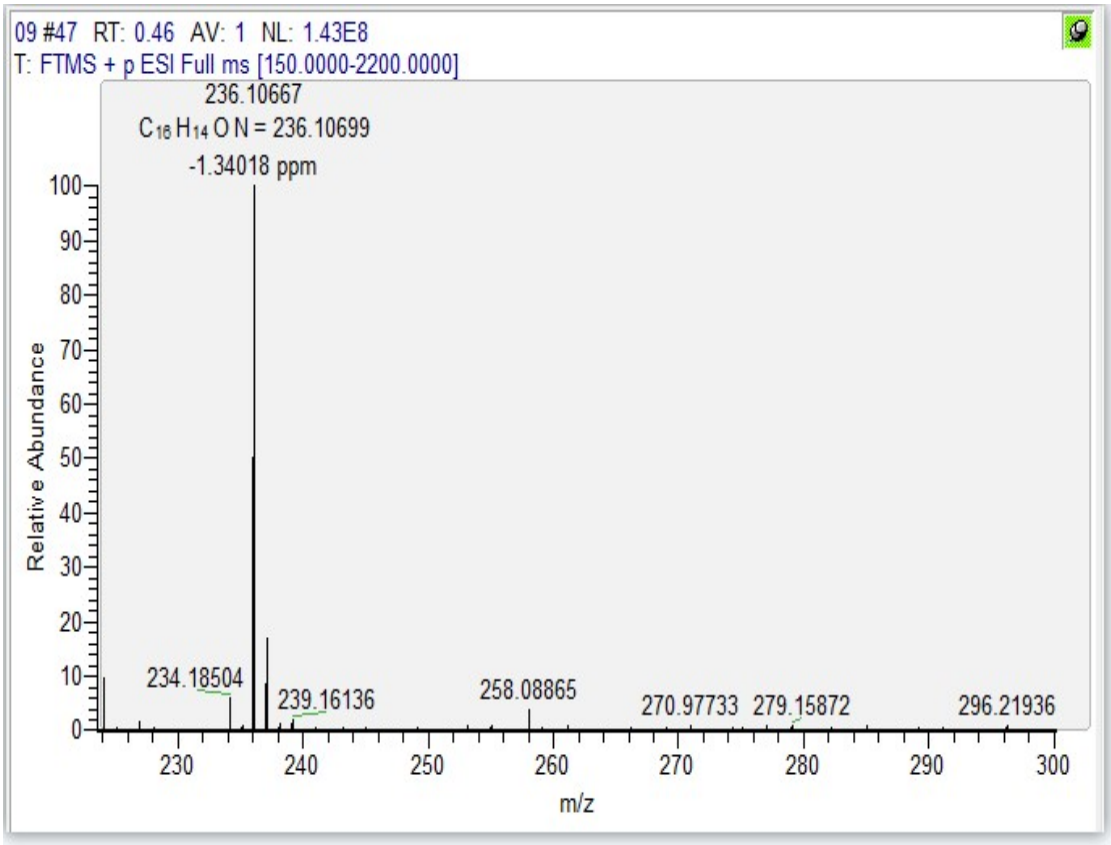

Fig. S25. HRMS spectrum of compound **3i**

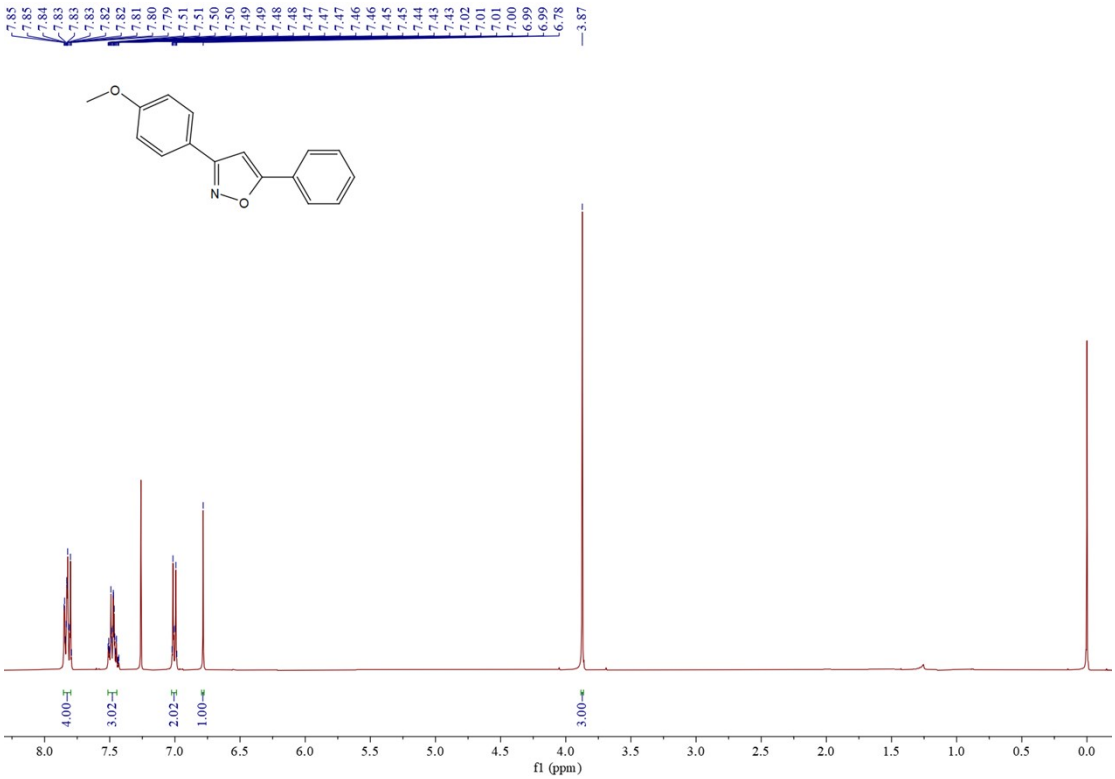

Fig. S26. ^{1}H NMR spectrum of compound **3j**

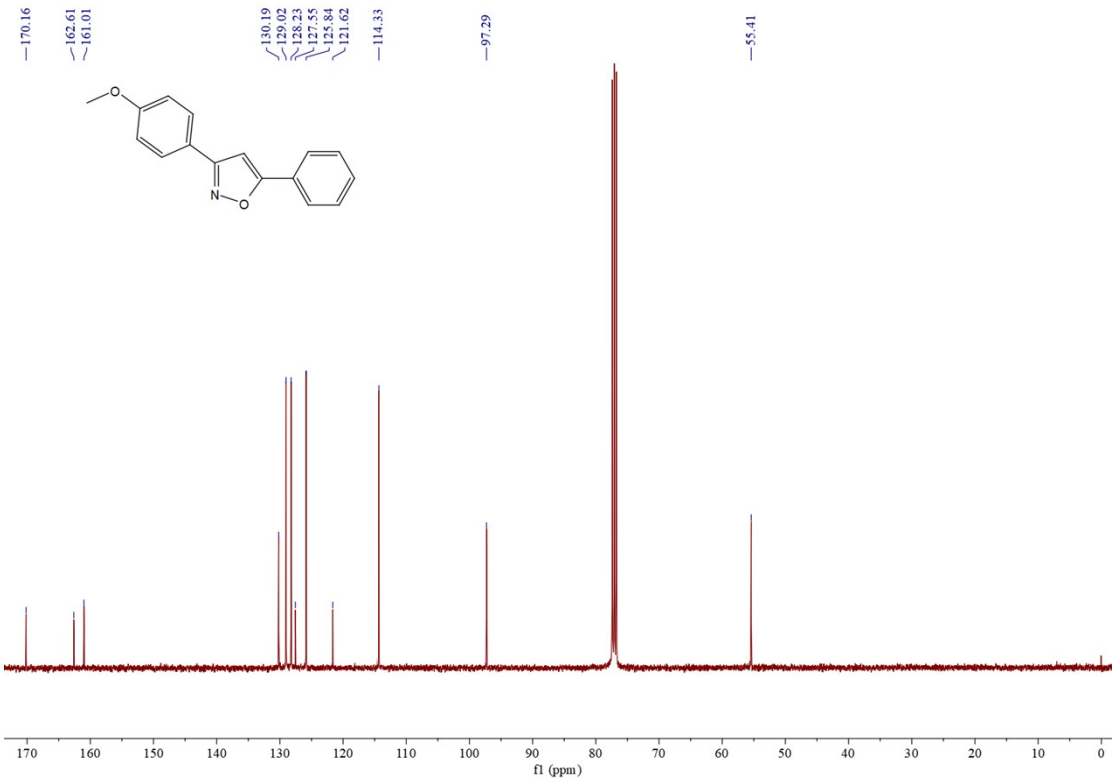

Fig. S27. ^{13}C NMR spectrum of compound **3j**

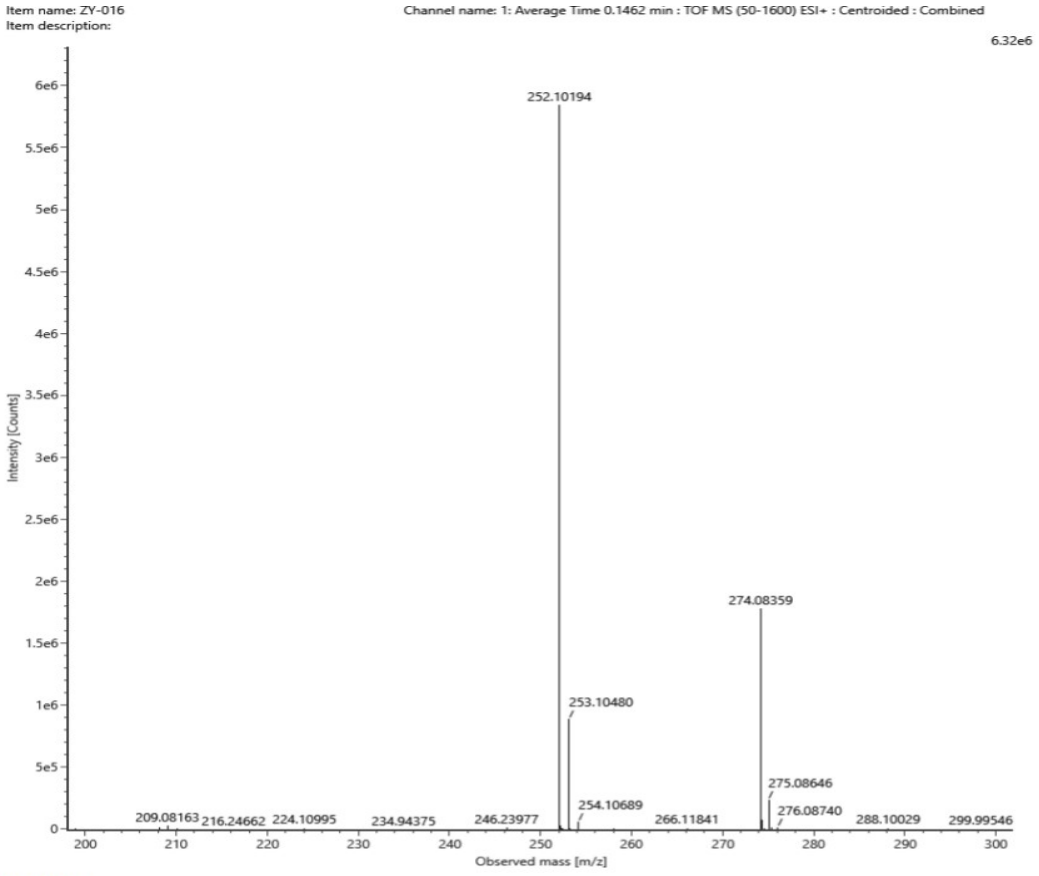

Fig. S28. HRMS spectrum of compound **3j**

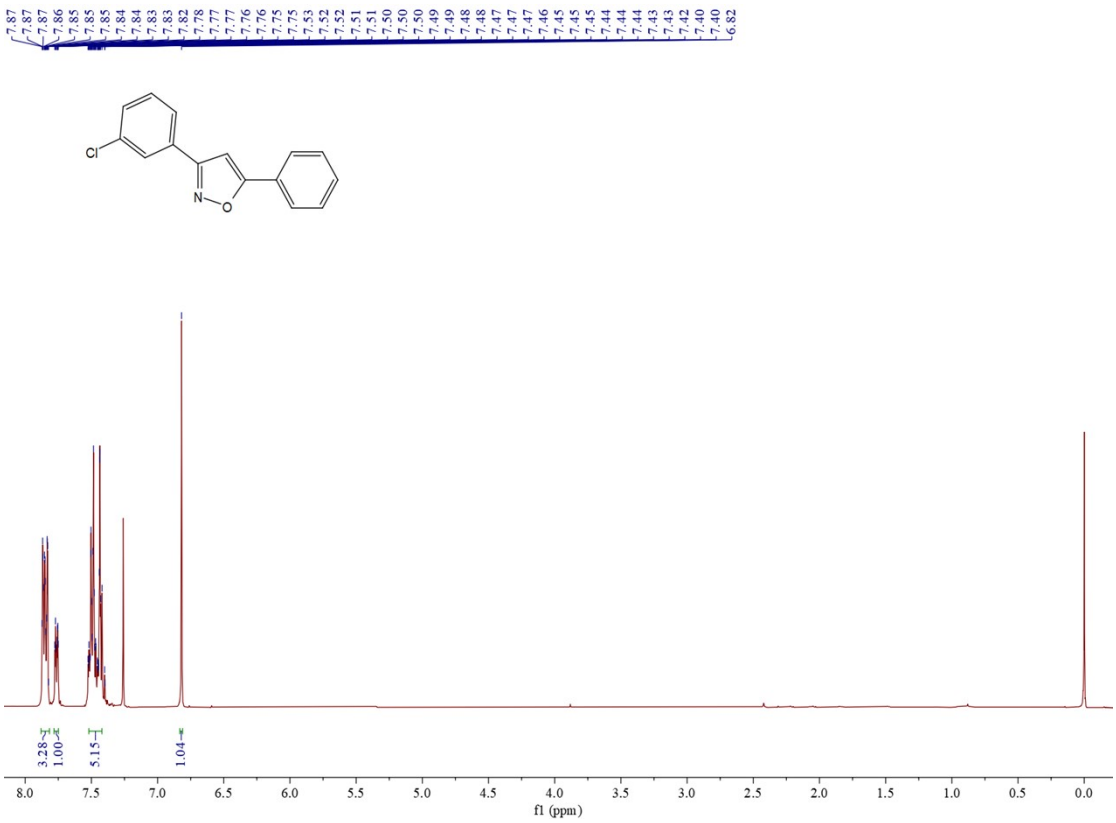

Fig. S29. ^{1}H NMR spectrum of compound **3k**

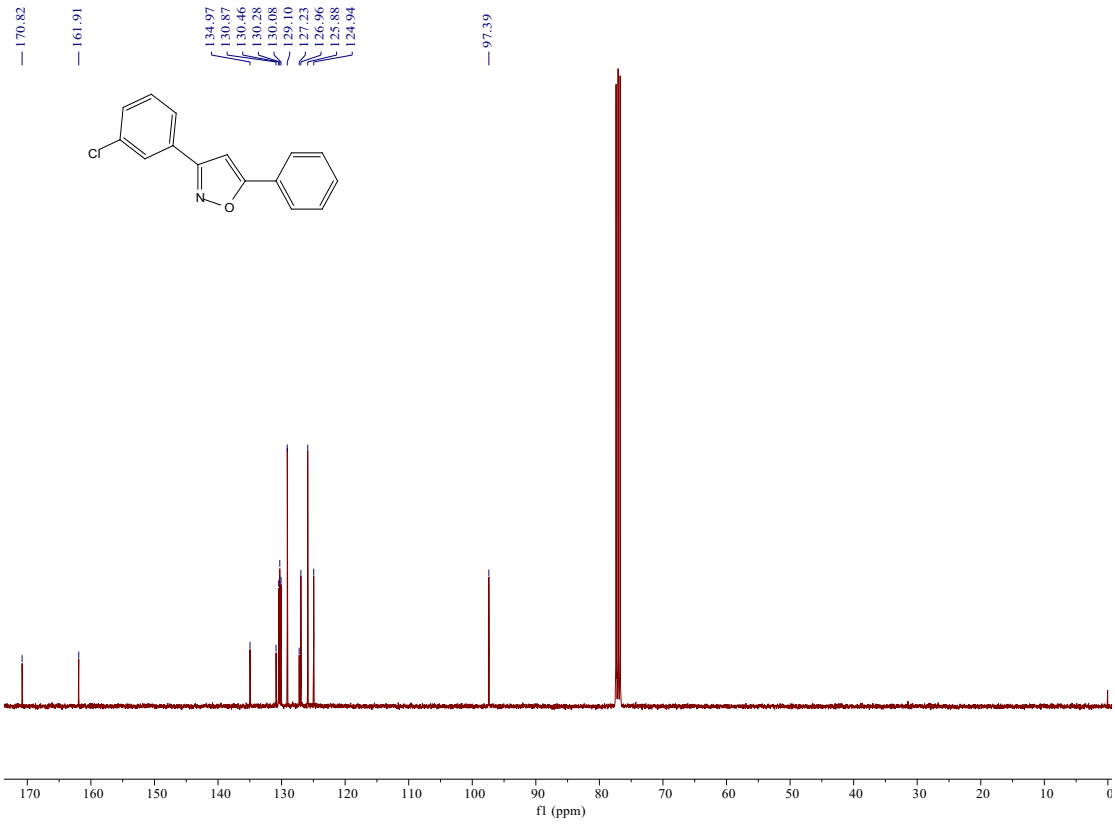

Fig. S30. ^{13}C NMR spectrum of compound **3k**

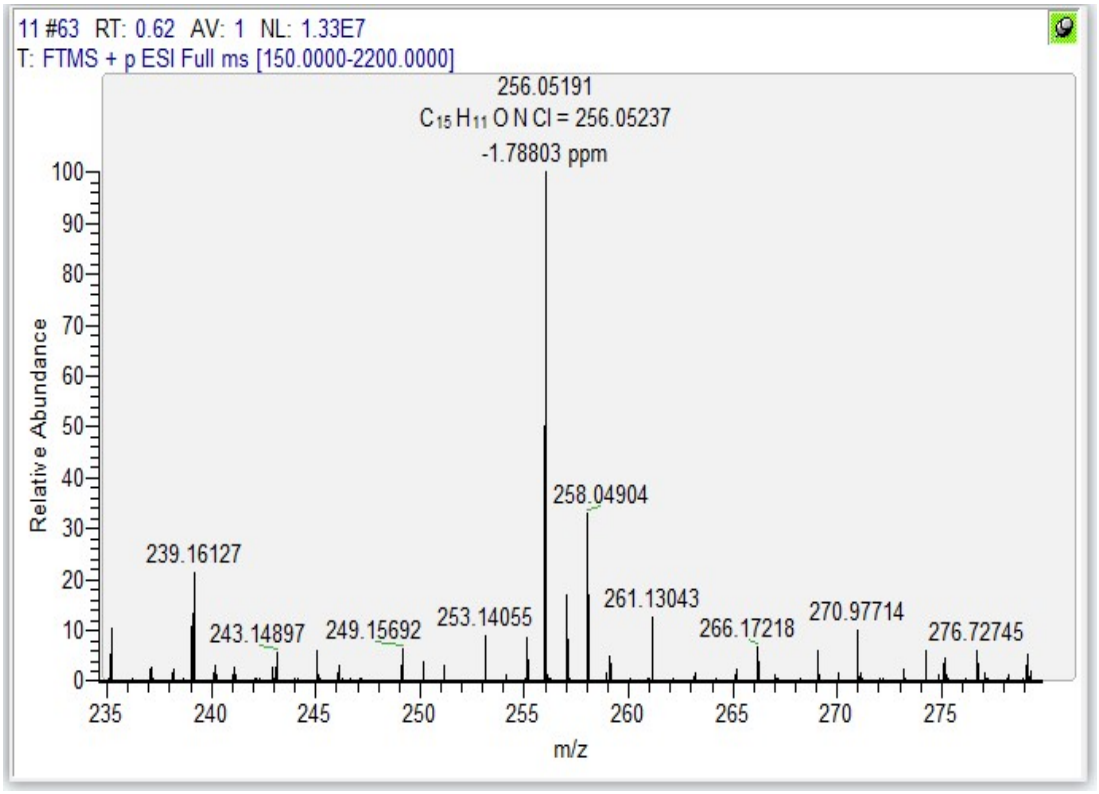

Fig. S31. HRMS spectrum of compound **3k**

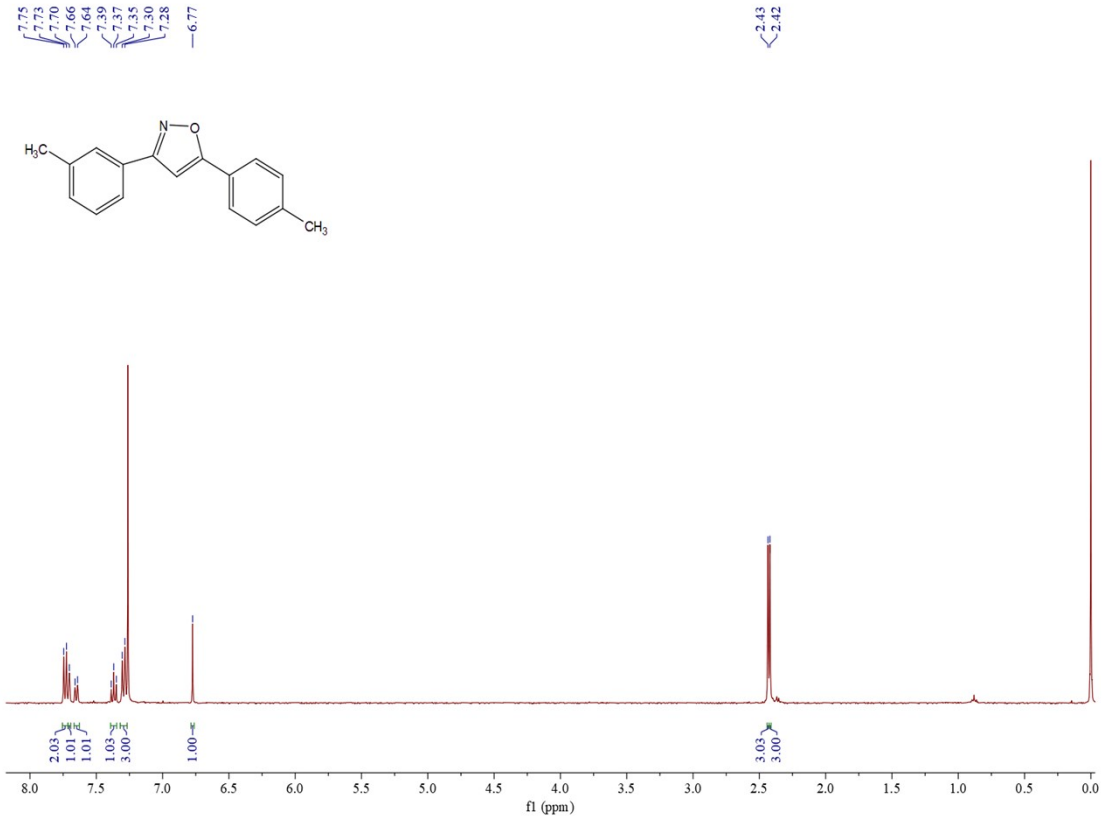

Fig. S32. ^{1}H NMR spectrum of compound **3l**

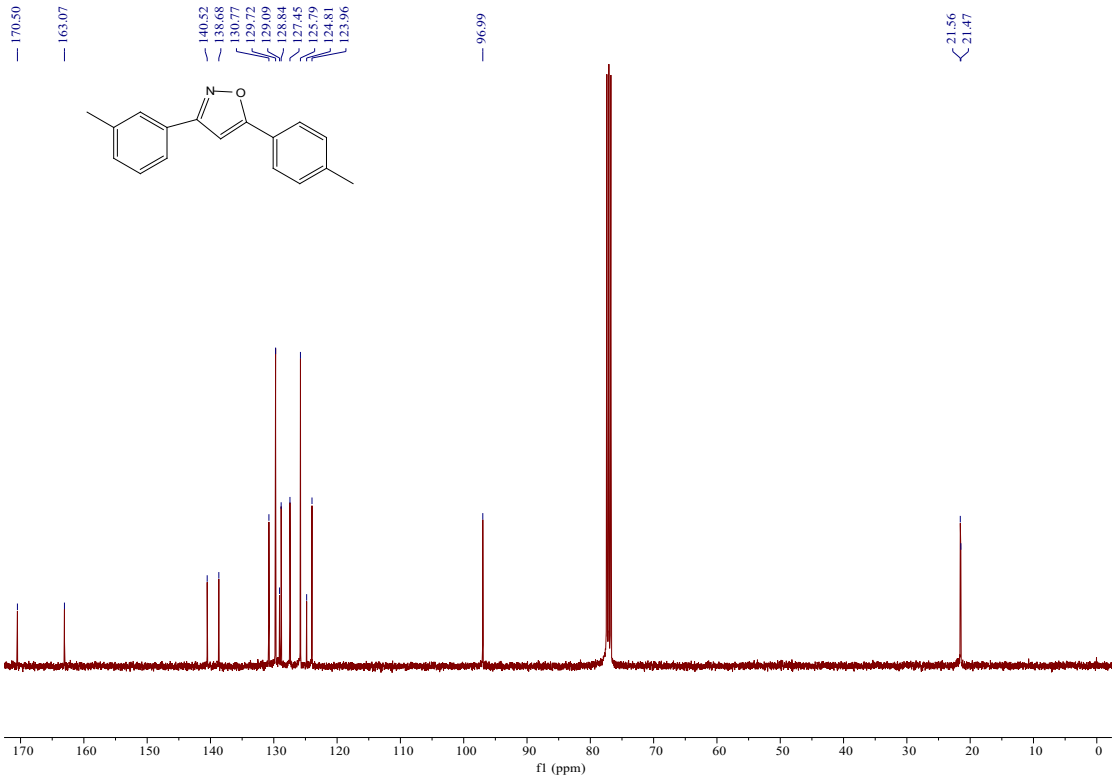

Fig. S33. ^{13}C NMR spectrum of compound **3l**

