ZrO_2-supported Cu (ll) - β-cyclodextrin complex: construction of 2, 4, 5-trisubstituted -1, 2, 3-triazoles via Azide-chalcone oxidative Cycloaddition and Post-Triazole Alkylation

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1. Experimental Section

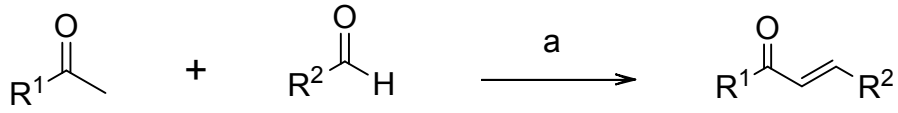
General Methods

Zirconium oxychloride ($ZrOCl_2.8H_2O$, >99.0%), ammonia ($NH_3.H_2O$, 25%) was purchased from S.D. FINE-CHEM LTD, India. β-cyclodextrin was purchased from Sigma-Aldrich India, deionized water was used for all workup procedures. Melting points were measured on secor INDIA apparatus and are uncorrected. ^1H NMR and ^{13}C NMR were recorded on VNMRS-400 (Agilent Technologies) NMR spectra in $CDCl_3$. Tetramethylsilane (TMS; δ = 0.00 ppm) served as internal standards for ^1H NMR. The corresponding residual non-deuterated solvent signal (CDCl3: δ = 77.00 ppm) was used as internal standards for 13C NMR. Performed Column chromatography on silica gel 60-120 mesh (Merck). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Mass spectra were measured with Micromass Q-Tof (HRESI-MS). DMF was dried over CaH_2 for 2 h and filtered. The catalyst was characterized by ATR-Fourier transform infrared (ATR-IR) were recorded using a Thermo Nicolet FTIR spectrometer (Model 5700, Madison, WI) fitted with a single bounce attenuated total reflectance (ATR) accessory with a ZnSe crystal of range 400-4000cm-1. X-ray powder diffraction (PXRD) was carried out on a XRD 7000, Shimandzu diffractometer with CuKα radiation. Scanning electron microscopy (SEM) images were obtained using a JEOL JXA-8530F microscope. Transmission electron microscopy (TEM) images were performed on PHILIPS CM200 electron microscopes at an acceleration voltage of 20-200kv. TGA thermograms of the nanoparticles were obtained under nitrogen on a Perkin–Elmer TGA 7 analyzer at a heating rate of 20°C min-1.

2. Starting material preparation:

2.1. General procedure for synthesis of α,β-unsaturated ketone

Starting materials, chalcone, were prepared from the corresponding aldehyde and ketone using general procedure as shown in the following Scheme and spectral data are in good agreement with the literature.

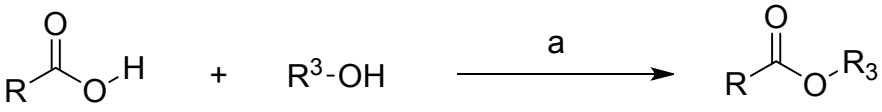


R^1 = 2-thiophenyl, aryl;
R^2 = benzo[1,3]dioxole , aryl;

Scheme 1. Preparation of α, β-unsaturated ketones: (a) 6N NaOH, MeOH at rt.

The following procedure is representative synthesis of all chalcones. The substituted acetophenone (0.05 mmol) and NaOH (0.01 mmol) were dissolved in 15 ml ethanol, and taken in a 50 mL round bottom of flask equipped with stirrer. The reaction was agitated at 0-5^{o}C; then the aldehyde was dissolved in 10 mL ethanol and added drop wise for 30 minutes, then the reaction was allowed to continue for 5 h at room temperature. The residual mass was quenched in the ice-water mixture and neutralized with 10% HCl solution. Then chromatography separation was followed by recrystallization from 95% ethanol in increasing order of polarity.

2.2. General procedure for synthesis of esters



R= aromatic;
R^3= alkyl;

Scheme 2. Preparation of esters from acids: (a) MeOH, H_2SO_4 (cat) at reflux temperature.

The substituted aromatic acid (0.05 mmol) were dissolved in 15 mL ethanol, and taken in a 50 ml round bottom of flask equipped with stirrer. The reaction was refluxed at 80 °c; then catalytic amount of $H_2SO_4$was dissolved in 10 mL ethanol and added dropwise for 30 minutes, then the reaction was allowed to continue for 5 h. When the reaction was complete (monitored by TLC), the reaction solvent was removed under reduced pressure, and then reaction mixture was extracted with ethyl acetate and work up with 5% HCl and 5% $NaHCO_3$

3. Preparation of Cu–β-cyclodextrin complex

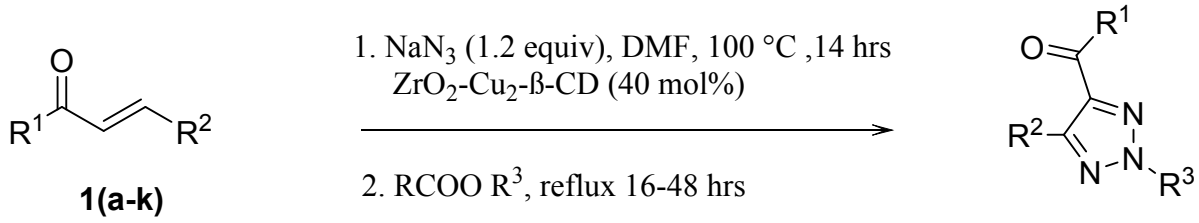
The complex was prepared following the method described by Matsui et al.[24] In a 250 ml Becker containing 50 ml of 0.5 M NaOH, β-cyclodextrin (1 mmol) was dissolved with stirring. To this clear solution 75 ml of 0.04 M $CuSO_4$•$(H_2O)_5$ (3 mmol) solution was added. A dark blue solution was obtained immediately and was stirred at room temperature for 6 h. Resulting solution was filtered to remove excess of copper salt which precipitated as a blue solid (copper hydroxide). To this blue solution was added ethanol (about 400 ml) until a light blue suspension was formed, then it was filtrated and washed with ethanol and air-dried at room temperature. This complex was converted to fine powder.

4. Preparation of ZrO_2-supported Cu (II)-β-cyclodextrin nanoparticles

The ZrO_2-supported Cu (II)-β-cyclodextrin nanoparticles were prepared by a traditional chemical co-precipitation method.[25] 1.5 g of Cu (II)-β-cyclodextrin and 2.42 g of zirconium oxychloride ($ZrOCl_2.8H_2O$) were dissolved in 50 mL of distilled deionized water under intense stirring at 90 °C. Subsequently, ammonia (25%) was added dropwise to the reaction mixture with stirring. The formed nanoparticles were collected by filteration under the reaction flask and the liquid reaction mixture was removed. The particles were washed with distilled water repeatedly and dried for 24 h at room temperature in a vacuum oven

(unsupported ZrO_2 nanoparticles were obtained according to the above procedure without adding Cu (II)-β-cyclodextrin).

4.1. General procedure for synthesis of N-2-substituted triazoles:



R^1 = 2-thiophenyl, aryl;
R^2 = benzo[1,3]dioxole , aryl ;
R^3 = aryl, alkyl;

The general procedure of the reaction between chalcones, sodium azide and aryl esters: regioselective synthesis of **2k** (5-(4-ethylphenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone:All reactions were performed on a 1 mmol scale relative to chalcones. 3-(4-ethylphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**1h**) (1 mmol), sodium azide (1.2 mmol), 40 mol % of ZrO_2-Cu_2-β-CD (50 mg, 0.036 mmol) and 3 mL DMF were taken in a round bottom flask equipped with stirrer. The reaction mixture was agitated at 100 ^oC for 14 h, then ester (1 mmol) was added to the mixture and the reaction continued at 100^oC for 16 h. The reaction mixture was diluted with water (4 mL), and extracted with ethyl acetate (6×10 mL). The combined organic phases were washed with brine (4×10 mL), dried over anhydrous Na_2SO_4 and concentrated in vaccum. The residue was subjected to column chromatography with hexanes/EtOAc as eluent to obtain the desired **2k** (77% yields). The remaining substituted triazoles were prepared in the similar manner.

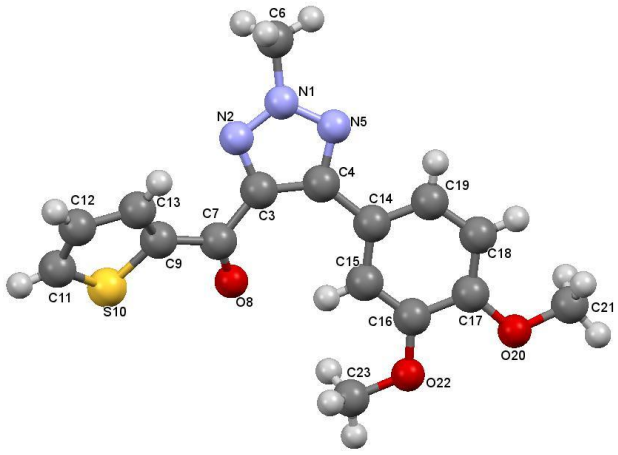
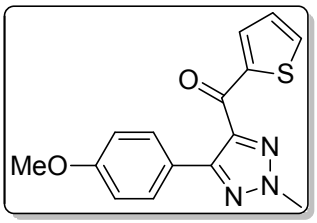


Fig. 5 ORTEP diagram of **2b** (CCDC 1009982)

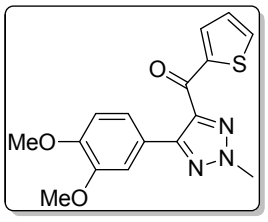
5. Characterization data of isolated triazole molecules (2a-2s):

(5-(4-methoxyphenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2a).



White solid, (m.p. 89-90 °C); R_f = 0.8 (Hexane: EtOAc 8: 2); IR (KBr): 3065, 2945, 1740, 1517, 1468, 1300, 1238, 1056, 838, 747, 656 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ= 8.22-8.21 (d, *J*=4 Hz, 1H , thiophene H), 7.87-7.85 (d, *J*=8Hz, 2H, ArH), 7.72-7.71 (d, *J*=4 Hz, 1H, thiophene H), 7.18-7.16 (t, *J*=4 Hz, 1H, thiophene H), 6.97-6.95 (d, *J*=8Hz, 2H, ArH), 4.32 (s, 3H, N-Me), 3.84 (s, 3H, OMe); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=178.4, 160.3, 149.8, 143.4, 141.2, 135.5, 134.8, 130.3, 128.0, 121.9, 113.6, 55.2, 42.2; HRMS (ESI) *m/z* Calculated for $C_{15}H_{13}N_3O_2SNa$ $(M+Na)^+$ 322.0626, Found 322.0631.

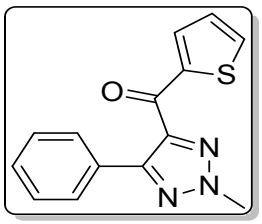
(5-(3, 4-dimethoxyphenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2b).



Pale Yellow solid, (m.p. 126-127 °C); R_f= 0.7 (Hexane: EtOAc 8: 2); IR (KBr): 3067, 2961, 1743, 1510, 1471, 1314, 1242, 1067, 838, 786, 668 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ=8.19-8.18 (d, *J* = 3.6 Hz, 1H,

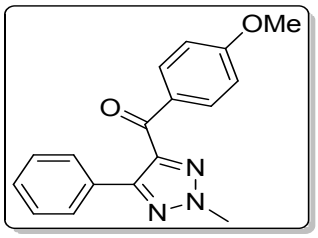
thiophene H), 7.73-7.72 (d, *J*=4.8 Hz, 1H, thiophene H), 7.55-7.54 (d, *J*=6.8 Hz, 2H, ArH), 7.19-7.16 (t, *J*=4.2 Hz, 1H, thiophene H), 6.94-6.92(d, *J*=8.8 Hz, 1H, ArH), 4.33 (s, 3H, N-Me), 3.95(s, 6H, OMe). 3.92(s, 6H, OMe); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=178.5, 149.7, 149.6, 148.5, 143.5, 141.3, 135.6, 134.9, 128.0, 122.1, 121.8, 112.0, 110.7, 55.9, 55.8, 42.3; HRMS (ESI) *m/z* Calculated for $C_{16}H_{15}N_3O_3SNa$ $(M+Na)^+$ 352.0732, Found 352.0731.

(2-methyl-5-phenyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2c).



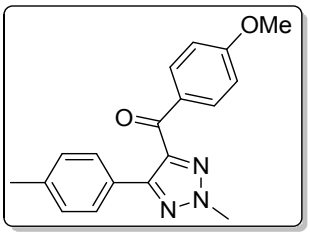
Pale yellow Oil, R_f = 0.7 (Hexane: EtOAc 8: 2); IR (Nujol): 3065, 2978, 1750, 1515, 1471, 1299, 1242, 1056, 845, 747, 678 cm$^{-1;}$ ^{1}H NMR (400 MHZ, $CDCl_3$): δ=8.22-8.21 (d, *J*=4 Hz, 1H, thiophene H), 7.88-7.86 (d, *J*=8Hz, 2H, ArH), 7.73-7.72 (d, *J*=4 Hz, 1H, thiophene H), 7.45-7.41 (m, 3H, ArH), 7.19-7.17 (t, *J*=4 Hz, 1H,thiophene H), 4.35 (s, 3H, N-Me); ^{13}C NMR (100 MHZ, $CDCl_3$); δ=178.4, 160.3, 149.9,143.9, 135.6, 135.0, 129.5, 129.1, 128.9, 128.2, 128.1, 42.3; HRMS (ESI) *m/z* Calculated for $C_{15}H_{13}N_3O_2SNa$ $(M+Na)^+$ 292.0521, Found 292.0520.

