Unprecedented stereoselective synthesis of 3-methylisoxazolidine-5-aryl-1,2,4-oxadiazoles via 1,3-dipolar cycloaddition and study of their *in vitro* antioxidant activity

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Experimental section

General methods: Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck). The plates were visualized by using UV light, gentle heating, or ninhydrin spray followed by heating in the case of amines. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX300 spectrometer with the residual solvent as the internal standard. The chemical shifts are expressed on the δ scale in parts per million (ppm). The following abbreviations are used to explain the observed multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; m, multiplet. NMR solvents were purchased from Eurisotop (Saint Aubin, France). High resolution (HR-ESI-QToF) mass spectra were recorded using a Bruker MicroToF-Q II XL spectrometer. 1D and 2D NMR spectroscopy which allowed signal assignments based on COSY and HSQC correlations.

General procedure (A) for the synthesis of Amidoxime.

To a solution of **2** (2 mmol, 610 mg) in 3 mL of EtOH was added hydroxyl amine 50% in water (1.8 equiv, 3.6 mmol, 120 mg) and a catalytic amount of acetic acid. The reaction mixture was stirred at 100°C for 10 min under microwaves irradiation. The mixture was extracted with EtOAc (3 x 100 mL), washed with brine and dried over anhydrous sodium sulfate. After removal of ethyl acetate by evaporation under reduced pressure, the residue obtained was purified by flash column chromatography using ethyl acetate (100%) as eluent to afford the desired amidoxime **3** (97%, 655 mg).

***General procedure (B) for the synthesis of 1,2,4-oxadiazoles* (4a-f).**

To a stirred solution of **3** (1.8 mmol, 600 mg) in 10 mL of freshly distilled toluene were added (1.1 eq, 1.98 mmol) of aldehyde, molecular sieve 4Å and a catalytic amount of PTSA. The reaction mixture stirred and heated under reflux (110°C) for 18 h. The solvent was evaporated

and the residue was extracted with EtOAc (3 x 100 mL). The combined organic layer are dried over (Na_2SO_4), filtered and evaporated. The crude product was purified by flash chromatography on silica gel (EtOAc/PE 8/2).

General procedure (C) for the acidic cleavage of the menthone chiral auxiliary.

1,2,4-Oxadiazole **4** (0.44 mmol) was dissolved in Ac_2O (2 mL), AcOH (3.2 mL), concentrated H_2SO_4 (0.8 mL), and the reaction was stirred at 50°C for 6.5h. After cooling to 0°C, the aqueous solution of 5% NaOH was added drop wise over a period of 2h until pH ~8. The mixture was then poured slowly into a saturated aqueous $NaHCO_3$ solution (280 mL). The resulting mixture was extracted with CH_2Cl_2 (3×100 mL), and the combined organic phases were dried with Na_2SO_4. After filtration and evaporation of the solvents under reduced pressure, the residue was purified by flash silica gel chromatography (EtOAc/PE 9/1) to afford the desired compound **5**.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2-isopropyl-5,5'-dimethyl-4'-oxotetrahydro-*2'H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-2'-yl)acetonitrile (2).

Nitrone **1** (2.5 mmol, 600 mg) and the allyl cyanide (12.5 mmol, 867 mg) were dissolved in toluene (15 mL) and heated at reflux for 48h, until TLC showed the complete conversion of the nitrone. The solution was concentrated and the residue was purified by flash chromatography (EtOAc/PE 8/2) to afford the desired cycloadduct **2** as a white solid (96%, 724 mg): mp 122-124°C; R_f = 0.67 [EtOAc 100%]; $[\alpha]^{22}$ = – 89.2 (c = 1; CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, 3H, CH_3, J = 6.4 Hz), 0.84 (d, 3H, CH_3, J = 6.8 Hz), 0.92 (m, 1H), 0.93 (d, 3H, CH_3, J = 6.2 Hz), 1.21 (t, 1H, H-13, J = 12.6 Hz), 1.37 (m, 2H), 1.67 (m, 2H), 1.82 (m, 1H), 2.07 (m, 2H), 2.29 (ddd, 1H, J = 6.2 Hz, J = 9.0 Hz, J = 12.4 Hz), 2.60 (t, 2H, J = 6.2 Hz), 2.73 (s, 3H, NCH_3), 2.79 (ddd, 1H, J = 5.6 Hz, J = 6.2 Hz, J = 12.4 Hz), 3.95 (d, 1H, J = 9.0 Hz), 4.20 (q, 1H, J = 6.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 22.3,

22.5, 22.6, 24.2, 24.5 (NCH_3), 26.1, 29.4, 34.9, 37.5, 41.1, 48.5, 65.1, 71.7, 89.1, 116.6, 172.5 (C=O) ppm; HR-ESI-QtoF: *m*/*z* calcd $C_{17}H_{28}N_3O_2$ $[M+H]^+$ = 305.2120, found: 305.2131.

(Z)-*N'*-hydroxy-2-((1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2-isopropyl-5,5'-dimethyl-4'-oxotetrahydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-2'-yl)acetimidamide (3).

Obtained as a white solid (97%, 655 mg) following general procedure (A): cycloadduct **2** (2, mmol, 610 mg) and hydroxylamine 50% in water (1.8 eq, 3.6 mmol, 120 mg): mp 164-166°C; R_f = 0.22 [EtOAc 100%]; $[\alpha]^{22}$ = + 51 (*c* = 1; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, 6H, $2CH_3$), 0.92 (d, 3H, CH_3, *J* = 4.2 Hz), 0.93 (m, 1H), 1.28 (t, 1H, *J* = 9 Hz), 1.37 (m, 2H), 1.63 (m, 2H), 1.83 (d, 1H, *J* = 12 Hz), 1.97 (m, 2H), 2.18 (m, 1H), 2.34 (dd, 1H, *J* = 8 Hz, *J* = 16 Hz), 2.46 (dd, 1H, *J* = 4 Hz, *J* = 18 Hz), 2.72 (s, 3H, NCH_3), 3.96 (d, 2H, *J* = 8 Hz), 4.98 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 22.3, 22.4, 24.3, 24.4, 26.2, 30.1, 34.2, 34.6, 38.7, 40.7, 48.1, 65.9, 75.6, 89.9, 152.3, 172.5 (C=O) ppm; HR-ESI-QtoF: *m*/*z* calcd $C_{17}H_{31}N_4O_3$ $[M+H]^+$ = 339.2391, found: 339.2381.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2-isopropyl-5,5'-dimethyl-2'-((5-phenyl-1,2,4-oxadiazol-3-yl)methyl)dihydro-*2'H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(*5'H*)-one (4a).

Obtained as a yellow liquid (70%, 530 mg) following general procedure (B): amidoxime **3** (600 mg, 1.8 mmol) and benzaldehyde (210 mg, 1.1 eq.). $[\alpha]^{22}$ = + 38 (*c* = 1; CH_2Cl_2); R_f = 0.73 [EtOAc 100%]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, 3H, CH_3, *J* = 8 Hz), 0.82 (t, 6H, 2 CH_3), 0.93 (m, 1H), 1.21 (t, 1H, *J* = 9 Hz), 1.32 (dd, 1H, *J* = 3.2 Hz, *J* = 8.8 Hz), 1.40 (m, 1H), 1.57 (dd, 1H, *J* = 3.2 Hz, *J* = 13.2 Hz), 1.69 (m, 2H), 1.97 (m, 2H), 2.35 (m, 1H), 2.72 (s, 3H, NCH_3), 2.80 (dd, 1H, *J* = 6 Hz, *J* = 8 Hz), 3.03 (dd, 1H, *J* = 5.6 Hz, *J* = 9.2 Hz), 3.12 (dd, 1H, *J* = 3.2 Hz, *J* = 7.6 Hz), 4.00 (d, 1H, H-3, *J* = 8.4 Hz), 4.30 (m, 1H, H-5), 7.51 (m, 2H), 7.58 (m, 1H), 8.10 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 22.3, 22.4,

24.3, 24.5, 26.2, 29.6, 30.0, 34.7, 38.5, 40.6, 48.2, 66.1, 74.3, 89.8, 124.2, 128.2, 129.2, 132.9, 168.2, 172.8, 175.7 (C=O) ppm; HR-ESI-QtoF: *m*/*z* calcd $C_{24}H_{33}N_4O_3$ $[M+H]^+$ = 425.2547, found: 425.2546.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2-isopropyl-5,5'-dimethyl-2'-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)dihydro-*2'H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(*5'H*)-one (4b). Obtained as a yellow liquid (58%, 377 mg) following general procedure (B): amidoxime **3** (600 mg, 1.8 mmol) and acetaldehyde (90 mg, 1.1 eq.). $[\alpha]^{22}$ = + 37.2 (*c* = 1; CH_2Cl_2); R_f = 0.75 [EtOAc 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, 3H, CH_3, *J* = 6.6 Hz), 0.86 (t, 6H, 2 CH_3), 0.93 (m, 1H), 1.28 (t, 1H), 1.33 (dd, 1H, *J* = 3.3 Hz, *J* = 12 Hz), 1.39 (m, 1H), 1.62 (dd, 1H, *J* = 3.3 Hz, *J* = 12.4 Hz), 1.79 (m, 2H), 2.03 (m, 2H), 2.34 (m, 1H), 2.55 (s, 3H, CH_3), 2.76 (s, 3H, NCH_3), 2.79 (d, 1H, *J* = 5.4 Hz), 2.94 (dd, 1H, *J* = 6.3 Hz, *J* = 15 Hz), 3.01 (dd, 1H, *J* = 6 Hz, *J* = 20 Hz), 3.99 (d, 1H, H-3, *J* = 8.7 Hz), 4.24 (m, 1H, H-5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3, 18.5, 22.3, 22.6, 24.4, 24.6, 26.1, 29.6, 30.0, 34.9, 38.6, 41.2, 48.5, 66.2, 74.3, 89.8, 167.7, 172.9, 176.5 (C=O) ppm; HR-ESI-QtoF: *m*/*z* calcd $C_{19}H_{31}N_4O_3$ $[M+H]^+$ = 363.2399, found: 363.2391.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2-isopropyl-5,5'-dimethyl-2'-((5-(*p*-tolyl)-1,2,4-oxadiazol-3-yl)methyl)dihydro-*2'H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(*5'H*)-one (4c). Obtained as a yellow liquid (65%, 512 mg) following general procedure (B): amidoxime **3** (600 mg, 1.8 mmol) and 4-tolualdehyde (240 mg, 1.1 eq.). $[\alpha]^{22}$ = + 34 (*c* = 1; CH_2Cl_2); R_f = 0.72 [EtOAc 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (d, 3H, CH_3, *J* = 6.3 Hz), 0.84 (t, 6H, 2 CH_3), 0.93 (m, 1H), 1.20 (t, 1H, *J* = 12,6 Hz), 1.31 (dd, 1H, *J* = 3.6 Hz, *J* = 6.6 Hz), 1.40 (m, 1H), 1.64 (dd, 1H, *J* = 2.7 Hz, *J* = 13.2 Hz), 1.81 (m, 2H), 2.00 (m, 2H), 2.35 (m, 1H), 2.43 (s, 3H, CH_3), 2.73 (s, 3H, NCH_3), 2.81 (dd, 1H, *J* = 7.2 Hz, *J* = 12.3 Hz), 3.00 (dd,

1H, *J* = 7 Hz, *J* = 16.2 Hz), 3.11 (dd, 1H, *J* = 6.9 Hz, *J* = 18.6 Hz), 4.00 (d, 1H, H-5, *J* = 8.7 Hz), 4.32 (m, 1H, H-3), 7.31 (d, 2H, *J* = 8.1 Hz), 8.00 (d, 2H, *J* = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 21.8, 22.3, 22.6, 24.3, 24.6, 26.2, 29.6, 30.2, 30.9, 35.0, 38.6, 48.5, 66.2, 74.4, 89.8, 128.2, 129.3, 129.9, 130.3, 168.2, 173.0, 176.0 (C=O) ppm; HR-ESI-QtoF: *m*/*z* calcd $C_{25}H_{35}N_4O_3$ $[M+H]^+$ = 439.2704, found: 439.2706.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2'-((5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)methyl)-2-isopropyl-5,5'-dimethyldihydro-*2'H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(*5'H*)-one (4d).

Obtained as a yellow liquid (62%, 480 mg) following general procedure (B): amidoxime **3** (600 mg, 1.8 mmol) and 4-chlorobenzaldehyde (280 mg, 1.1 eq.). $[\alpha]^{22}$ = + 42 (*c* = 1; CH_2Cl_2); R_f = 0.70 [EtOAc 100%]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, 3H, CH_3, *J* = 6.4 Hz), 0.79 (d, 3H, CH_3, *J* = 6.8 Hz), 0.82 (d, 3H, CH_3, *J* = 6.8 Hz), 0.877 (m, 1H), 1.18 (t, 1H, *J* = 12 Hz), 1.32 (dd, 1H, *J* = 3.2 Hz, *J* = 12 Hz), 1.38 (m, 1H), 1.56 (dd, 1H, *J* = 3.2 Hz, *J* = 13.2 Hz), 1.66 (dd, 2H, *J* = 2.4, *J* = 9,3 Hz), 1.95 (m, 2H), 2.35 (m, 1H), 2.71 (s, 3H, NCH_3), 2.77 (dd, 1H, *J* = 5.2 Hz, *J* = 12.4 Hz), 3.01 (dd, 1H, *J* = 6 Hz, *J* = 8.8 Hz), 3.11 (dd, 1H, *J* = 7.2 Hz, *J* = 14.8 Hz), 3.99 (d, 1H, H-3, *J* = 8.8 Hz), 4.27 (m, 1H, H-5), 7.48 (d, 2H, *J* = 8.8 Hz), 8.02 (d, 2H, *J* = 8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 22.3, 22.4, 24.2, 24.4, 26.2, 29.5, 30.0, 34.7, 38.5, 40.6, 48.2, 66.1, 74.1, 89.7, 122.6, 129.4, 129.6, 139.3, 168.3, 172.8, 174.8 (C=O) ppm; HR-ESI-QtoF: *m*/*z* calcd $C_{24}H_{32}ClN_4O_3$ $[M+H]^+$ = 459.2167, found: 459.2157.

(*1S,2S,2'S,3a'S,5R*)-2-isopropyl-2'-((5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)methyl-5,5-dimethyldihydro-*2'H*-spiro[cyclohexane-1,6'-imidazol[1,5-*b*]isoxazol]-4'-(*5'H*)-one (4e).