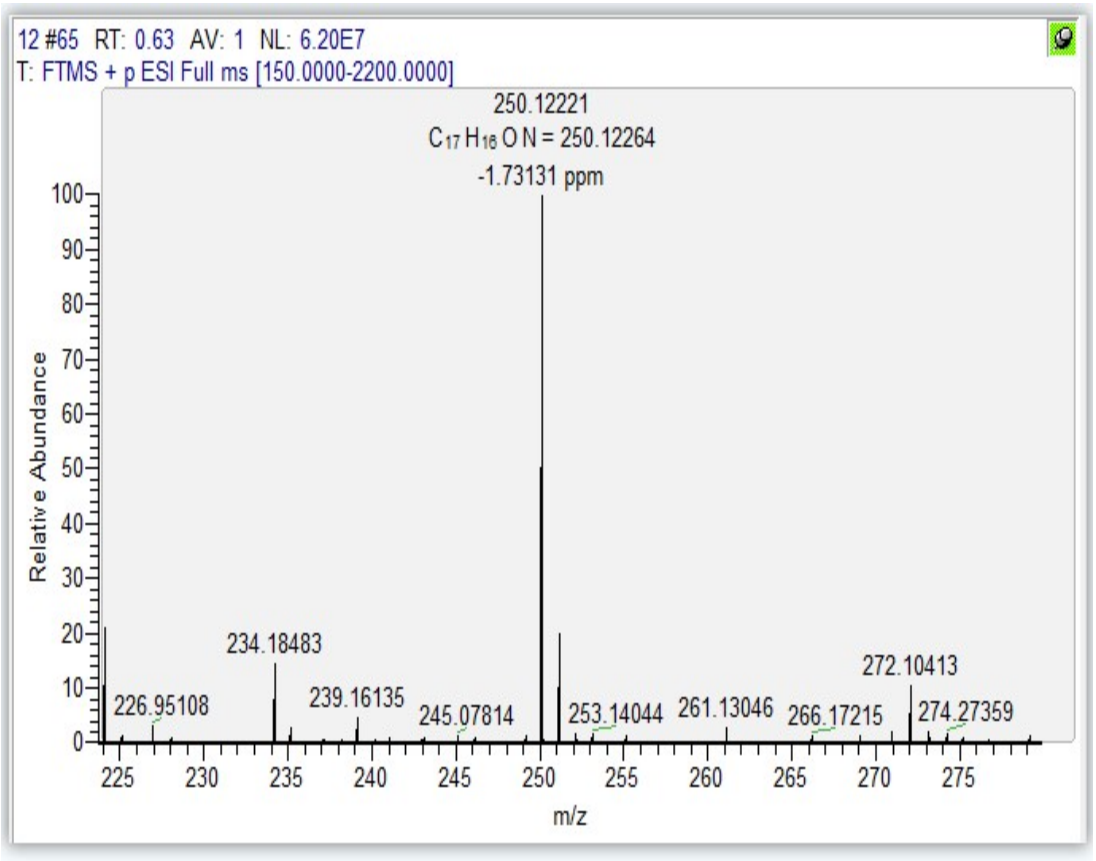

Fig. S34. HRMS spectrum of compound **3l**

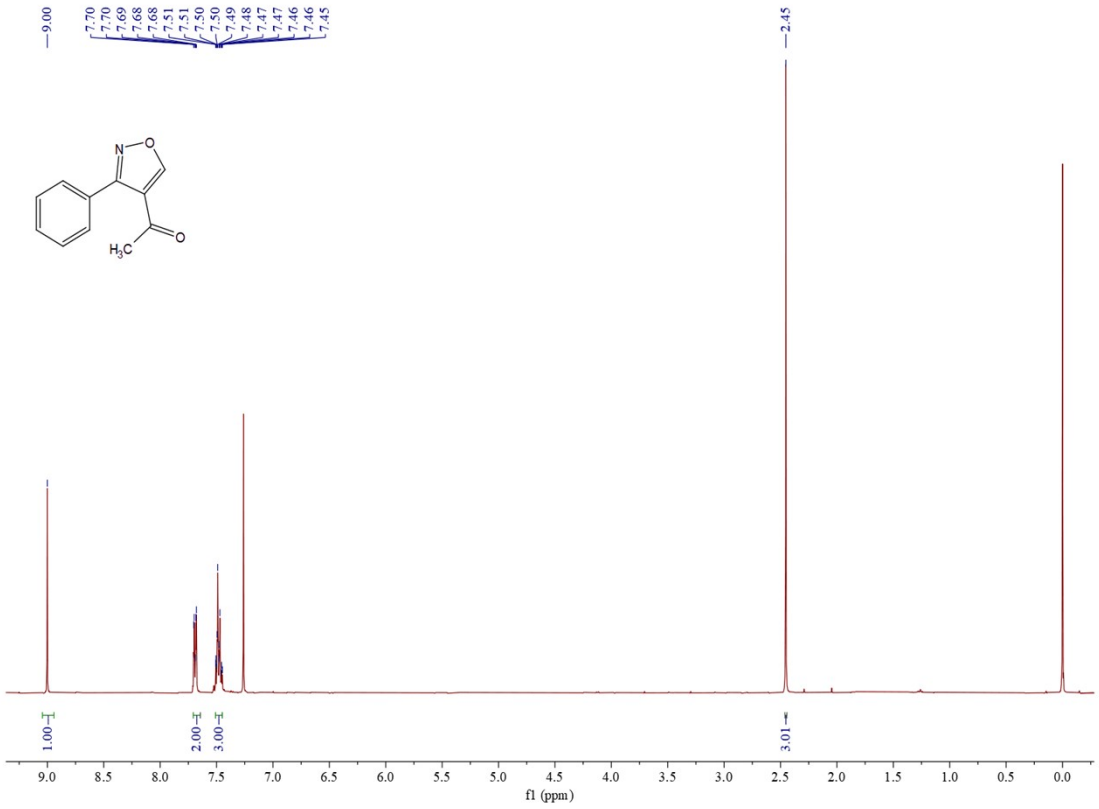

Fig. S35. ^{1}H NMR spectrum of compound **5a**

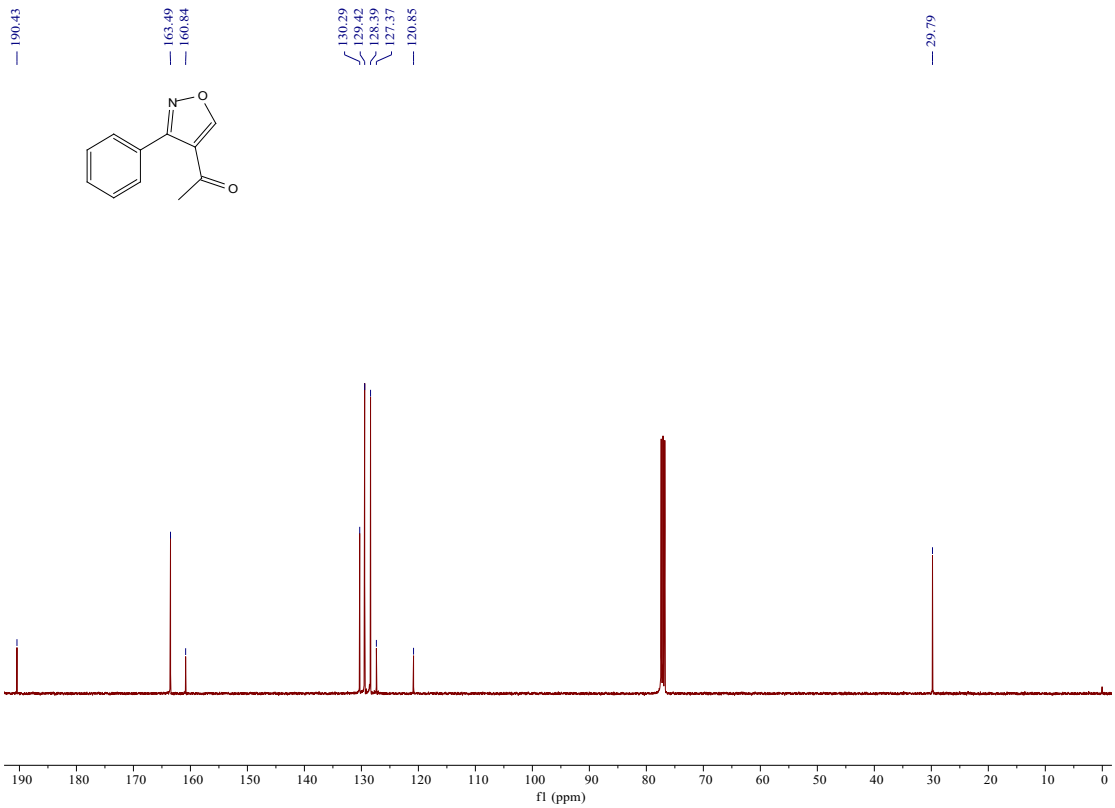

Fig. S36. ^{13}C NMR spectrum of compound **5a**

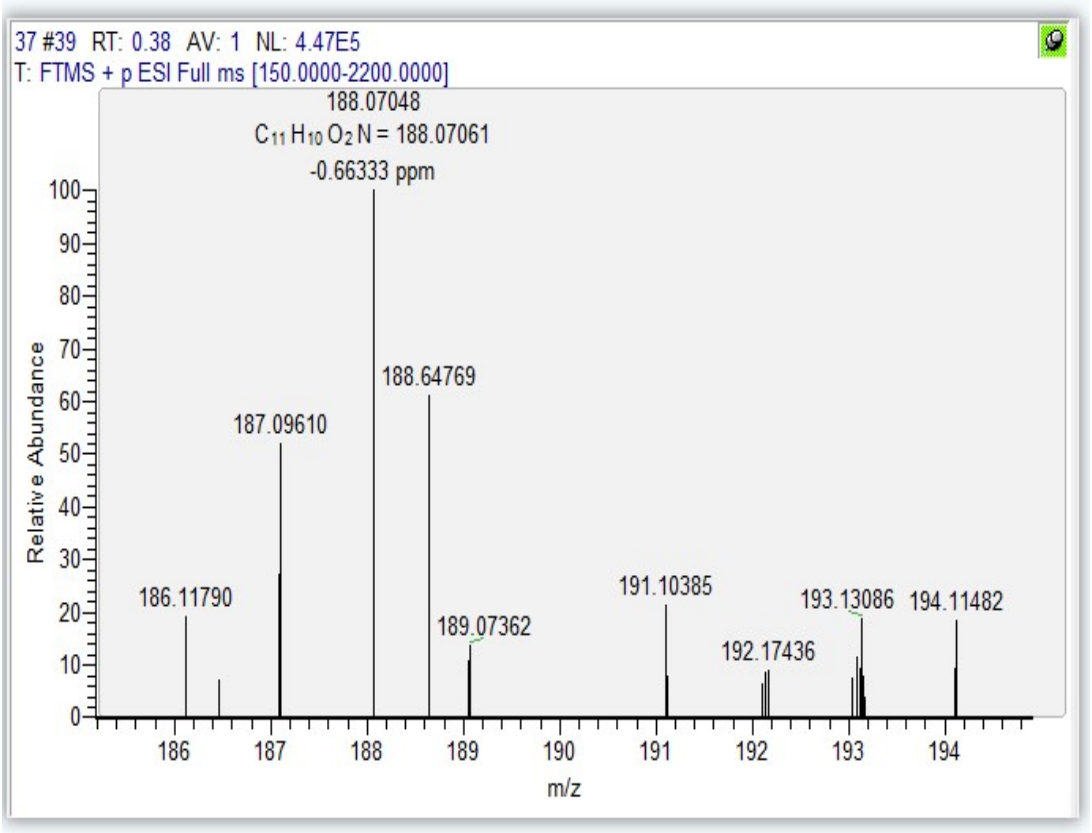

Fig. S37. HRMS spectrum of compound **5a**

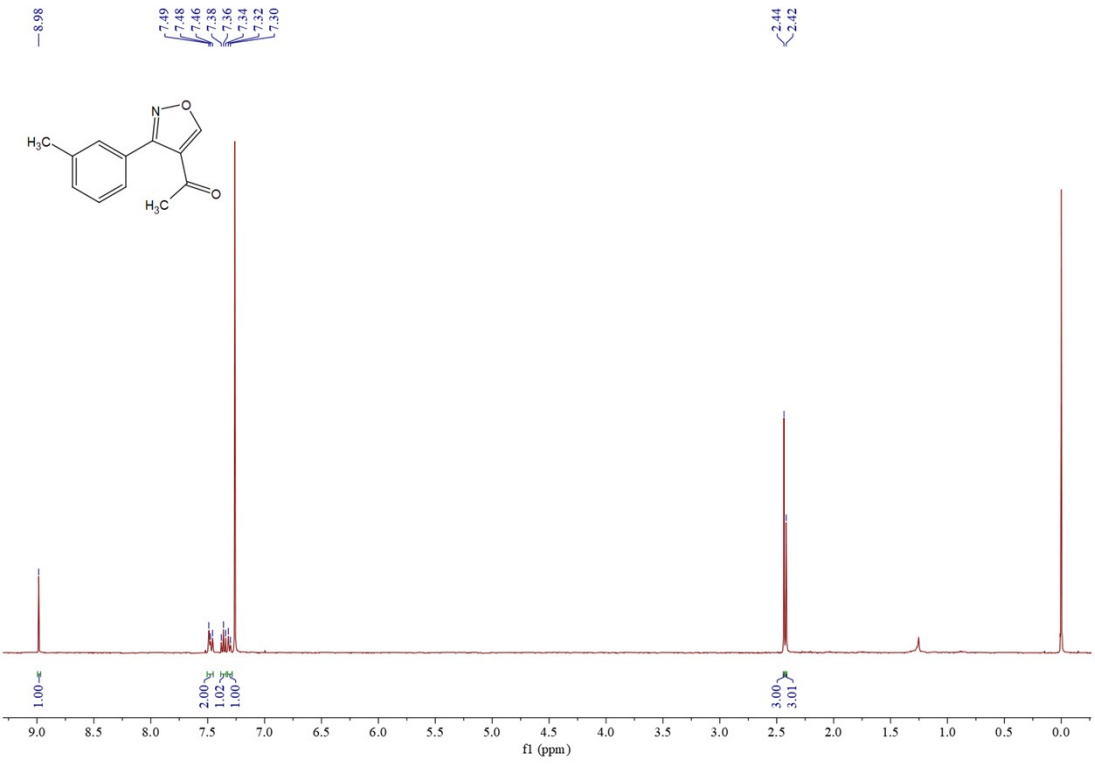

Fig. S38. [1]H NMR spectrum of compound **5b**

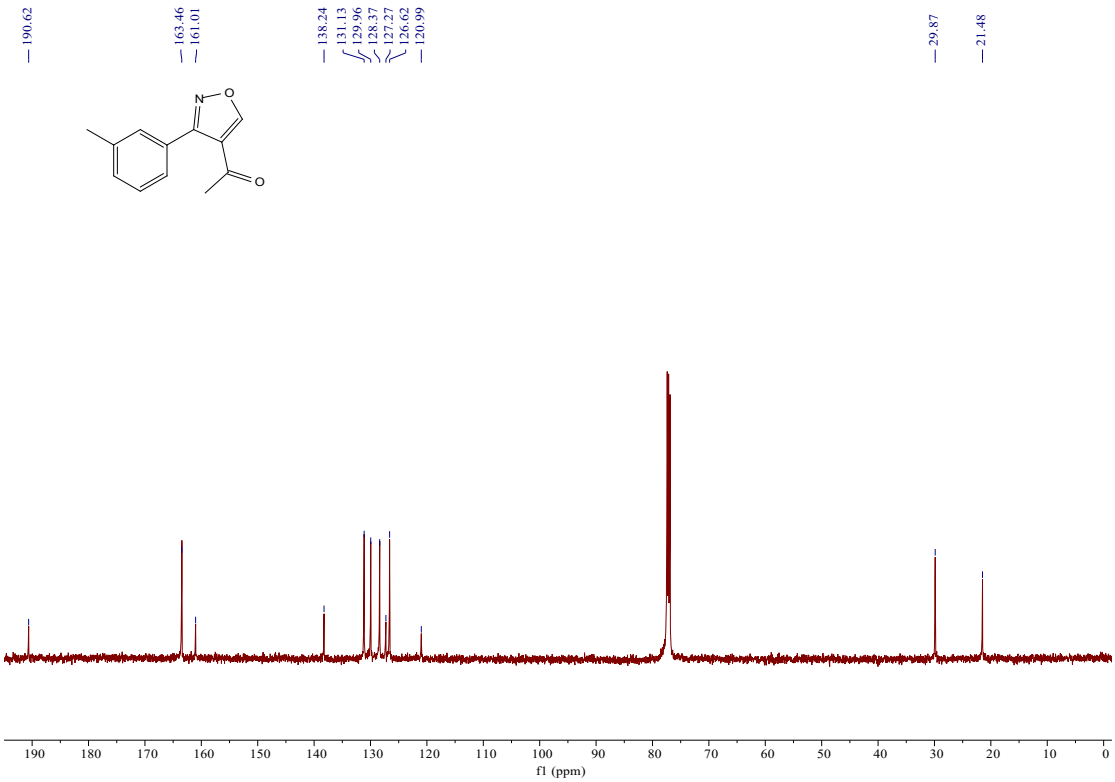

Fig. S39. ^{13}C NMR spectrum of compound **5b**

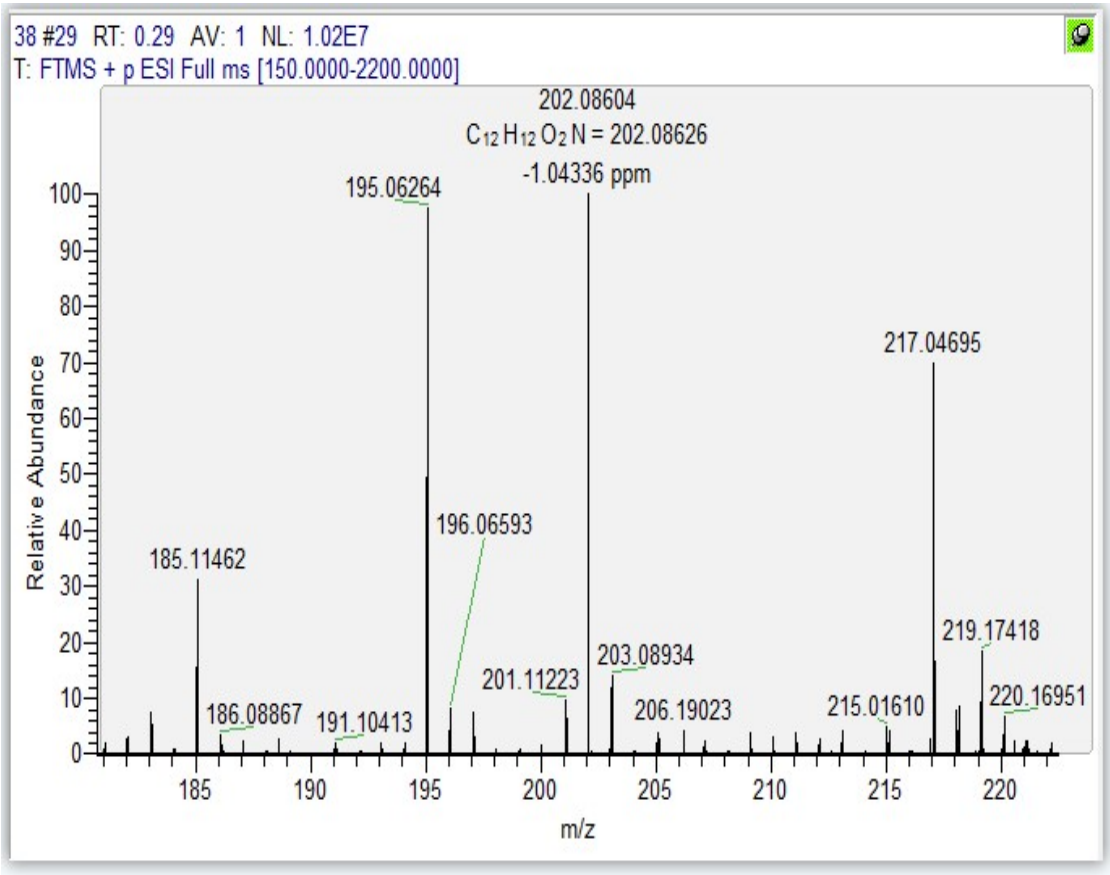

Fig. S40. HRMS spectrum of compound **5b**

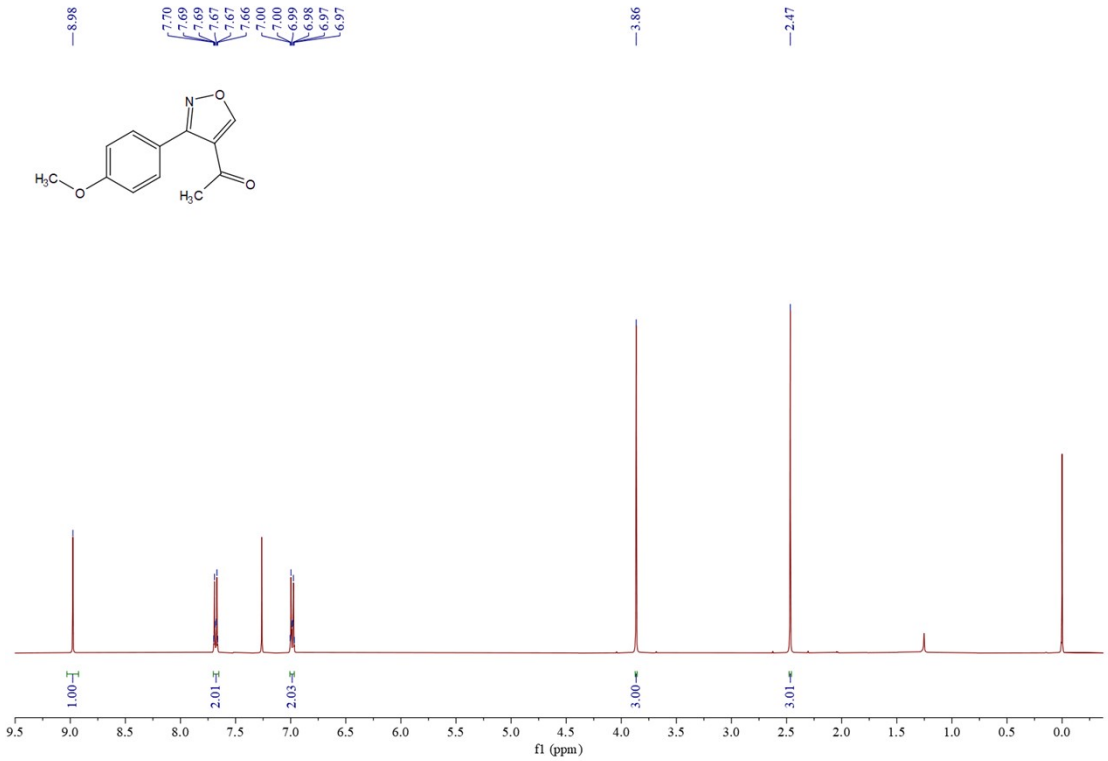

Fig. S41. ^{1}H NMR spectrum of compound **5c**

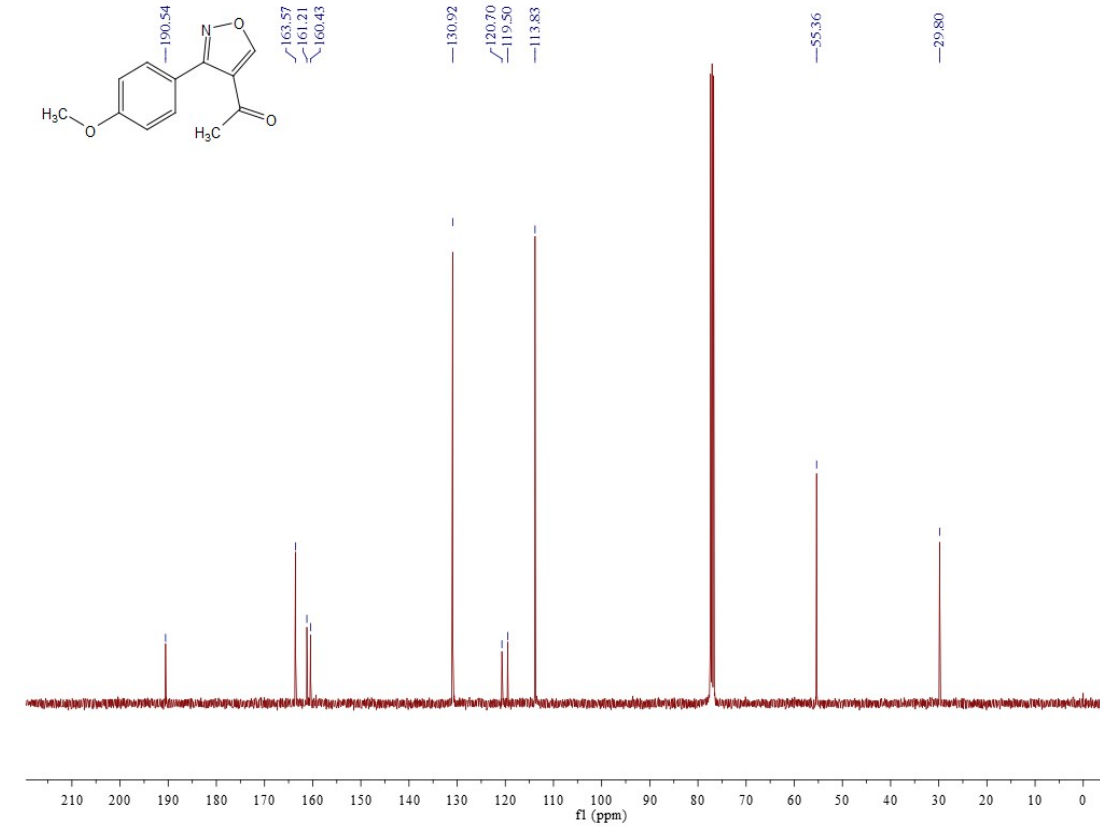

Fig. S42. ^{13}C NMR spectrum of compound **5c**