(4-methoxyphenyl)(2-methyl-5-phenyl-2H-1, 2, 3-triazol-4-yl) methanone (2d).



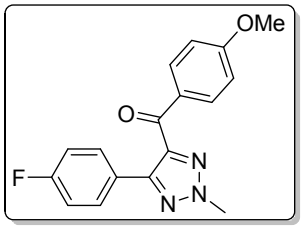
White solid, (m.p. 89-90 °C); R_f = 0.8 (Hexane: EtOAc 8 : 2); IR (KBr): 3005, 1738, 1575, 1533, 1310, 1258, 1100, 834, 767, 664 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$): δ=8.09-8.06 (d, *J*=8.8 Hz, 2H, ArH), 7.79-7.77 (d, *J*=8.0Hz, 2H, ArH), 6.96-6.94 (d, *J*=8.8 Hz, 2H, ArH), 4.31 (s, 3H, N-Me), 3.87(s, 3H, OMe); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=186.3, 163.8, 149.3, 142.3, 132.7, 130.0, 129.6, 128.9, 128.4, 128.3, 113.5, 55.4, 42.1; HRMS (ESI) *m/z* Calculated for $C_{17}H_{15}N_3O_2Na$ $(M+Na)^+$ 316.1062, Found 316.1069.

(4-methoxyphenyl)(2-methyl-5-(p-tolyl)-2H-1, 2, 3-triazol-4-yl) methanone (2e).



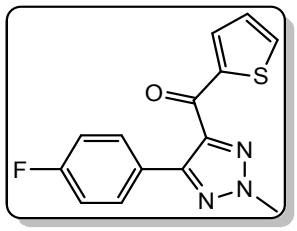
White crystalline solid, (m.p. 98-99 °C); R_f = 0.8 (Hexane: EtOAc 8: 2); IR (KBr): 3005, 1738, 1575, 1533, 1290, 1258, 1017, 834, 782 664 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ=8.08-8.05 (d, *J*=9.2Hz, 2H ArH), 7.68-7.66 (d, *J*=8.4Hz, 2H ArH), 7.20-7.18 (d, *J*=7.6, 2H ArH), 6.95-6.93 (d, *J*=9.2Hz, 2H ArH), 4.29 (s, 3H, N-Me), 3.87 (s, 3H, OMe), 2.36 (s, 3H, Me); ^{13}CNMR (100 MHZ, $CDCl_3$): δ=186.4, 163.8, 149.4, 142.2, 138.8, 132.7, 131.0, 130.2, 129.0,128.7, 128.3, 126.8, 113.5, 55.4, 42.1, 21.3; HRMS (ESI) *m/z* Calculated for $C_{18}H_{17}N_3O_2Na$ $(M+Na)^+$ 330.1218, Found 330.1221.

(5-(4-fluorophenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(4-methoxyphenyl) methanone (2f).



Pale Yellow solid, (m.p. 96-97 °C); IR (KBr): 3005, 1738, 1575, 1533, 1300, 1258, 1015, 830, 792, 664 cm^{-1}; R_f = 0.7 (Hexane: EtOAc 9 : 1); ^1H NMR (400 MHZ, $CDCl_3$): δ= 8.09-8.07 (d, *J*=9.2Hz, 2H, ArH), 7.82-7.79 (m, 2H, ArH), 7.11-7.07 (m, 2H, ArH), 6.97-6.94 (d, *J* = 8.8Hz, 2H, ArH), 4.31 (s, 3H, N-Me), 3.88 (s, 3H, OMe); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=186.2, 164.4, 163.9, 148.6, 142.1, 132.8, 130.59, 130.51, 130.0, 115.4, 115.2, 113.6, 55.5, 42.2; HRMS (ESI) *m/z* Calculated for $C_{17}H_{14}FN_3O_2Na$ $(M+Na)^+$ 334.0968, Found 334.0974.

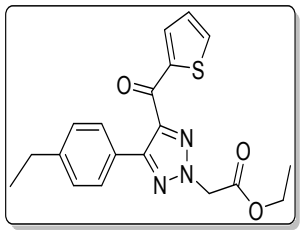
(5-(4-fluorophenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2g).



White solid, (m.p. 75-77 °C); R_f = 0.8 (Hexane: EtOAc 8: 2); IR (KBr): 3076, 2978, 1748, 1510, 1469, 1318, 1265, 1086, 838, 787, 678cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ=8.24-8.23 (d, *J*=4.4 Hz, 1H

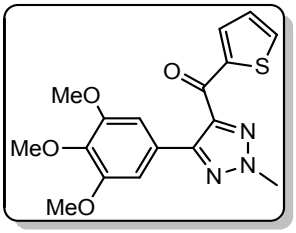
thiophene H), 7.92-7.89 (m, 2H, ArH), 7.74-7.73 (d, *J*=5.6 Hz, 1H thiophene H), 7.19-7.17 (d, *J* = 8.4Hz, 1H thiophene H), 7.14-7.10 (m, 2H, ArH), 4.29 (s, 3H, N-Me); ^{13}C NMR (100 MHZ, $CDCl_3$); *δ*=178.2, 164.5, 149.1, 143.2, 141.4, 135.6, 135.0, 131.0, 130.9, 128.1, 125.6, 115.3, 42.3 HRMS (ESI) *m/z* Calculated for $C_{14}H_{10}FN_3OSNa$ $(M+Na)^+$ 310.0426 Found 310.0427.

Ethyl 2-(4-(4-ethylphenyl)-5-(thiophene-2-carbonyl)-2H-1, 2, 3-triazol-2-yl) acetate (2h).



Pale yellow oil, R_f = 0.30 (Hexane: EtOAc 8: 2); IR (Nujol): 3066, 2967, 1738, 1515, 1465, 1300, 1245, 1078, 838, 767, 678 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$): *δ*=8.21-8.20 (d, *J*=5.2Hz, 1H, thiophene H), 7.81-7.79 (d, *J*=8.4Hz, 2H ArH), 7.71-7.69 (d, *J*=6.4Hz, 1H, thiophene H), 7.27-7.25 (d, *J*=8.4Hz, 2H ArH), 7.17-7.15 (t, *J*=4.6Hz, 1H, thiophene H), 5.28 (s, 2H, N-CH_2), 4.61-4.56 (q, 2H, CH_2), 2.71-2.65 (q, 2H, CH_3), 1.70-1.66 (t, 3H, CH_3), 1.27-1.25 (t, 3H, CH_3); ^{13}C NMR (100 MHZ, $CDCl_3$):*δ*=178.5, 167.7, 149.7,145.3, 143.5, 141.2, 135.4, 134.8, 132.4,130.8, 128.9, 127.7, 127.0, 68.1, 53.4, 30.3, 15.4, 14.6; HRMS (ESI) *m/z* Calculated for $C_{19}H_{19}N_3OSNa$ $(M+Na)^+$ 392.1045, Found 392.1047.

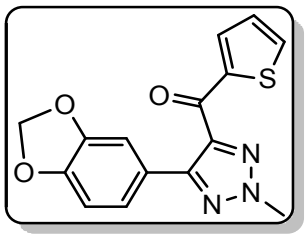
(2-methyl-5-(3, 4, 5-trimethoxyphenyl)-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2i)



Pale Yellow solid, (m.p. 70- 72 °C); R_f = 0.7 (Hexane: EtOAc 8: 2); IR (KBr): 3080, 2969, 1745, 1500, 1471, 1380, 1242, 1067, 838, 797, 686 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$): *δ*=8.15-8.14 (d, *J*=4.8 Hz, 1H, thiophene H), 7.73-7.72 (d, *J*=5.6 Hz, 1H, thiophene H), 7.267-7.261 (d, *J*=2.4 Hz, 2H, ArH), 7.18-7.16 (d, *J*=8.8 Hz, 1H, thiophene H), 4.34 (s, 3H, N-Me), 3.92 (s, 6H, OMe), 3.89 (s, 3H,OMe); ^{13}C NMR (100 MHZ, $CDCl_3$): *δ*=178.6, 152.9, 149.5, 143.5, 141.6, 138.9, 135.6,

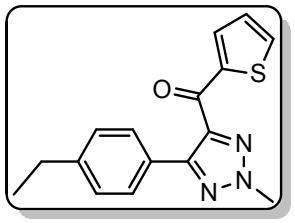
134.9, 128.7, 128.0, 124.8, 106.3, 60.8, 56.2, 42.3; HRMS (ESI) *m/z* Calculated for $C_{17}H_{17}N_3O_4SNa$ $(M+Na)^+$ 382.0837, Found 382.0842.

(5-(benzo[d][1,3]dioxol-5-yl)-2-methyl-2H-1,2,3-triazol-4-yl)(thiophen-2-yl) methanone (2j).



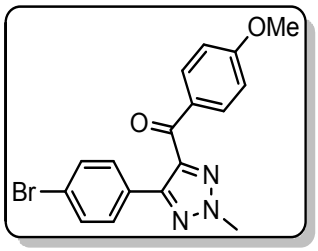
Pale Yellow oil; $R_{f=}$ 0.8 (Hexane: EtOAc 8: 2); IR (Nujol): 3056, 2961, 1737, 1511, 1471, 1270, 1242, 1067, 856, 778, 657 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ=8.20-8.19 (d, *J*=4.4 Hz, 1H, thiophene H), 7.72-7.70 (d, *J*=6.4 Hz, 1H, thiophene H), 7.45-7.42 (d, *J*=10.4 Hz, 1H, ArH), 7.40-7.39 (d, *J*=1.6 Hz, 1H, ArH), 7.17-7.15 (t, *J*=4.6 Hz, 1H, thiophene H), 6.87-6.85 (d, J=7.6 Hz, ArH), 4.30 (s, 3H, N-Me); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=178.4, 149.6, 148.4, 147.5, 143.4, 141.2, 135.5, 134.9, 128.0, 123.3, 123.2, 109.4, 108.1, 101.2, 42.2 HRMS (ESI) *m/z* Calculated for $C_{15}H_{11}N_3O_3SNa$ $(M+Na)^+$ 336.0419, Found 336.0420.

(5-(4-ethylphenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2k).



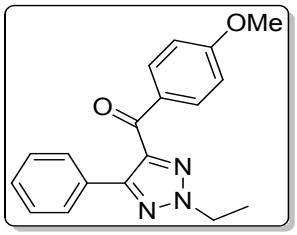
Pale Yellow solid, (m.p. 98- 100 °C); R_f = 0.8 (Hexane: EtOAc 8: 2); IR (KBr): 3076, 2961, 1745, 1515, 1471, 1300, 1242, 1067, 838, 747 678 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ= 8.21-8.19 (d, *J*=5.2 Hz, 1H, thiophene H), 7.79-7.77 (d, *J*=8.0 Hz, 2H, ArH), 7.72-7.70 (d, *J*=6.0 Hz, 1H, thiophene H), 7.27-7.25 (d, *J*=8.4 Hz, 2H, ArH), 7.17-7.15 (t, *J*=4.2Hz, 1H, thiophene H), 4.32 (s, 3H, N-Me), 2.71-2.65 (q, 2H, CH_2), 1.27-1.23 (t, 3H, CH_3); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=178.4, 150.0, 145.4, 143.4, 141.4, 135.5, 134.8, 128.9, 128.0, 127.7, 126.8, 42.2, 28.7, 15.4; HRMS (ESI) *m/z* Calculated for $C_{16}H_{15}N_3OSNa$ $(M+Na)^+$ 320.0834, Found 320.0836.

(5-(4-bromophenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(4-methoxyphenyl) methanone (2l).



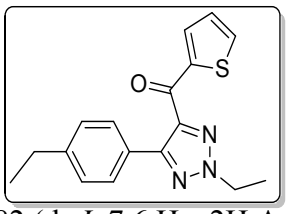
Pale Yellow solid, (m.p. 110-112 °C); R_f = 0.7 (Hexane: EtOAc 8: 2); IR (KBr): 3005, 1744, 1575, 1533, 1308, 1258, 1017, 834, 772, 664 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ=8.09-8.07 (d, J=9.2 Hz, 2H ArH), 7.71-7.68 (d, J=9.2 Hz, 2H ArH), 7.53-7.51 (d, J=8.8 Hz, 2H, ArH), 6.97-6.94 (d, J=8.8 Hz, 2H, ArH), 4.30 (s, 3H, N-Me), 3.88 (s, 3H, OMe); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=186.1, 163.9, 148.3, 142.3, 132.8, 131.5, 130.1, 129.9, 128.7, 123.2, 113.6, 55.5, 42.2; HRMS (ESI) *m/z* Calculated for $C_{17}H_{14}BrN_3O_2Na$ $(M+Na)^+$ 394.0617, Found 394.0618.

(4-methoxyphenyl)(2-methyl-5-phenyl-2H-1, 2, 3-triazol-4-yl) methanone (2m).