Obtained as a yellow liquid (68%, 512 mg) following general procedure (B): amidoxime **3** (600 mg, 1.8 mmol) and 4-methoxybenzaldehyde (269 mg, 1.1 eq.). $[\alpha]^{22}$ = + 29.5 (*c* = 1; CH_2Cl_2); R_f = 0.69 [EtOAc 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (d, 3H, CH_3, *J* = 6.3 Hz), 0.84 (t, 6H, 2 CH_3), 0.93 (m, 1H), 1.24 (t, 1H, *J* = 15 Hz), 1.35 (dd, 1H, *J* = 3.3 Hz, *J* = 12.3 Hz), 1.46 (m, 1H), 1.70 (dd, 1H, *J* = 3 Hz, *J* = 12.6 Hz), 1.85 (m, 2H), 2.02 (m, 2H), 2.35 (m, 1H), 2.73 (s, 3H, NCH_3), 2.81 (dd, 1H, *J* = 4.8 Hz, *J* = 12 Hz), 3.01 (dd, 1H, *J* = 6.6 Hz, *J* = 15.3 Hz), 3.12 (dd, 1H, *J* = 6.9 Hz, *J* = 15.3 Hz), 3.90 (s, 3H, OCH_3), 4.00 (d, 1H, H-3, *J* = 9 Hz), 4.33 (m, 1H, H-5), 7.01 (d, 2H, *J* = 9 Hz), 8.08 (d, 2H, *J* = 8.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6, 22.3, 22.5, 24.3, 24.6, 26.2, 29.6, 29.8, 30.1, 34.9, 38.6, 40.8, 48.4, 66.2, 74.5, 89.8, 114.7, 115.0, 130.1, 130.5, 163.4, 168.1, 175.7 (C=O) ppm; HR-ESI-QtoF: *m*/*z* calcd $C_{25}H_{35}N_4O_4$ $[M+H]^+$ = 455.2664, found: 455.2653.

(1*S*,2*S*,2'*S*,3a'*S*,5*R*)-2'-((5-([1,1'-biphenyl]-4-yl)-1,2,4-oxadiazol-3-yl)methyl)-2-isopropyl-5,5'-dimethyldihydro-*2'H*-spiro[cyclohexane-1,6'-imidazo[1,5-*b*]isoxazol]-4'(*5'H*)-one (4f).

Obtained as a yellow liquid (51%, 450 mg) following general procedure (B): amidoxime **3** (600 mg, 1.8 mmol) and biphenyl-4-carboxaldehyde (360 mg, 1.1 eq.). $[\alpha]^{22}$ = + 30.4 (*c* = 1; CH_2Cl_2); R_f = 0.71 [EtOAc 100%]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, 3H, CH_3, *J* = 6.4 Hz), 0.82 (t, 6H, 2 CH_3), 0.91 (m, 1H), 1.21 (t, 1H, *J* = 12 Hz), 1.33 (dd, 1H, *J* = 2.8 Hz, *J* = 12 Hz), 1.40 (m, 1H), 1.58 (dd, 1H, *J* = 3.6 Hz, *J* = 10 Hz), 1.66 (m, 2H), 1.99 (m, 2H), 2.37 (m, 1H), 2.73 (s, 3H, NCH_3), 2.81 (dd, 1H, *J* = 5.2 Hz, *J* = 7.2 Hz), 3.03 (dd, 1H, *J* = 5.6 Hz, *J* = 14.8 Hz), 3.14 (dd, 1H, *J* = 7.2 Hz, *J* = 14.8 Hz), 4.01 (d, 1H, H-3, *J* = 8.8 Hz), 4.27 (m, 1H, H-5), 7.40 (t, 1H), 7.47 (t, 2H), 7.64 (d, 2H, *J* = 7.2 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 8.16 (d, 2H, *J* = 8.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 22.3, 22.4, 24.3, 24.4, 26.2, 29.6, 30.1, 34.7, 38.5, 40.6, 48.2, 66.1, 74.3, 89.7, 122.9,127.3, 127.8, 128.5, 128.6, 129.1, 139.7,

145.6, 168.2, 172.8, 175.6 (C=O) ppm; HR-ESI-QtoF: *m/z* calcd $C_{30}H_{37}N_4O_3$ $[M+H]^+$ = 501.2860, found: 501.2841.

(3*S*,5*S*)-2-Acetyl-*N*-methyl-5-((5-phenyl-1,2,4-oxadiazol-3-yl)methyl)isoxazolidine-3-carboxamide (5a) and (3*S*,5*S*)-*N*-methyl-5-((5-phenyl-1,2,4-oxadiazol-3-yl)methyl)isoxazolidine-3-carboxamide (5'a).

5a and **5'a** were obtained from **4a** (190 mg, 0.44 mmol) following general procedure (C).

(5a) Yield (52%); yellow solid: mp 148-150°C; R_f = 0.45 [EtOAc 100%]; $[\alpha]^{22}$ = +36.6 (*c* = 1; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H), 2.39 (m, 1H), 2.81 (d, 3H, CH_3), 2.97 (dd, 1H, *J* = 5.2, *J* = 14.8 Hz), 3.09 (dd, 1H, *J* = 7.6, *J* = 14.8 Hz), 3.17 (m, 1H), 4.89 (m, 2H, H-3, H-5), 7.53 (t, 2H), 7.61 (t, 1H, *J* = 7,6 Hz), 8.11 (d, 2H, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 26.6, 30.1, 35.1, 58.2, 78.6, 124.0, 128.3, 129.3, 133.9, 167.3, 169.1, 171.7 (C=O), 176.2 (C=O) ppm; HR-ESI-QtoF: *m/z* calcd $C_{16}H_{19}N_4O_4$ $[M+H]^+$ = 331.1410, found: 331.1401.

(5'a) Yield (28%): mp 132-134°C; R_f = 0.40 [EtOAc 100%]; $[\alpha]^{22}$ = +36.6 (*c* = 1; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (m, 1H), 2.68 (d, 3H, CH_3, *J* = 4.6 Hz), 2.90 (m, 1H), 3.10 (dd, 1H, *J* = 5.8 Hz, *J* = 13.6 Hz), 3.18 (dd, 1H, *J* = 7.2 Hz, *J* = 14.8 Hz), 4.19 (d, 1H, H-3, *J* = 8.2 Hz), 4.72 (m, 1H, H-5), 7.51 (t, 2H, *J* = 6.2 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 8.10 (d, 2H, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 25.6, 30.9, 60.4, 78.6, 124.0, 128.3, 129.3, 133.1, 167.4, 167.8, 169.1 (C=O) ppm; HR-ESI-QtoF: *m/z* calcd $C_{14}H_{16}N_4O_3$ $[M+H]^+$ = 289.1242, found: 289.1260.

(3*S*,5*S*)-*N*,2-dimethyl-5-((5-(*p*-tolyl)-1,2,4-oxadiazol-3-yl)methyl)isoxazolidine-3-carboxamide (5c).

5c Was obtained from **4c** (190 mg, 0.43 mmol) following general procedure (C). Yield (60%); yellow solid: mp 166-168°C; R_f = 0.42 [EtOAc 100%]; $[\alpha]^{22}$ = +32.6 (c = 1; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (m, 1H), 2.43 (s, 3H, CH_3), 2.81 (d, 3H, CH_3, J = 4.8 Hz), 2.93 (m, 1H), 3.03 (dd, 1H, J = 5.6, J = 15.2 Hz), 3.11 (dd, 1H, J = 6.0, J = 15.6 Hz), 4.10 (d, 1H, H-3, J = 8 Hz), 4.68 (m, 1H, H-5), 7.31 (d, 2H, J = 8 Hz), 7.78 (d, 2H, J = 8.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 26.2, 38.5, 62.5, 78.8, 121.3, 128.3, 130.0, 143.9, 167.7, 171.4, 176.2 (C=O) ppm; HR-ESI-QtoF: m/z calcd $C_{15}H_{19}N_4O_3$ $[M+H]^+$ = 303.1452, found: 303.1449.

(3*S*,5*S*)-5-((5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-yl)methyl)-*N*,2-dimethylisoxazolidine-3-carboxamide (5d).

5d Was obtained from **4d** (190 mg, 0.41 mmol) following general procedure (C). Yield (57%); yellow solid: mp 154-156°C; R_f = 0.48 [EtOAc 100%]; $[\alpha]^{22}$ = +42 (c = 1; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (m, 1H), 2.81 (t, 3H, CH_3, J = 4.8 Hz), 2.96 (dd, 1H, J = 5.2, J = 14.8 Hz), 3.03 (dd, 1H, J = 5.6, J = 15.2 Hz), 3.11 (dd, 1H, J = 6.8, J = 15.2 Hz), 4.13 (d, 1H, H-3, J = 7.2), 4.68 (m, 1H, H-5), 7.51 (m, 2H), 8.04 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 30.0, 38.6, 62.4, 78.5, 122.4, 129.5, 129.7, 139.6, 168.0, 171.2, 175.1 (C=O) ppm; HR-ESI-QtoF: m/z calcd $C_{14}H_{16}ClN_4O_3$ $[M+H]^+$ = 323.0905, found: 323.0893.

(3*S*,5*S*)-2-Acetyl-5-((5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)-*N*-methyl-isoxazolidine-3-carboxamide (5e).

5e Was obtained from **4e** (190 mg, 0.42 mmol) following general procedure (C). Yield (68%); yellow solid: mp 190-192°C; R_f = 0.42 [EtOAc 100%]; $[\alpha]^{22}$ = +32.6 (c = 1; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3), 2.40 (m, 1H), 2.81 (d, 3H, CH_3, J = 4 Hz),

2.94 (dd, 1H, J = 4.4, J = 12 Hz), 3.06 (dd, 1H, J = 6, J = 12 Hz), 3.16 (m, 1H), 3.90 (s, 3H, CH_3), 4.88 (m, 2H, H-3, H-5), 7.02 (d, 2H, J = 7.2 Hz), 8.05 (d, 2H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 26.6, 29.9, 32.1, 55.7, 58.2, 78.7, 114.7, 116.6, 123.4, 130.2, 163.5, 167.2, 169.1, 176.0 (C=O) ppm; HR-ESI-QtoF: m/z calcd $C_{15}H_{19}N_4O_3$ $[M+H]^+$ = 361.2452, found: 361.2449.

DPPH free radical scavenging activity

The ability of 3-methylisoxazolidine-5-aryl-1,2,4-oxadiazoles to scavenge free radical was tested using a synthetic compound, 2,2 -diphenyl-1-picrylhydrazyl (DPPH), as reported by Daoud *et al.*[1] with slightly modification. In its radical form, DPPH absorbs at 517 nm. Briefly, 2 mL of DPPH (0.005g DPPH/100 mL of ethanol) was added to the samples at different concentrations. The mixture was mixed (vortexes) for 30sg then was kept in the dark for 20 min at room temperature (Daoud et al, 2015).1 Ethanol alone was used as negative control, DPPH without extract as control for total activity (DPPH), while ascorbic acid was used as positive control. The percentage of activity was calculated as:

% Activity= [(absorbance DPPH−absorbance of test sample)/absorbance DPPH] ×100

The concentration of extract capable of inhibiting 50% of the DPPH activity was designated as IC50. This last was calculated by plotting the percentage of radical scavenging activity against different concentrations of sample.

Ferric reducing antioxidant power (FRAP)

In this assay, the yellow color of the test solution changes to green depending on the reducing power of test specimen. The presence of reductants in the solution causes the reduction of the $Fe^{3+/}$ferricyanide complex to the ferrous form. Therefore, Fe^{2+} can be monitored by the measurement of the absorbance at 700 nm (Sana et al., 2015).[2] 1 mL of different

concentrations of extract were mixed with 2.5 mL of a 0.2 M sodium phosphate buffer (pH 6.6, prepared from 62.5 mL of a 0.2 M Na_2HPO_4 and 37.5 mL of 0.2 M $NaH_2PO_4.H_2O$) and 2.5 mL of 1% $K_3Fe(CN)_6$ and incubated in a aqueous bath at 50ºC for 20 min. Then, 2.5 mL of 10% trichloroacetic acid were added to the mixture that was centrifuged at 650 g-force for 10 min. The supernatant (2.5 mL) was then mixed with 2.5 mL distilled aqueous and 0.5 mL of 0.1% ferric chloride solution. The intensity of the blue-green colour was measured at 700 nm. The EC_{50} value (mg/mL) is the extract concentration at which the absorbance was 0.5 for the reducing power and was calculated from the graph of absorbance at 700 nm against extract concentration. Ascorbic acid was used as a positive control. Tests were carried out in triplicate.

Table 1. Antioxidant activity: IC_{50} values of the DPPH free radical scavenging.

Samples	**0**	**0.25**	**0.50**	**1.00**	**1.50**	**2.00**	**IC_{50}(mg/mL)**
5a	0	36.08±0.10	38.65±0.40	49.072±1.03	53.81±0.06	58.45±0.34	1.4 ± 0.15
5'a	0	29.17±0.37	39.48±0.25	47.11± 0.11	56.18±0.15	68.65±0.27	1.2 ± 0.20
5c	0	39.17±0.20	48.04±0.16	53.40±0.06	55.77±0.20	60.20±0.64	0.64 ± 0.20
5d	0	39.16±0.15	47.01±0.27	56.70±0.17	66.80±0.19	65.67±0.15	0.62 ± 0.06
5e	0	33.50±1.02	37.11±0.20	50.20± 0.20	61.54±0.09	68.86±0.41	0.88 ± 0.60
Ascorbic acid	0	45.71±0.15	61.26±0.15	77.52± 0.06	88.55±0.09	87.65±0.10	0.41 ± 0.05

IC_{50} (mg/mL): Values corresponding to the amount of extract required to scavenge 50% of radicals present in the reaction mixture.