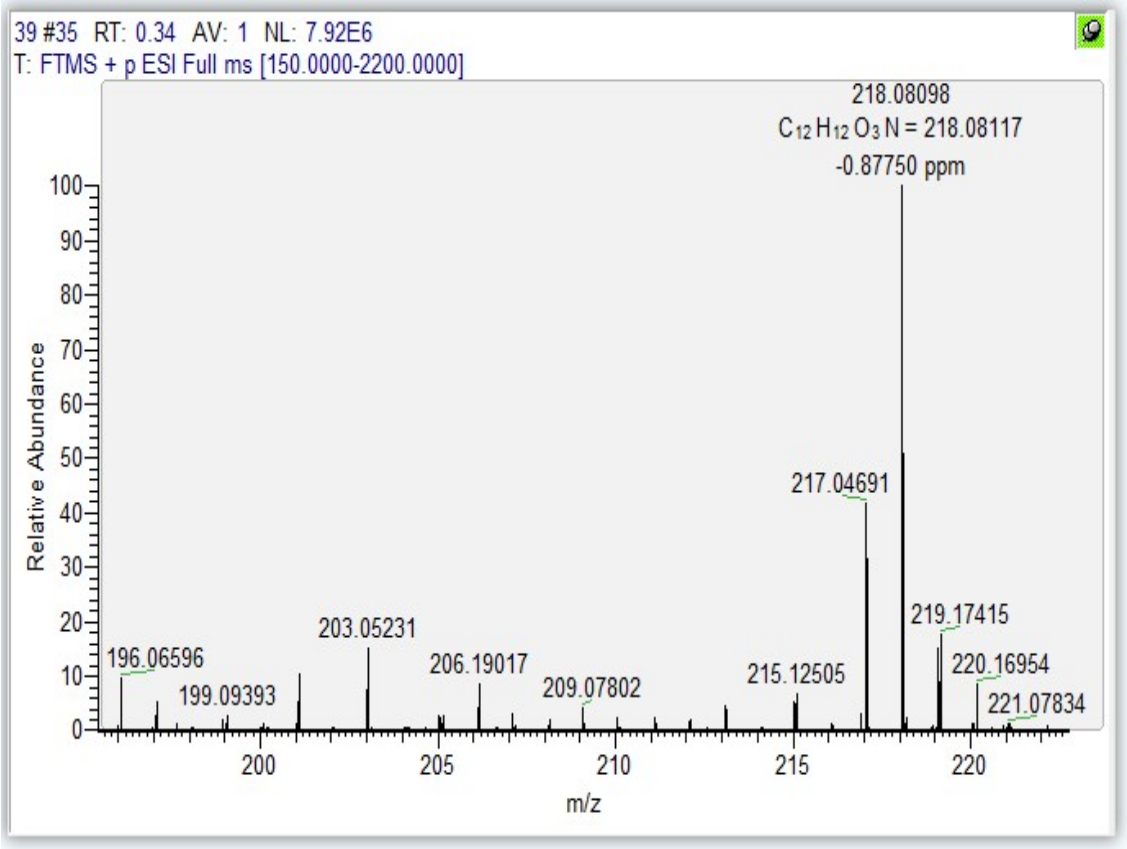

Fig. S43. HRMS spectrum of compound **5c**

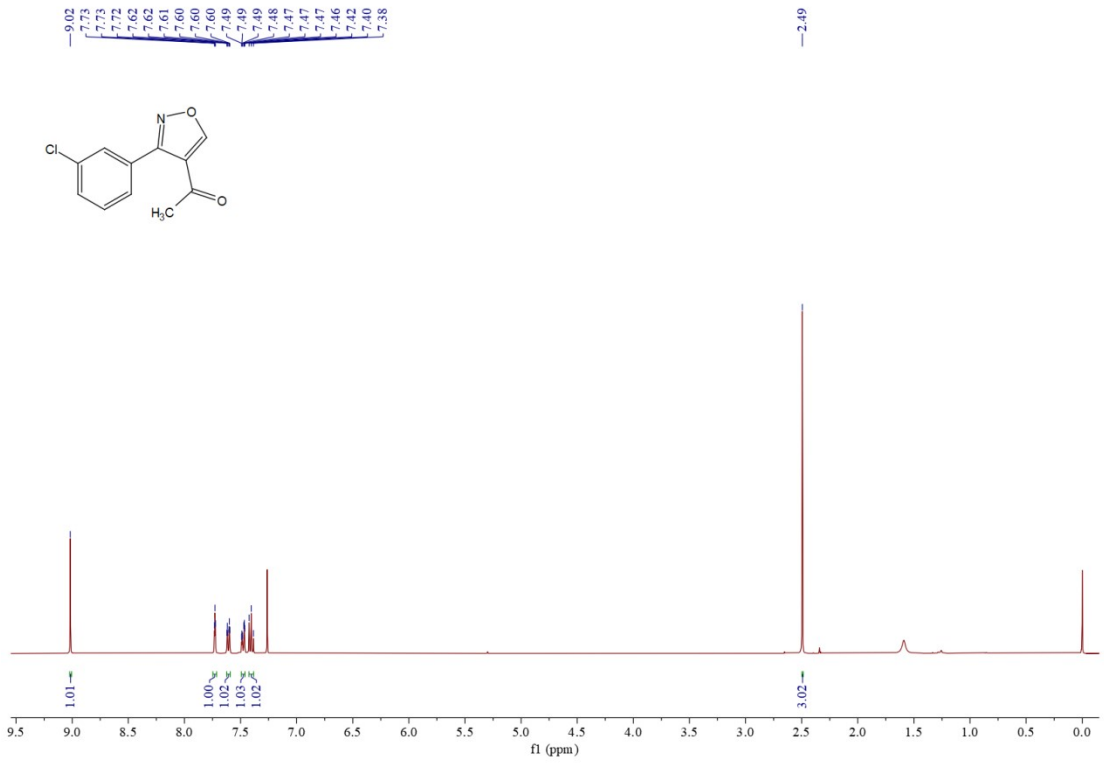

Fig. S44. [1]H NMR spectrum of compound **5d**

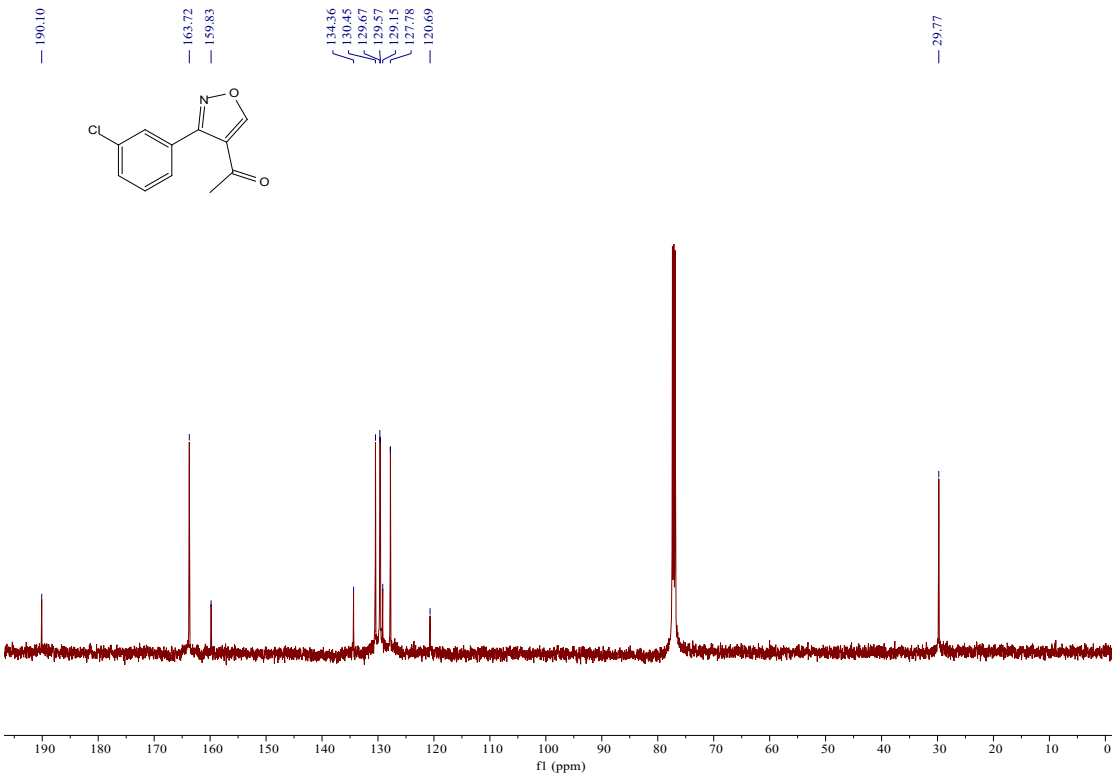

Fig. S45. ^{13}C NMR spectrum of compound **5d**

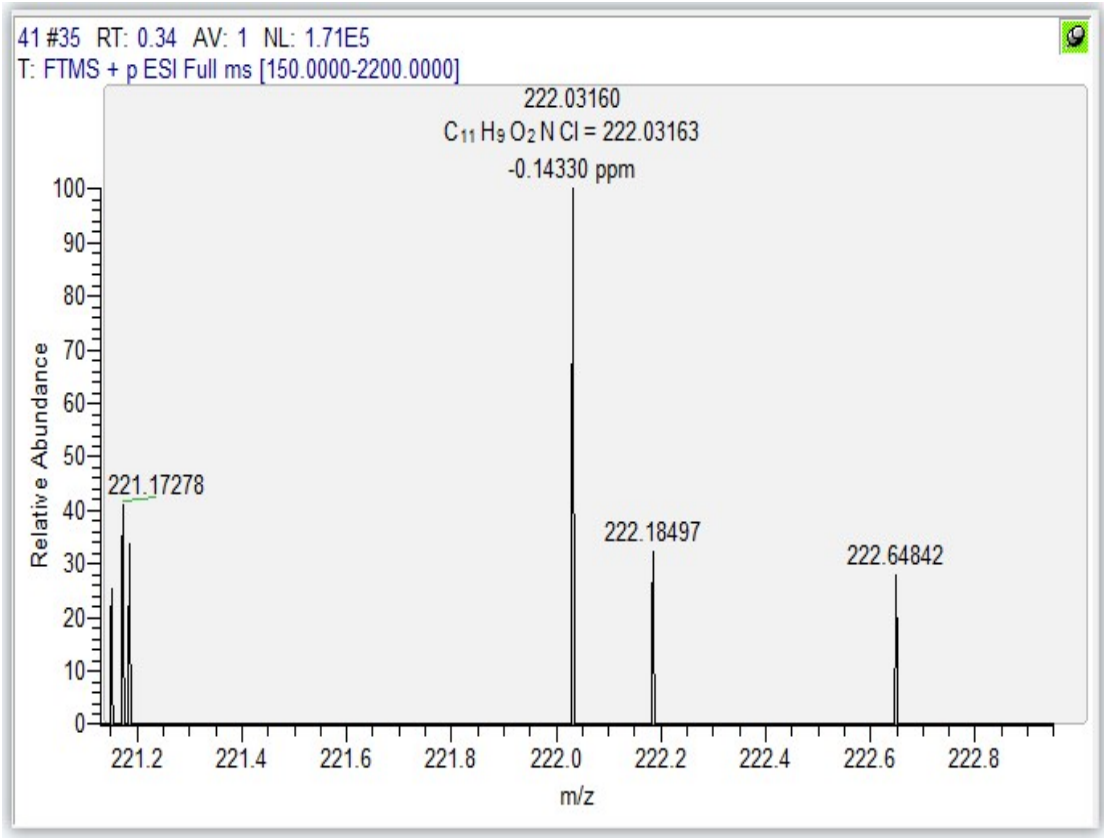

Fig. S46. HRMS spectrum of compound **5d**

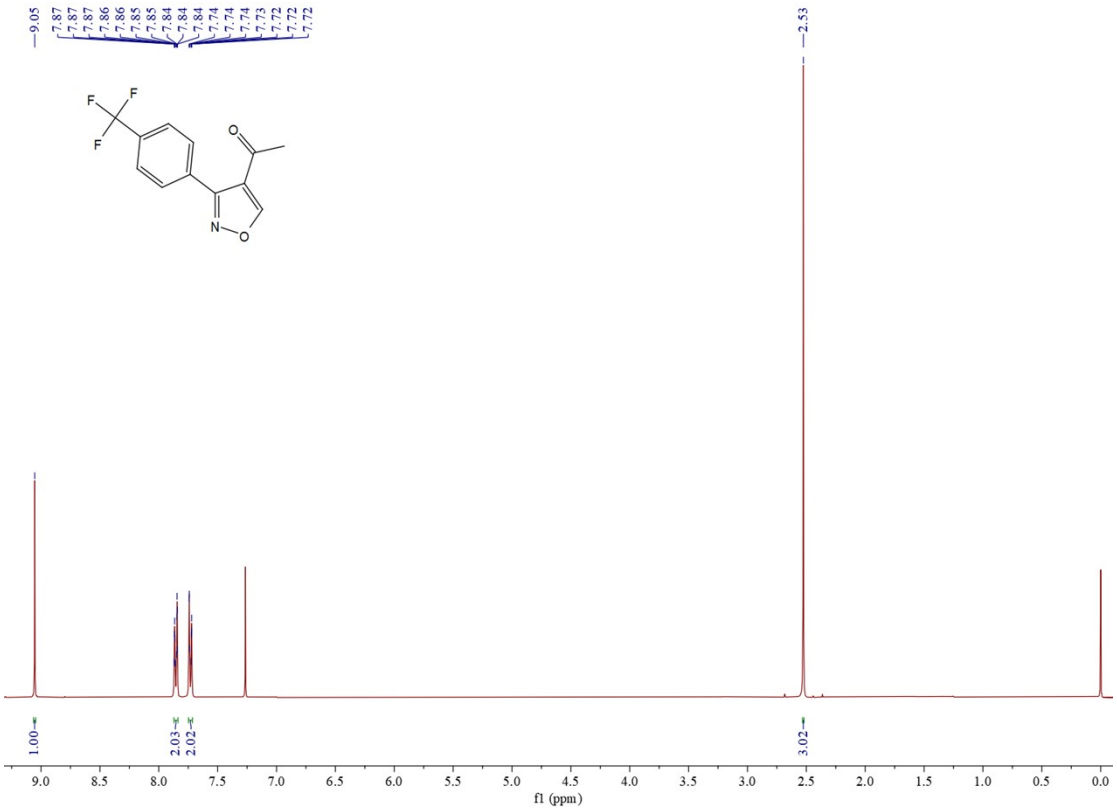

Fig. S47. ^{1}H NMR spectrum of compound **5e**

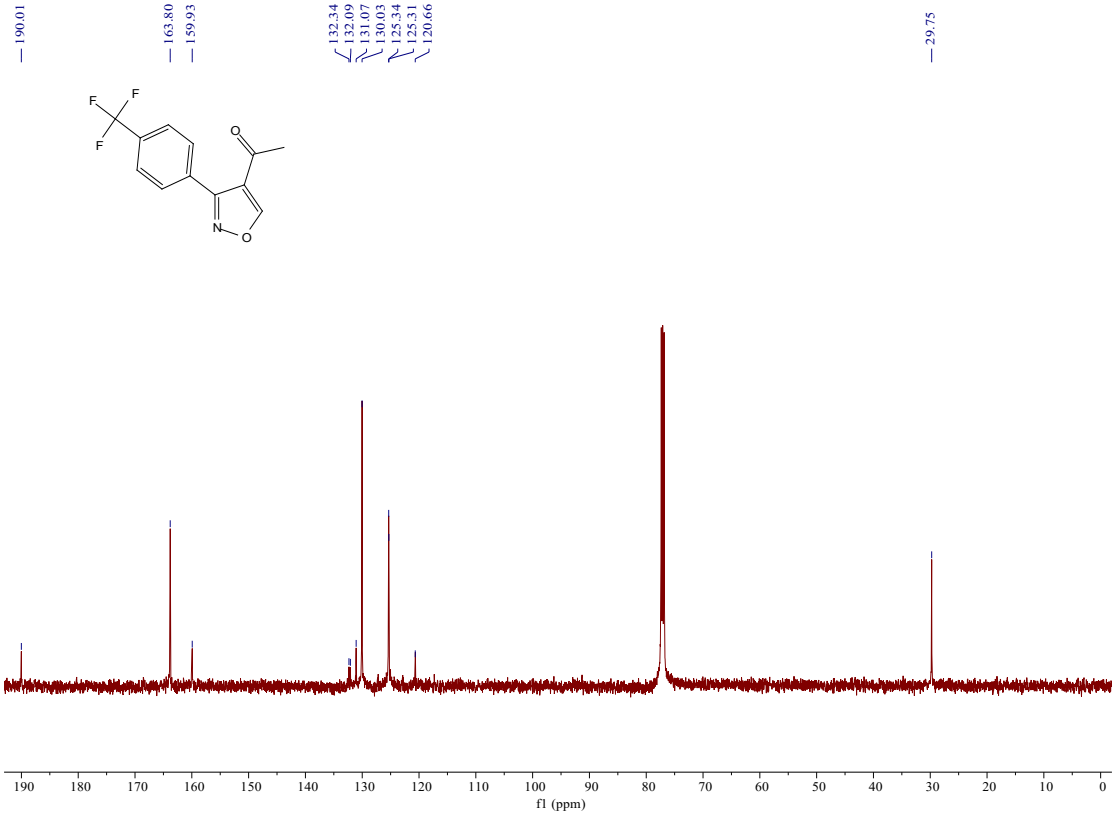

Fig. S48. ^{13}C NMR spectrum of compound **5e**

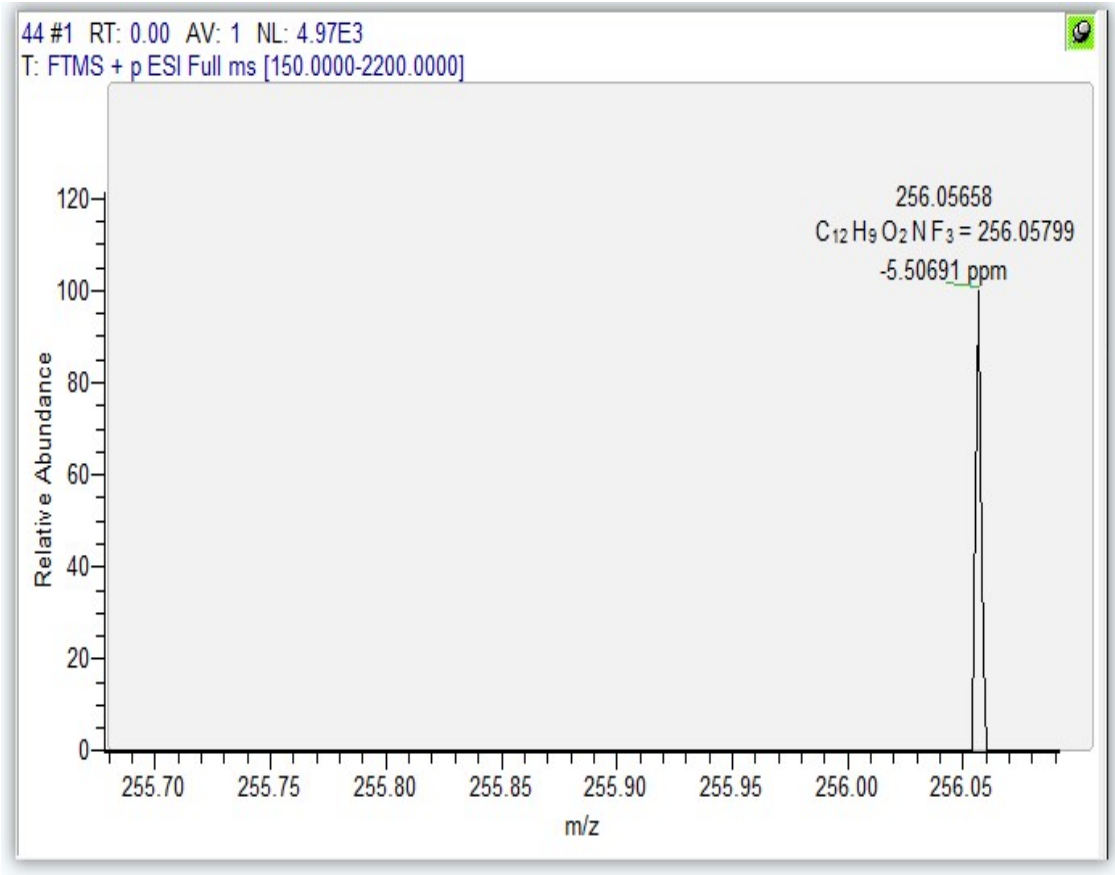

Fig. S49. HRMS spectrum of compound **5e**

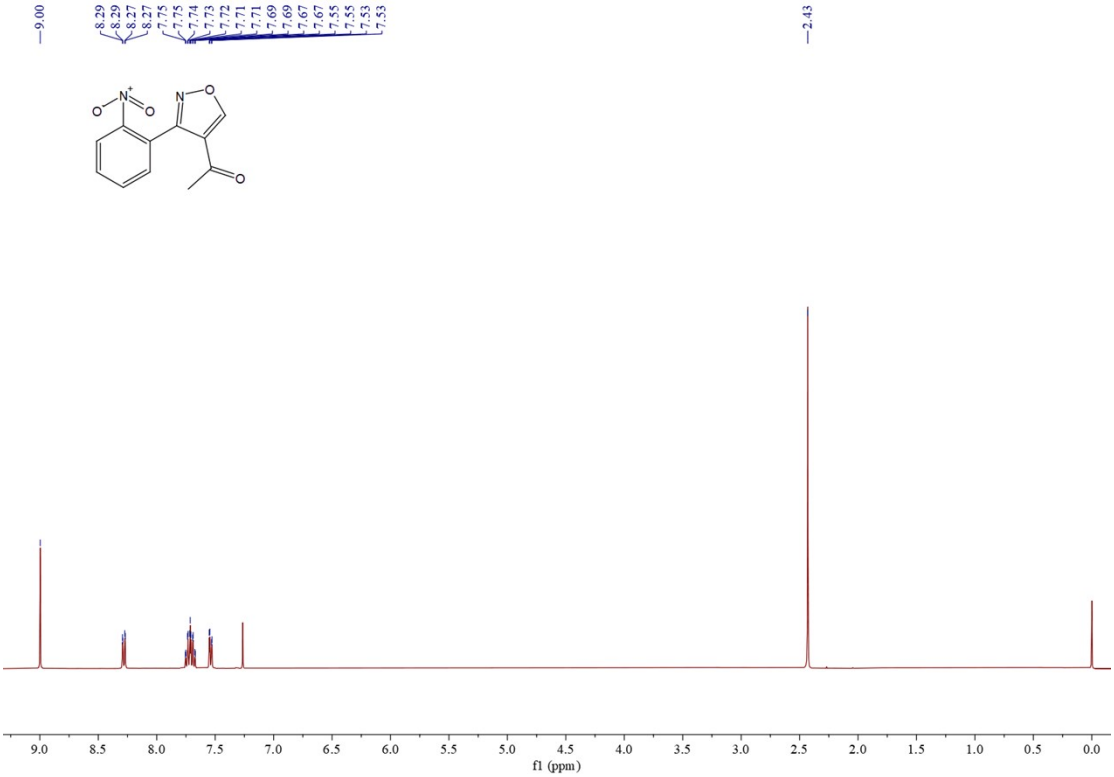

Fig. S50. [1]H NMR spectrum of compound **5f**

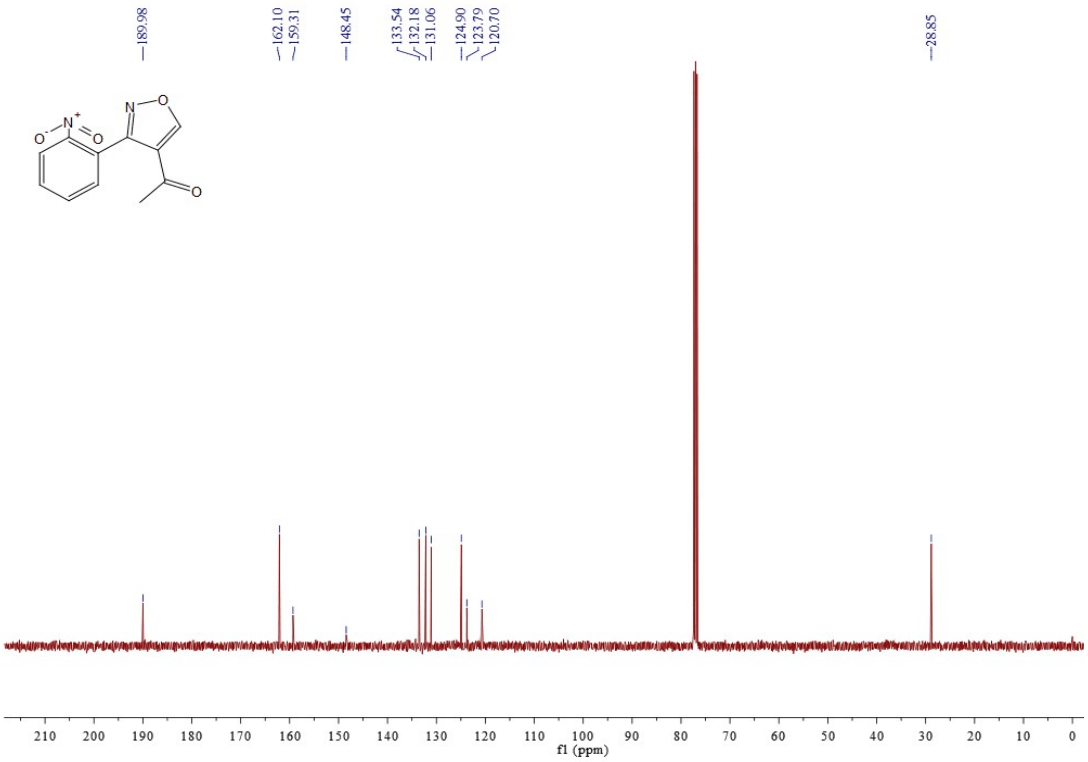