White solid, (m.p. 89-90 °C); R_f = 0.7 (Hexane: EtOAc 8: 2); IR (KBr): 3005, 1743, 1575, 1530, 1300, 1258, 1017, 834, 762, 664 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ=8.09-8.07 (d, J=9.2 Hz, 2H, ArH), 7.80-7.77 (m, 2H, ArH), 7.41-7.34 (m, 3H, ArH), 6.96-6.94 (d, J=8.8 Hz, 2H, ArH), 4.61-4.55 (q, 2H, N-CH_2), 3.88 (s, 3H, OMe), 1.68-1.64 (t, 3H, CH_3); HRMS (ESI) *m/z* Calculated for $C_{18}H_{17}N_3NaO_2Na$ $(M+Na)^+$ 330.1218, Found 330.1223.

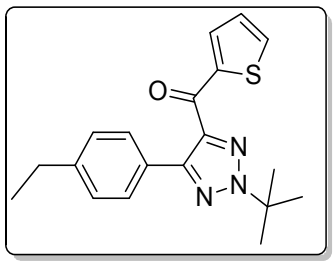
(2-ethyl-5-(4-ethylphenyl)-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2n).



Pale yellow liquid, R_f = 0.8 (Hexane: EtOAc 8: 2); IR (Nujol) 3067, 2978, 1740, 1468, 1287, 1234, 1100, 838, 747 678 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ=8.22-8.21 (d, J=4.0Hz, 1H, thiophene H), 7.84-7.82 (d, J=7.6 Hz, 2H ArH), 7.68-7.66 (d, J=5.2Hz, 1H, thiophene H), 7.26-7.24 (d, J=6.4Hz, 2H ArH), 7.14-7.12 (t, J=4.4 Hz, 1H, thiophene H), 4.58-4.53 (q, 2H, N-CH_2), 2.71-2.65 (q, 2H, CH_2), 1.67-1.64 (t, 3H, CH_3), 1.27-1.23 (t, 3H, CH_3); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=178.5,

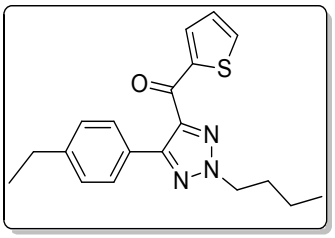
149.7, 145.3, 143.5, 141.2, 135.5, 134.8, 129.0, 128.0, 127.7, 50.7, 28.7, 15.4, 14.6; HRMS (ESI) *m/z* Calculated for $C_{17}H_{17}N_3OSNa$ $(M+Na)^+$ 334.0990, Found 334.0991.

(2-(tert-butyl)-5-(4-ethylphenyl)-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2p).



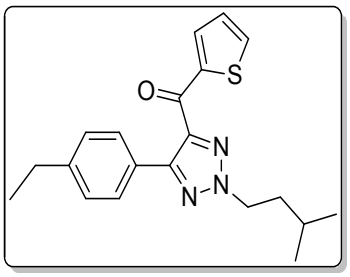
Pale yellow liquid, R_f = 0.8 (Hexane: EtOAc 8: 2); IR (Nujol): 3076, 2961, 1730, 1515, 1471, 1300, 1242, 1067, 838, 747 678cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$): δ=8.22-8.21 (d, *J*=4.0 Hz, 1H, thiophene H), 7.81-7.79 (d, *J*=8.4 Hz, 2H ArH), 7.71-7.69 (d, *J*=8.8 Hz, 1H, thiophene H), 7.27-7.25 (d, *J*=6.8 Hz, 2H ArH), 7.18-7.16 (t, *J*=4.6 Hz, 1H, thiophene H), 2.71-2.65 (q, 2H, CH_2), 1.71-1.64 (t, 3H, CH_3), 1.25 (s, 9H, t-butyl); ^{13}C NMR (100 MHZ, $CDCl_3$); δ=178.5, 145.3, 143.4, 141.2, 135.4, 134.8, 130.8, 128.9, 128.7, 128.0, 127.7, 68.1, 29.6, 28.9, 14.6; HRMS(ESI) *m/z* Calculated for $C_{19}H_{21}N_3OSNa$ $(M+Na)^+$ 362.1303, Found 362.1305.

(2-butyl-5-(4-ethylphenyl)-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2q).



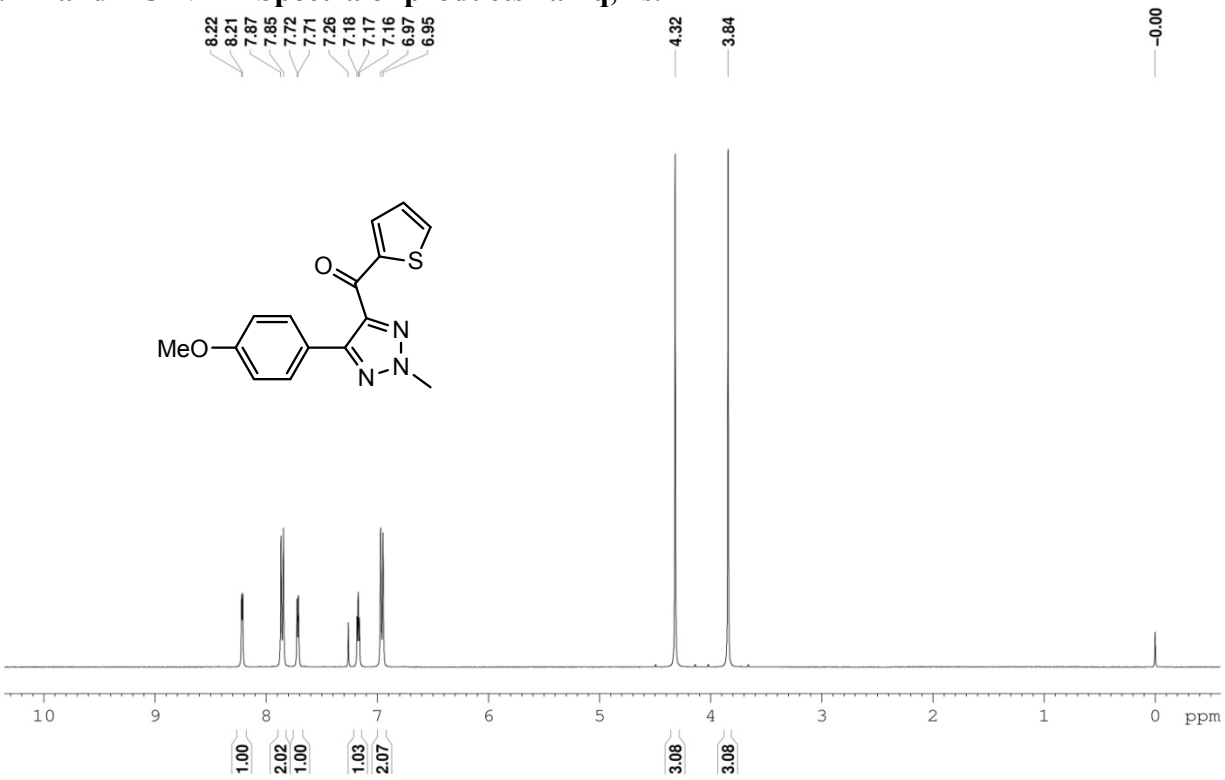
Pale yellow liquid, R_f = 0.8 (Hexane: EtOAc 8: 2); IR (Nujol); 3076, 2961, 1745, 1515, 1471, 1300, 1242, 1067, 838, 740 658 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$): δ=8.21-8.20 (d, *J*=4.0 Hz, 1H, thiophene H), 7.82-7.80 (d, *J*=8.4 Hz, 2H ArH), 7.71-7.69 (d, *J*=6.4 Hz, 1H, thiophene H), 7.27-7.25 (d, *J*=8.8 Hz, 2H ArH), 7.17-7.15 (t, *J*=4.4 Hz, 1H, thiophene H), 4.55-4.52 (t, 2H, N-CH_2), 2.71-2.65 (q, 2H, CH_2), 2.08-2.05 (t, 2H, CH_2), 1.46-1.39 (m, 2H, CH_2), 1.01-0.97 (t, 3H, CH_3), 0.94-0.91 (t, 3H, CH_3); ^{13}C NMR (100 MHZ, $CDCl_3$); δ=178.5, 145.3,143.5, 141.1, 135.4, 134.8, 128.9, 128.7, 128.0, 127.7, 68.1, 31.5, 28.9, 19.7, 14.0, 13.4; HRMS (ESI) *m/z* Calculated for $C_{19}H_{21}N_3OSNa$ $(M+Na)^+$ 362.1303, Found 334.1304.

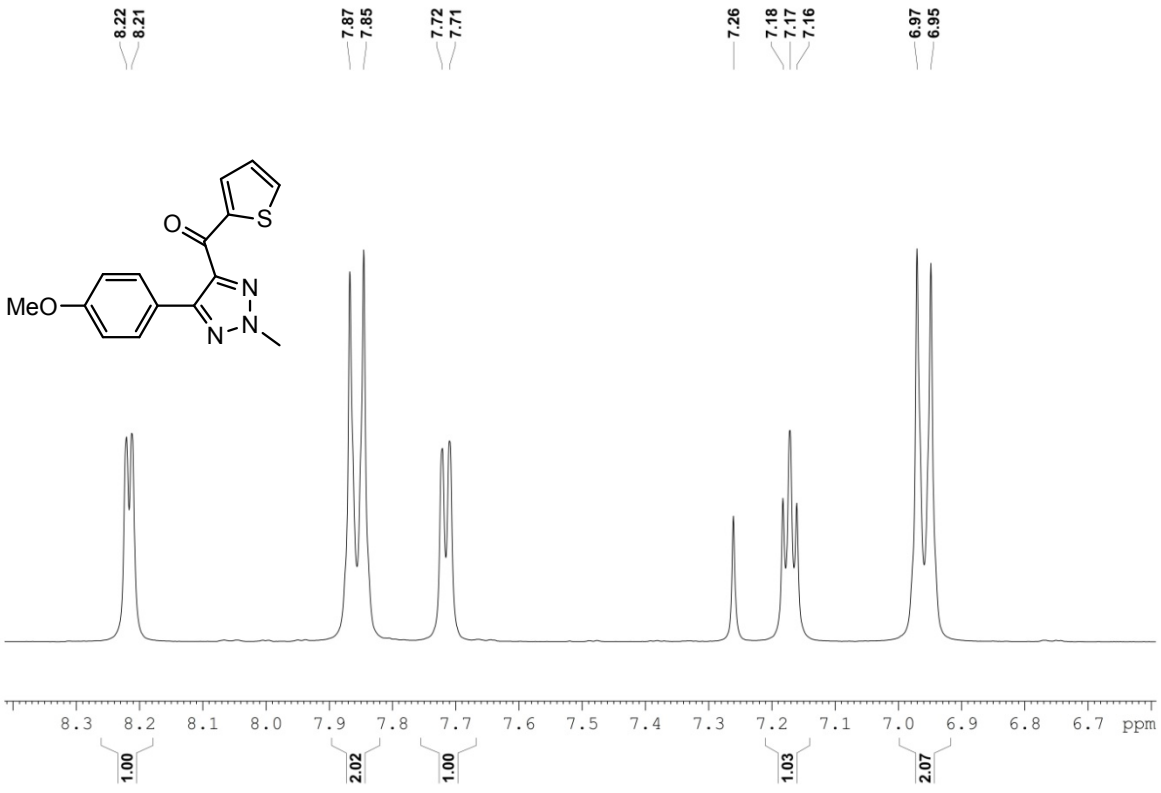
(5-(4-ethylphenyl)-2-isopentyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone (2s).