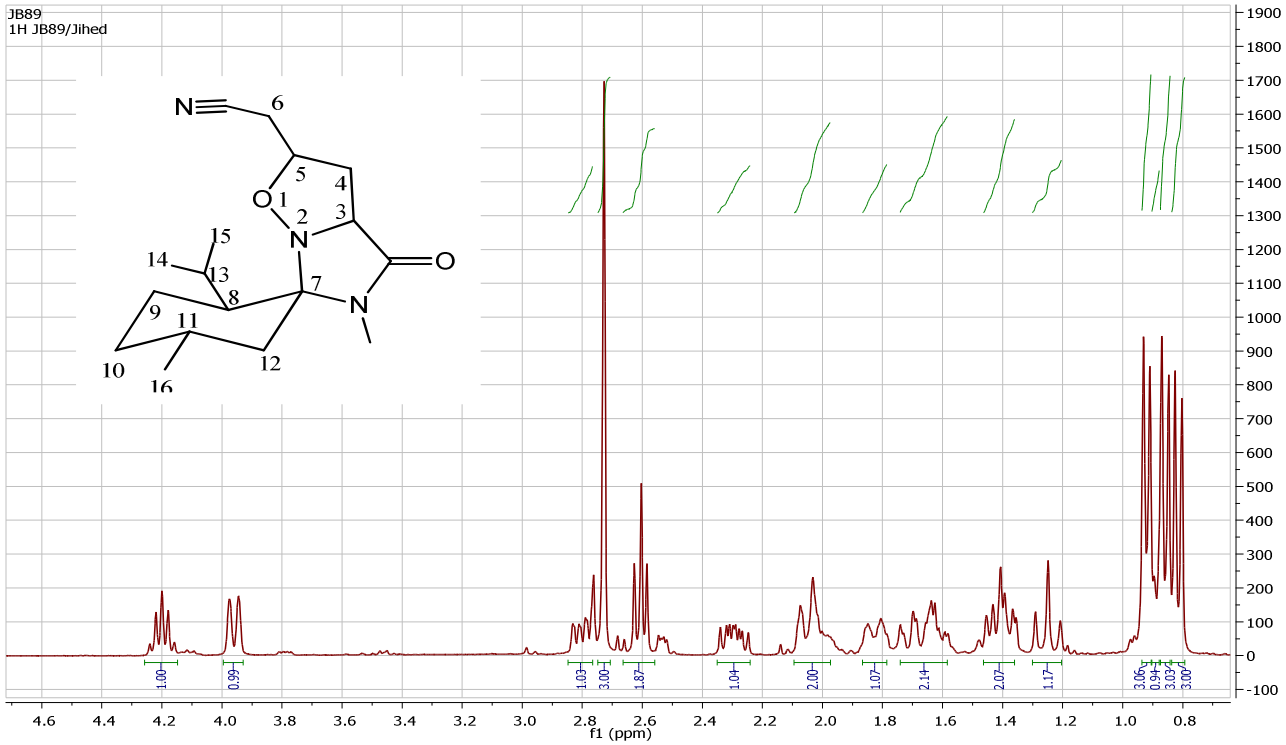
Table 2. Antioxidant activity: EC_{50} values of the FRAP assay.

Samples	0	0.25	0.50	1.00	1.50	2.00	EC_{50}(mg/mL)
5a	0	0.05 ±0.11	0.11 ±0.03	0.21 ±0.03	0.28±0.05	0.47 ±0.05	-
5'a	0	0.08 ±0.02	0.18 ±0.05	0.35 ±0.07	0.50 ±0.08	0.55 ±0.17	1.50 ± 0.11
5c	0	0.18 ±0.12	0.29 ±0.05	0.39±0.15	0.60 ±0.07	0.64 ±0.04	1.25 ± 0.05
5d	0	0.19 ±0.05	0.30 ±0.05	0.45 ±0.11	0.55 ±0.01	0.74 ±0.02	1.17 ± 0.15
5e	0	0.14 ±0.10	0.25 ±0.05	0.31 ±0.05	0.39 ±0.05	0.54±0.01	1.81 ± 0.15
Ascorbic acid	0	0.21 ±0.05	0.40 ±0.02	0.60 ±0.07	0.85 ±0.05	0.98 ±0.02	0.85 ± 0.04

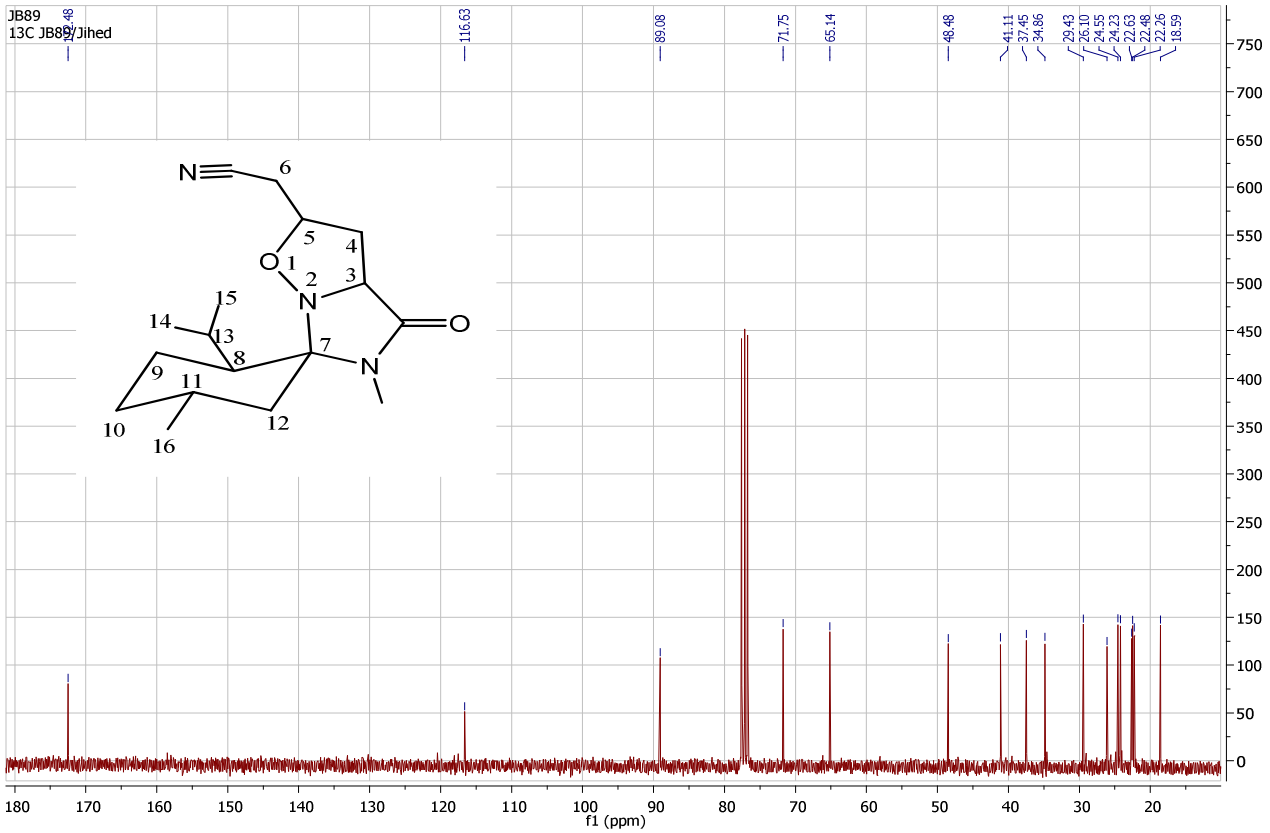
EC_{50}(mg/mL): Effective concentration corresponding to the value of absorbance (0.5).

[1] Daoud, A., Drira, M., Bakari, S., Hfaiedh, N., Mnafgui, K., Kadri, A., & Gharsallah, N. *Arab. J. Chem.,* **2015**, *8*, 1–12.

[2] Bakari, S.; Ncir, M.; Felhi, S.; Hajlaoui, H.; Saoudi, M.; Gharsallah, N.; Kadri, A. *Food Sci. Biotechnol*. **2015**, *24*, 1943-1949.



^{1}H NMR of compound (**2**)



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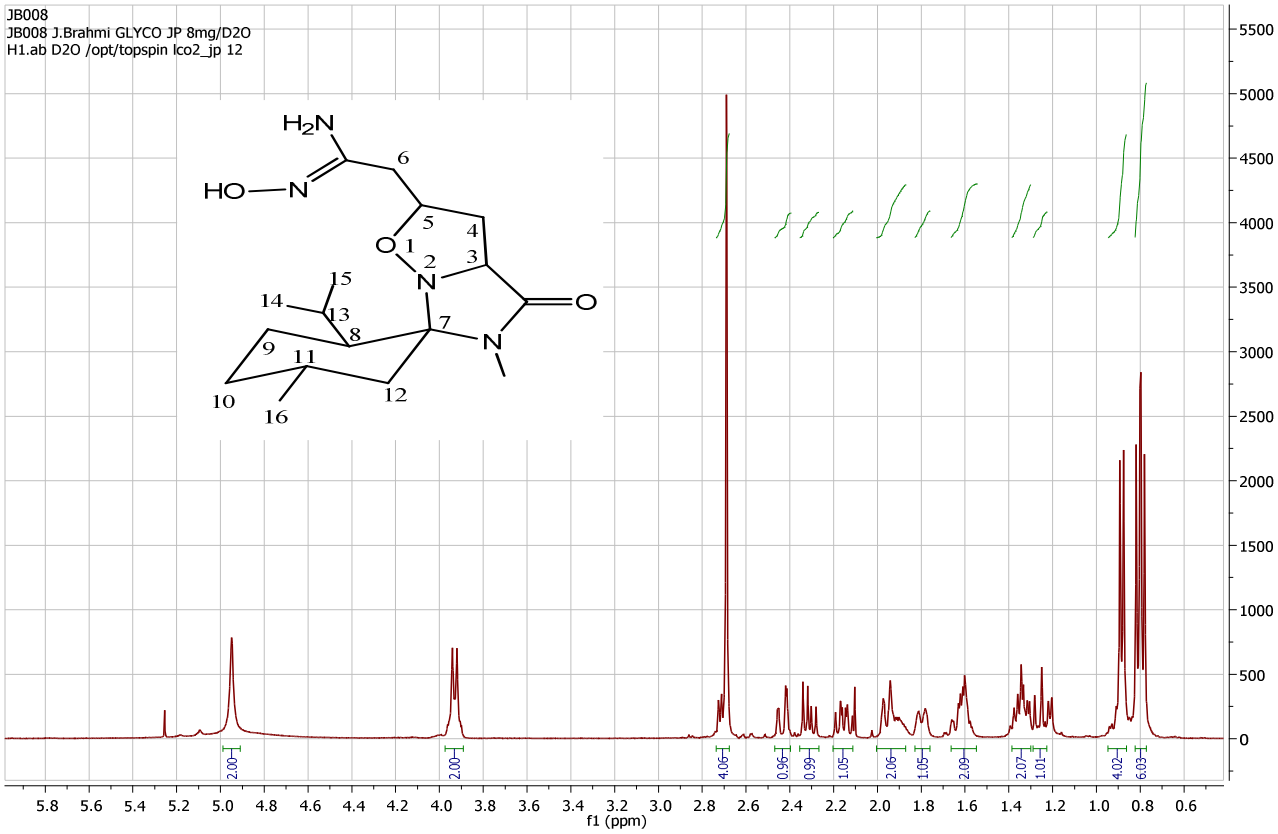

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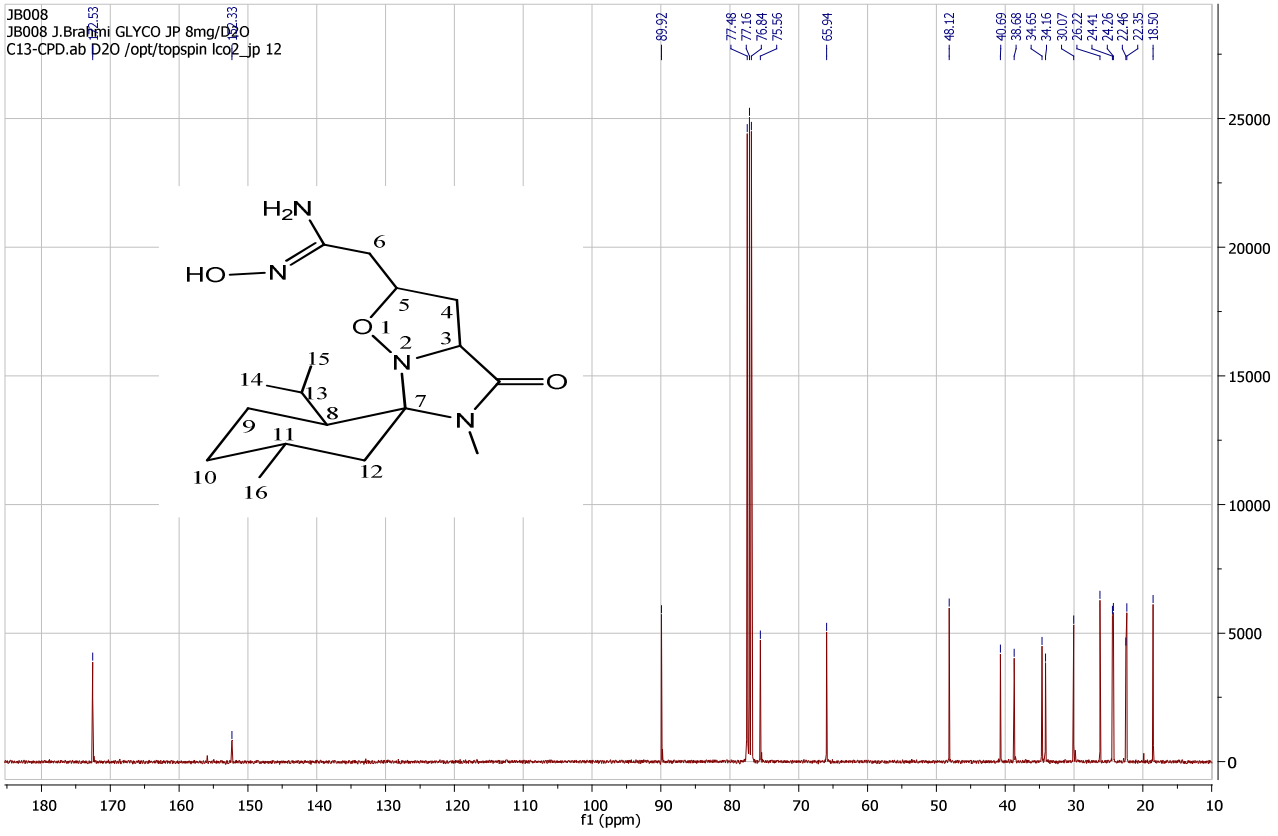
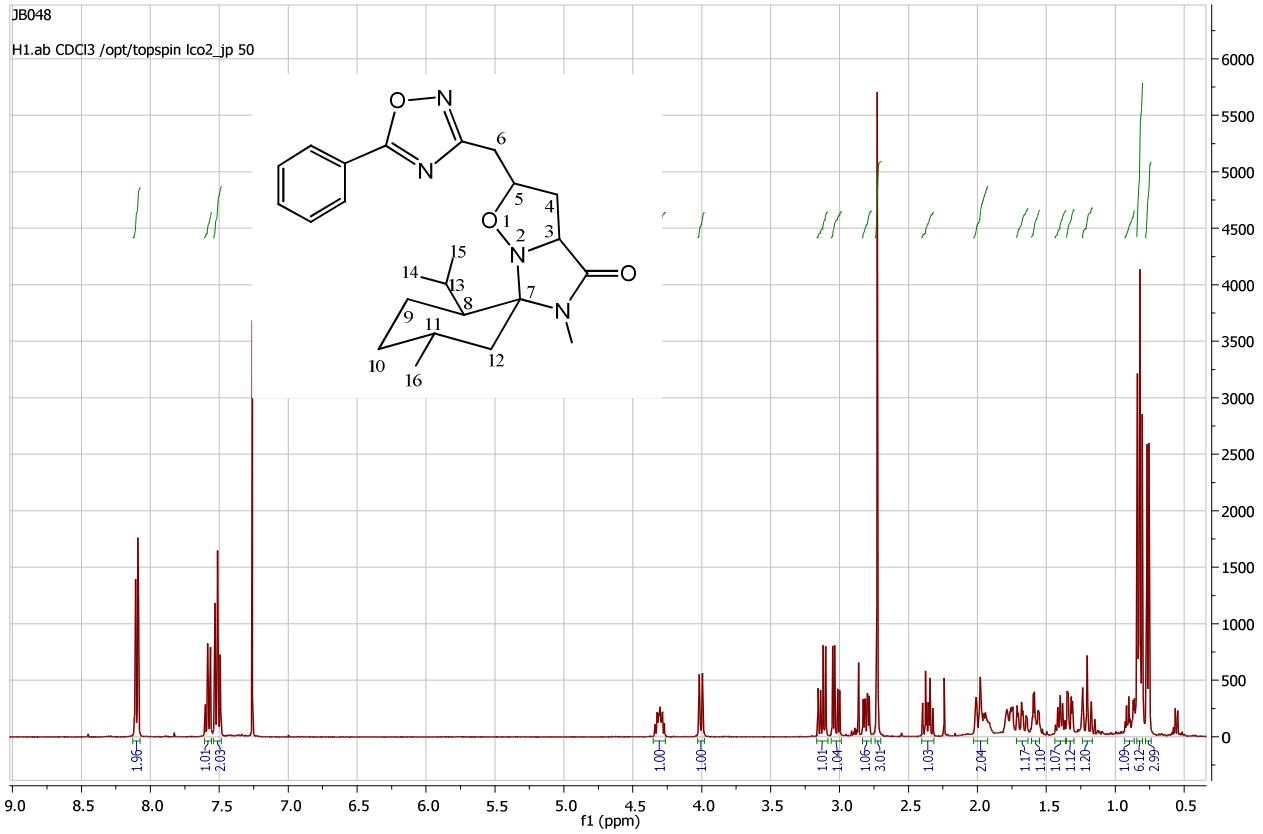