Fig. S51. ^{13}C NMR spectrum of compound **5f**

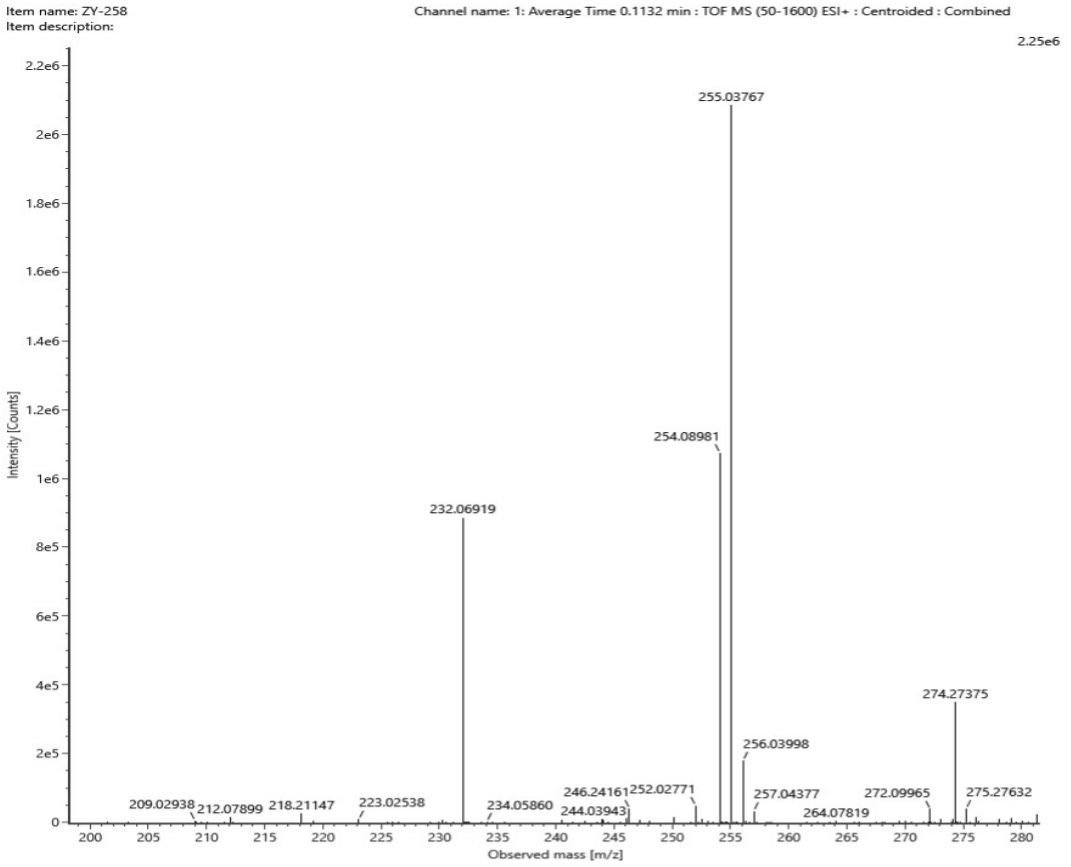

Fig. S52. HRMS spectrum of compound **5f**

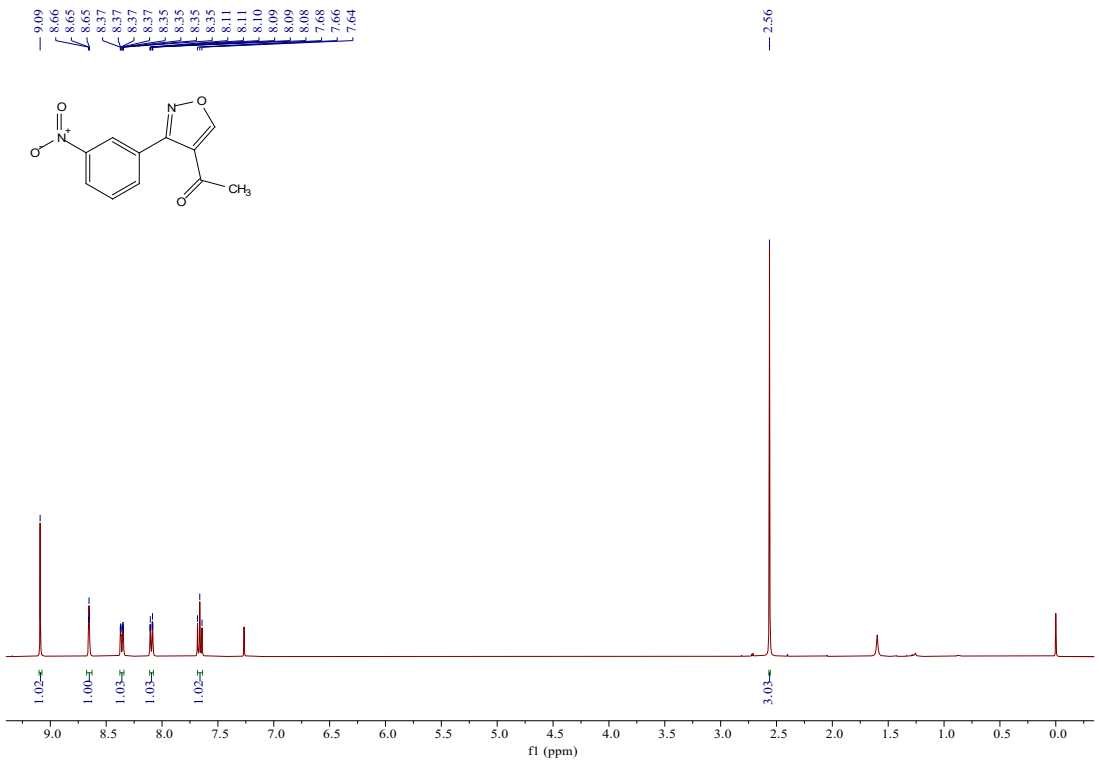

Fig. S53. ^{1}H NMR spectrum of compound **5g**

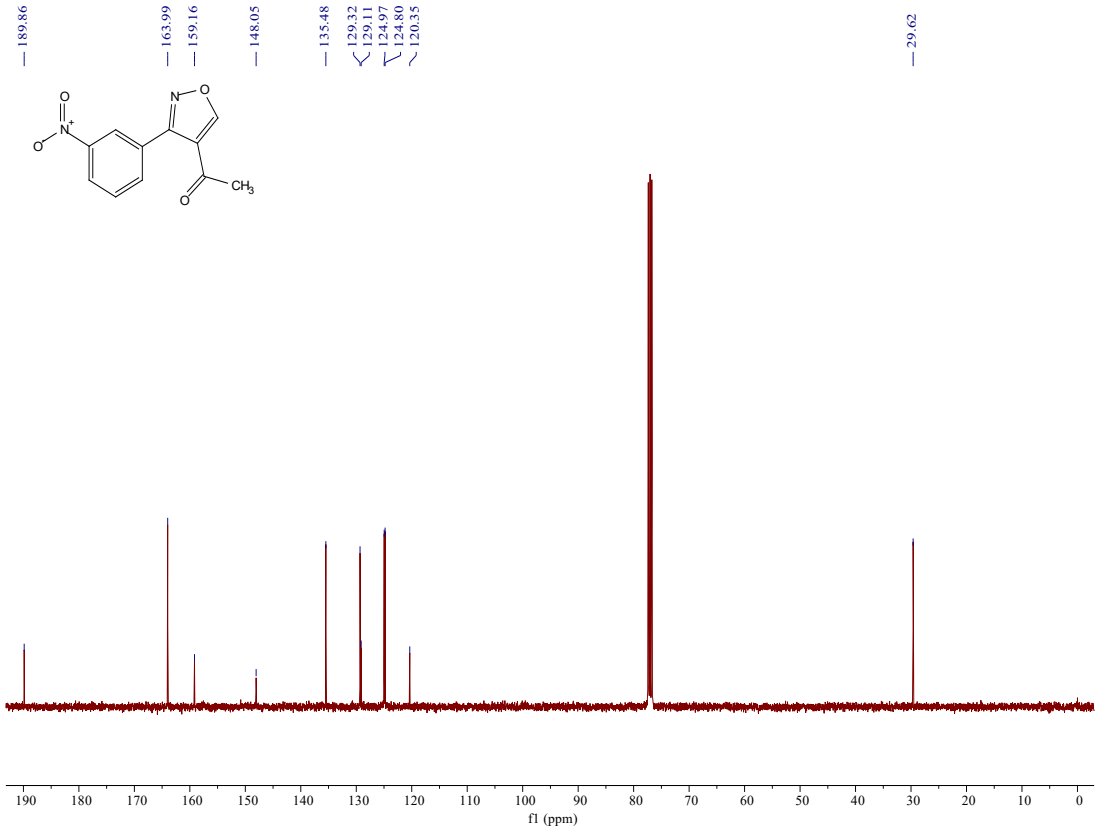

Fig. S54. ^{13}C NMR spectrum of compound **5g**

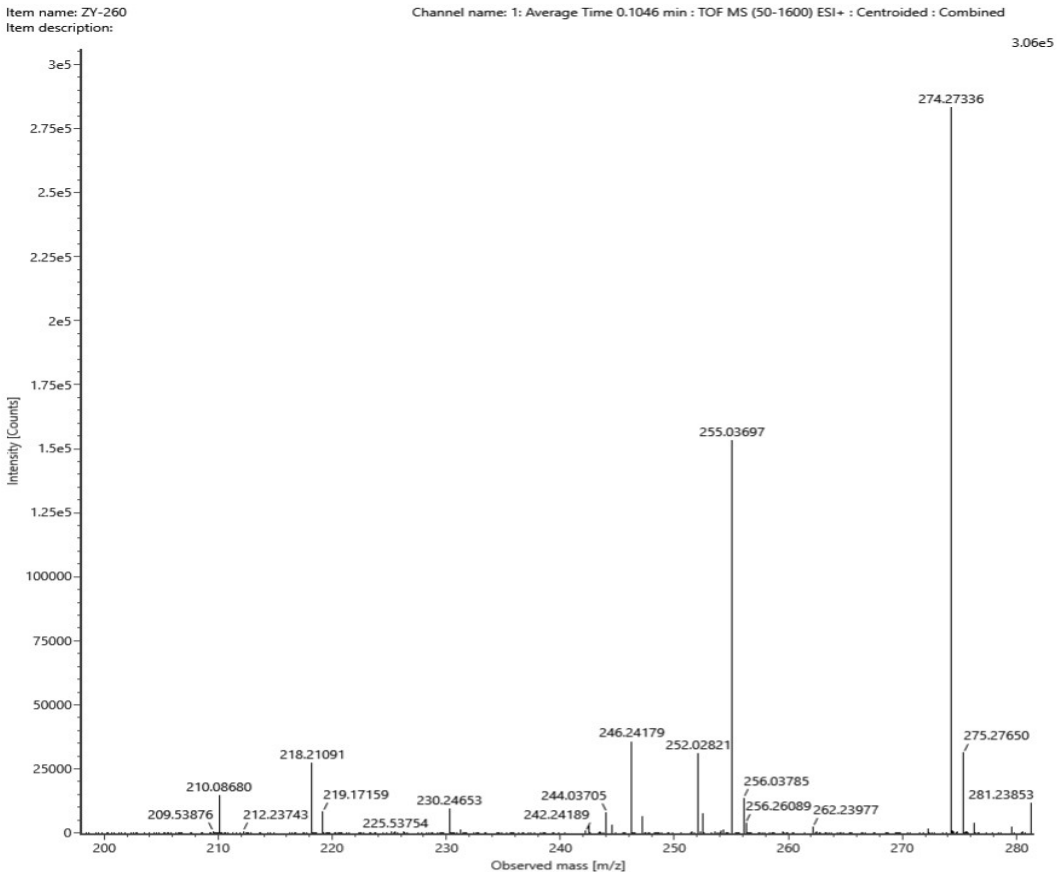

Fig. S55. HRMS spectrum of compound **5g**

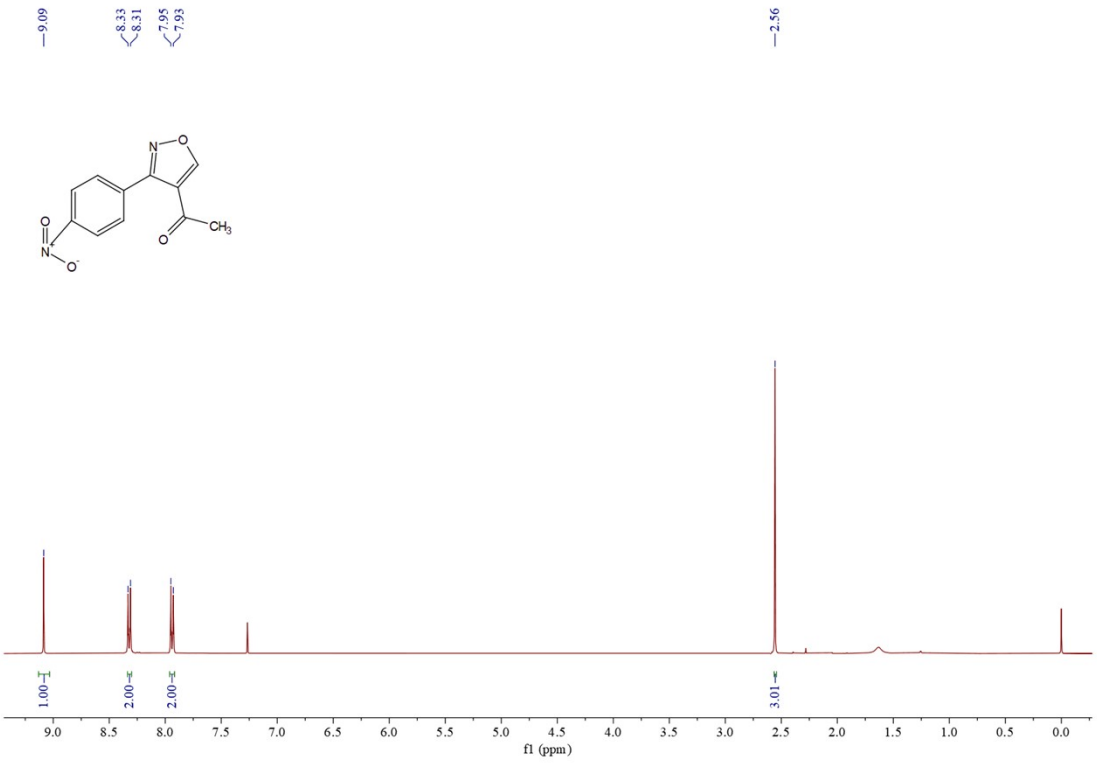

Fig. S56. ^{1}H NMR spectrum of compound **5h**

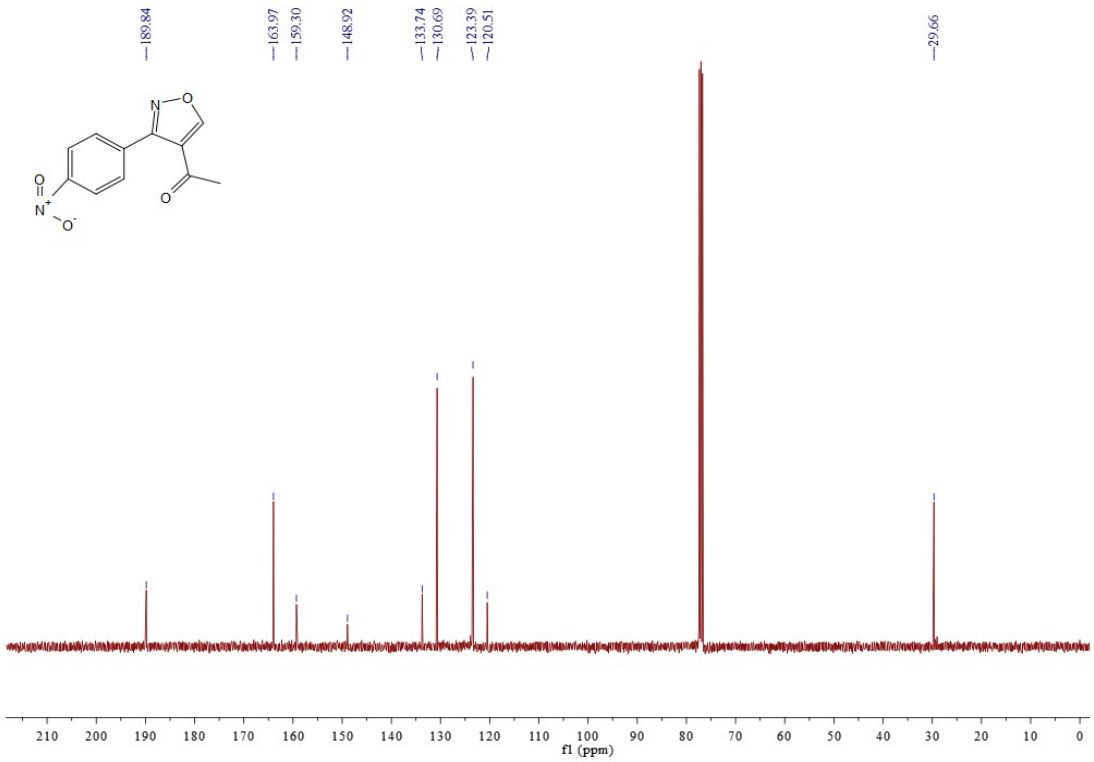

Fig. S57. ^{13}C NMR spectrum of compound **5h**

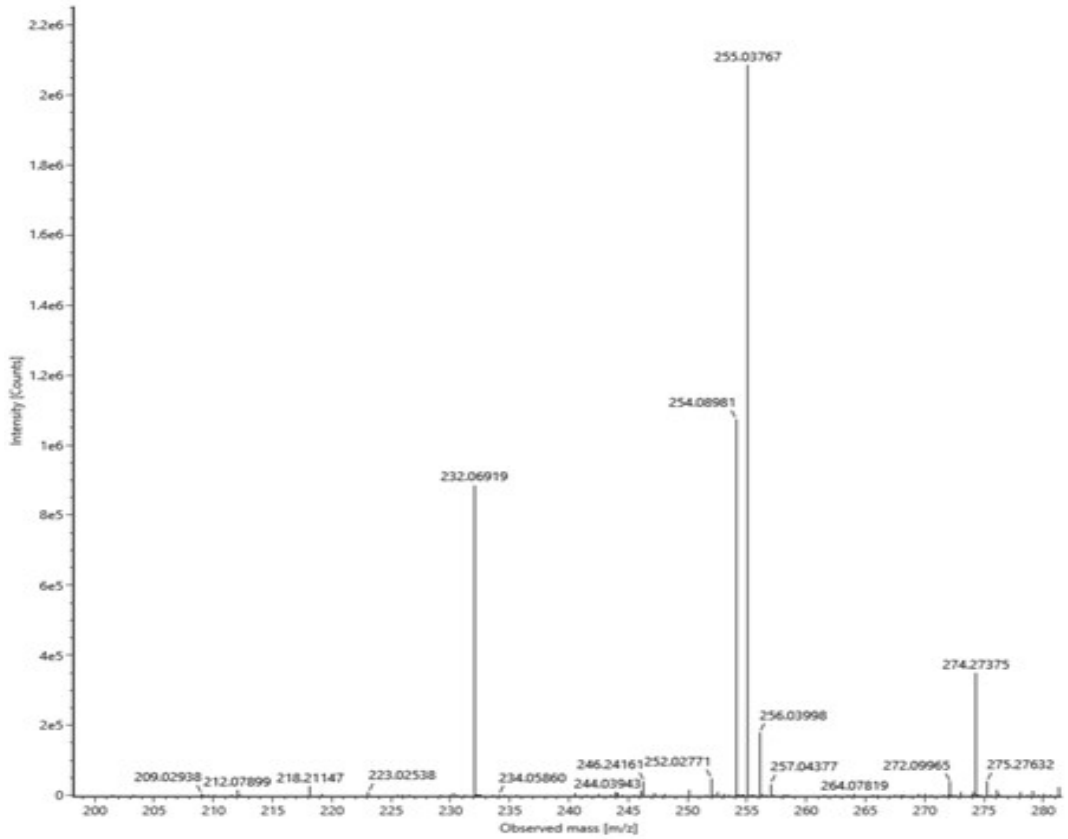

Fig. S58. HRMS spectrum of compound **5h**

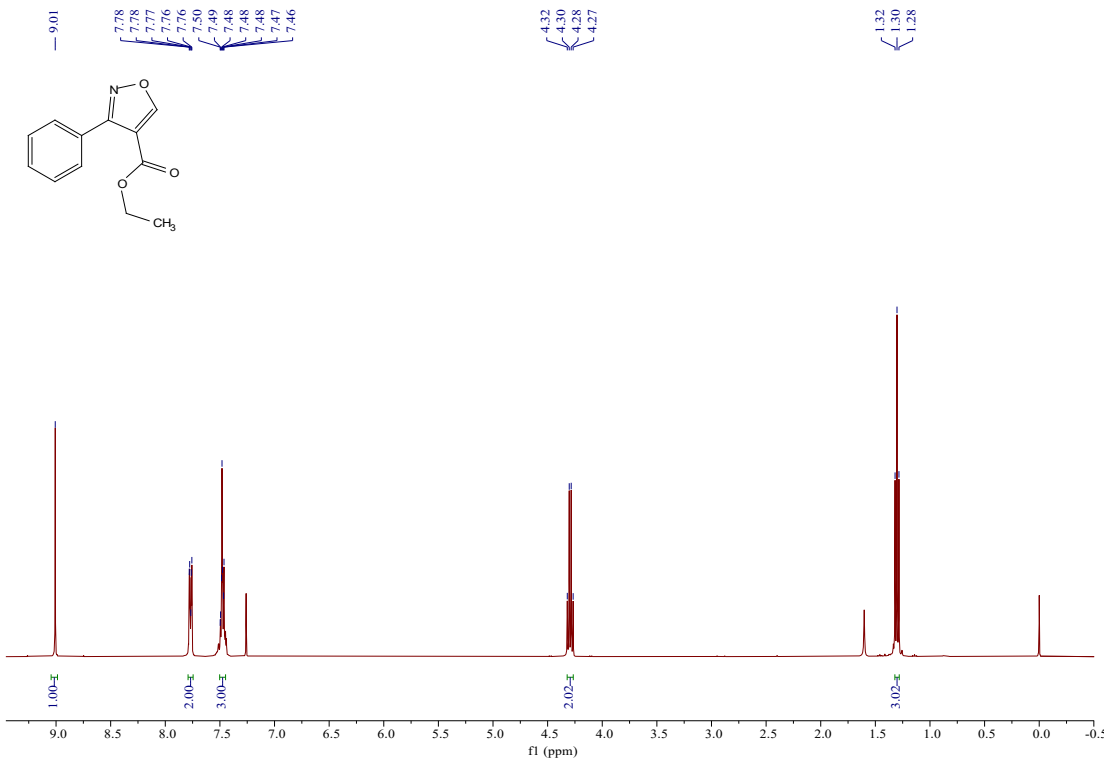

Fig. S59. ^{1}H NMR spectrum of compound **5i**

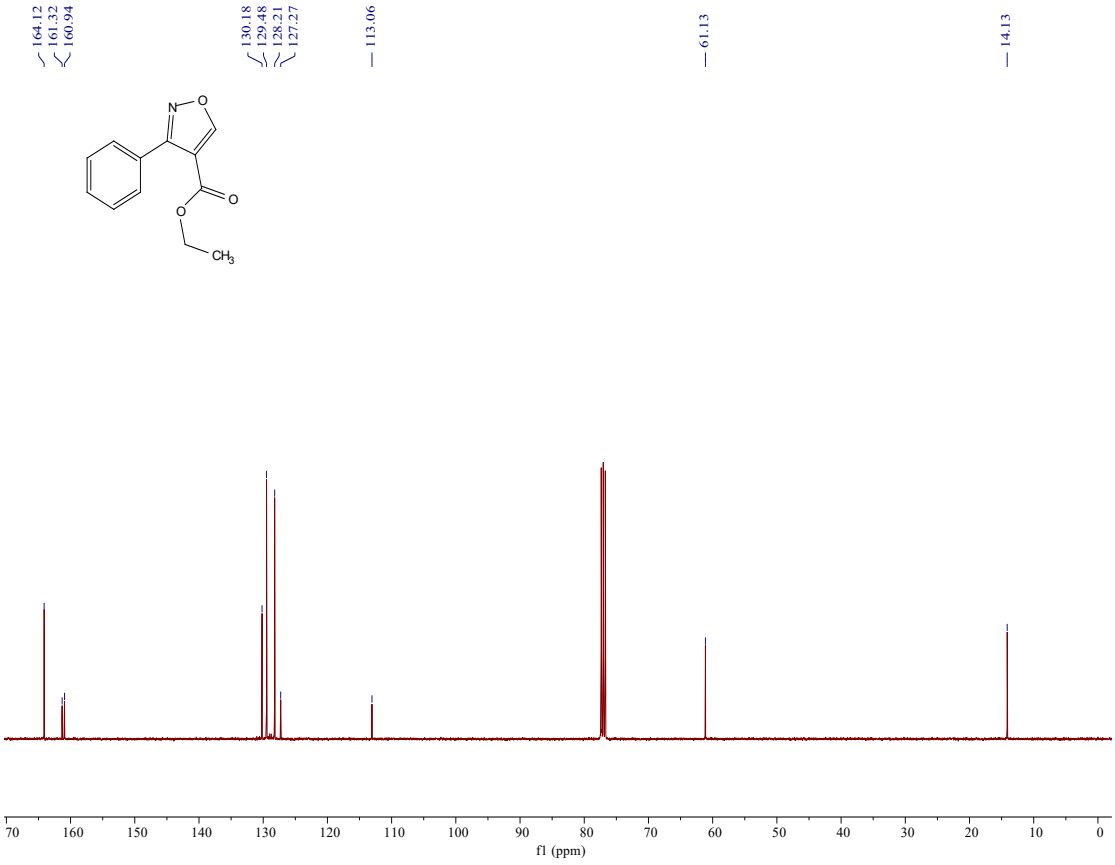