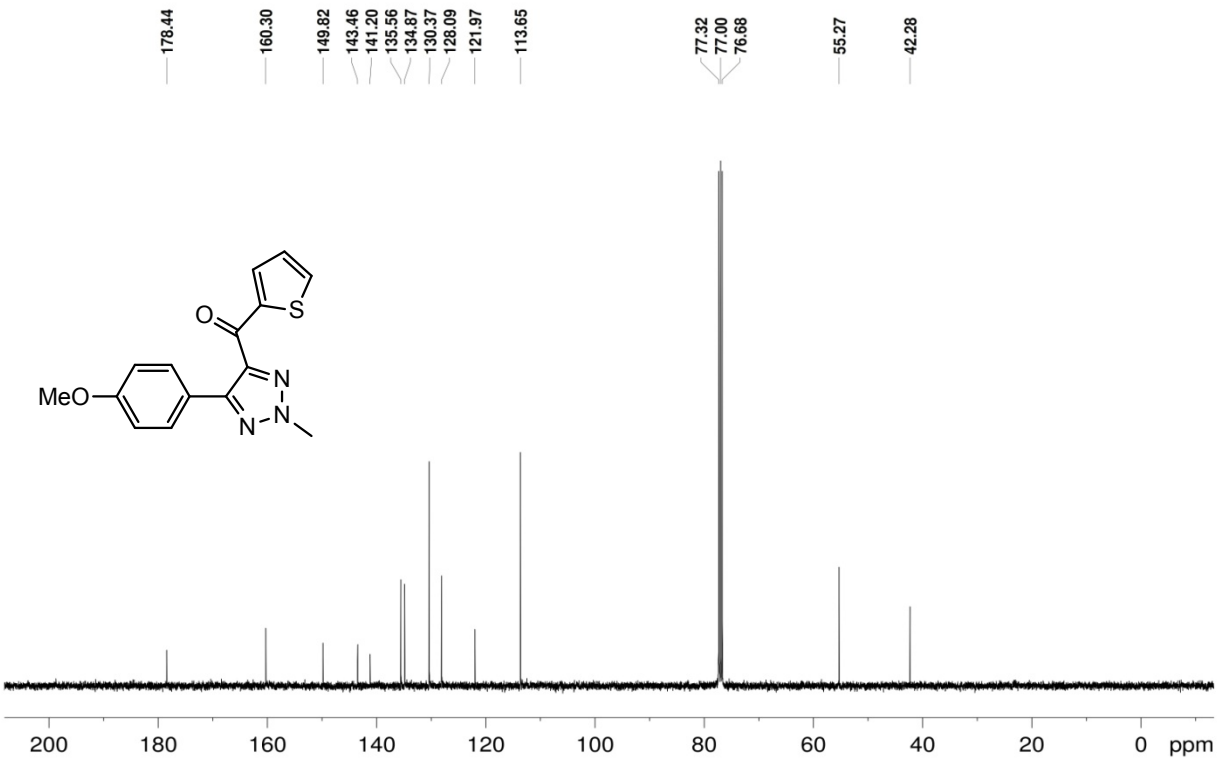


Pale yellow oil, R_f= 0.8 (Hexane: EtOAc 8 : 2); ; IR (Nujol); 3060, 2954, 1730, 1515, 1471, 1320, 1242, 1057, 838, 737, 688 cm^{-1}; ^1H NMR (400 MHZ, $CDCl_3$): δ=8.32-8.31 (d, J=5.2 Hz, 1H, thiophene H), 7.94-7.92 (d, J=7.6 Hz, 2H, ArH), 7.83-7.80 (m, 1H, thiophene H), 7.39-7.37 (d, J=7.6 Hz, 2H, ArH), 7.29-7.27 (t, J=5.0 Hz, 1H, thiophene H), 4.69-4.65 (t, 2H, N-CH_2), 2.83-2.77 (q, 2H, CH_2), 2.12-2.06 (q, 2H, CH_2), 1.83-1.74 (m, 2H, CH_2), 1.13-1.11 (d, 6H, $(CH_3)_2$), 1.04-1.00 (t, 3H, CH_3); ^{13}C NMR (100 MHZ, $CDCl_3$): δ=178.5, 145.3, 143.5, 141.1, 135.4, 134.8, 128.9, 128.7, 128.0, 127.7, 54.0, 38.2, 29.3, 25.5, 22.2, 14.0. 19.7, 14.0 HRMS (ESI) *m/z* Calculated for $C_{20}H_{23}N_3OSNa$ $(M+Na)^+$ 376.1460, Found 376.1462.

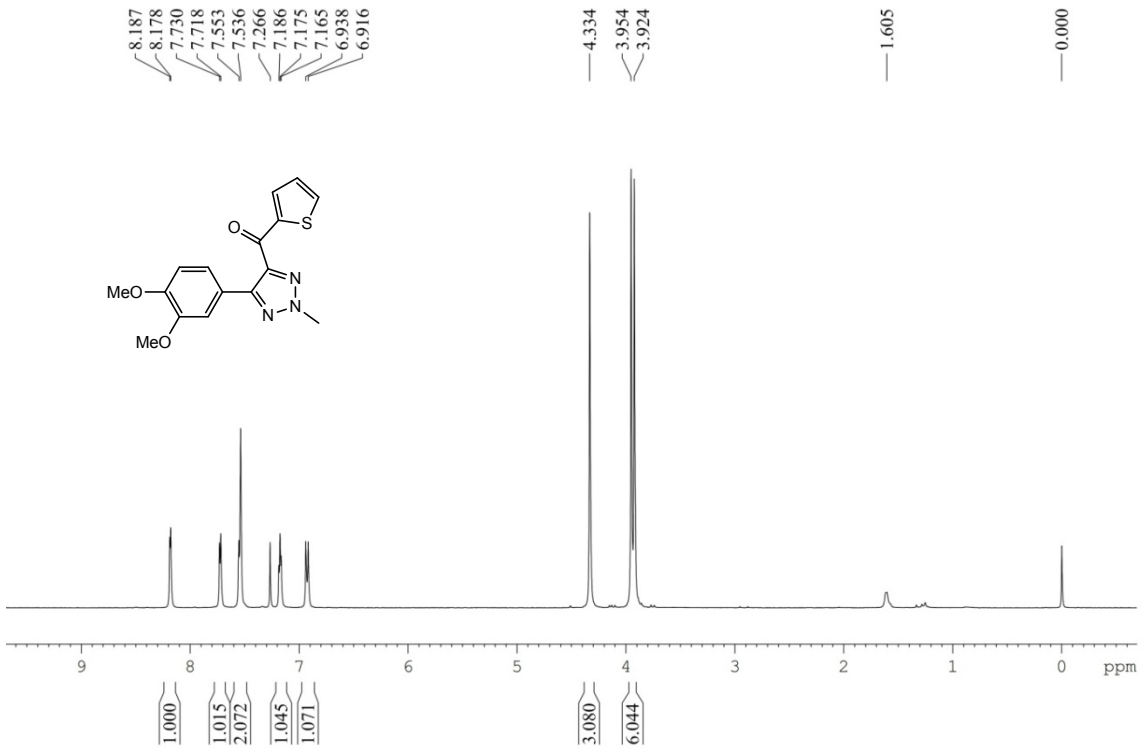
4. ^{1}H and ^{13}C-NMR Spectra of products 2a-2q, 2s.







^{1}H and ^{13}C NMR Spectra of Compound **(**5-(4-methoxyphenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone **(2a)**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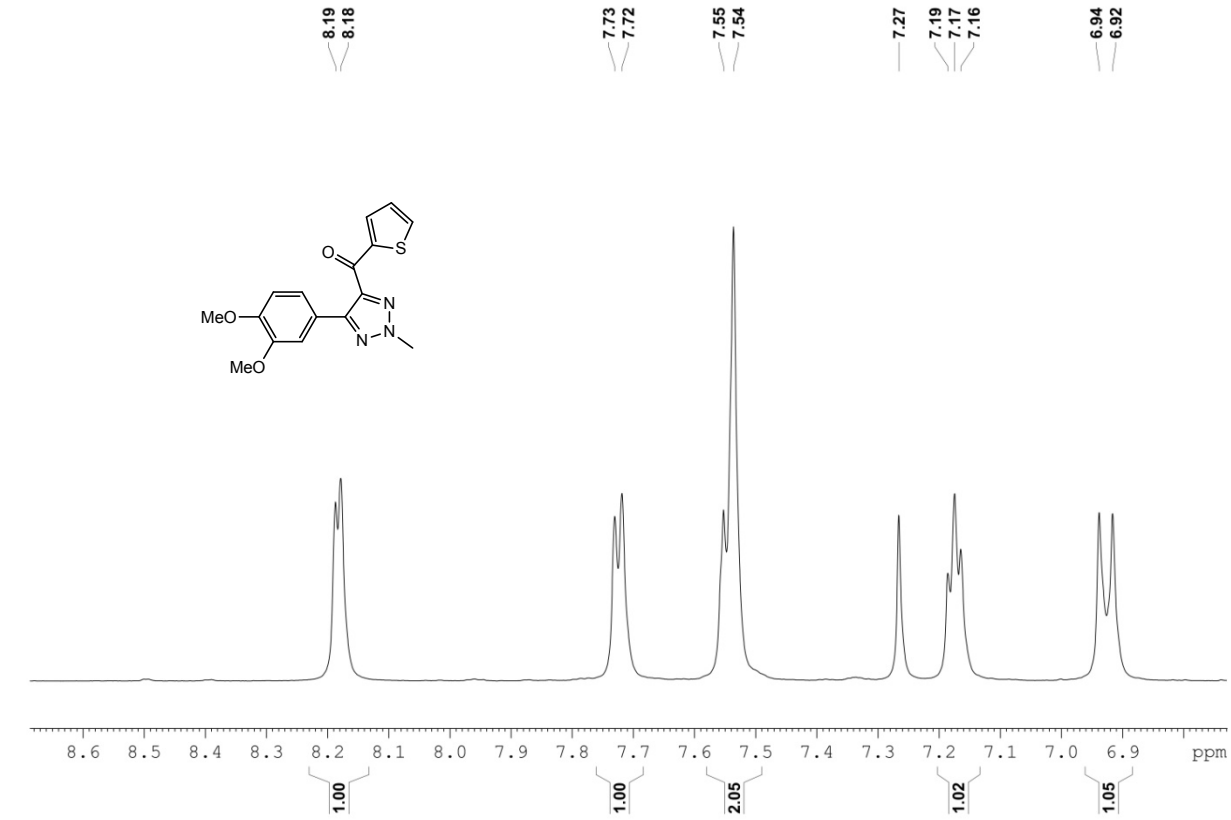
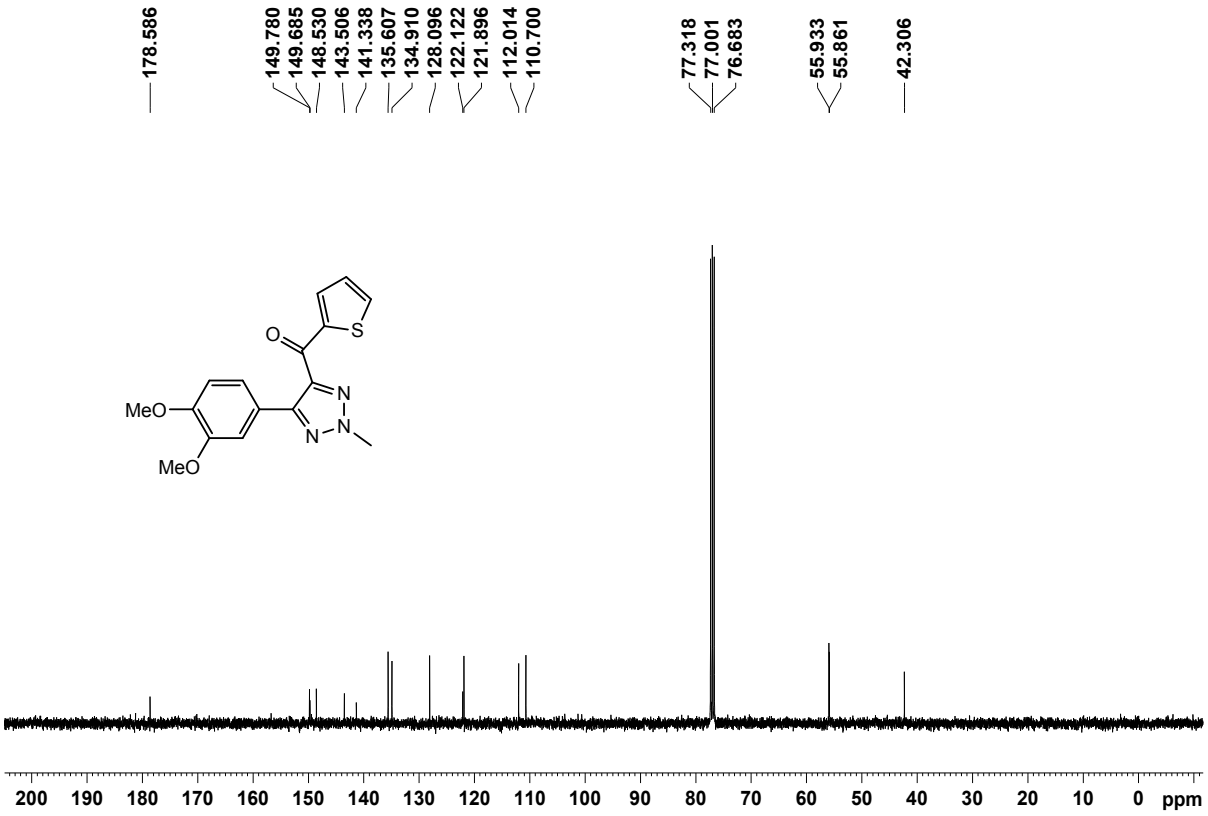
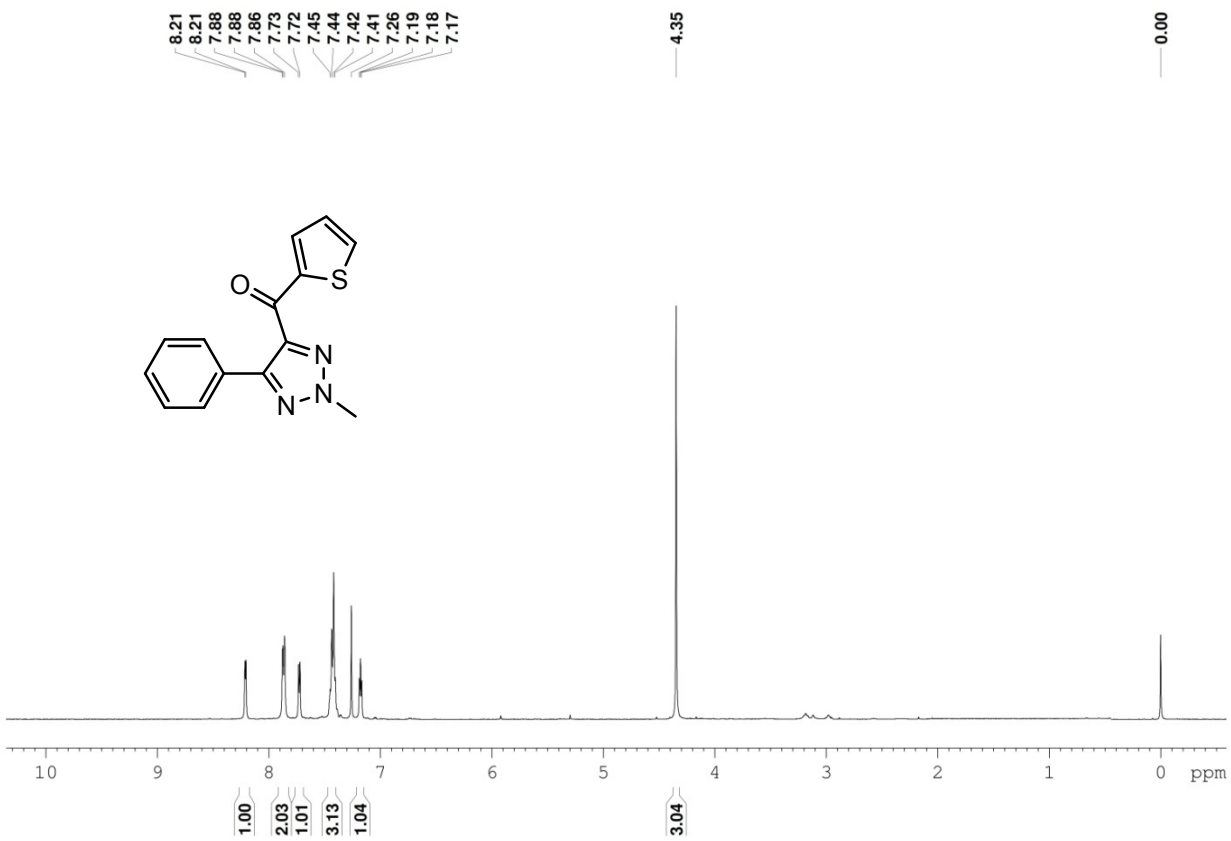
8.178
7.730
7.718
7.553
7.536
7.266
7.186
7.175
7.165
6.938
6.916
4.334
3.954
3.924
1.605
0.000
MeO
MeO
O
S
N
N
N
9
8
7
6
5
4
3
2
1
0
ppm
1.000
1.015
2.072
1.045
1.071
3.080
6.044