^{13}C NMR of compound (**3**)



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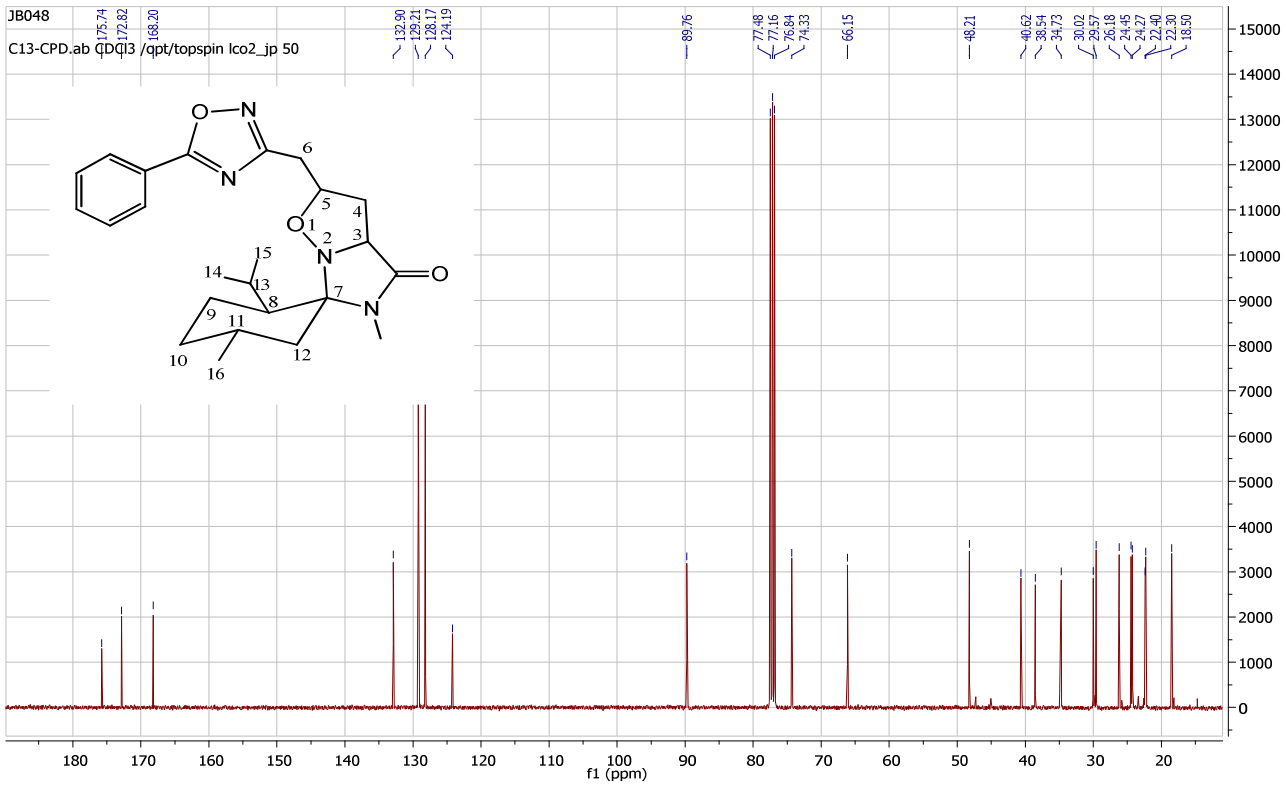

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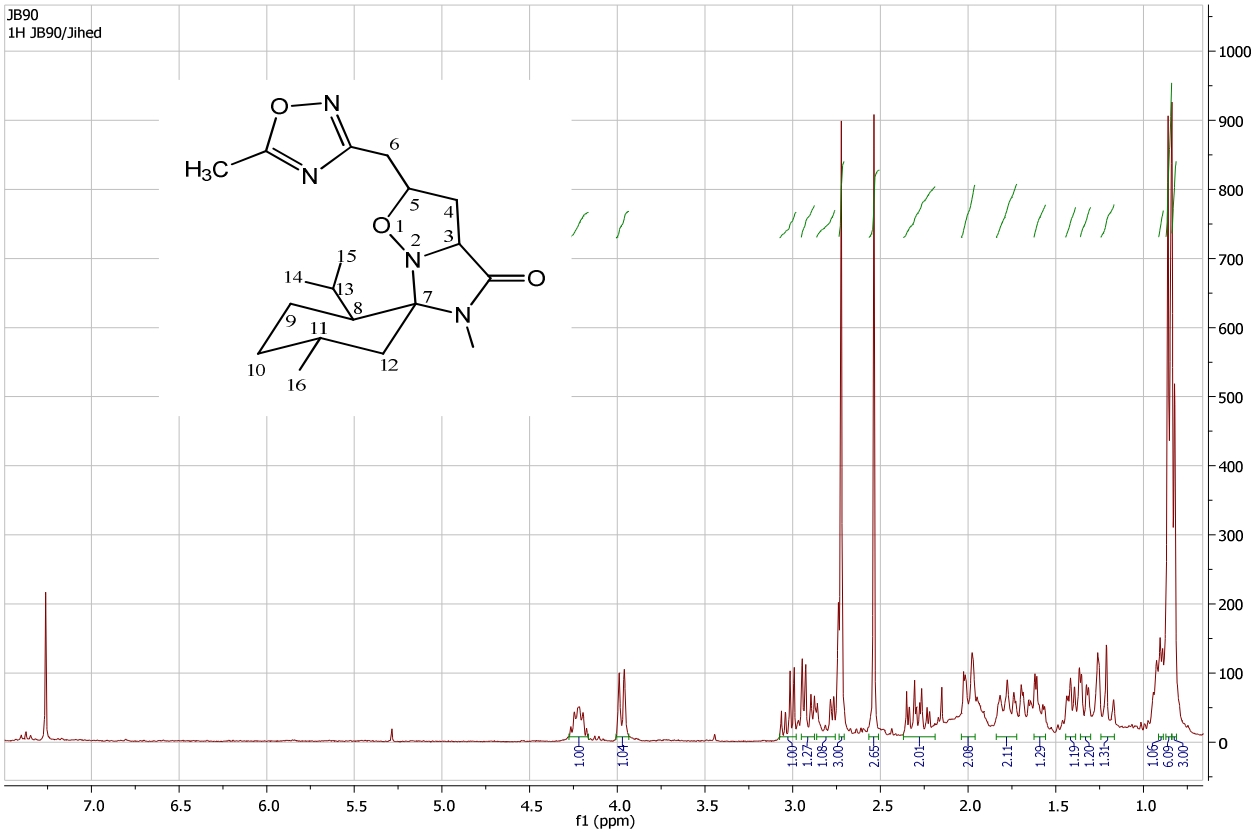
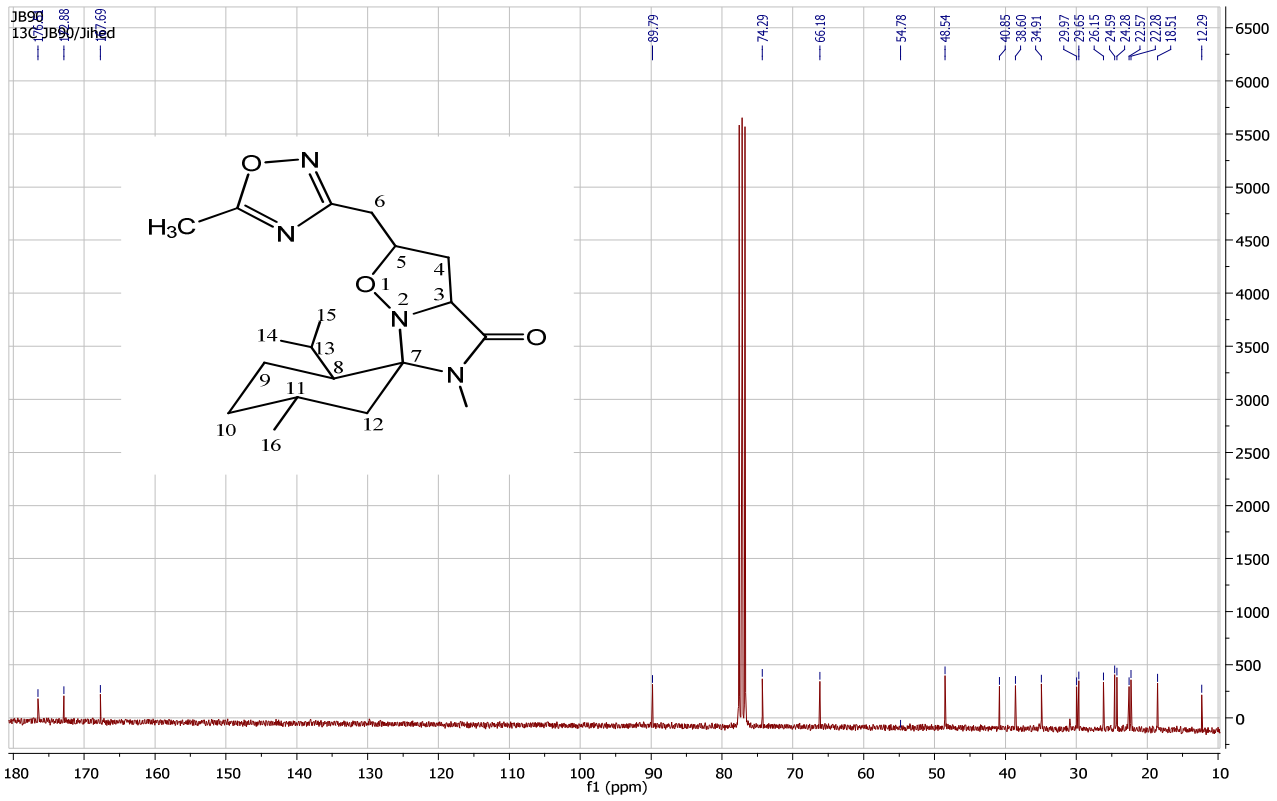


^{1}H NMR of compound (**4b**)



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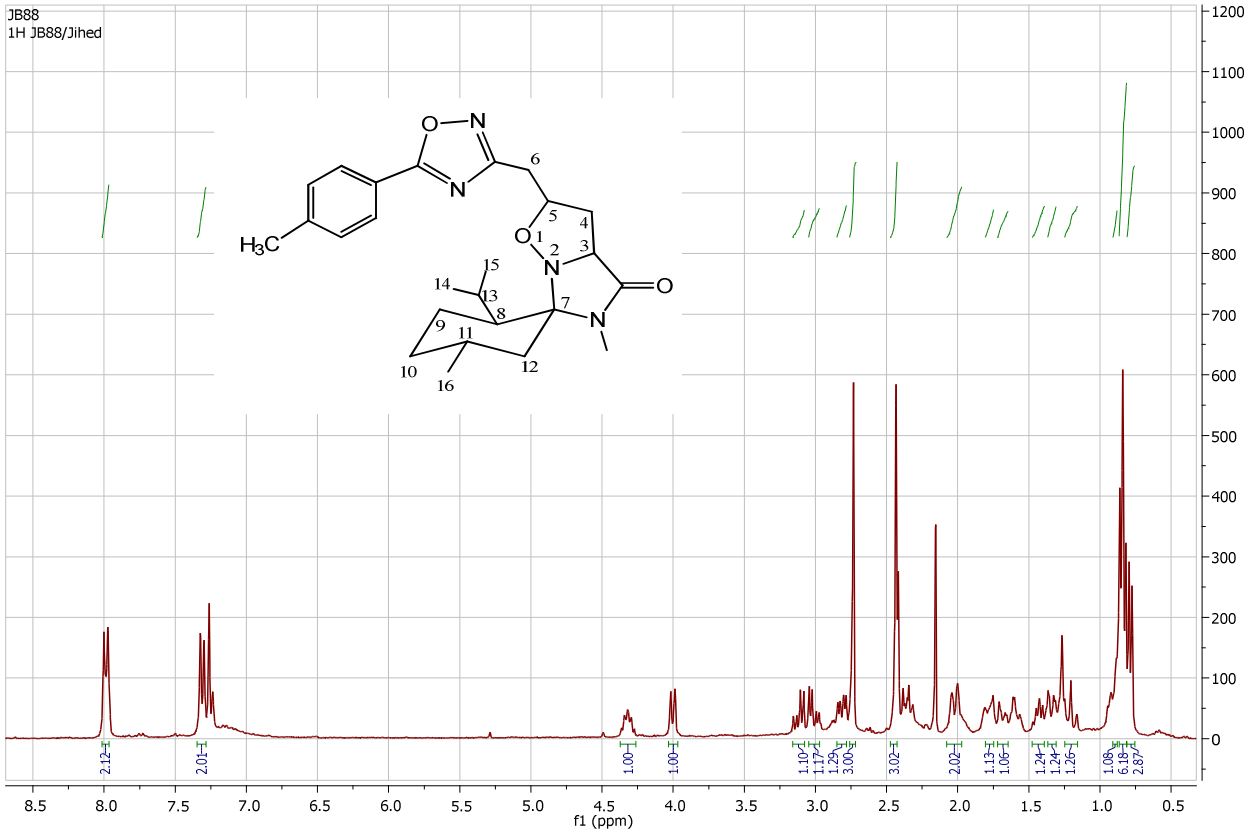