Fig. S60. ^{13}C NMR spectrum of compound **5i**

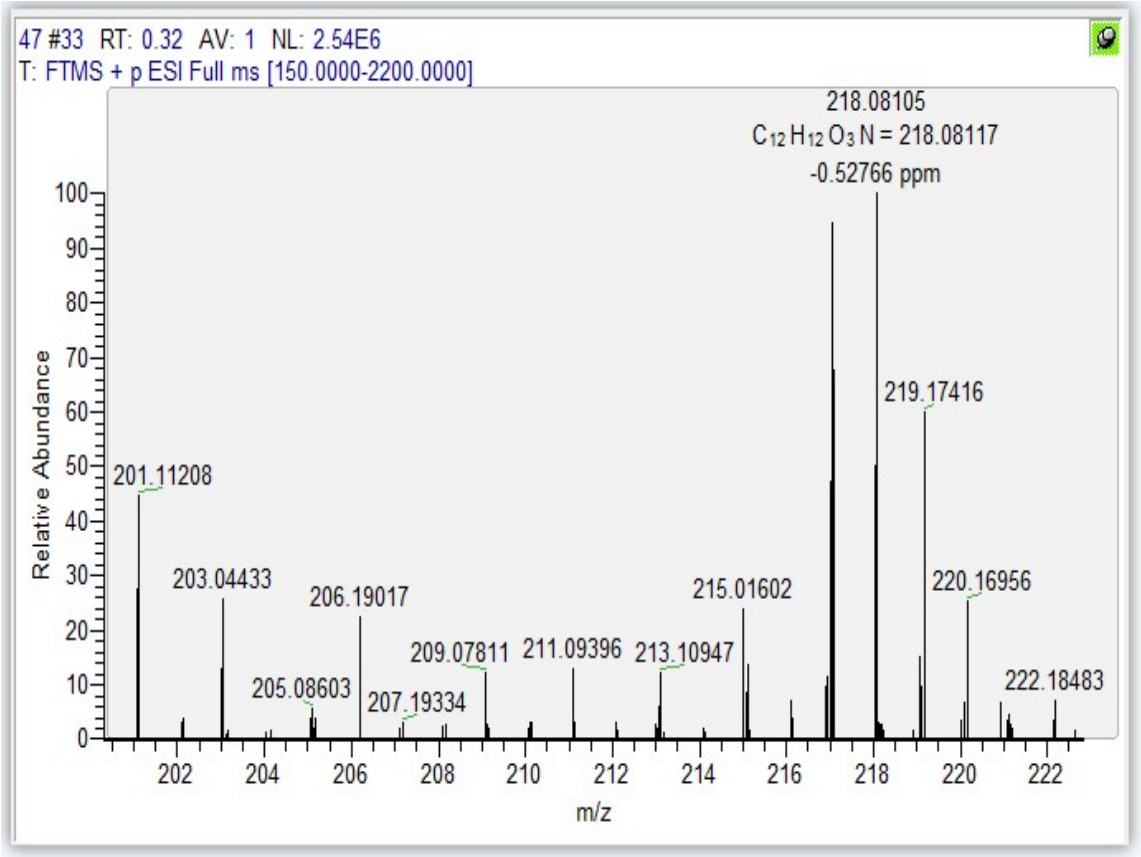

Fig. S61. HRMS spectrum of compound **5i**

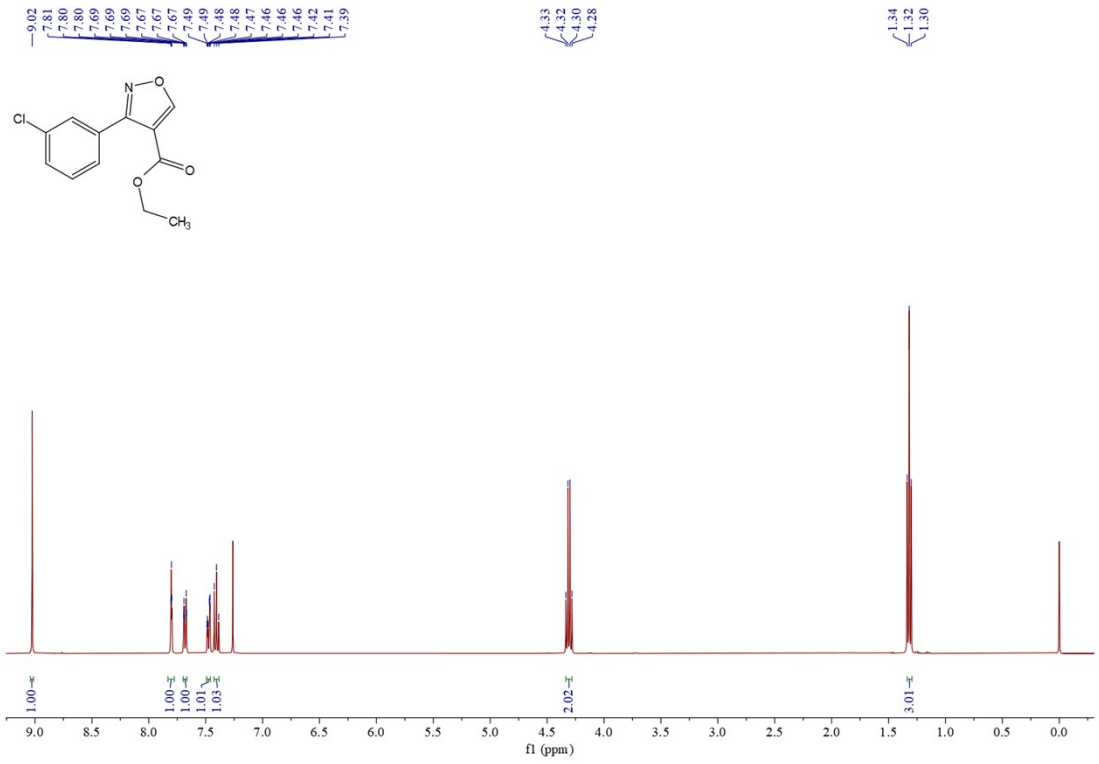

Fig. S62. ^{1}H NMR spectrum of compound **5j**

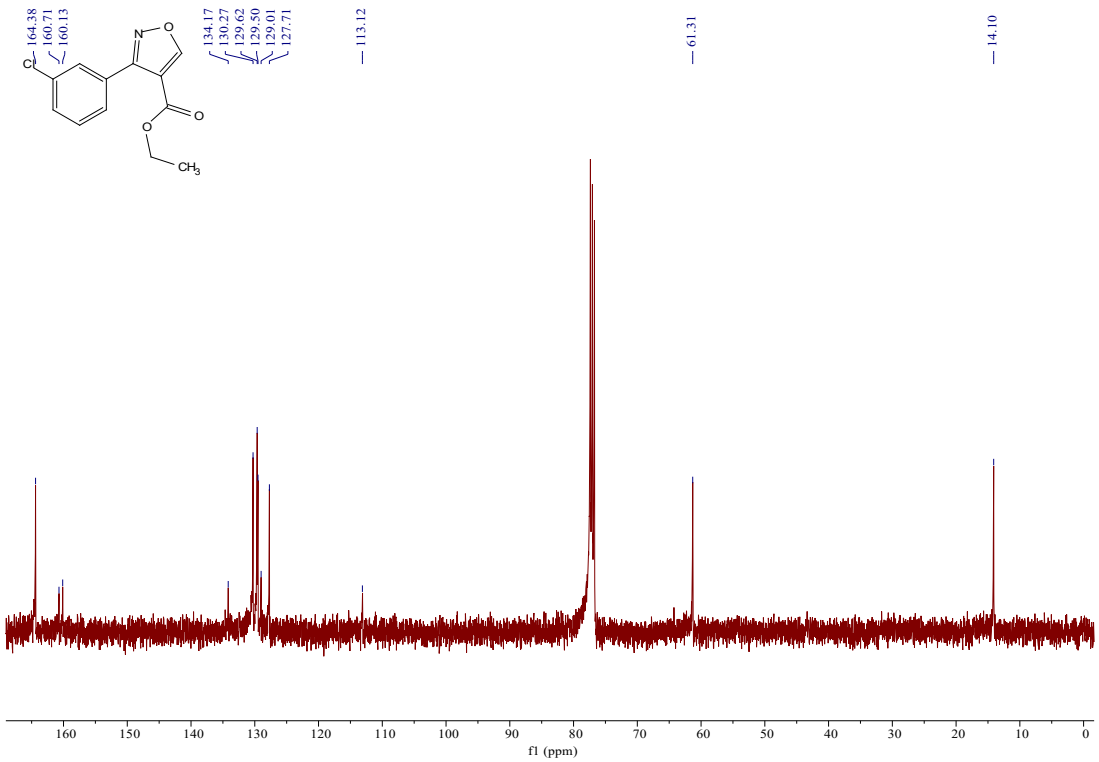

Fig. S63. ^{13}C NMR spectrum of compound **5j**

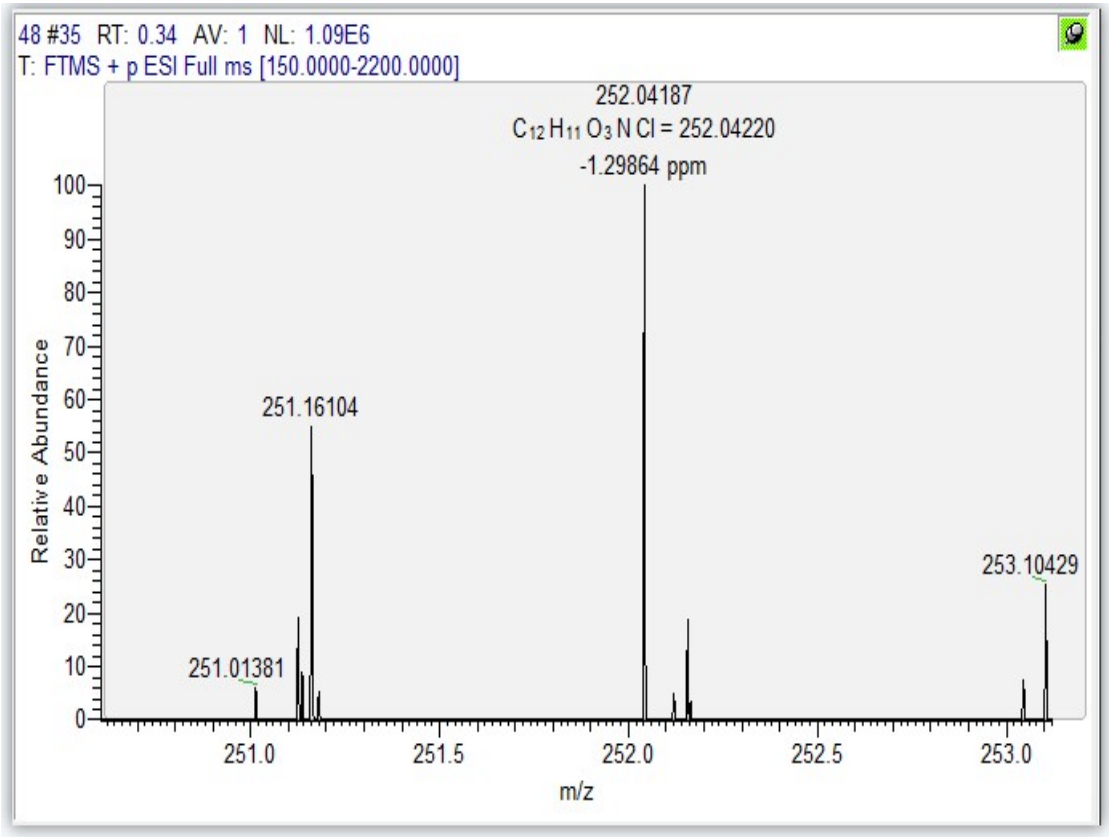

Fig. S64. HRMS spectrum of compound **5j**

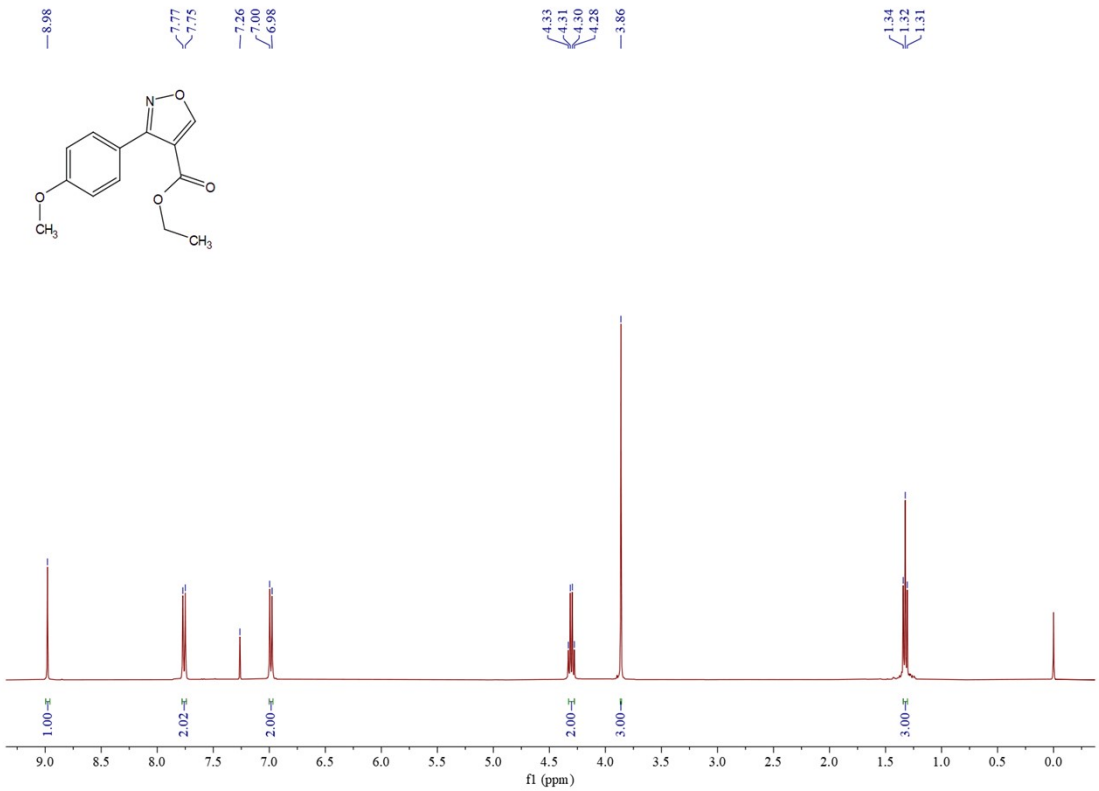

Fig. S65. [1]H NMR spectrum of compound **5k**

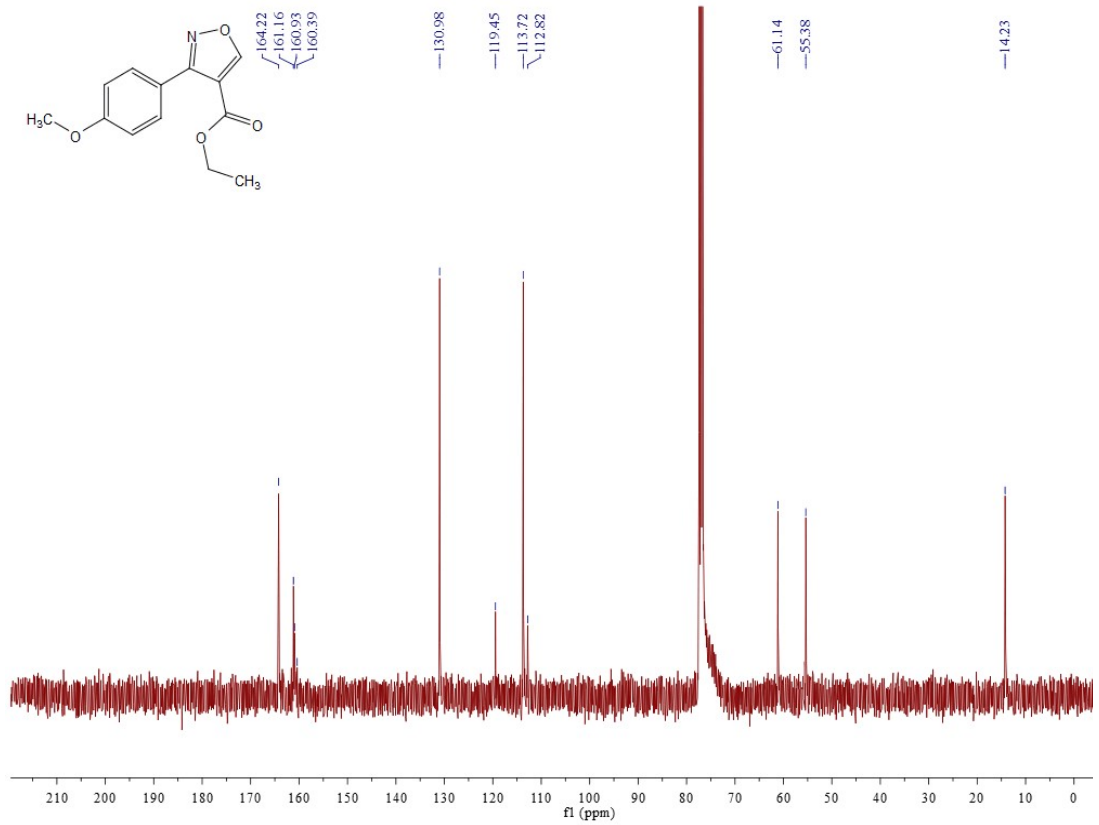

Fig. S66. [13]C NMR spectrum of compound **5k**

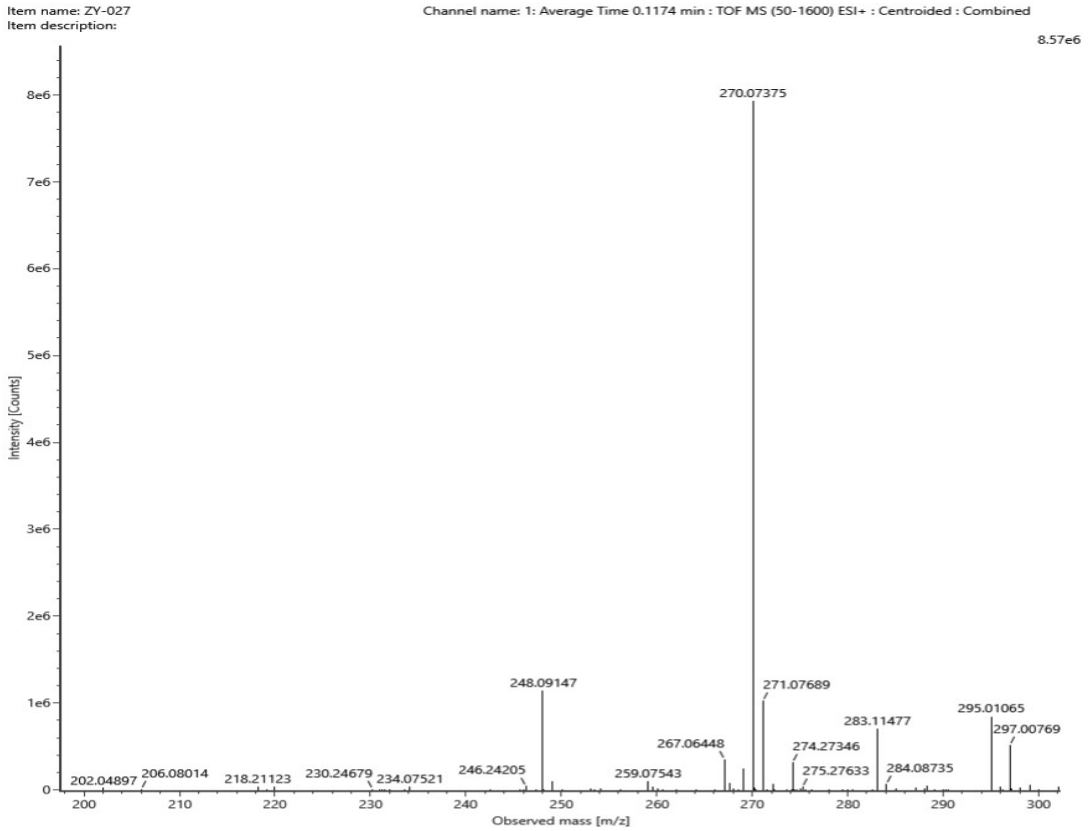

Fig. S67. HRMS spectrum of compound **5k**

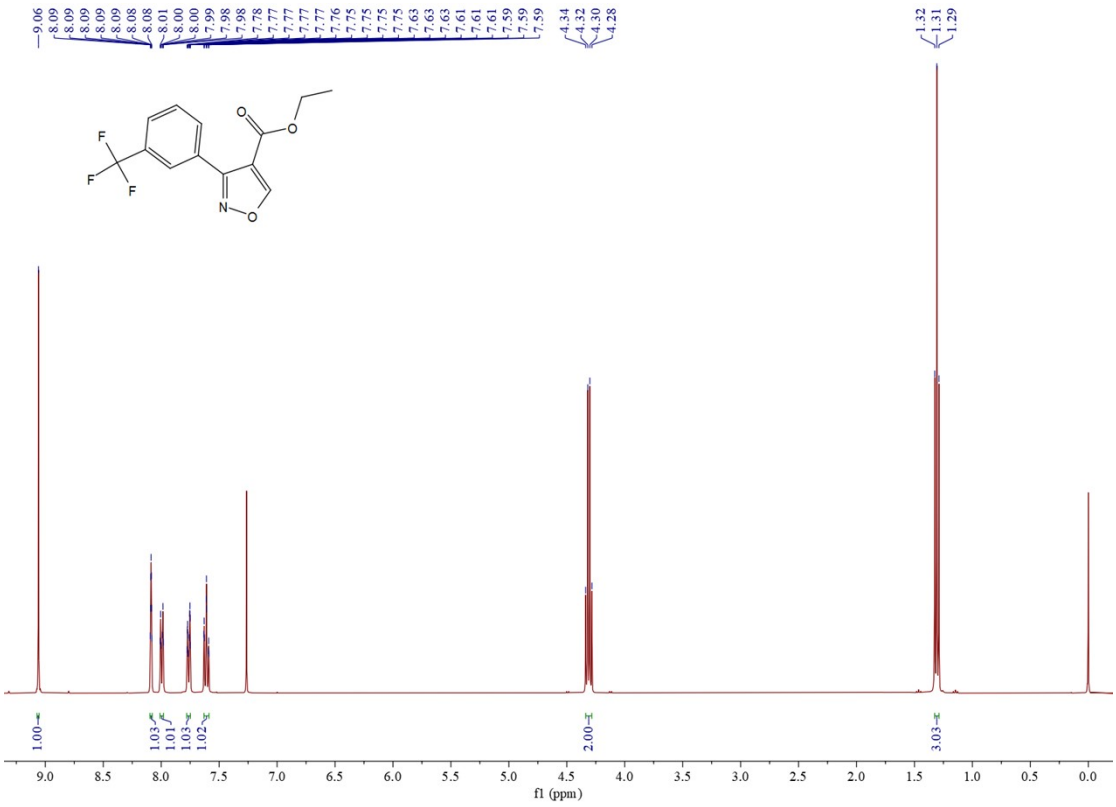

Fig. S68. ^{1}H NMR spectrum of compound **5l**

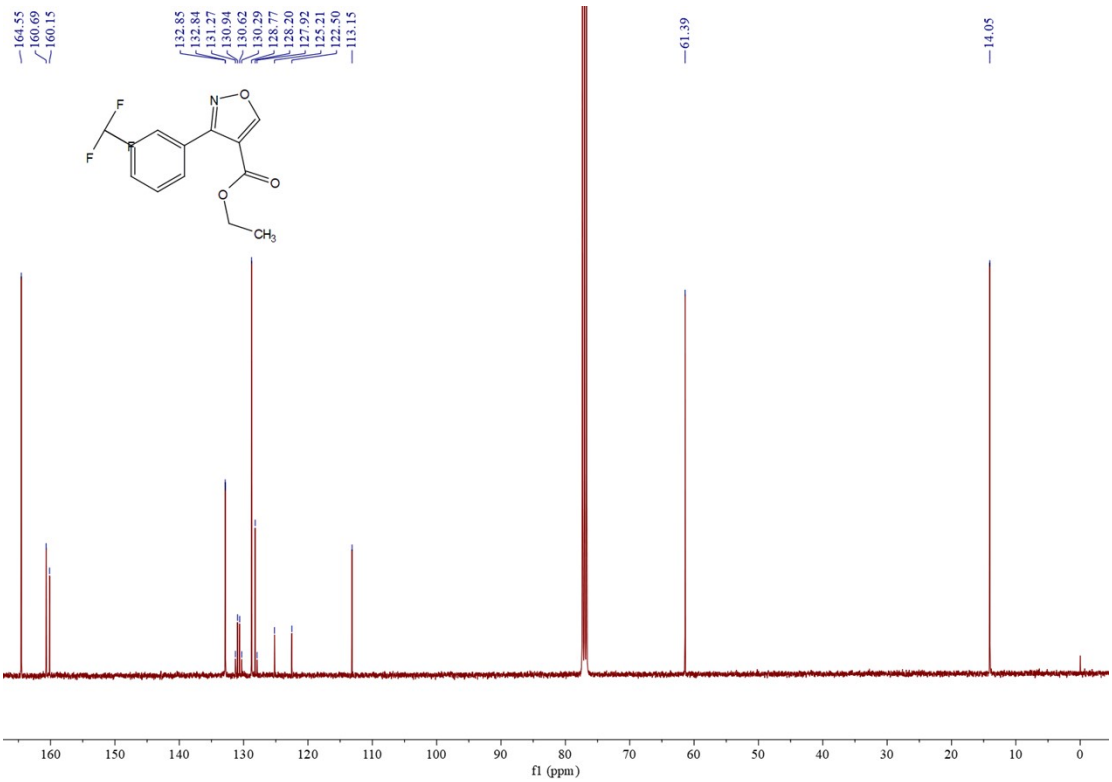