8.19
8.18
7.73
7.72
7.55
7.54
7.27
7.19
7.17
7.16
6.94
6.92
MeO
MeO
O
S
N
N
N
8.6
8.5
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
ppm
1.00
1.00
2.05
1.02
1.05



^{1}H and ^{13}C NMR Spectra of Compound (5-(3, 4-dimethoxyphenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone **(2b)**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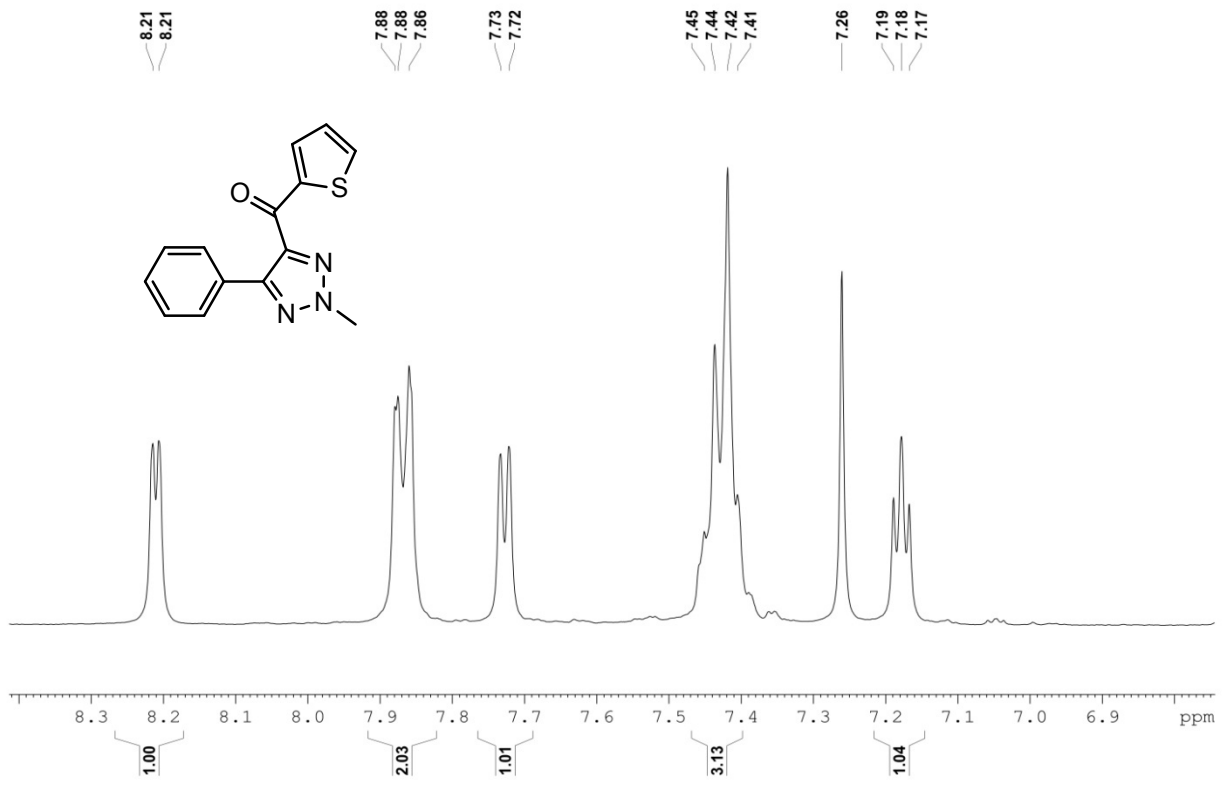
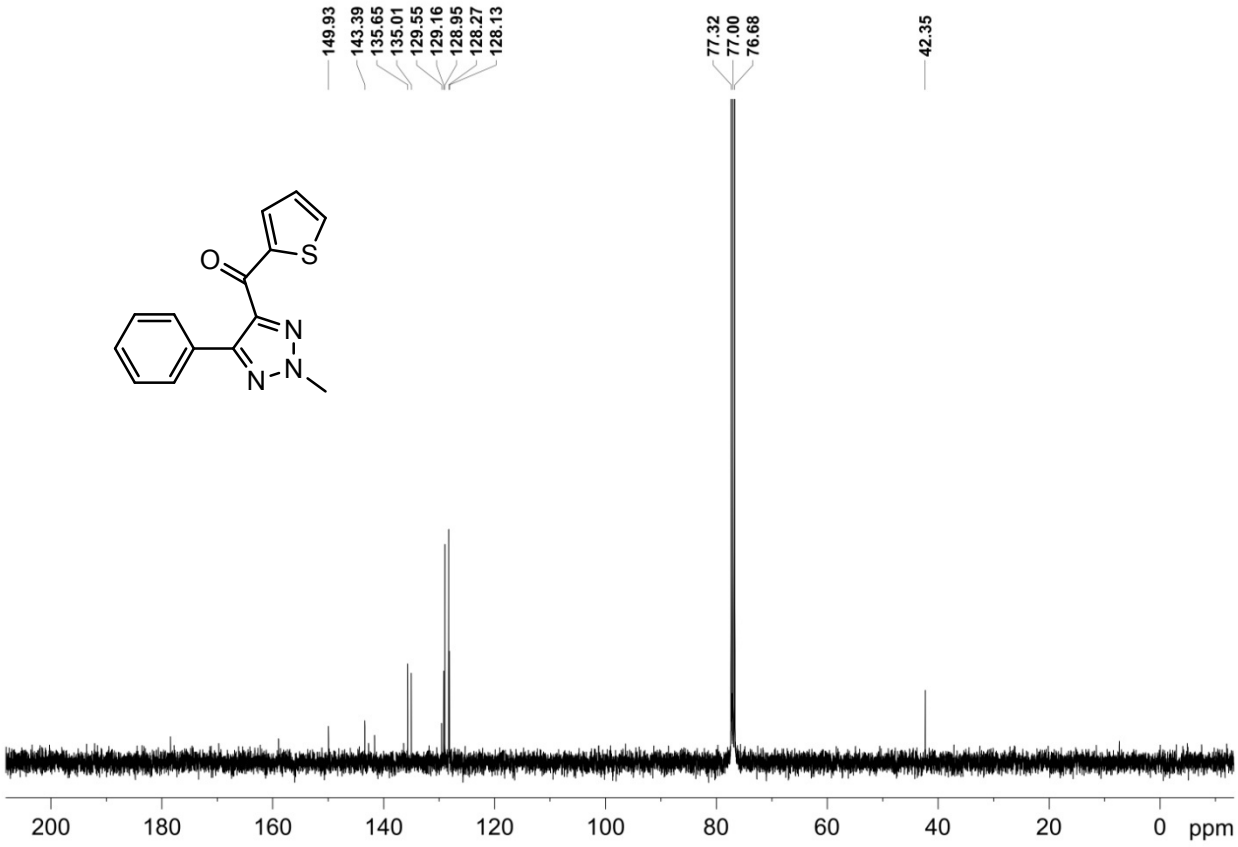
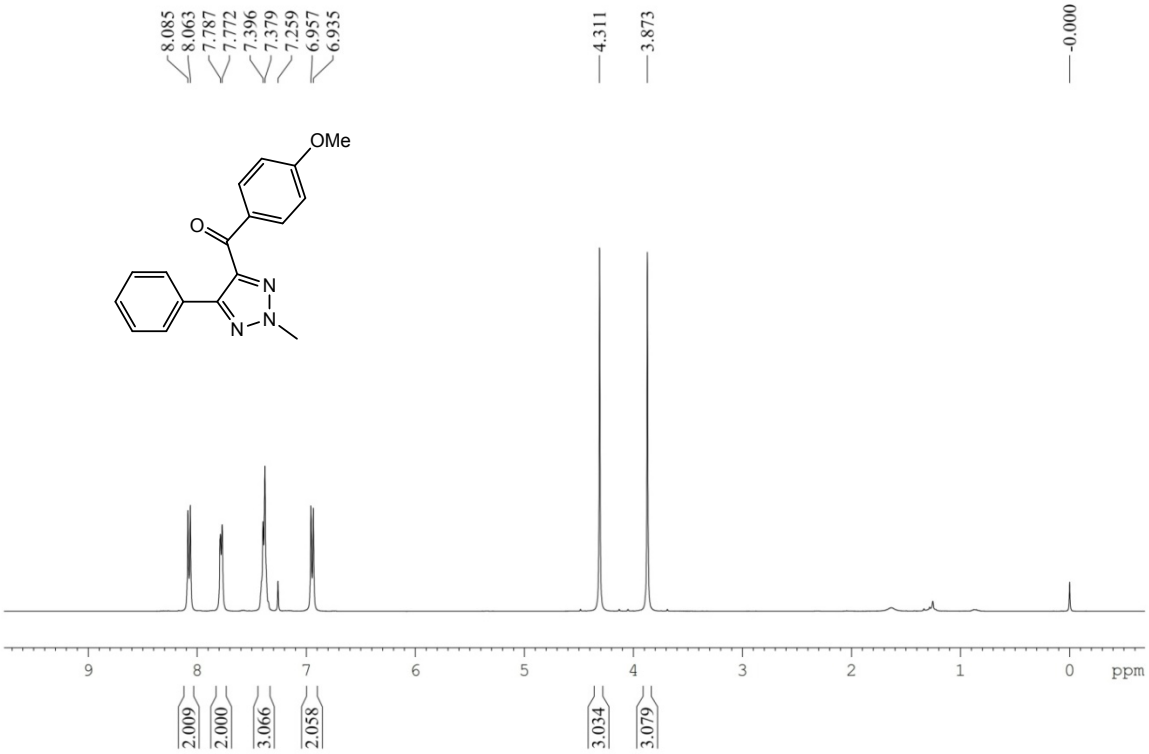
8.21
7.88
7.88
7.86
7.73
7.72
7.45
7.44
7.42
7.41
7.26
7.19
7.18
7.17
4.35
0.00
O
S
N
N
N
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.03
1.01
3.13
1.04
3.04


8.21
8.21
7.88
7.88
7.86
7.73
7.72
7.45
7.44
7.42
7.41
7.26
7.19
7.18
7.17
O
S
N
N
N
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
ppm
1.00
2.03
1.01
3.13
1.04