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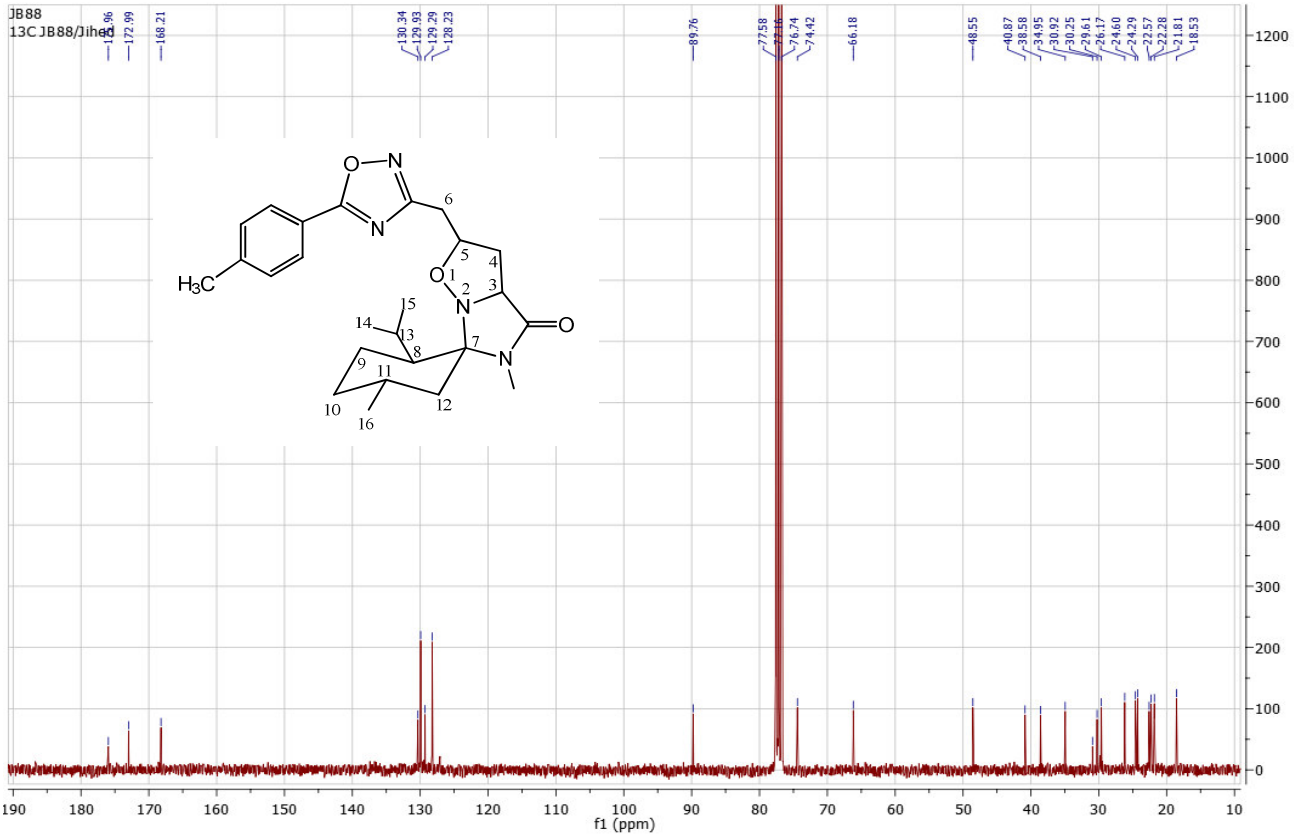

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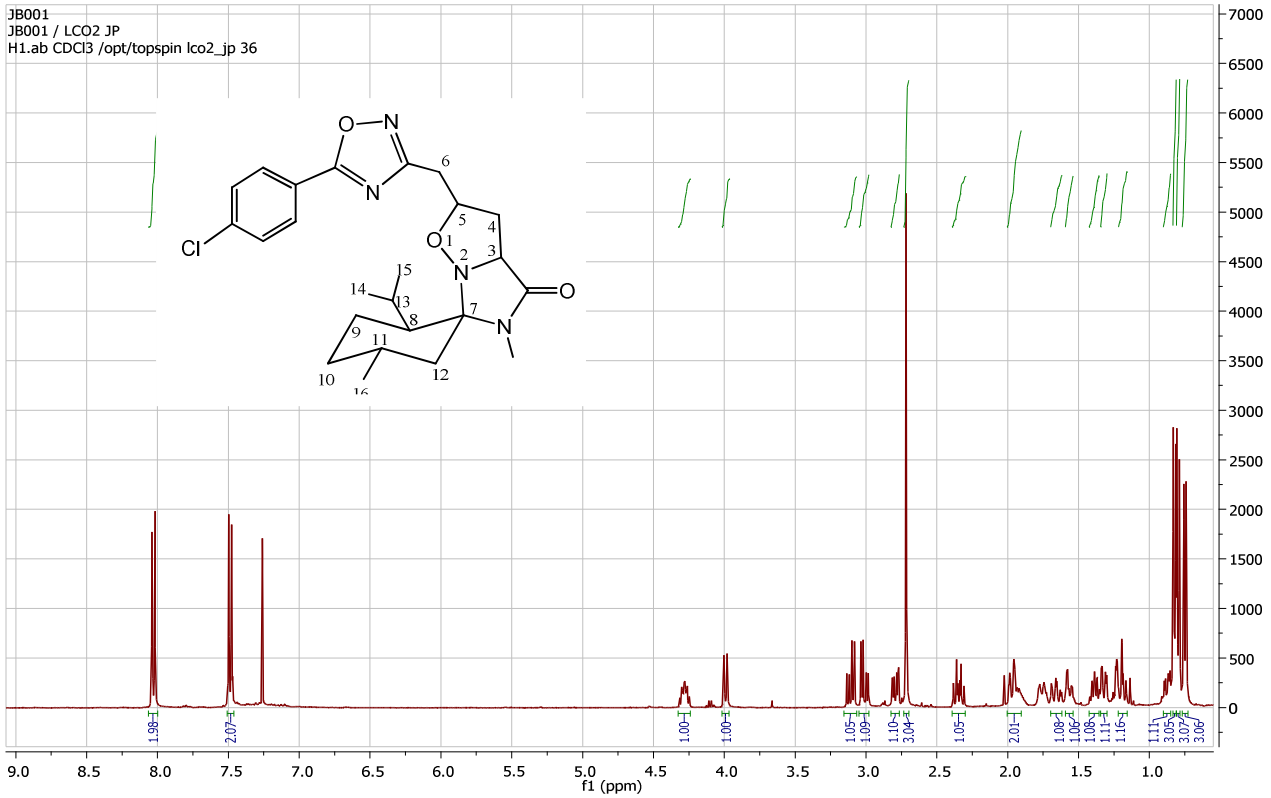

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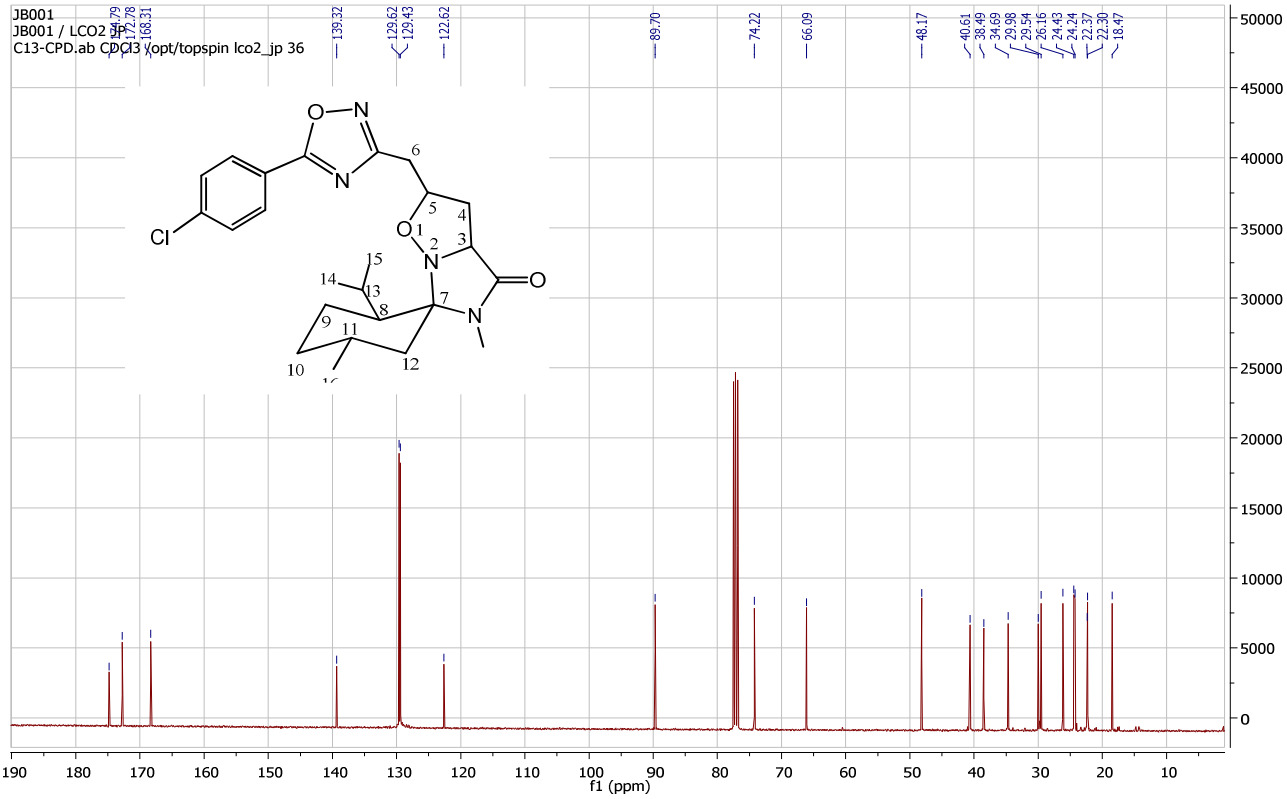

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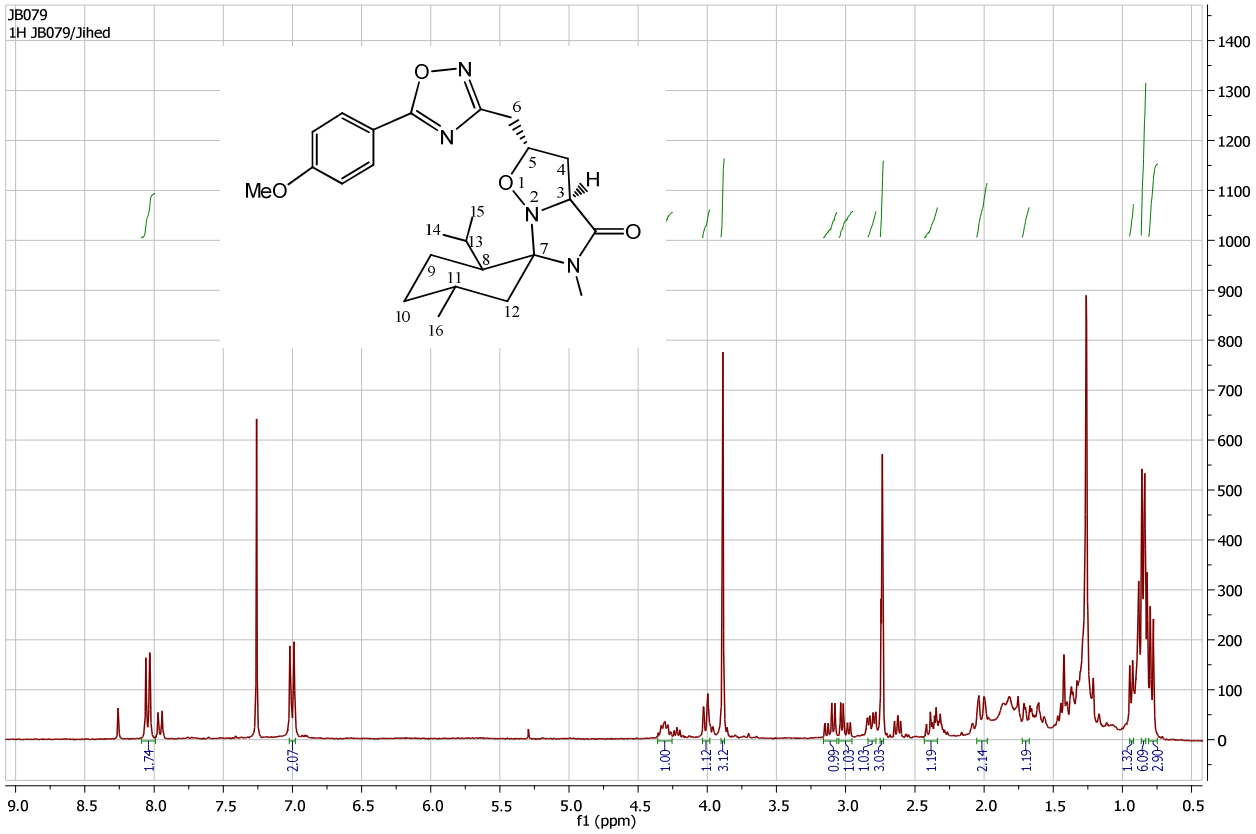