Fig. S69. ^{13}C NMR spectrum of compound **5l**

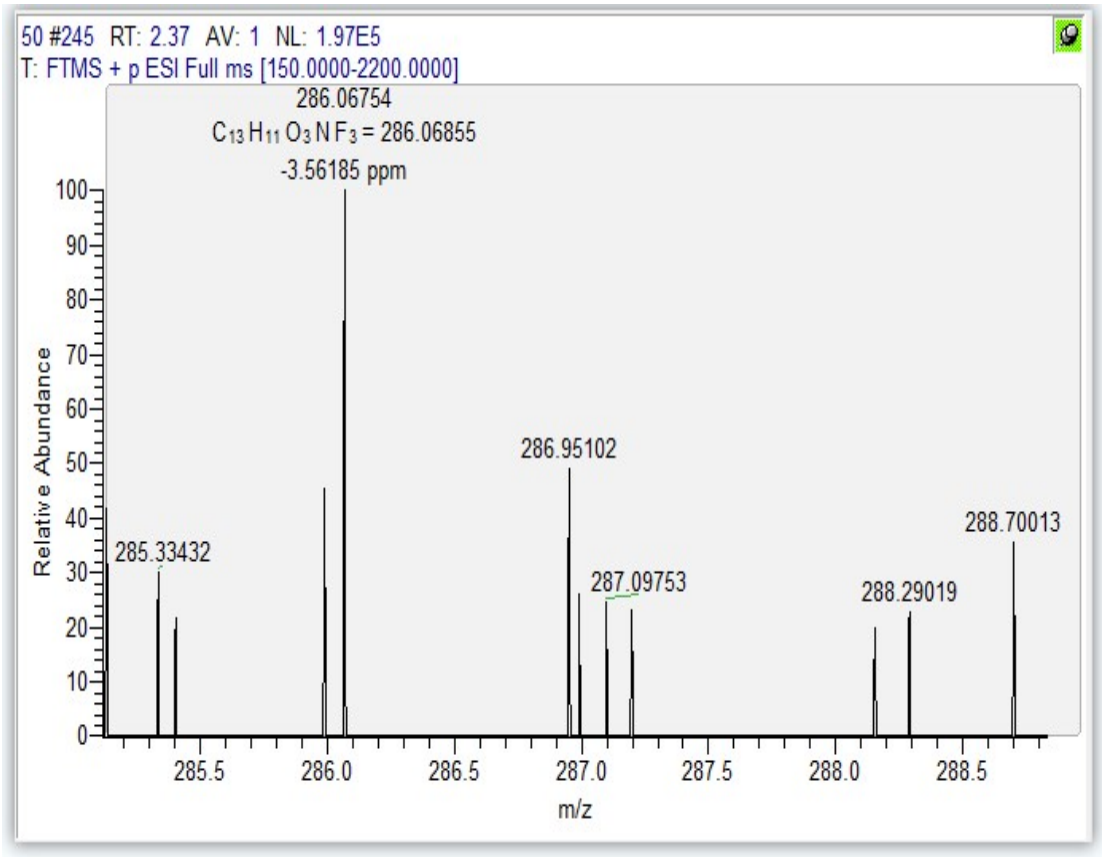

Fig. S70. HRMS spectrum of compound **5l**

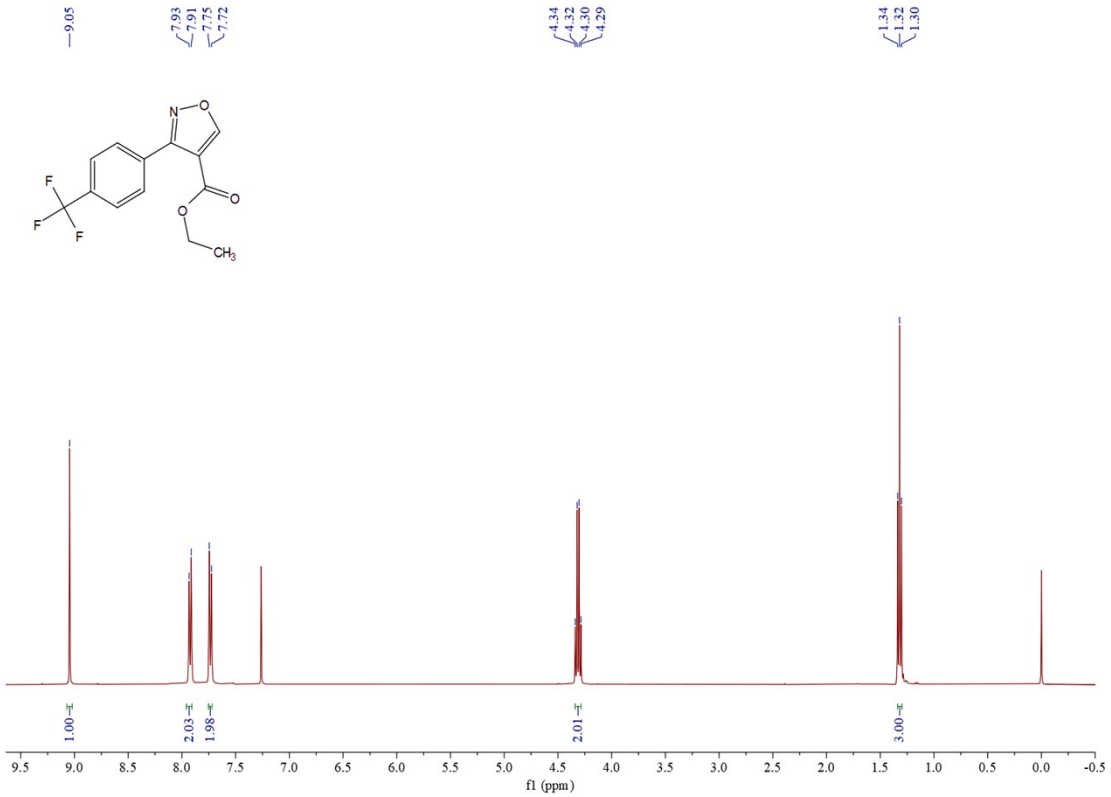

Fig. S71. [1]H NMR spectrum of compound **5m**

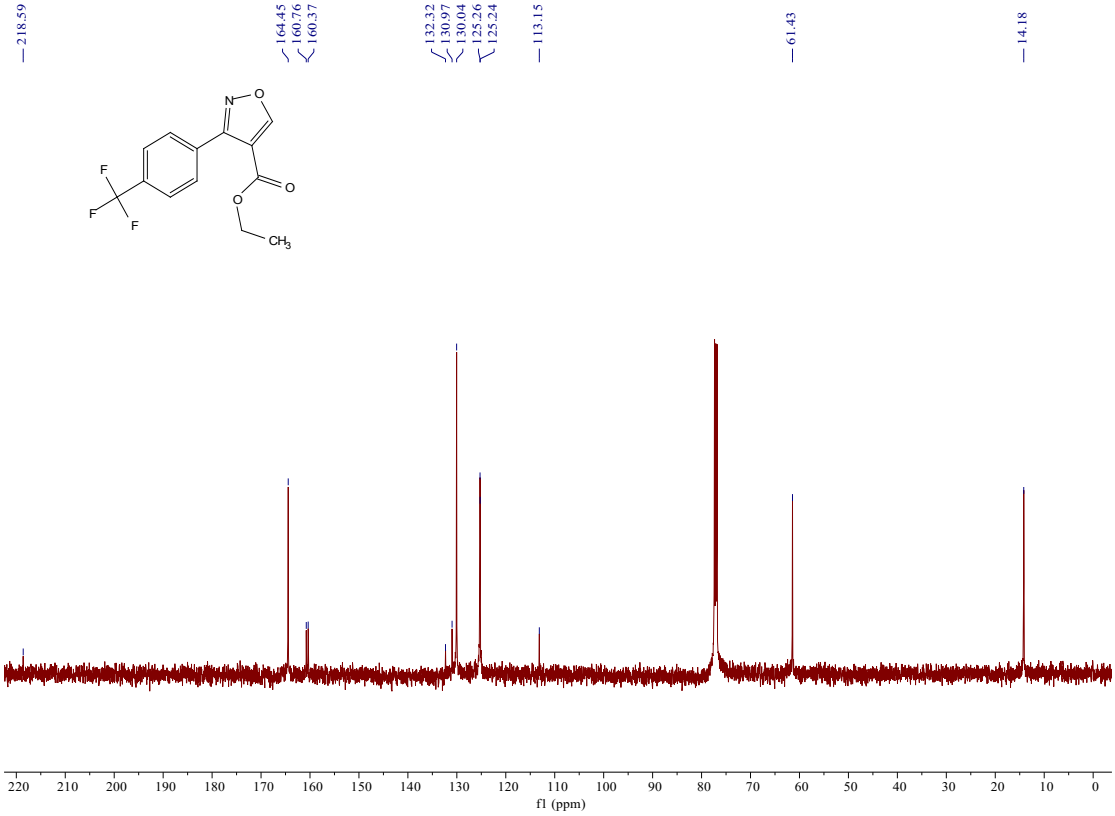

Fig. S72. [13]C NMR spectrum of compound **5m**

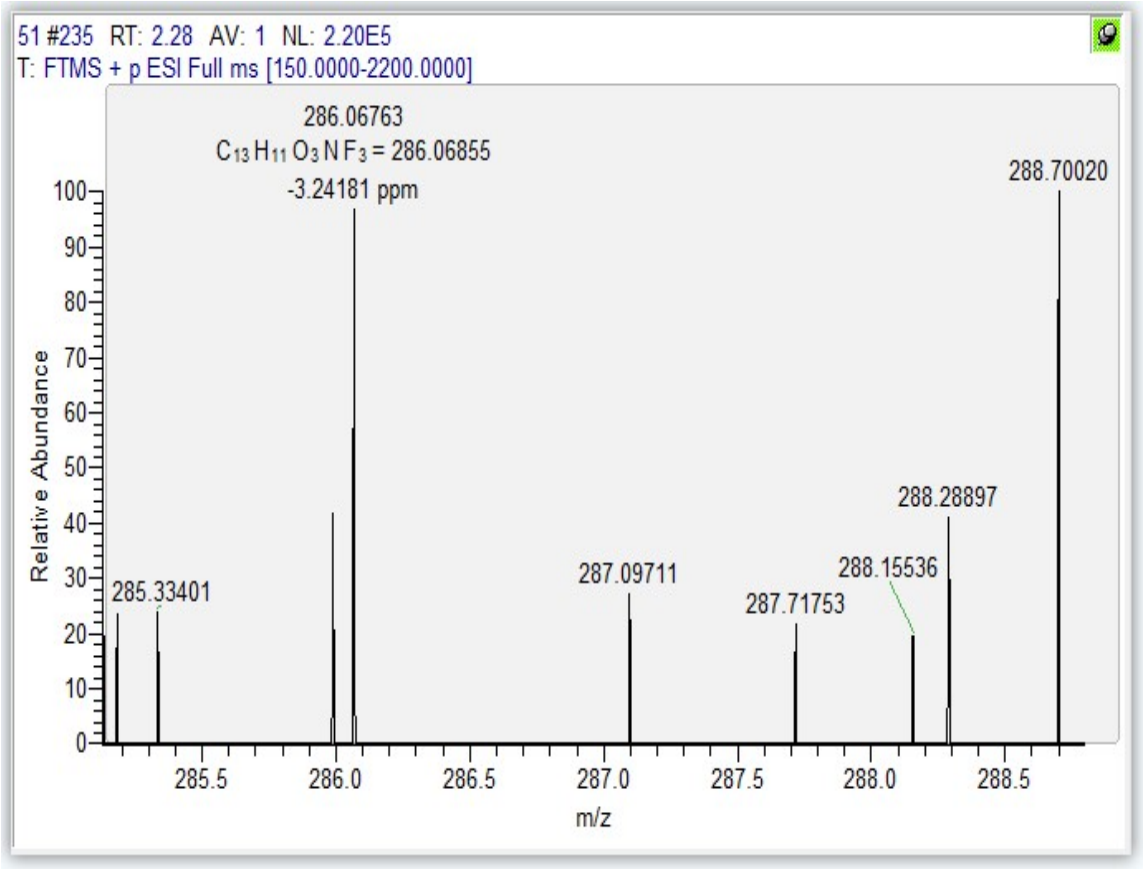

Fig. S73. HRMS spectrum of compound **5m**

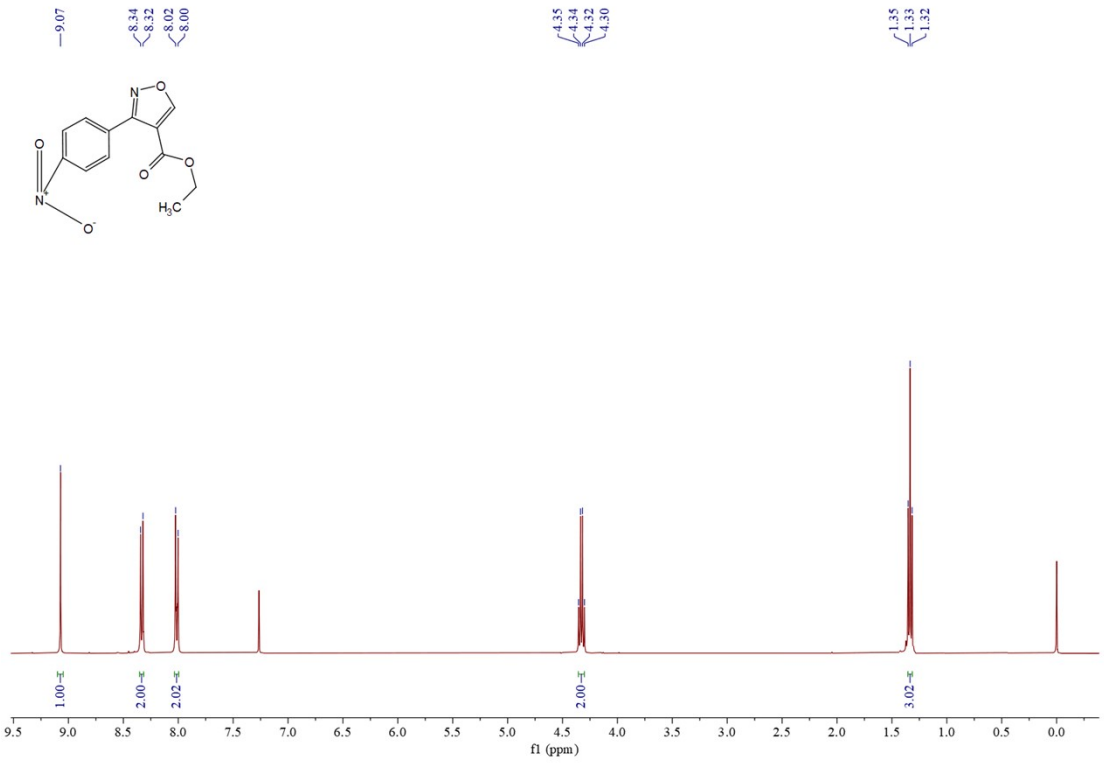

Fig. S74. [1]H NMR spectrum of compound **5n**

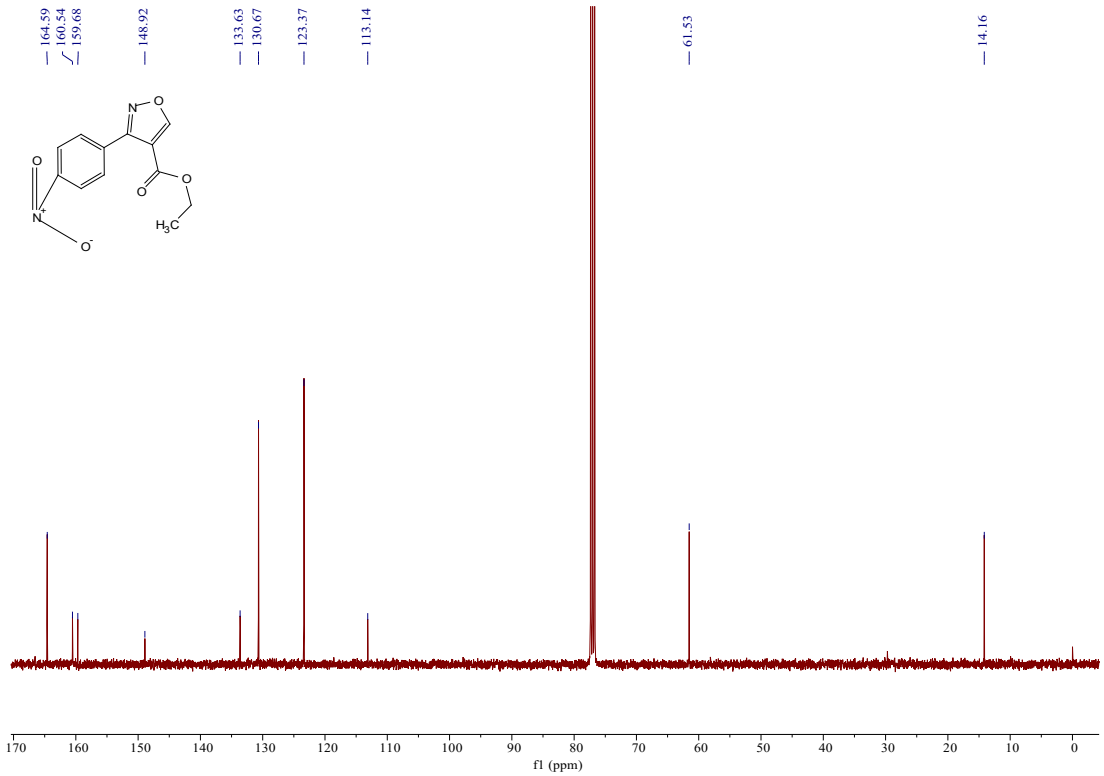

Fig. S75. ^{13}C NMR spectrum of compound **5n**

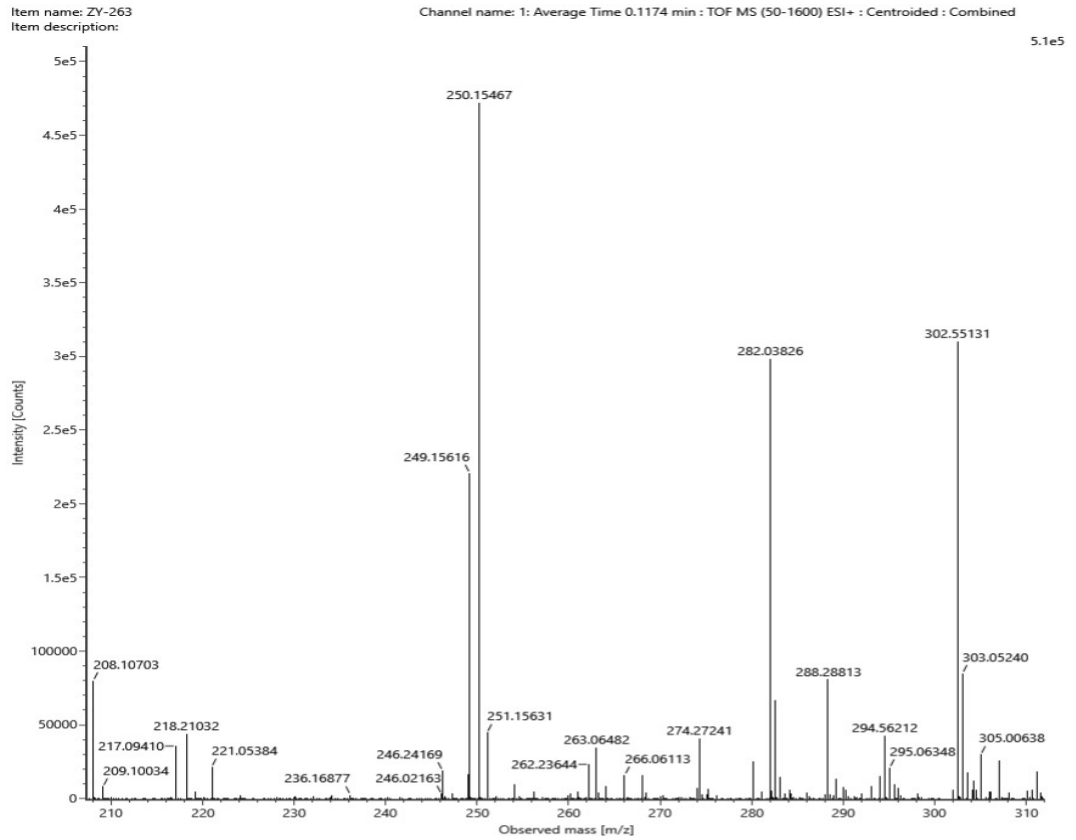

Fig. S76. HRMS spectrum of compound **5n**

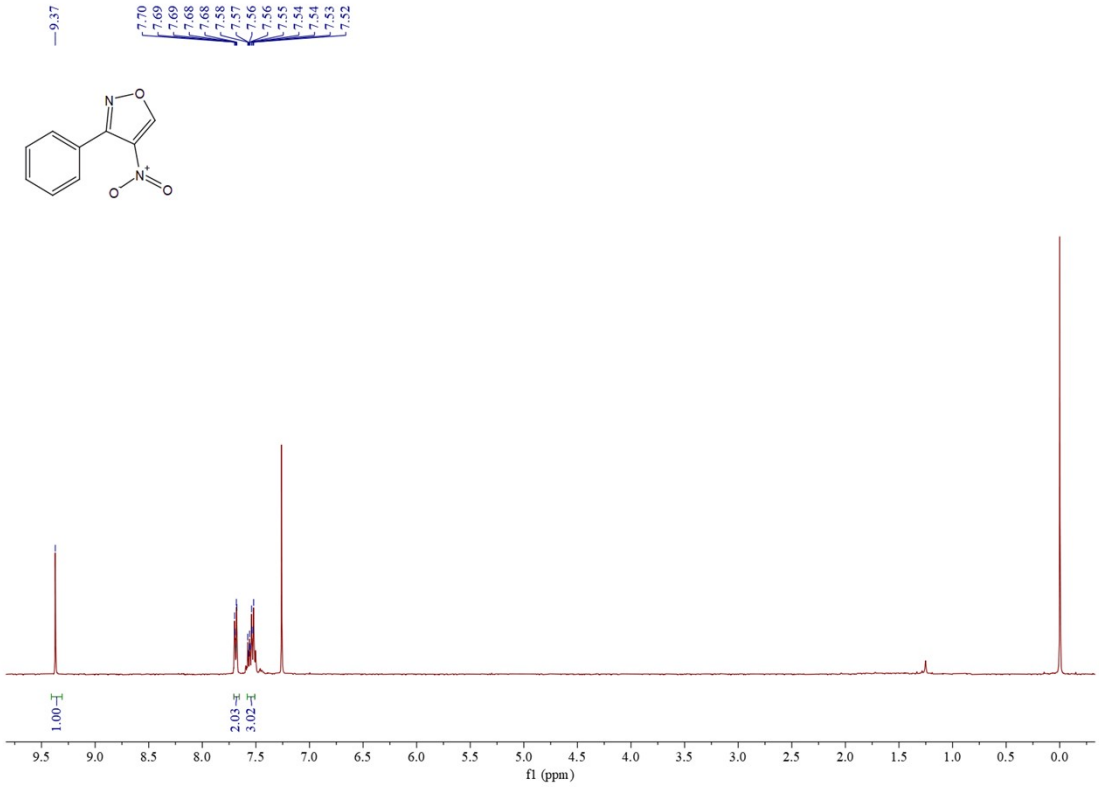

Fig. S77. [1]H NMR spectrum of compound **5o**

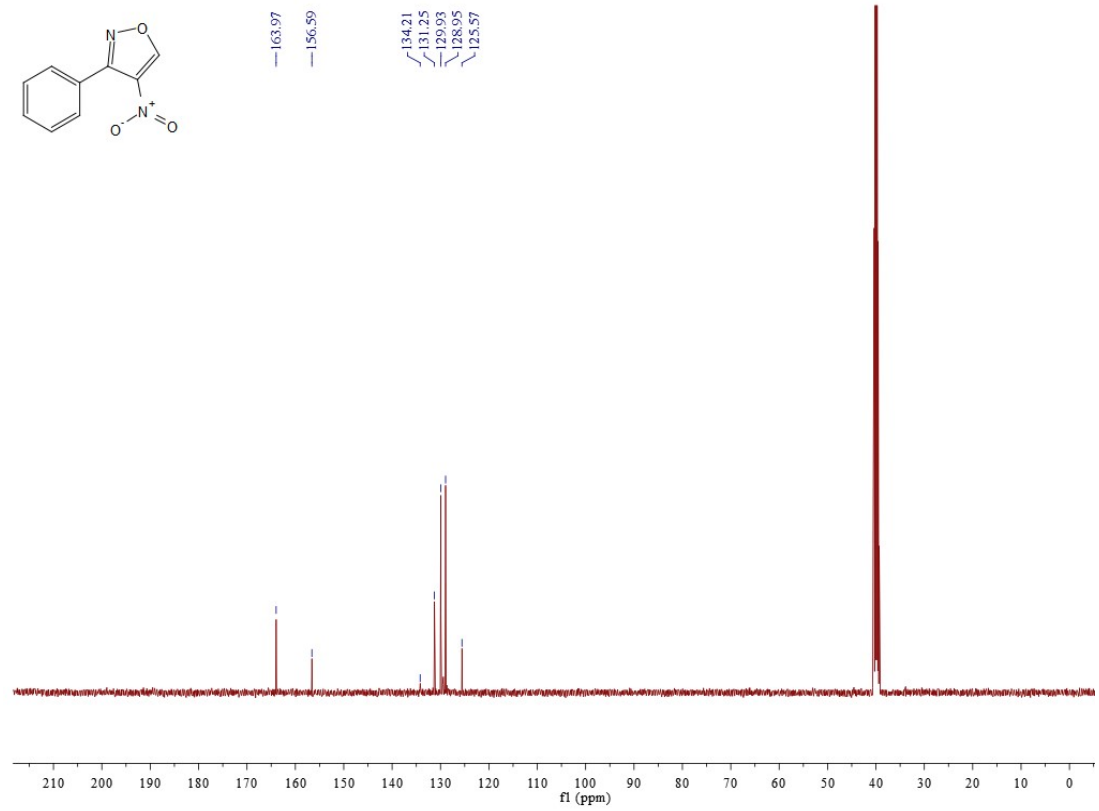