^{1}H and ^{13}C NMR Spectra of Compound (2-methyl-5-phenyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone **(2c)**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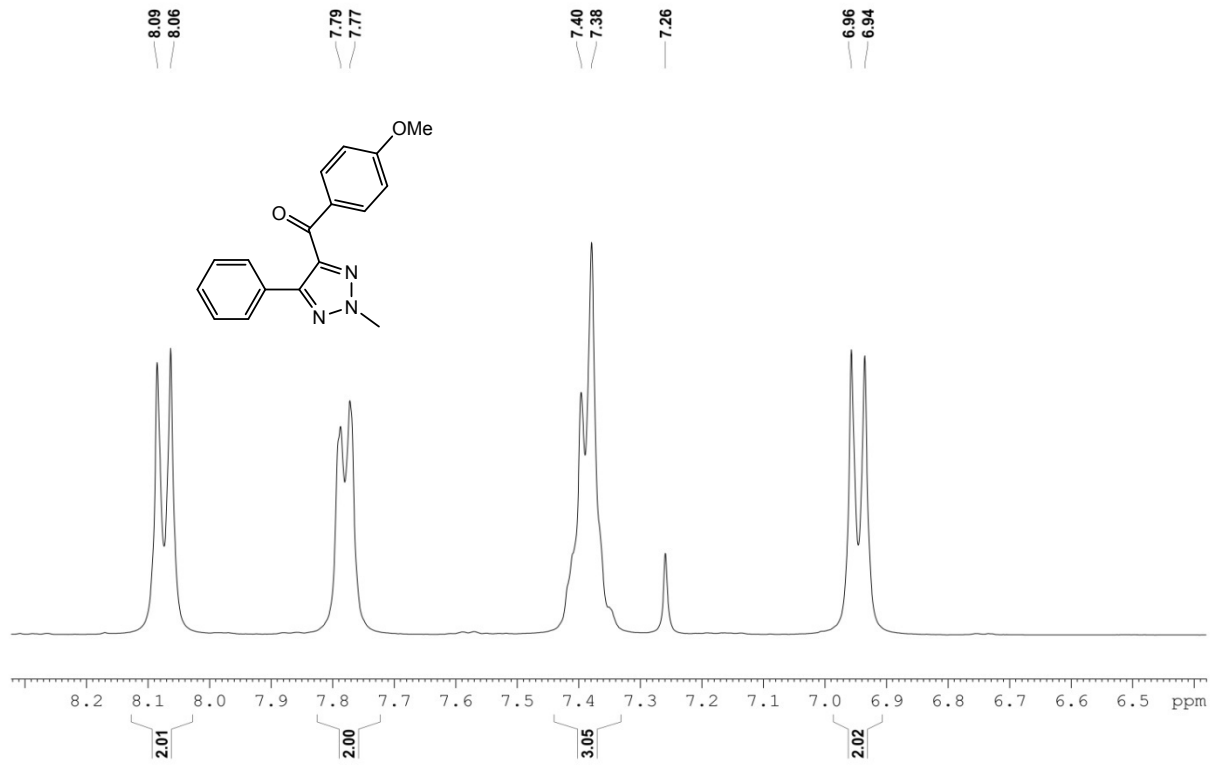
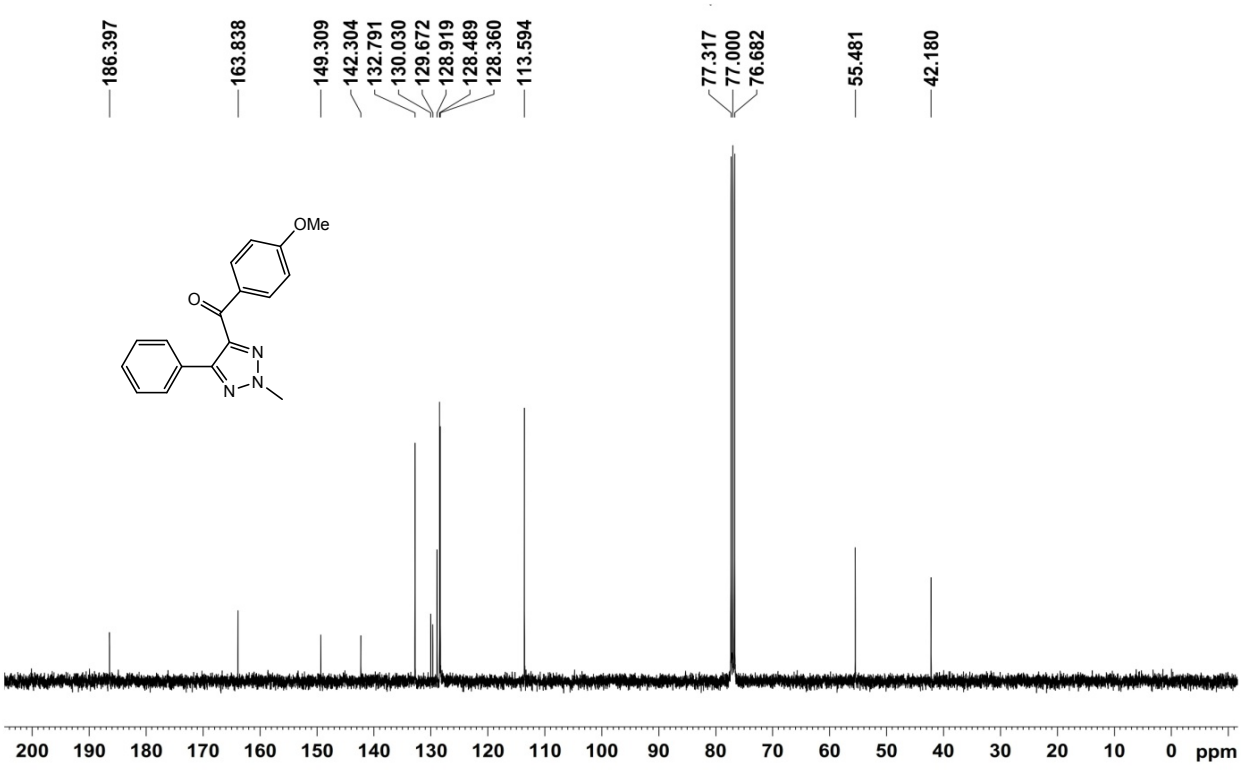
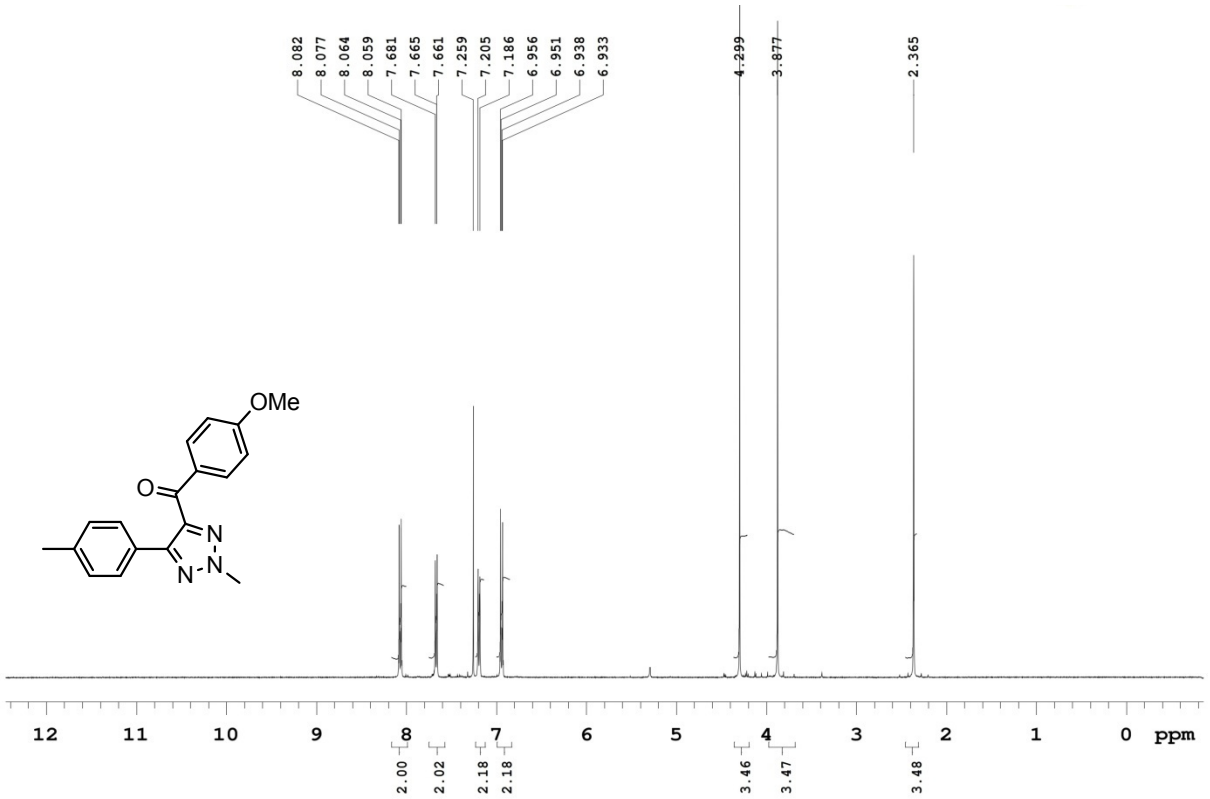
7.379
7.259
6.957
6.935
4.311
3.873
-0.000
OMe
O
N
N
N
9
8
7
6
5
4
3
2
1
0
ppm
2.009
2.000
3.066
2.058
3.034
3.079


8.09
8.06
7.79
7.77
7.40
7.38
7.26
6.96
6.94
OMe
O
N
N
N
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
ppm
2.01
2.00
3.05
2.02



^{1}H and ^{13}C NMR Spectra of Compound (4-methoxyphenyl)(2-methyl-5-phenyl-2H-1, 2, 3-triazol-4-yl) methanone **(2d)**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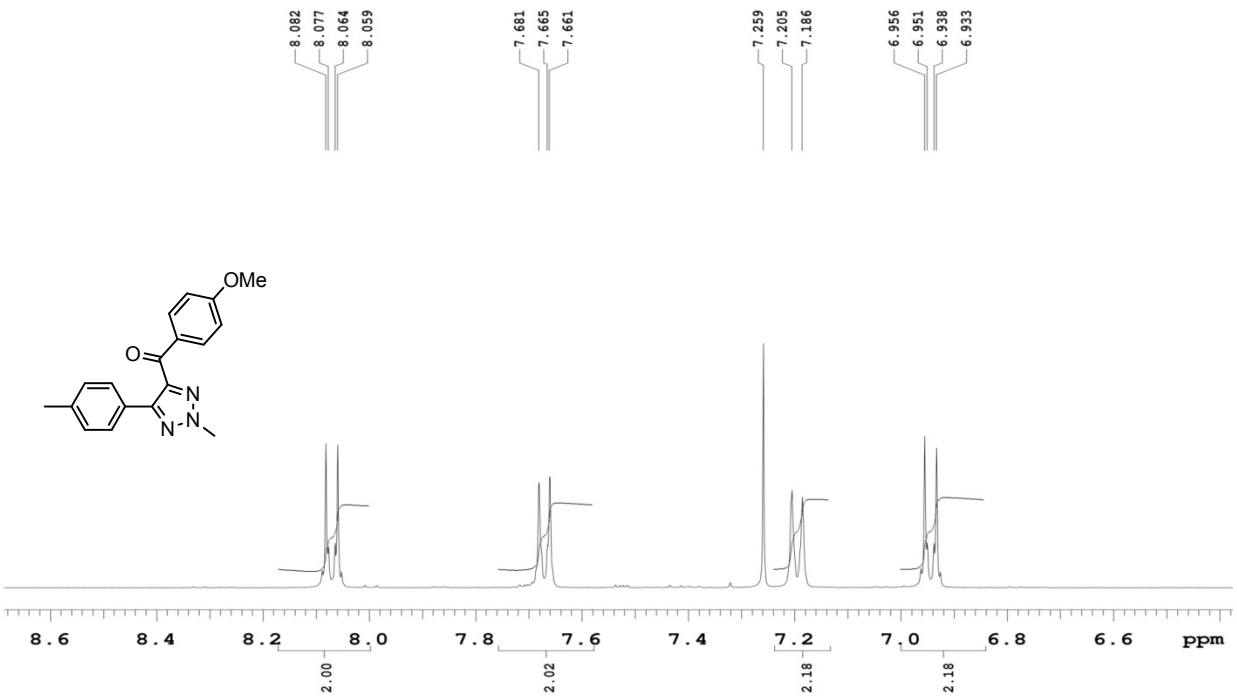
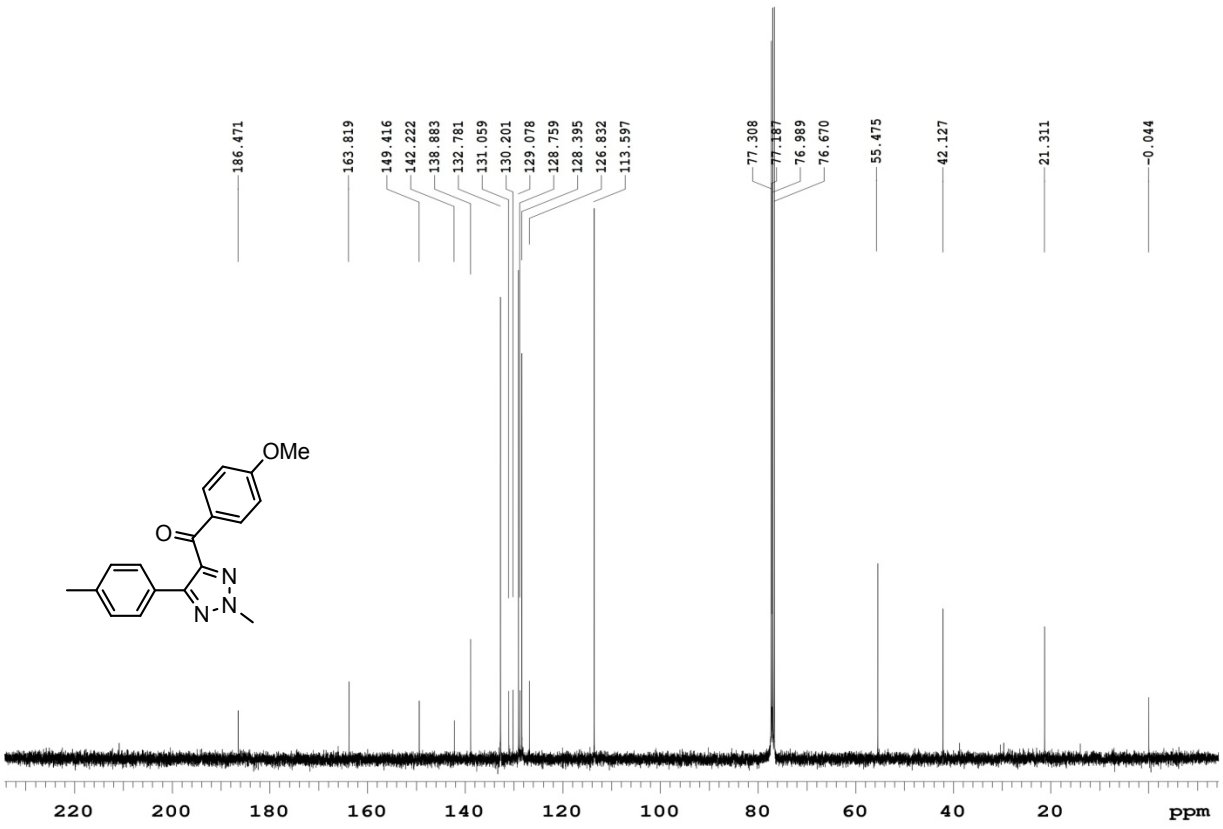
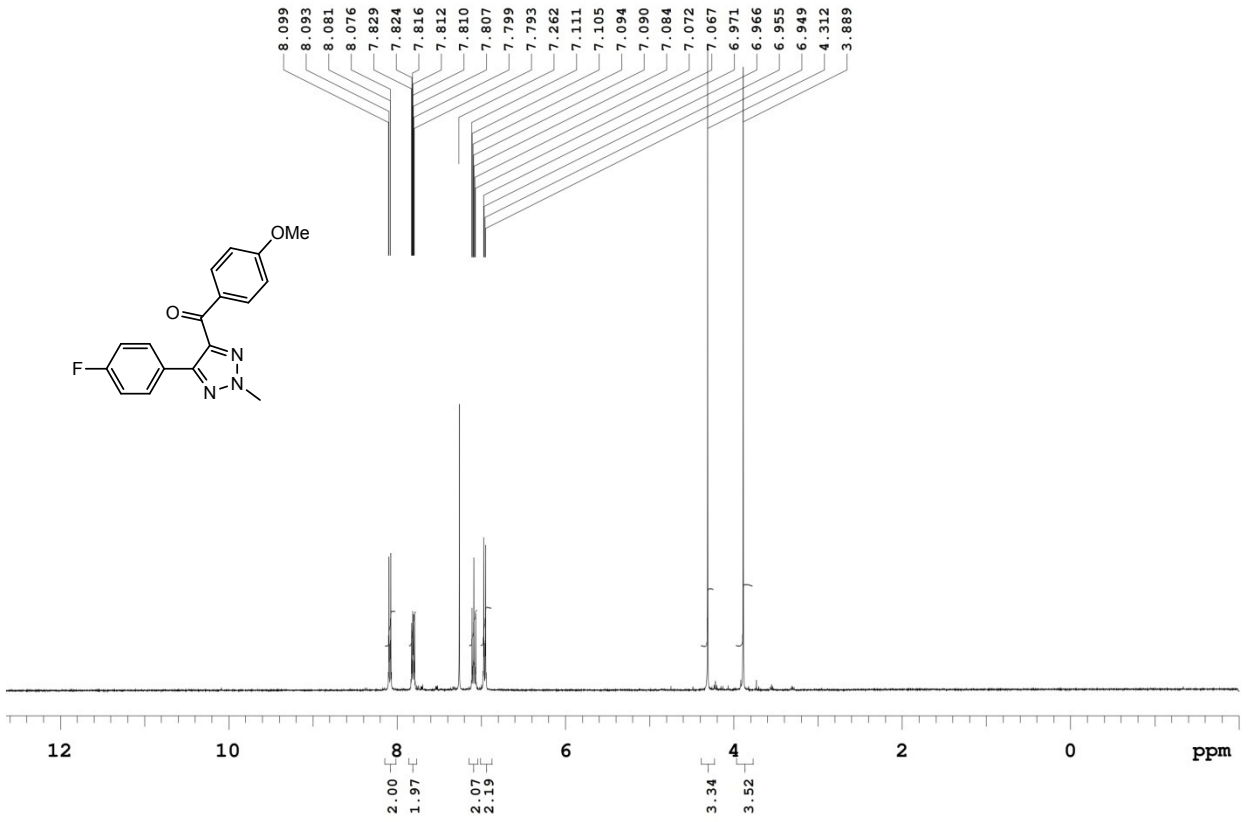
8.077
8.064
8.059
7.681
7.665
7.661
7.259
7.205
7.186
6.956
6.951
6.938
6.933
4.299
3.877
2.365
OMe
O
N
N
N
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.02
2.18
2.18
3.46
3.47
3.48