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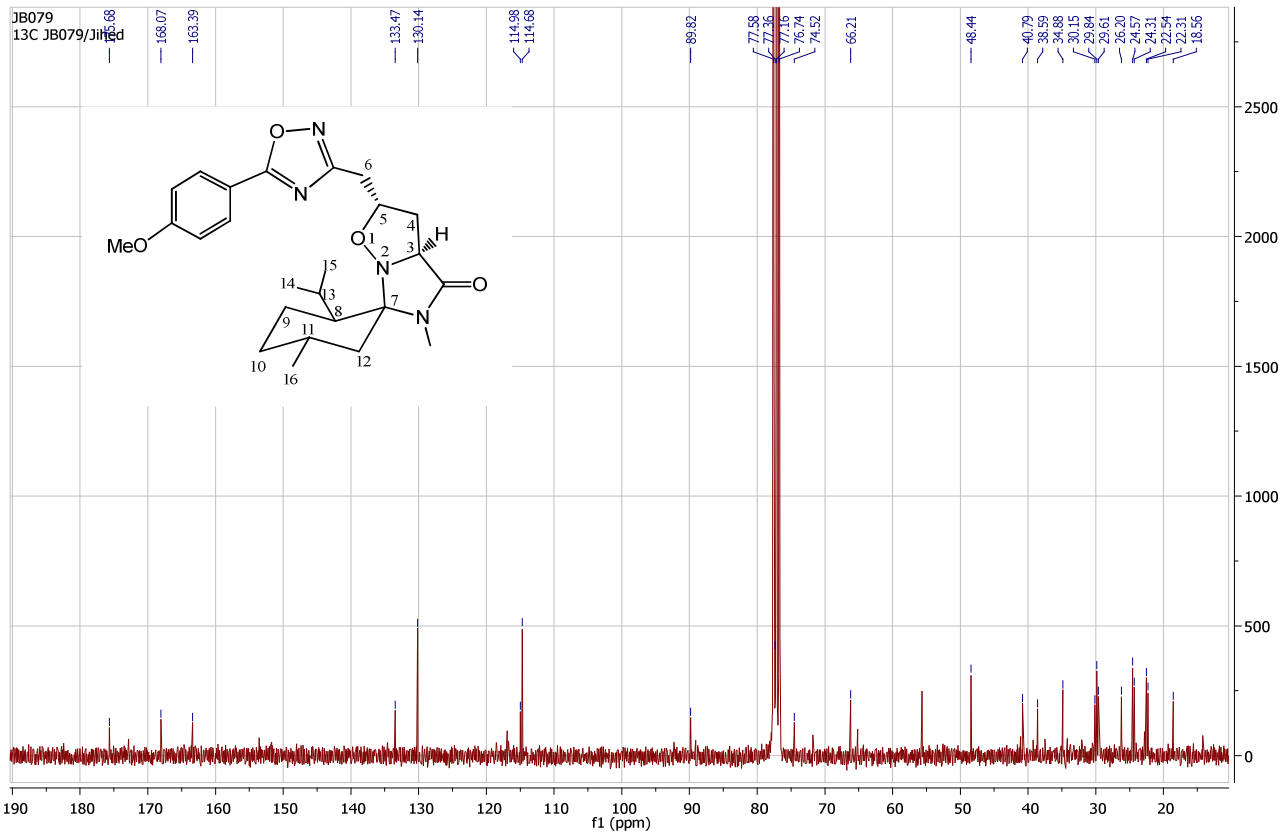

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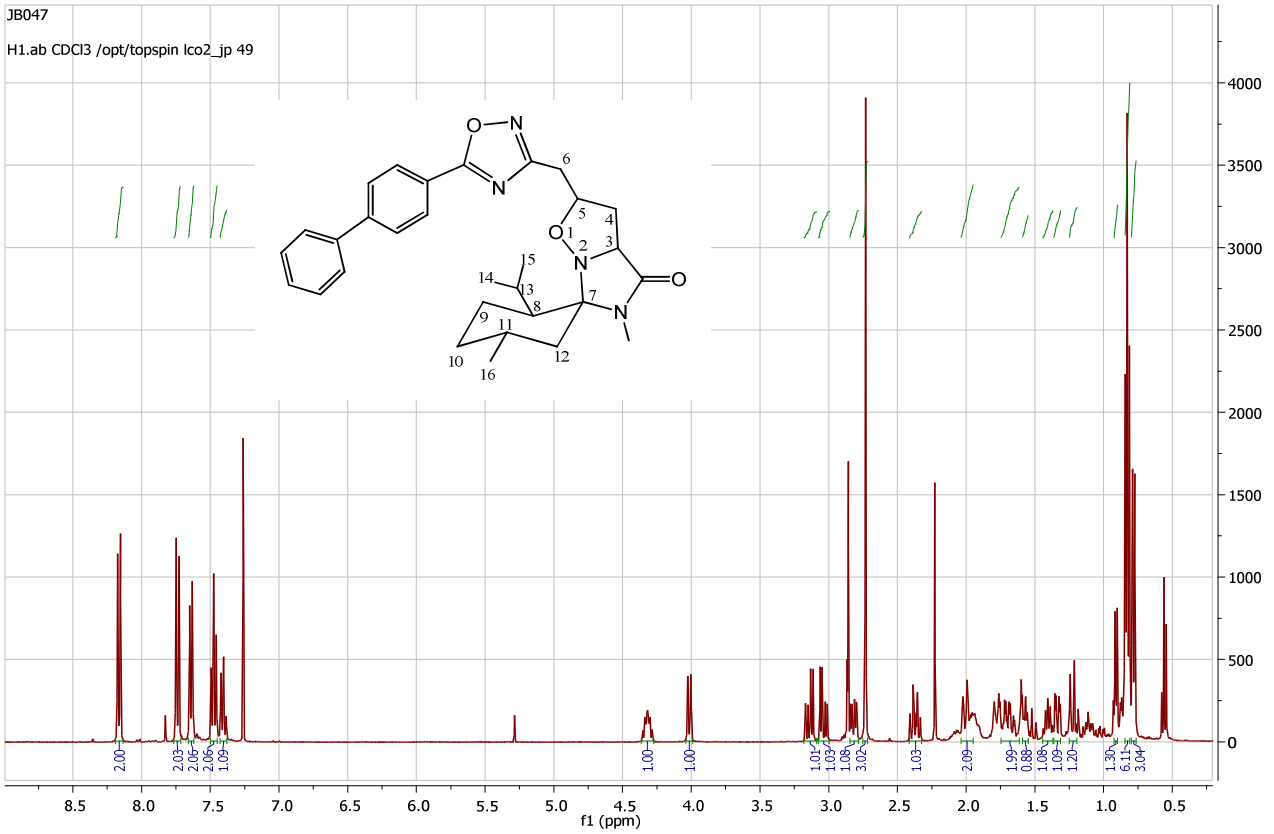
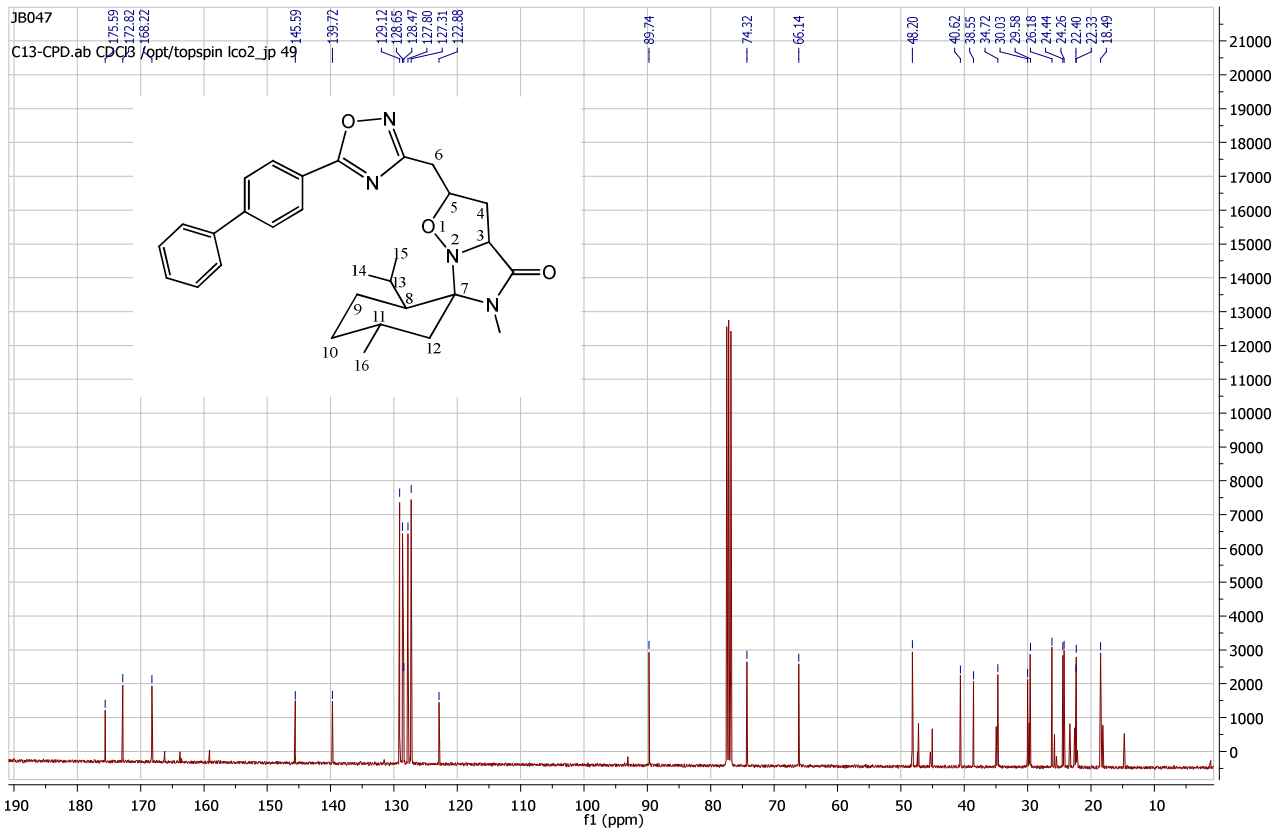


^{1}H NMR of compound (**4f**)



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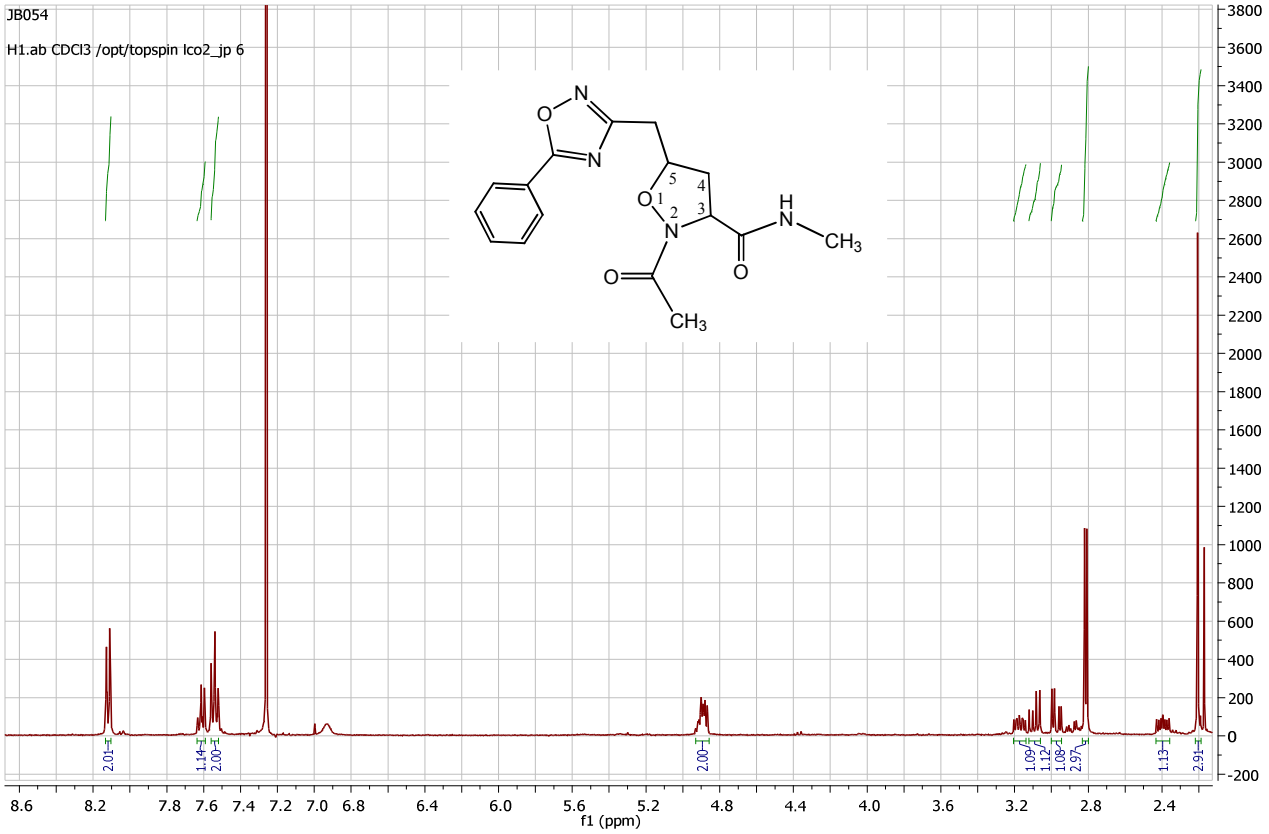
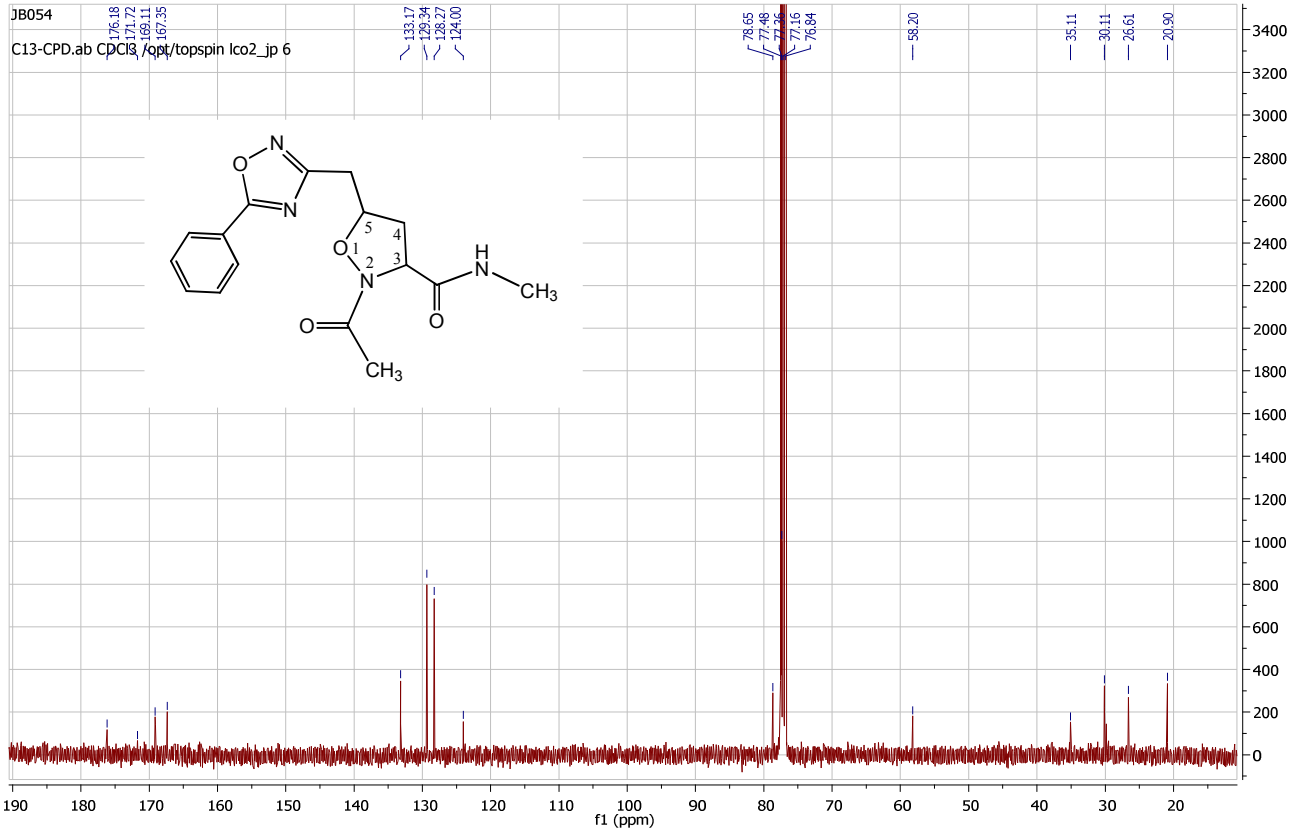