Fig. S78. [13]C NMR spectrum of compound **5o**

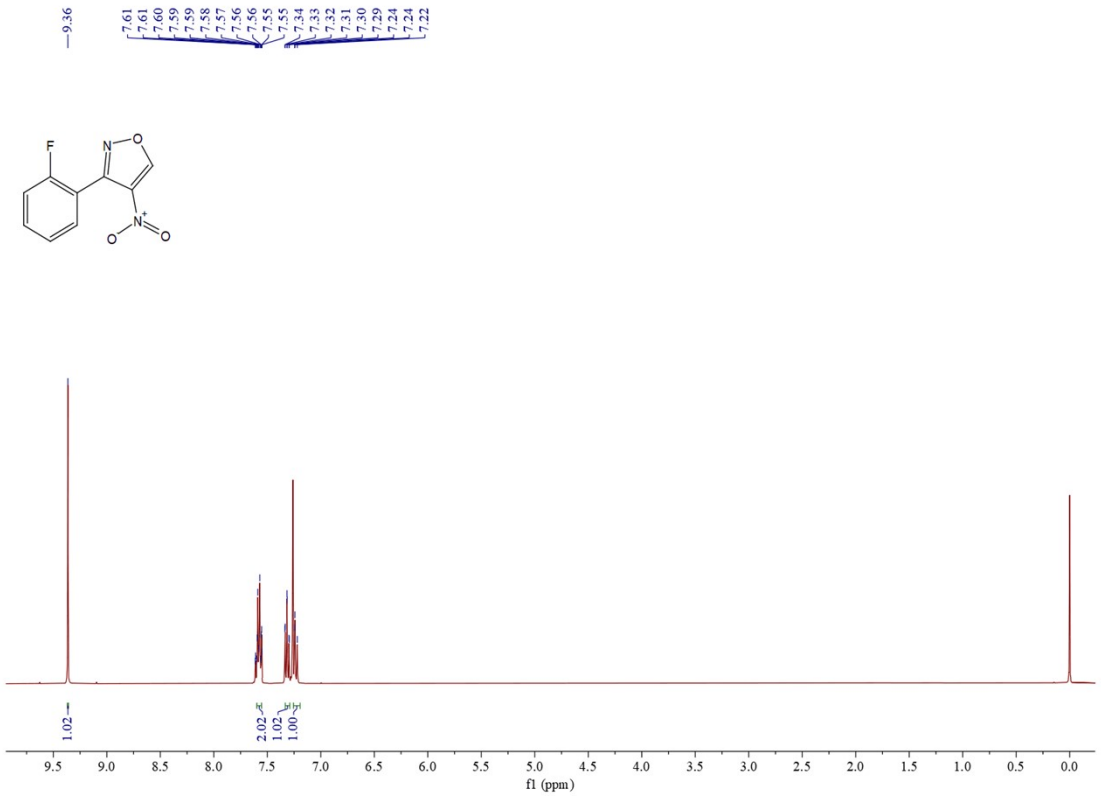

Fig. S79. ^{1}H NMR spectrum of compound **5p**

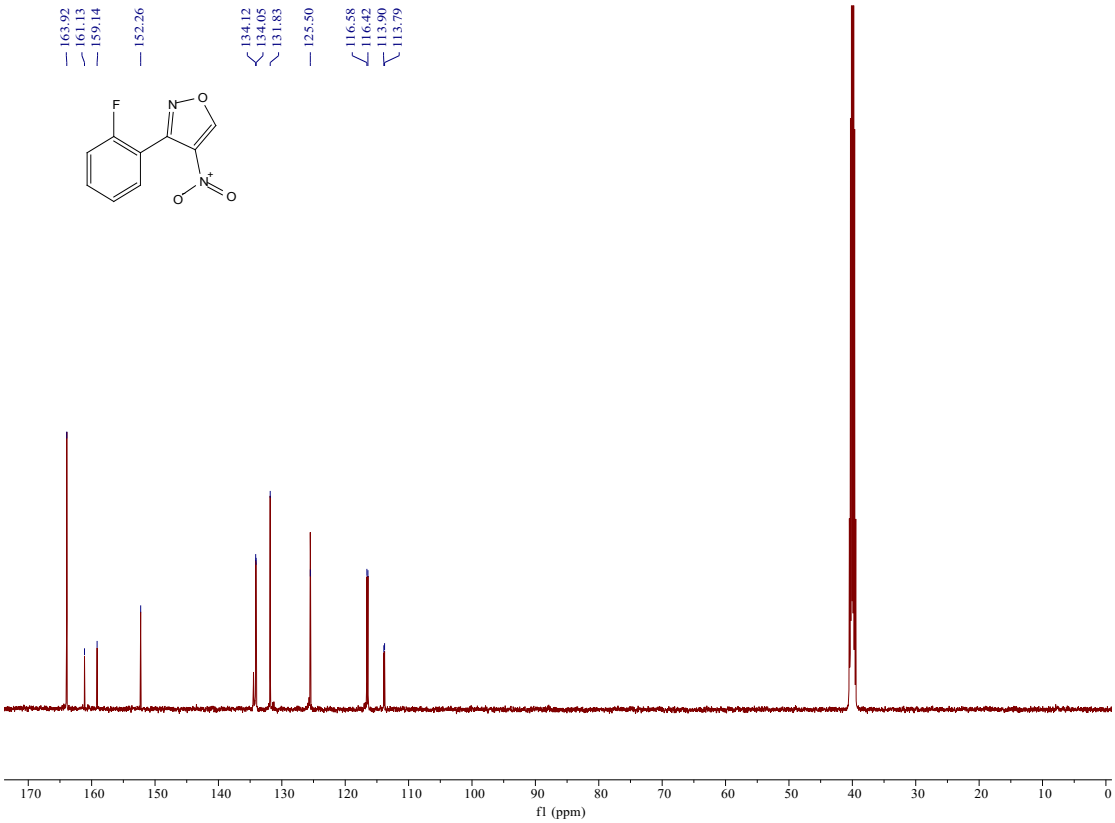

Fig. S80. ^{13}C NMR spectrum of compound **5p**

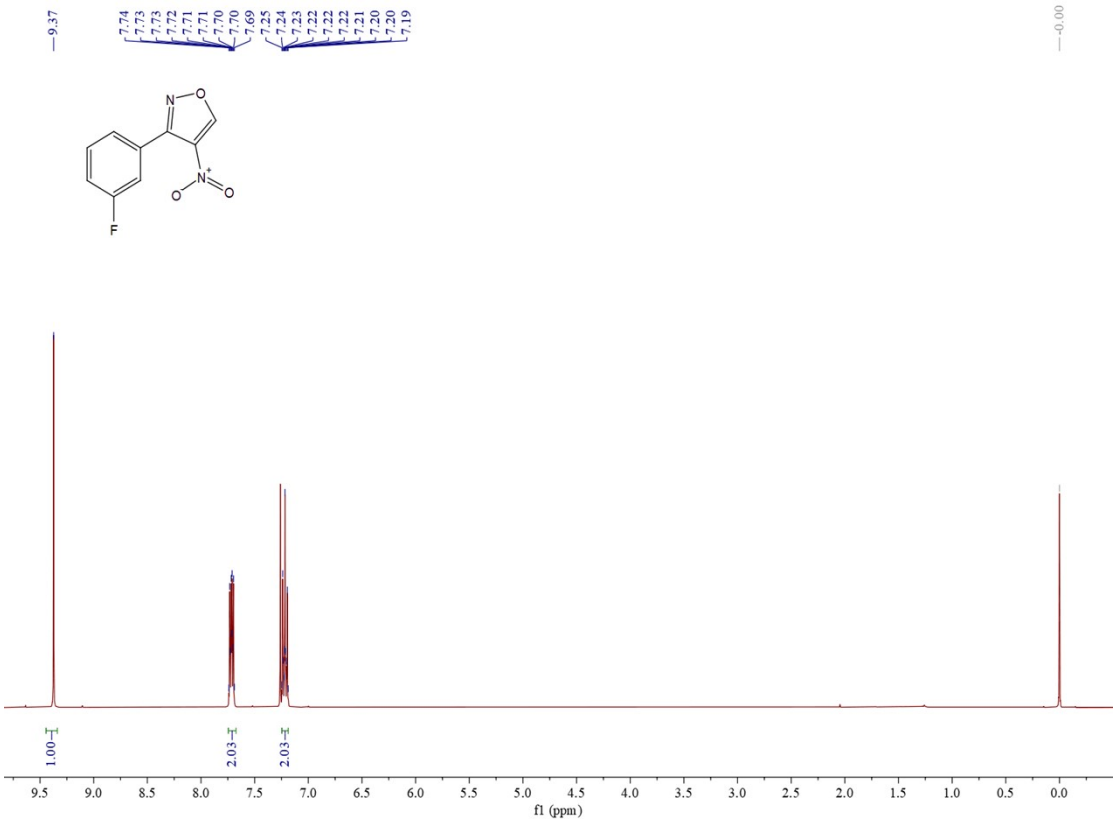

Fig. S81. ^{1}H NMR spectrum of compound **5q**

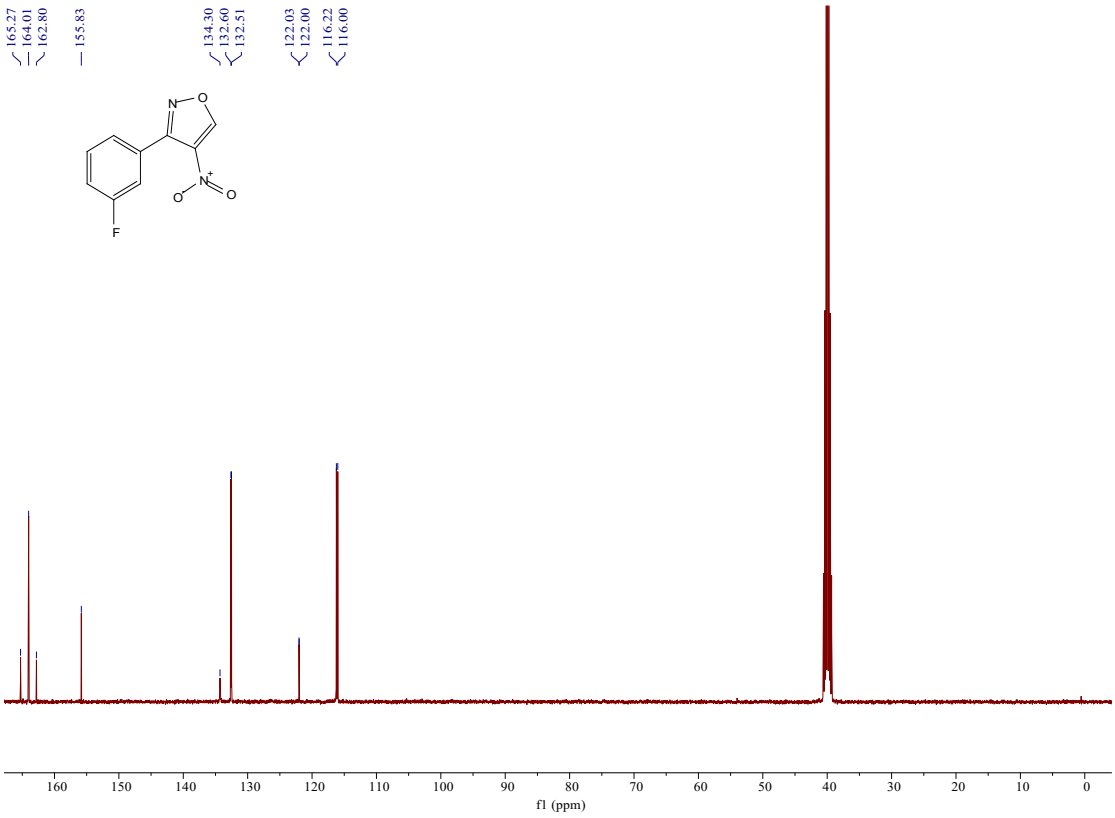

Fig. S82. ^{13}C NMR spectrum of compound **5q**

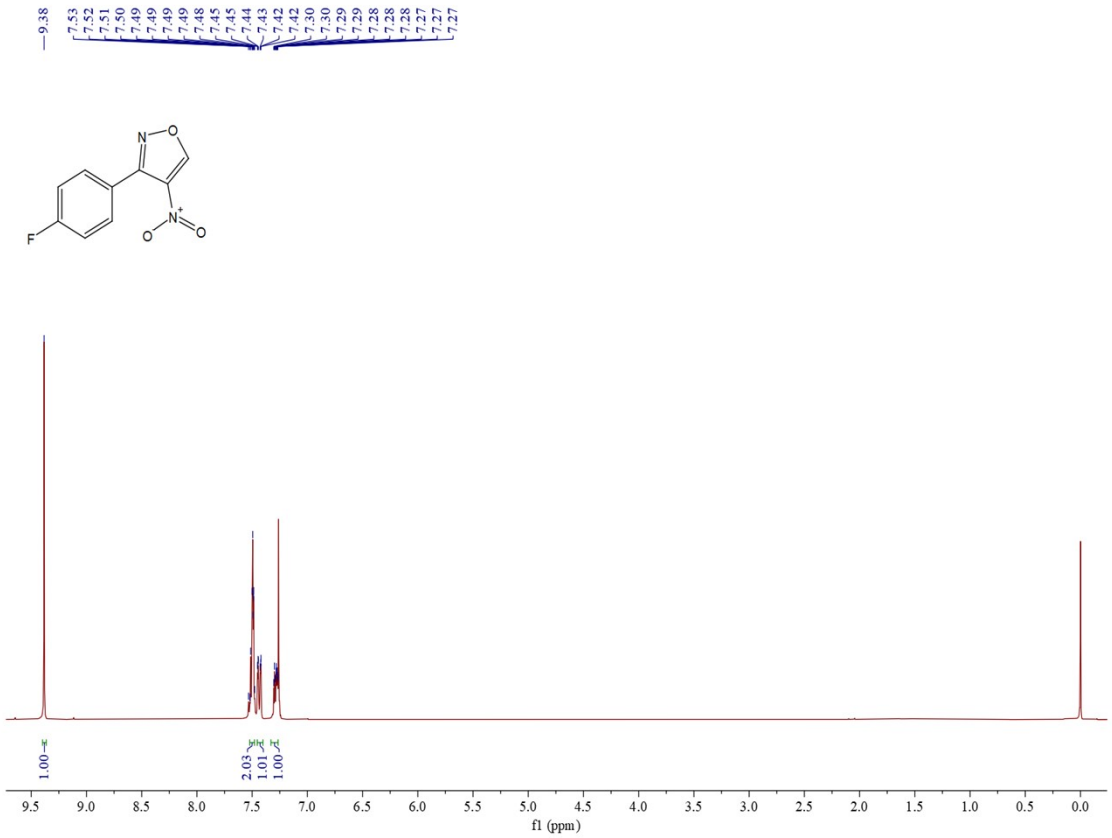

Fig. S83. [1]H NMR spectrum of compound **5r**

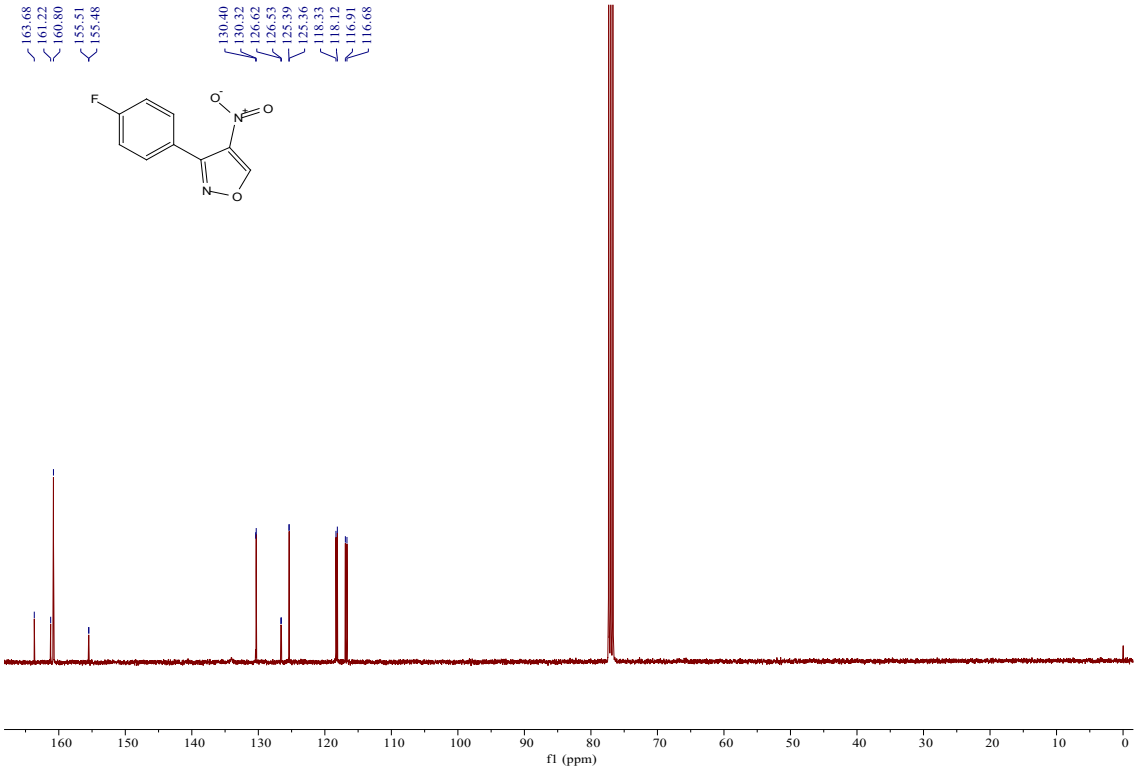

Fig. S84. [13]C NMR spectrum of compound **5r**

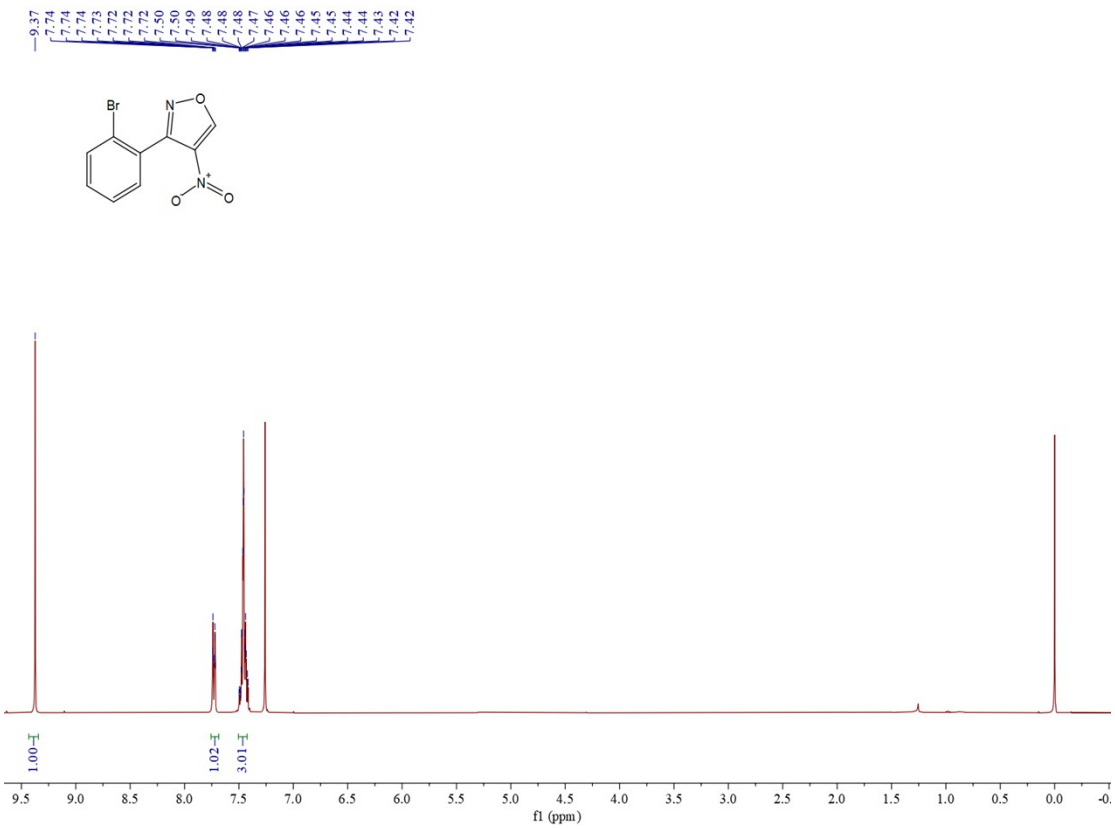

Fig. S85. ^{1}H NMR spectrum of compound **5s**

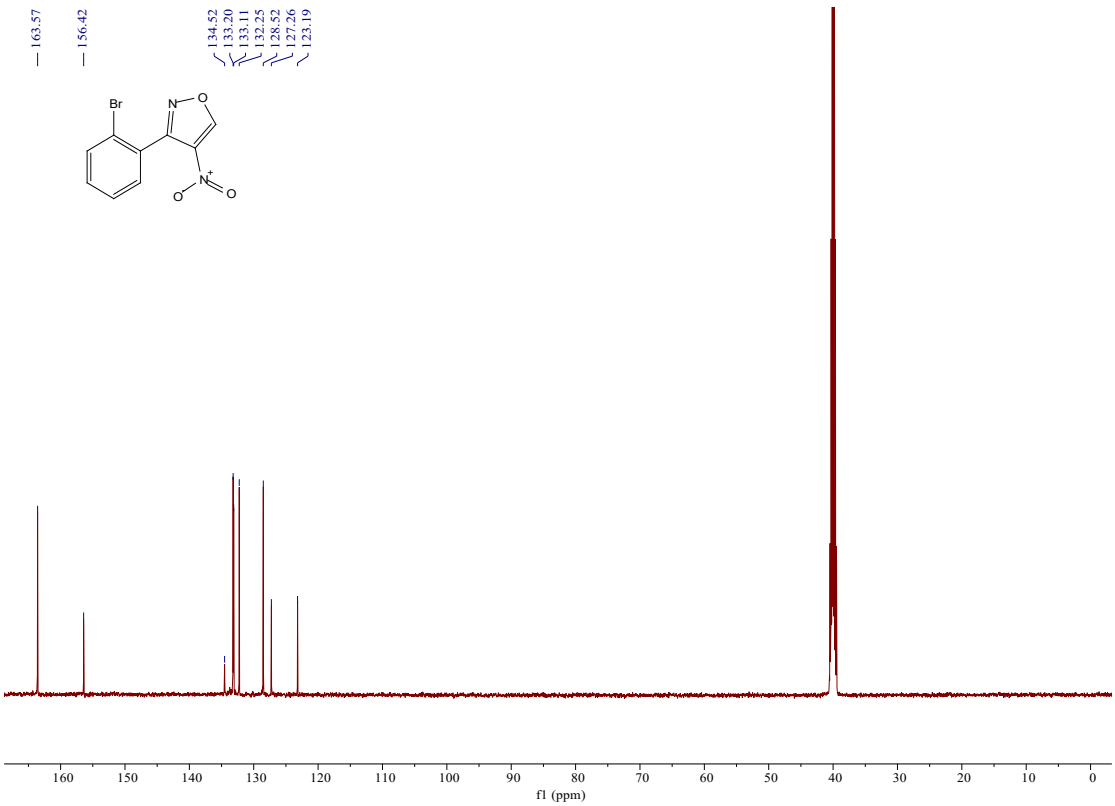

Fig. S86. ^{13}C NMR spectrum of compound **5s**