8.082
8.077
8.064
8.059
7.681
7.665
7.661
7.259
7.205
7.186
6.956
6.951
6.938
6.933
OMe
O
N
N
N
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
2.00
2.02
2.18
2.18



^{1}H and ^{13}C NMR Spectra of Compound (4-methoxyphenyl)(2-methyl-5-(p-tolyl)-2H-1, 2, 3-triazol-4-yl) methanone **(2e)**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8.081
8.076
7.829
7.824
7.816
7.812
7.810
7.807
7.799
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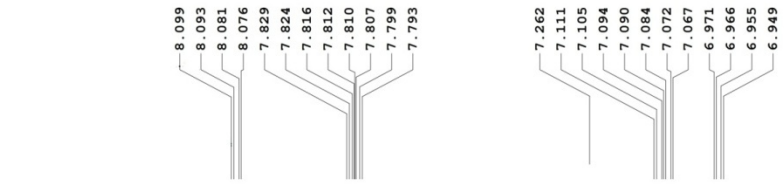
7.262
7.111
7.105
7.094
7.090
7.084
7.072
7.067
6.971
6.966
6.955
6.949
4.312
3.889
OMe
O
N
N
N
F
12
10
8
6
4
2
0
ppm
2.00
1.97
2.07
2.19
3.34
3.52


8.099
8.093
8.081
8.076
7.829
7.824
7.816
7.812
7.810
7.807
7.799
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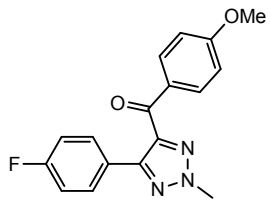
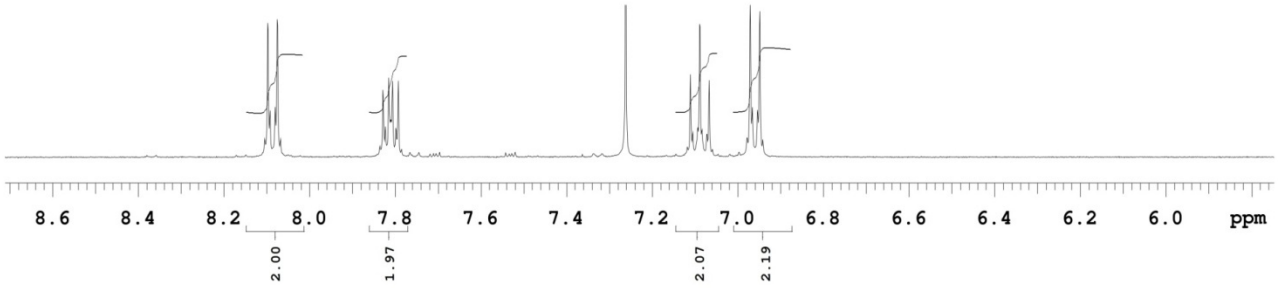
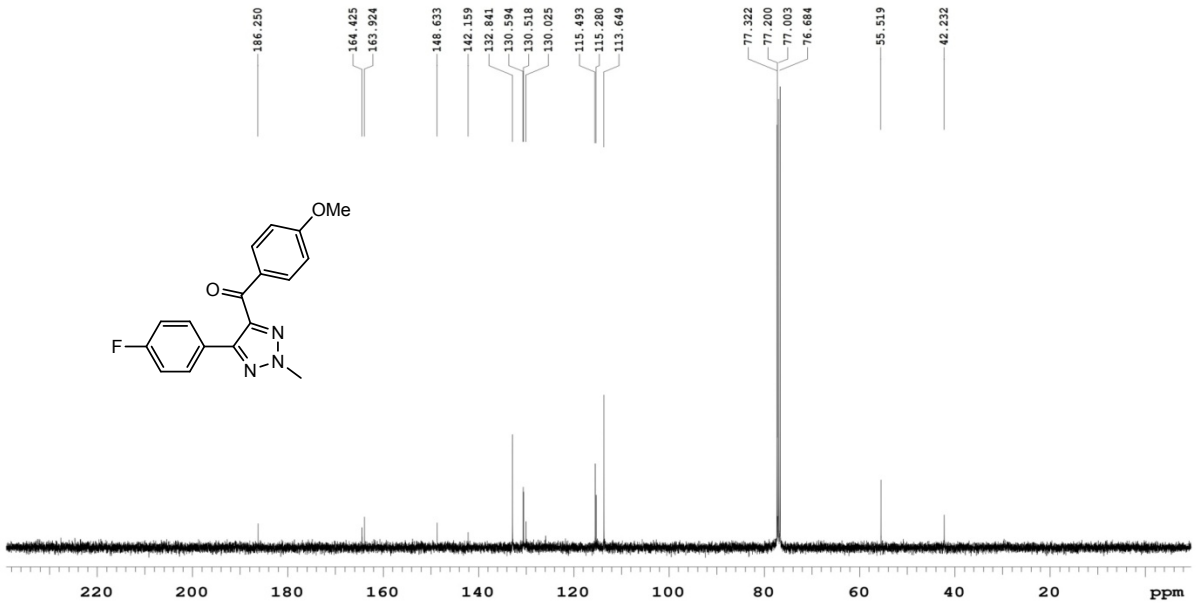
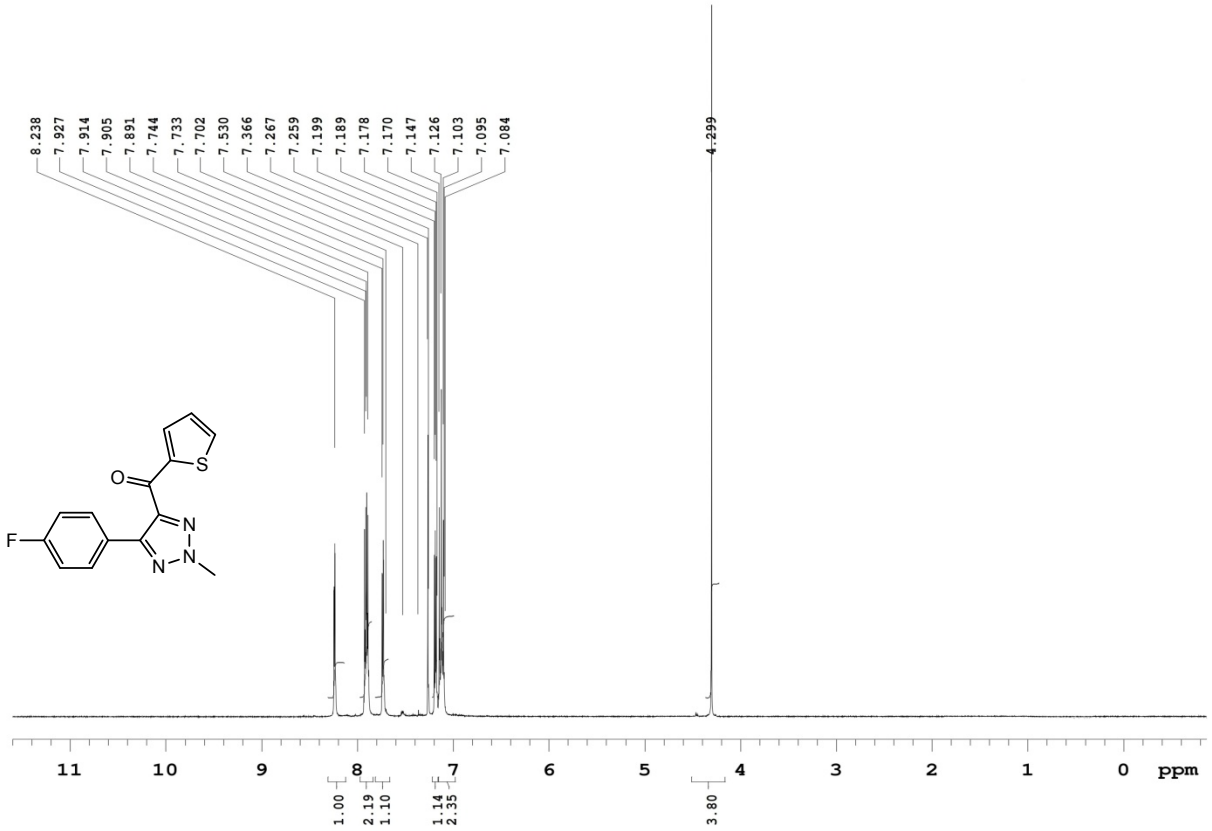
7.262
7.111
7.105
7.094
7.090
7.084
7.072
7.067
6.971
6.966
6.955
6.949