^{1}H NMR of compound (**5a**)



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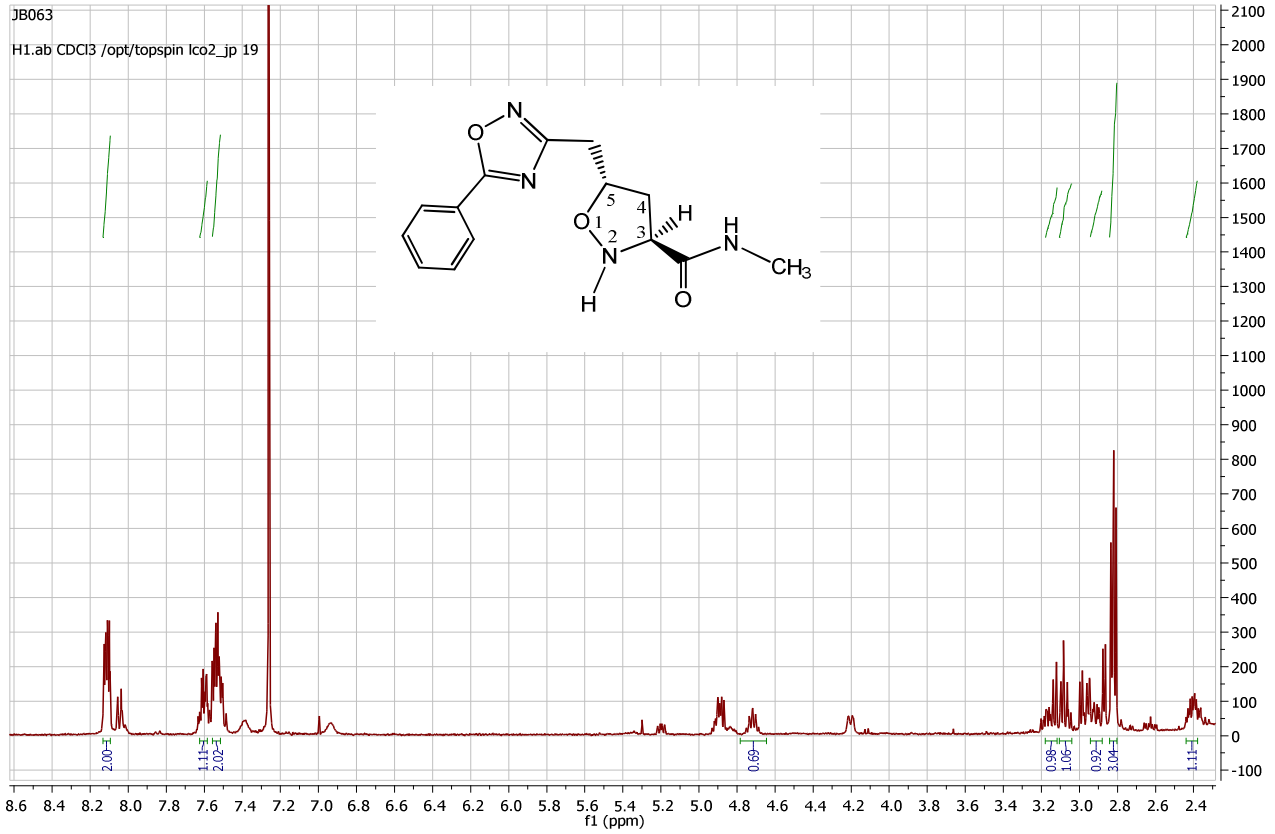
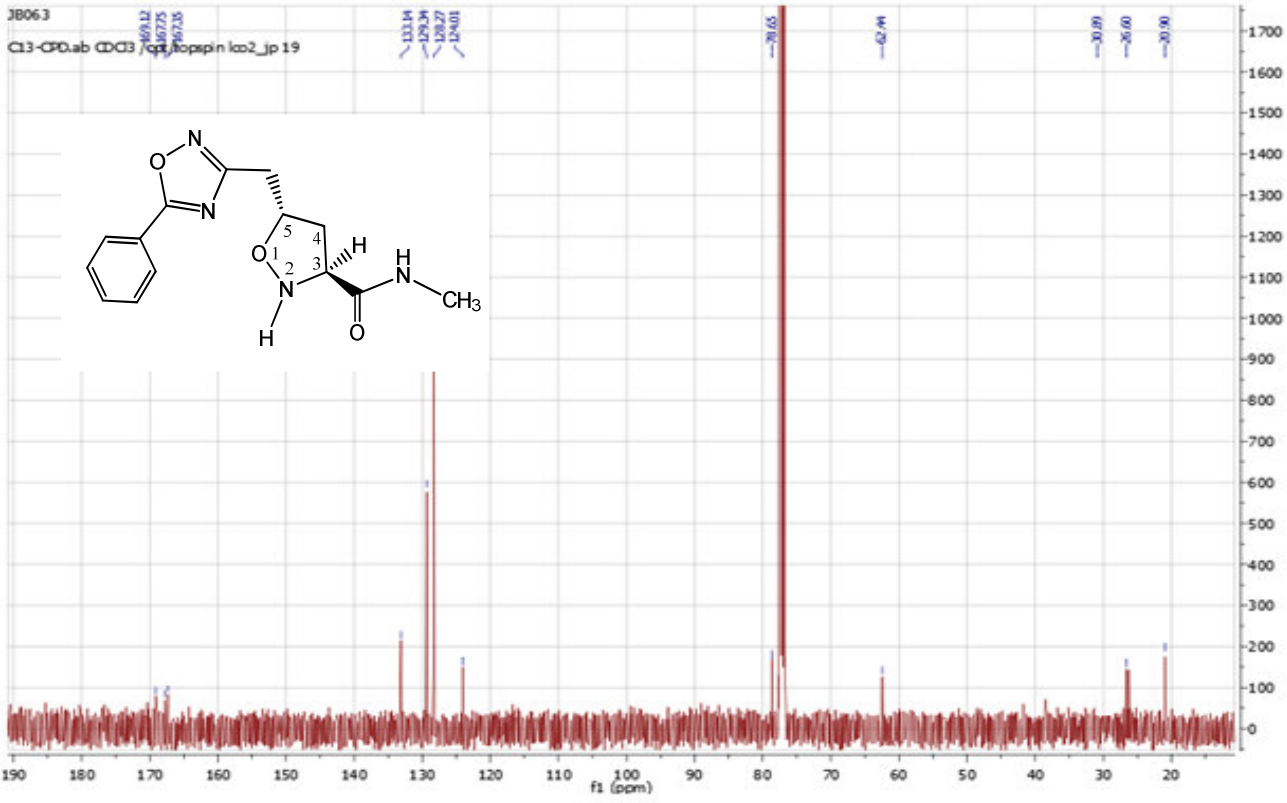


^{1}H NMR of compound (**5'a**)



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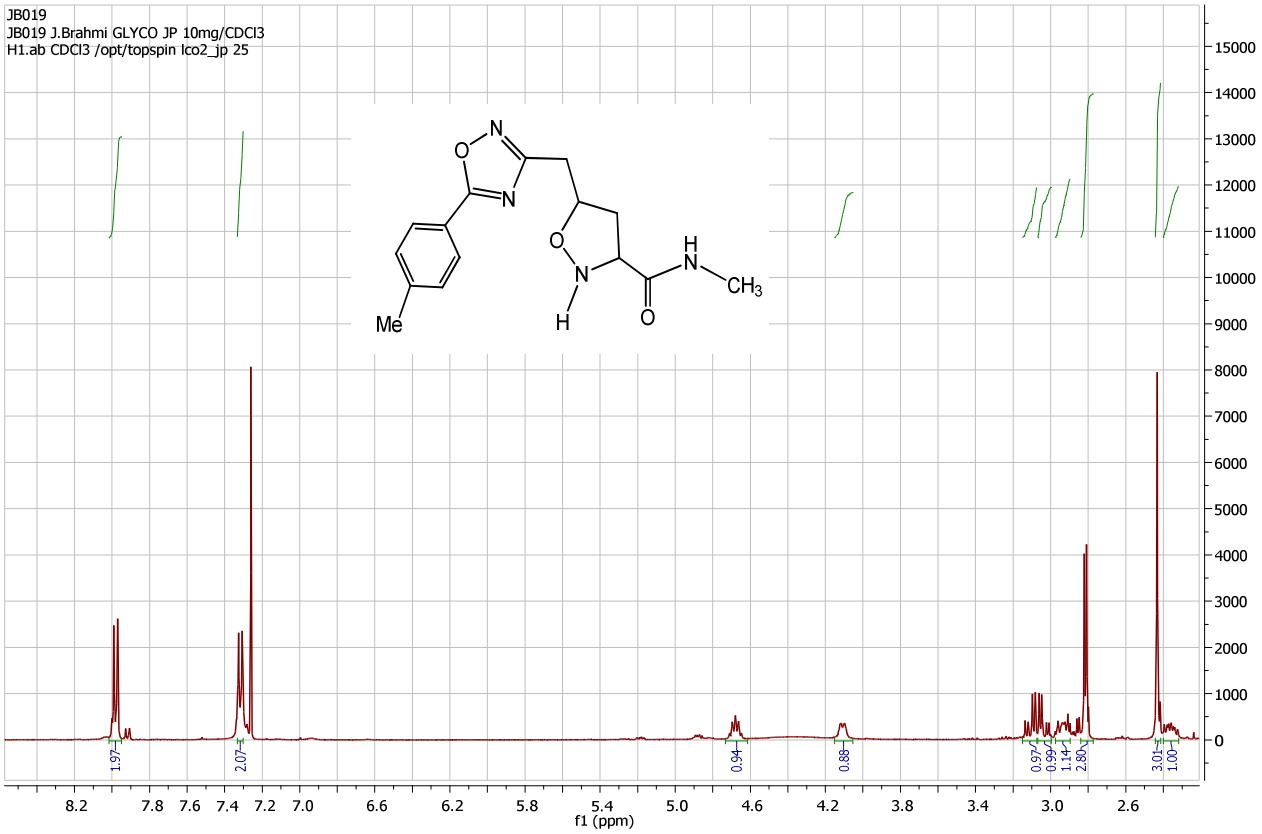

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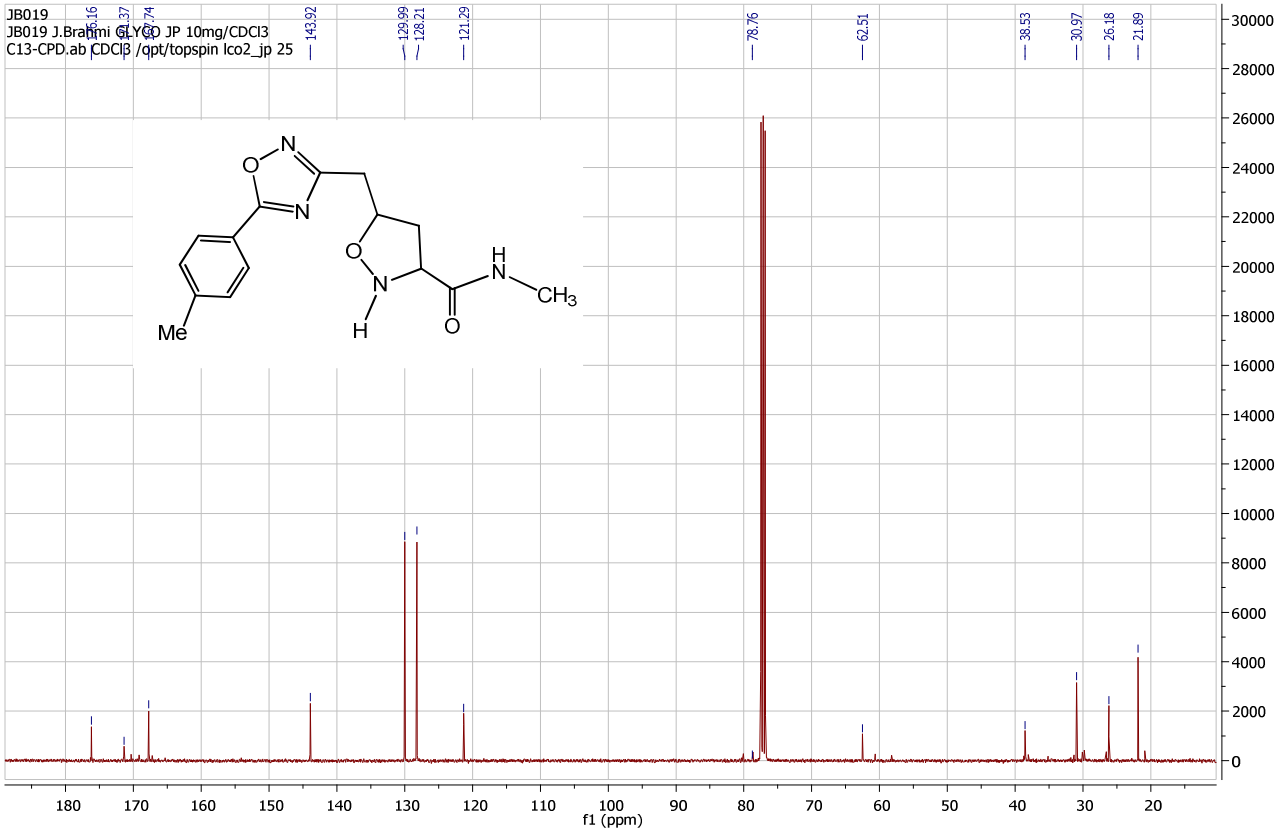