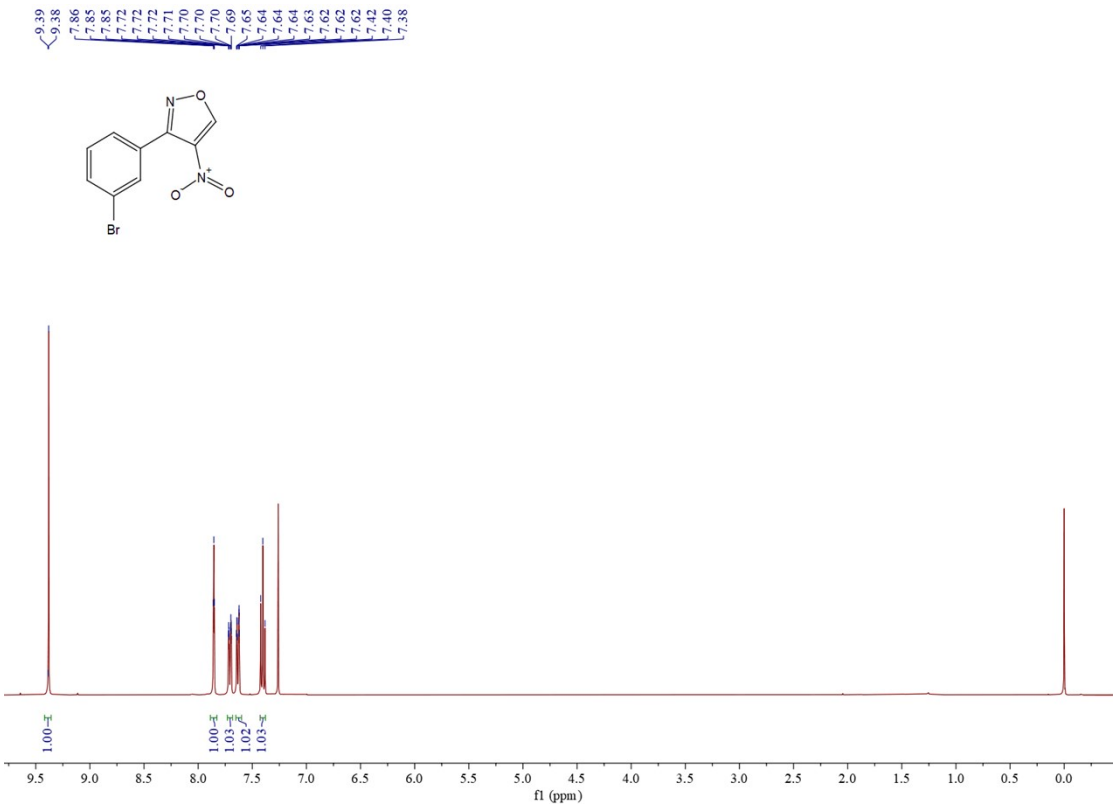

Fig. S87. ^{1}H NMR spectrum of compound **5t**

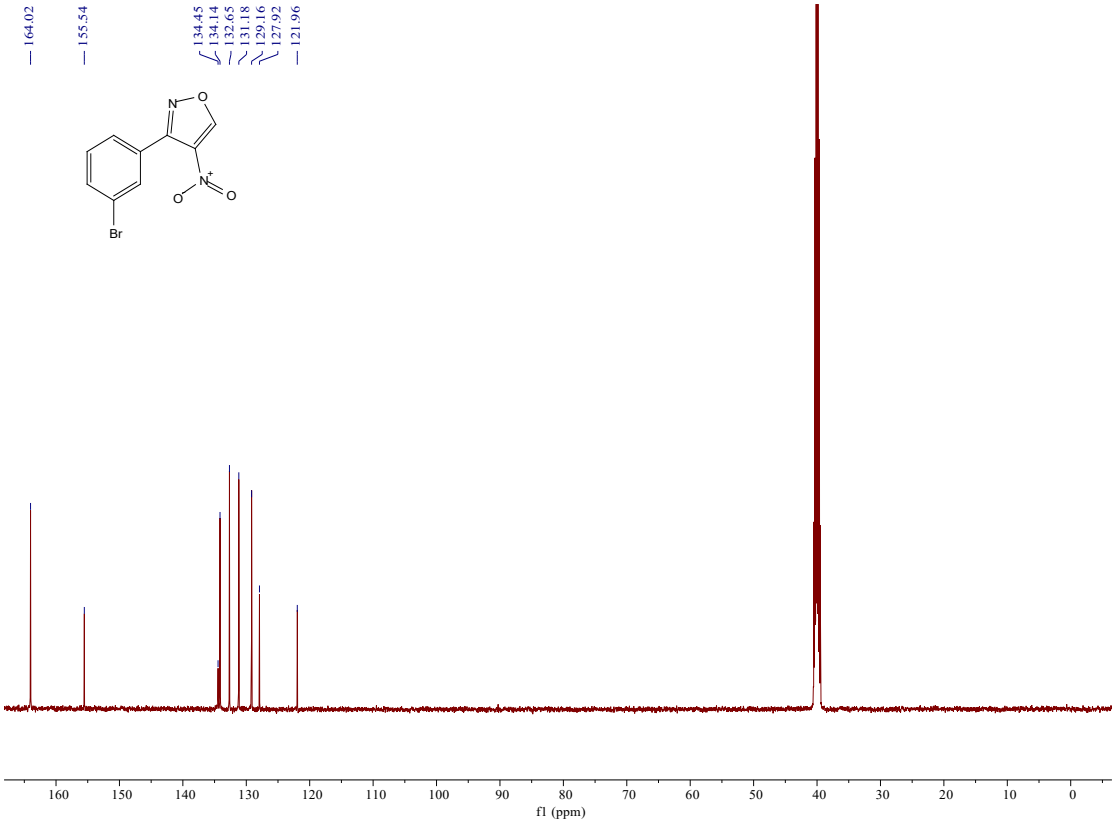

Fig. S88. ^{13}C NMR spectrum of compound **5t**

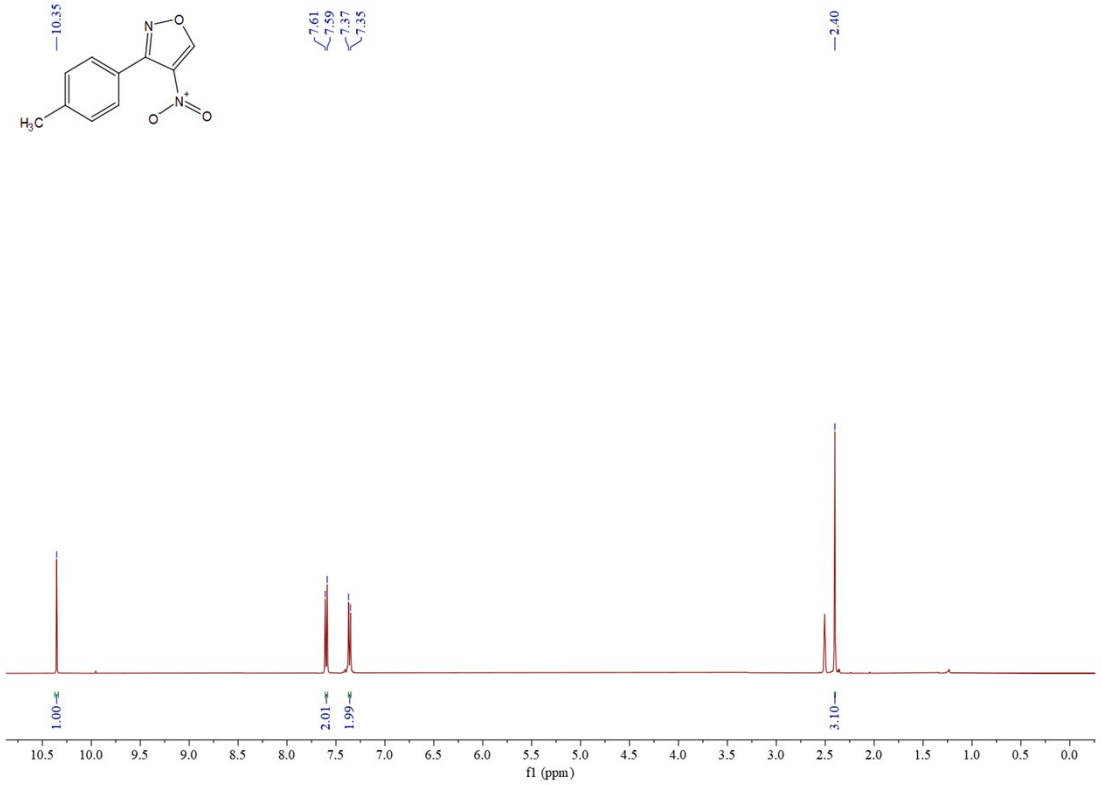

Fig. S89. ^{1}H NMR spectrum of compound **5u**

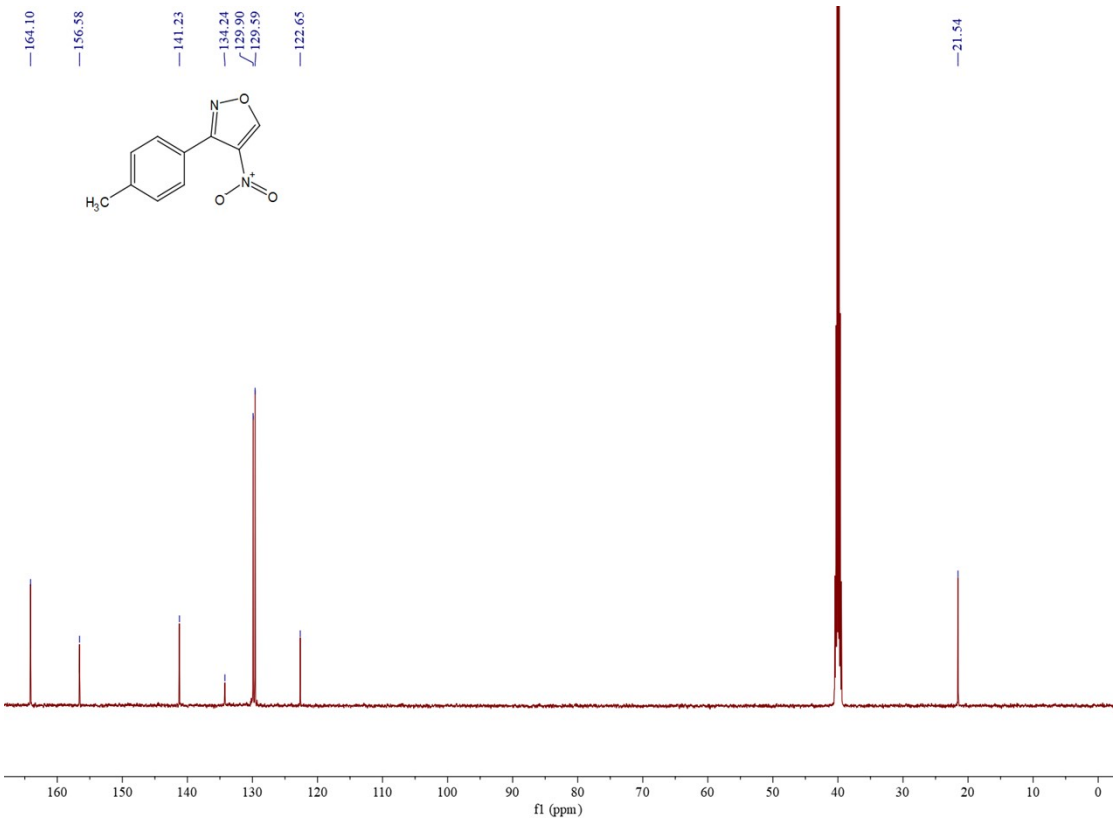

Fig. S90. ^{13}C NMR spectrum of compound **5u**

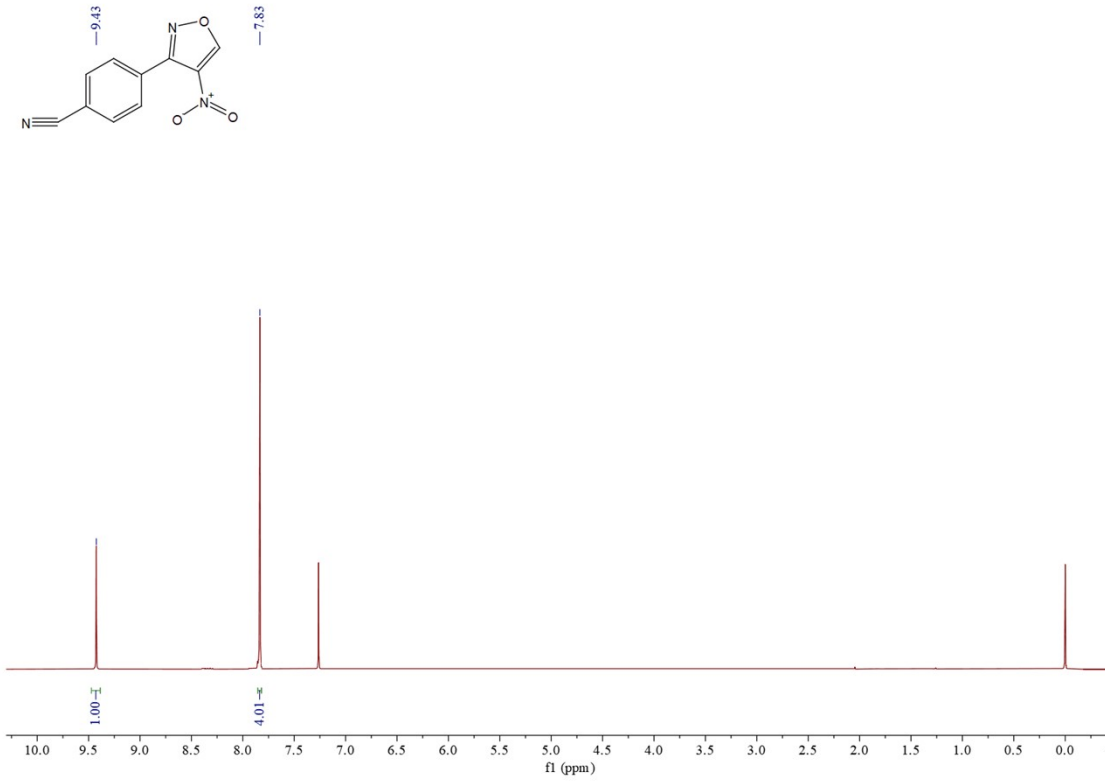

Fig. S91. [1]H NMR spectrum of compound **5v**

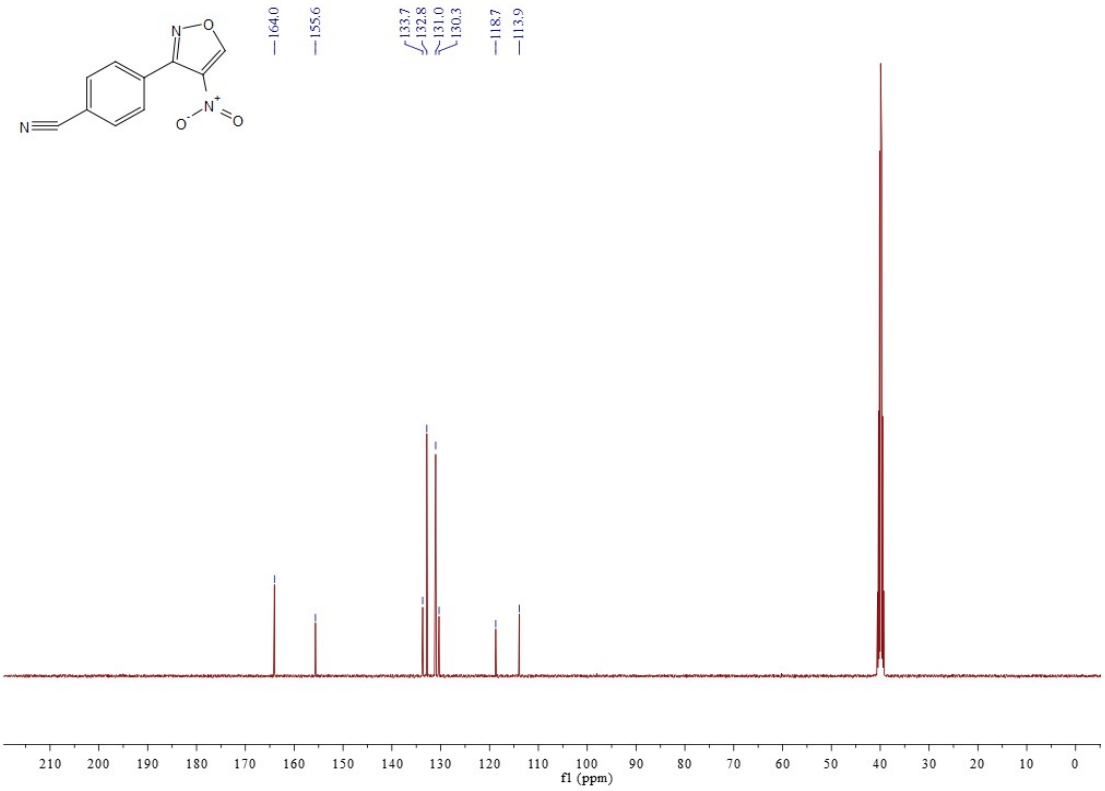

Fig. S92. [13]C NMR spectrum of compound **5v**

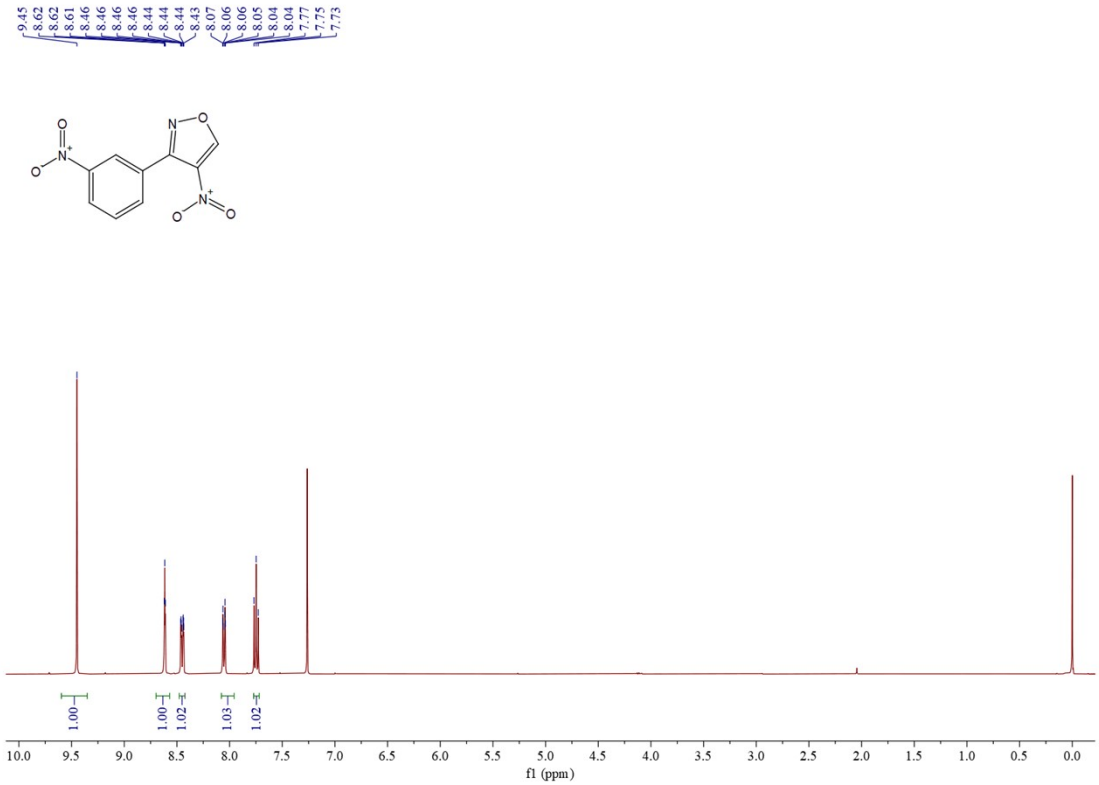

Fig. S93. ^{1}H NMR spectrum of compound **5w**

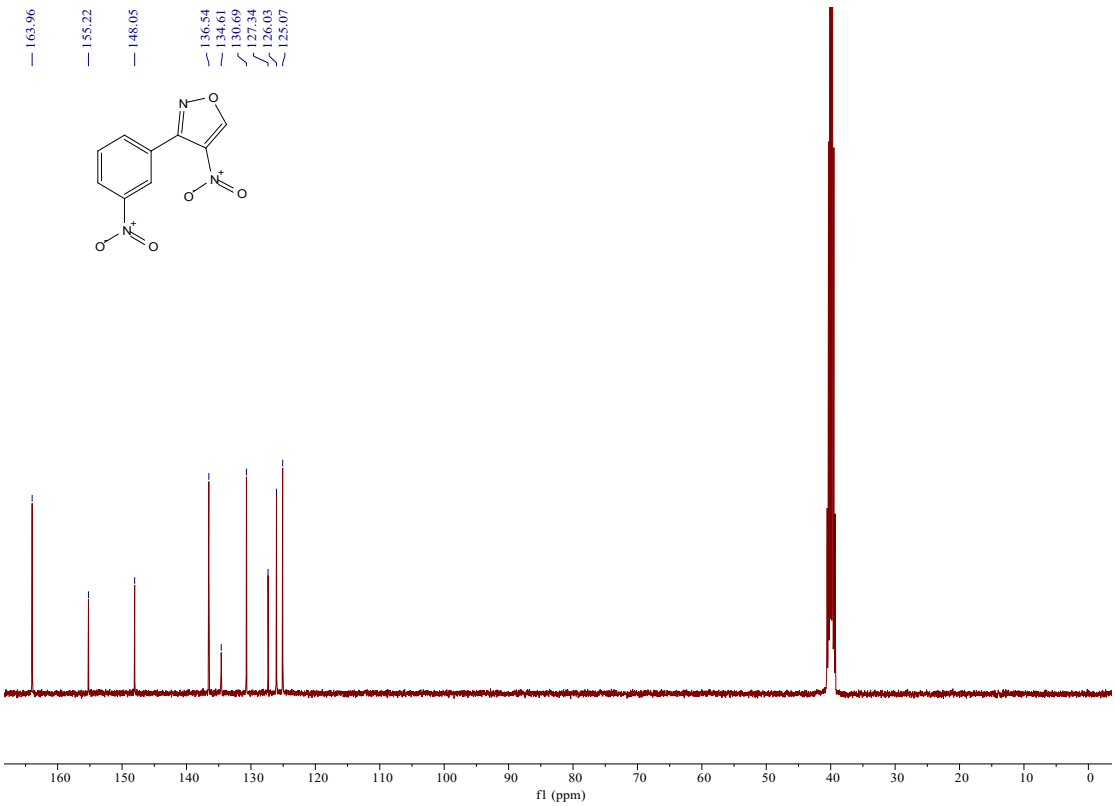

Fig. S94. ^{13}C NMR spectrum of compound **5w**

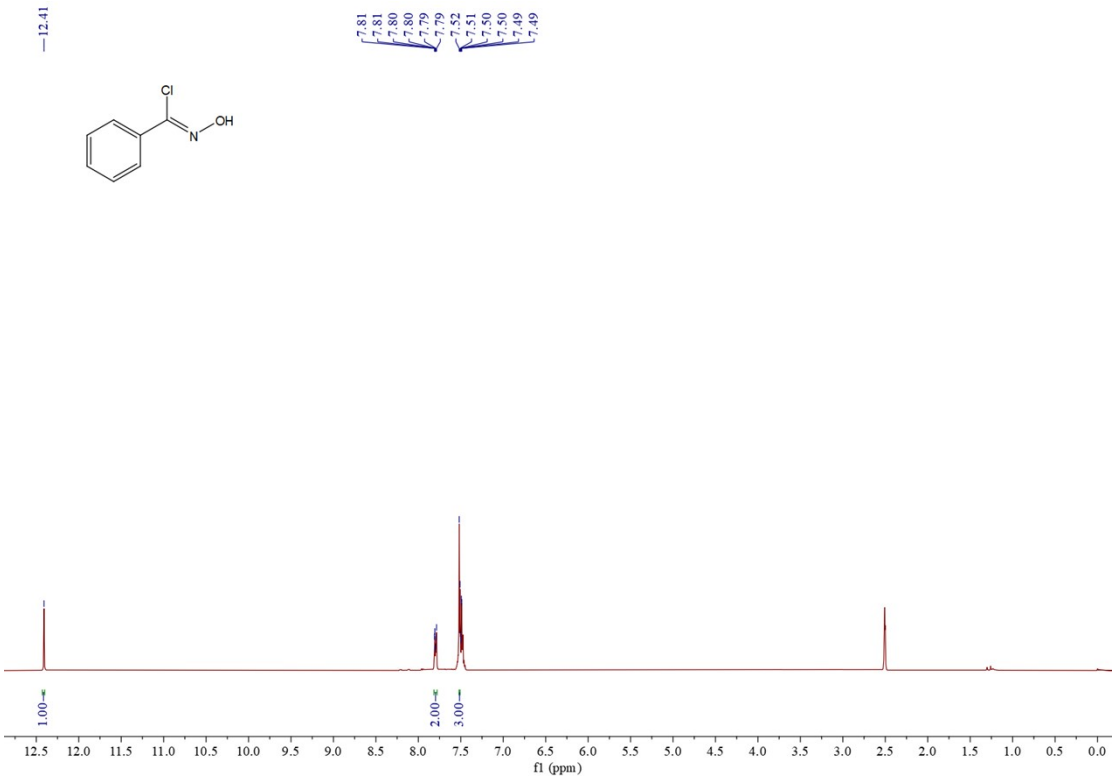

Fig. S95. ^{1}H NMR spectrum of compound **6**