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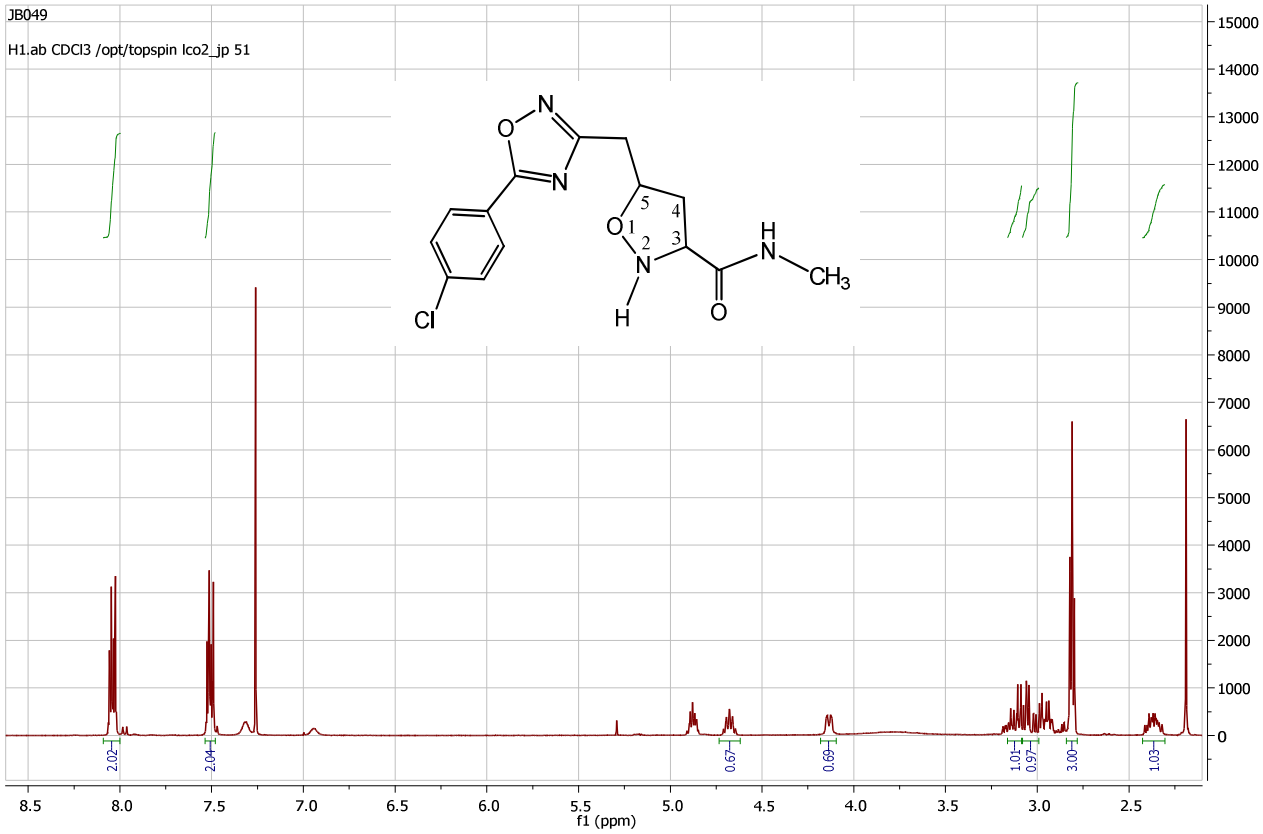

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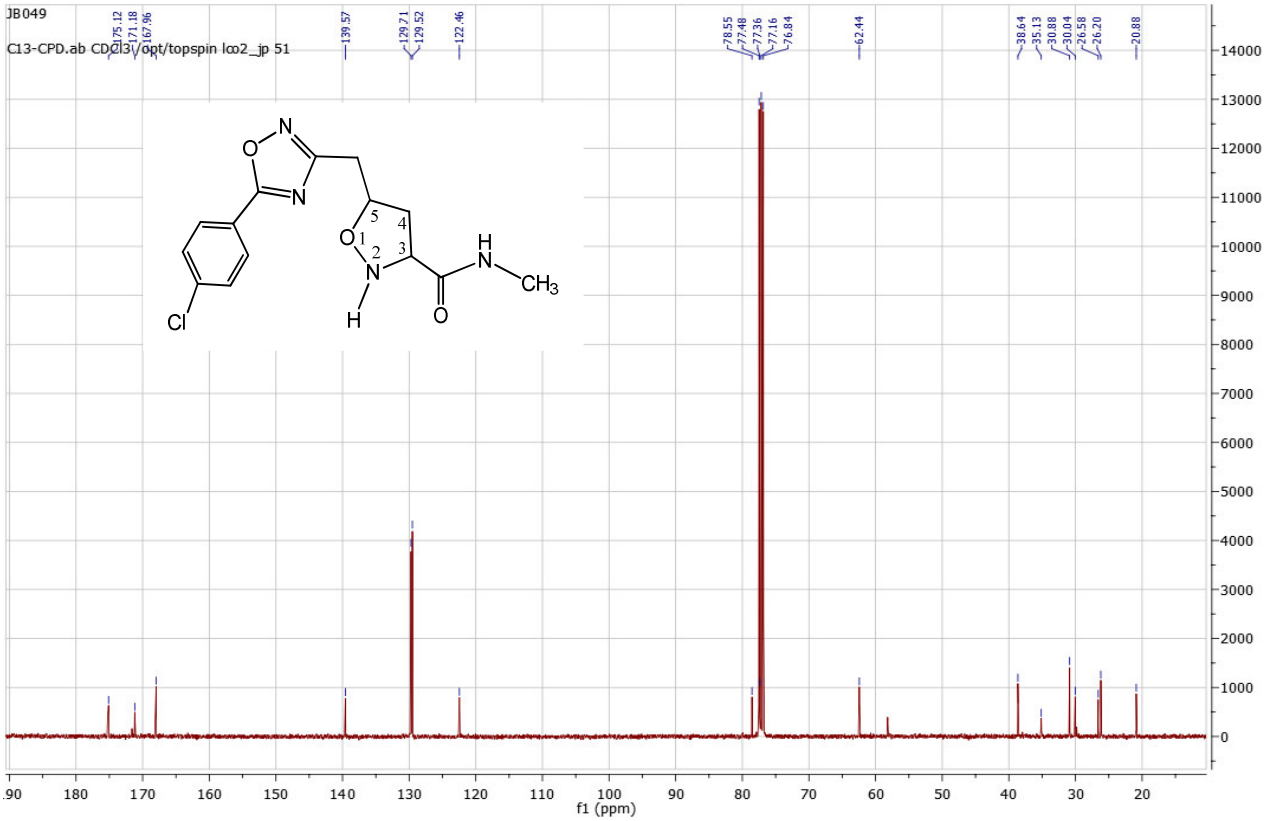

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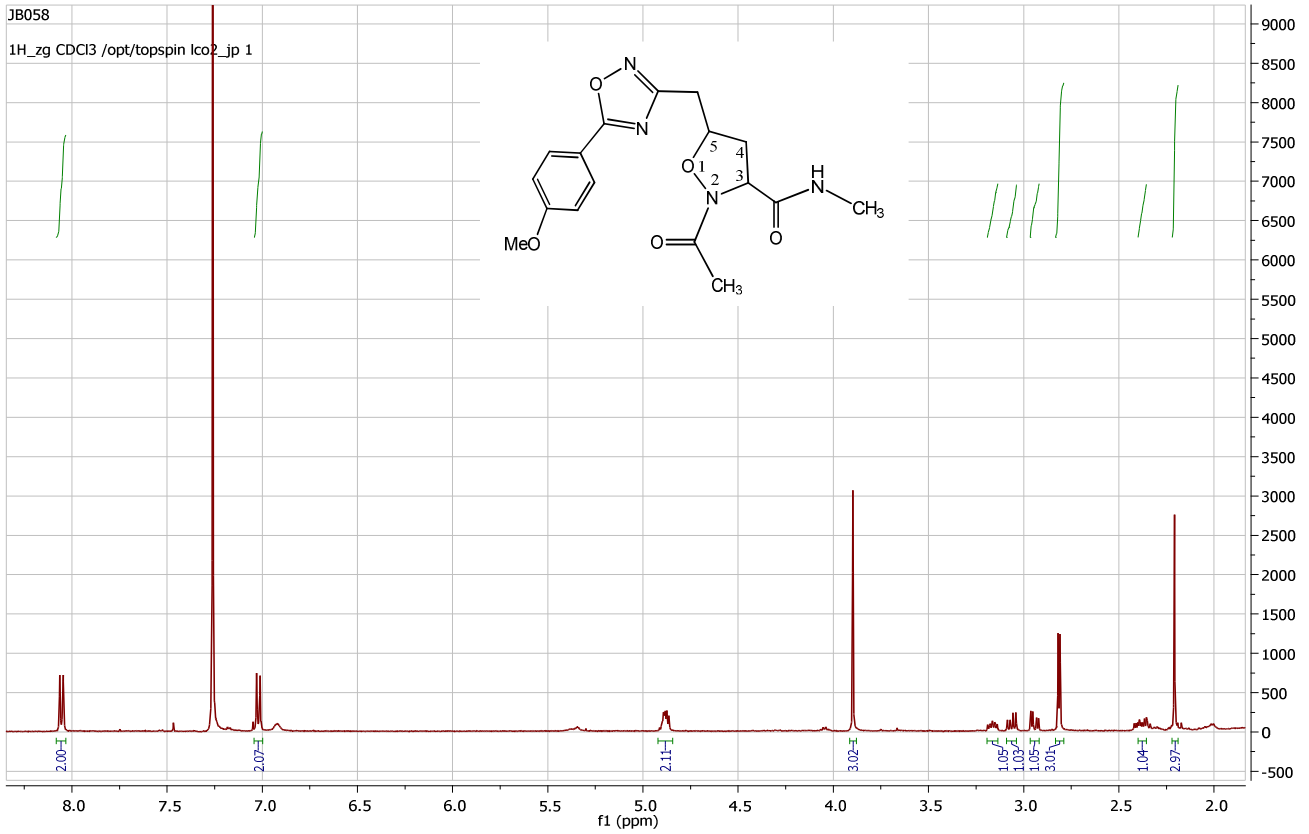

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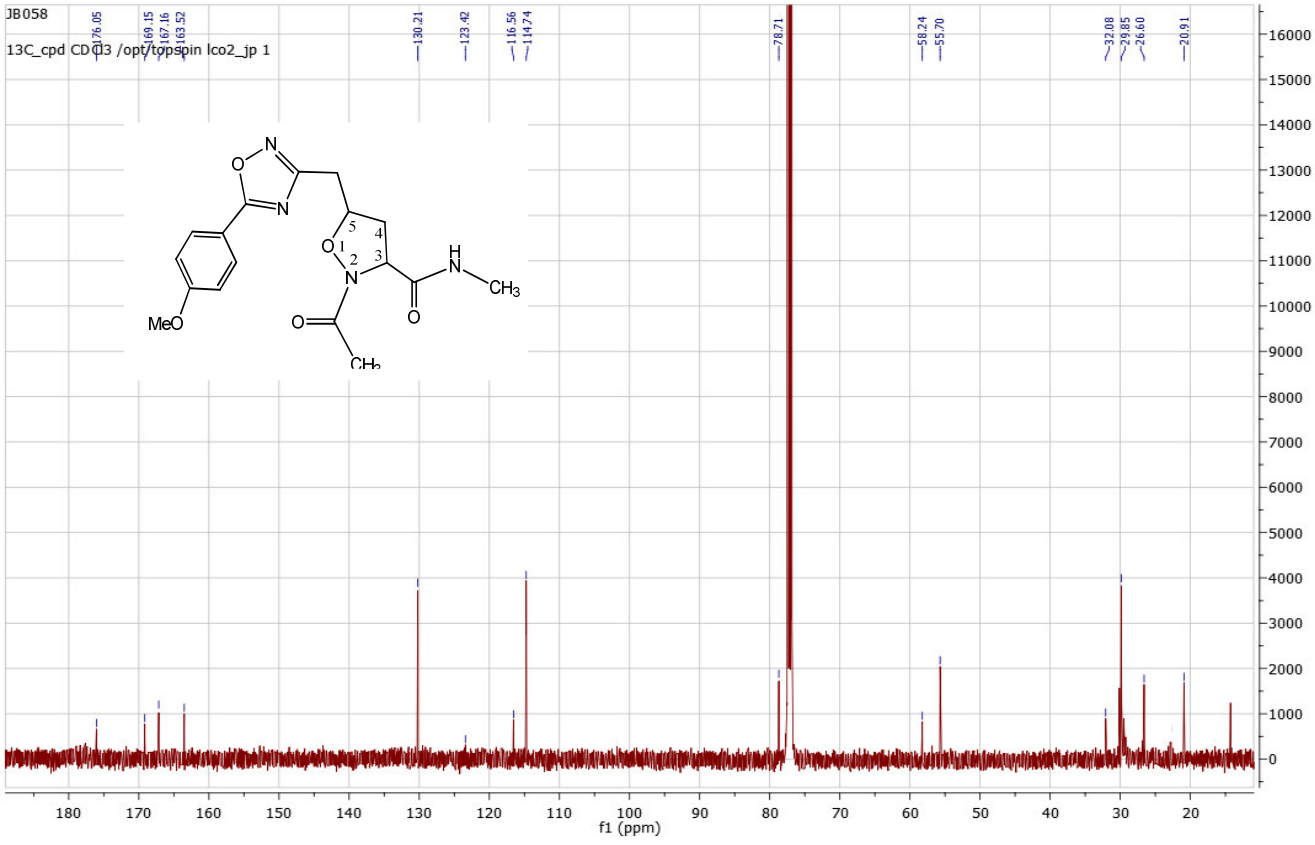

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