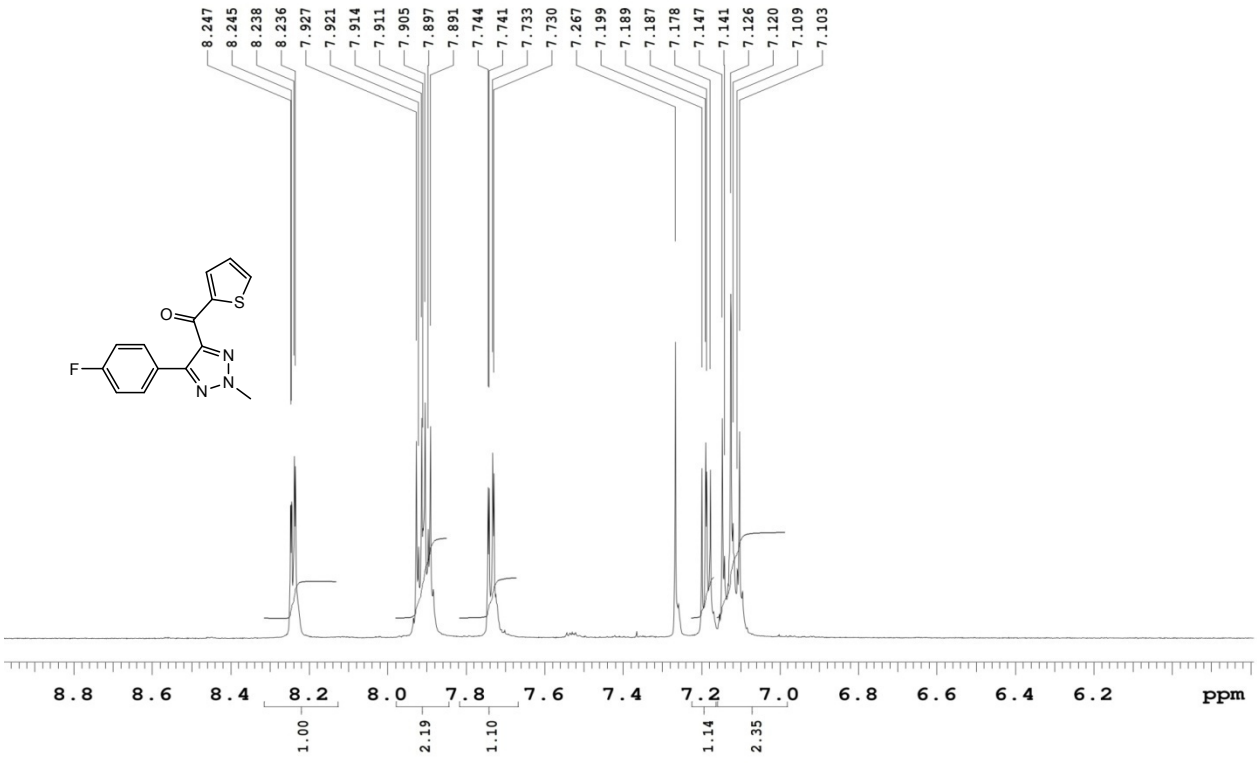

OMe
O
N
N
N
F

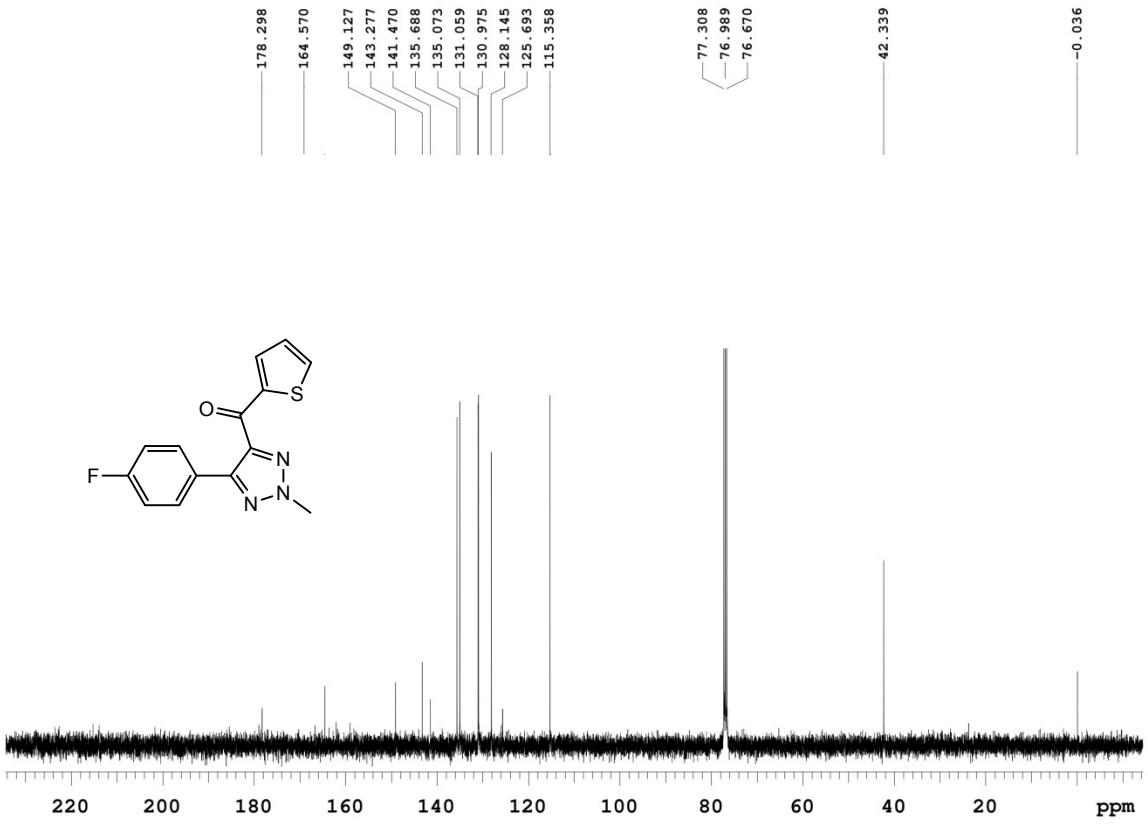

8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
ppm
2.00
1.97
2.07
2.19



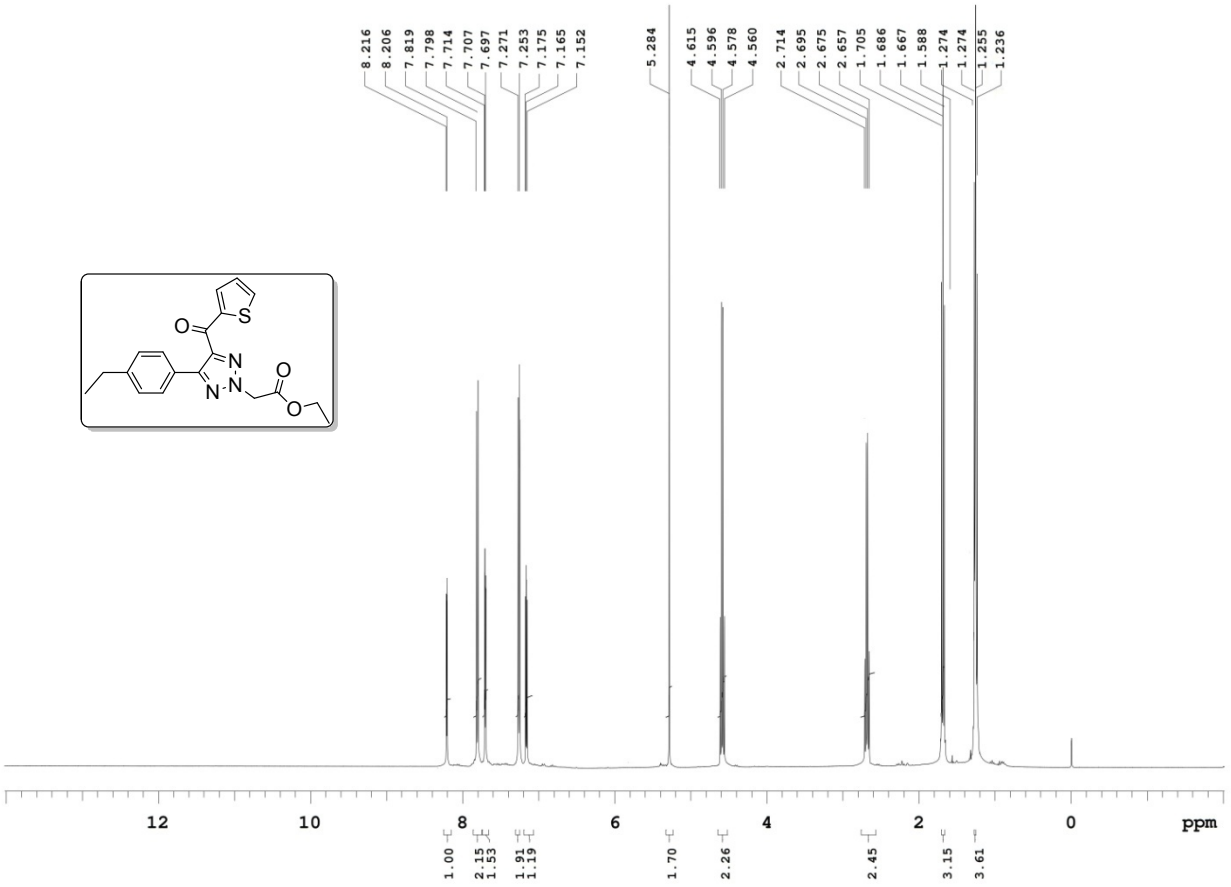
^{1}H and ^{13}C NMR Spectra of Compound (5-(4-fluorophenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(4-methoxyphenyl) methanone **(2f)**

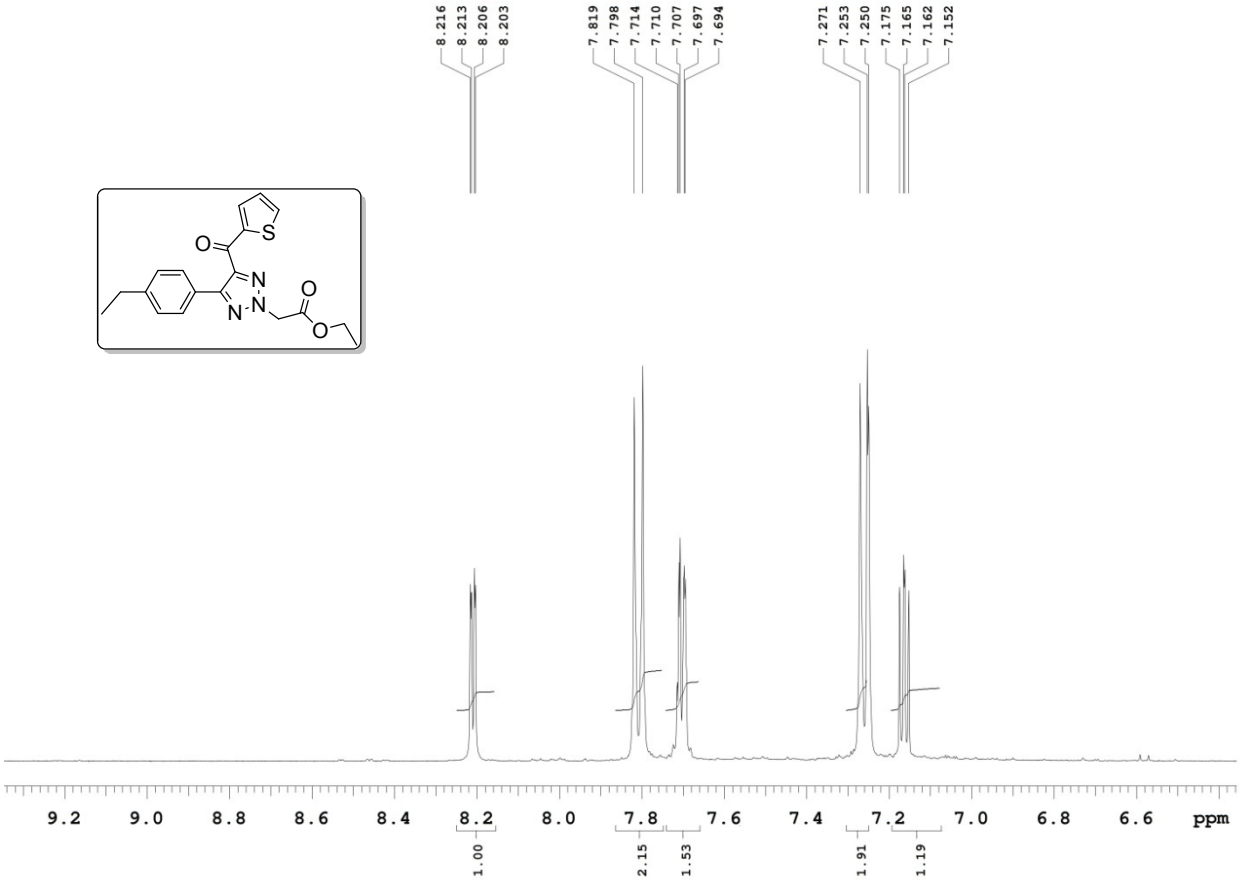

8.238
7.927
7.914
7.905
7.891
7.744
7.733
7.702
7.530
7.366
7.267
7.259
7.199
7.189
7.178
7.170
7.147
7.126
7.103
7.095
7.084
4.299
O
S
N
N
N
F
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.19
1.10
1.14
2.35
3.80

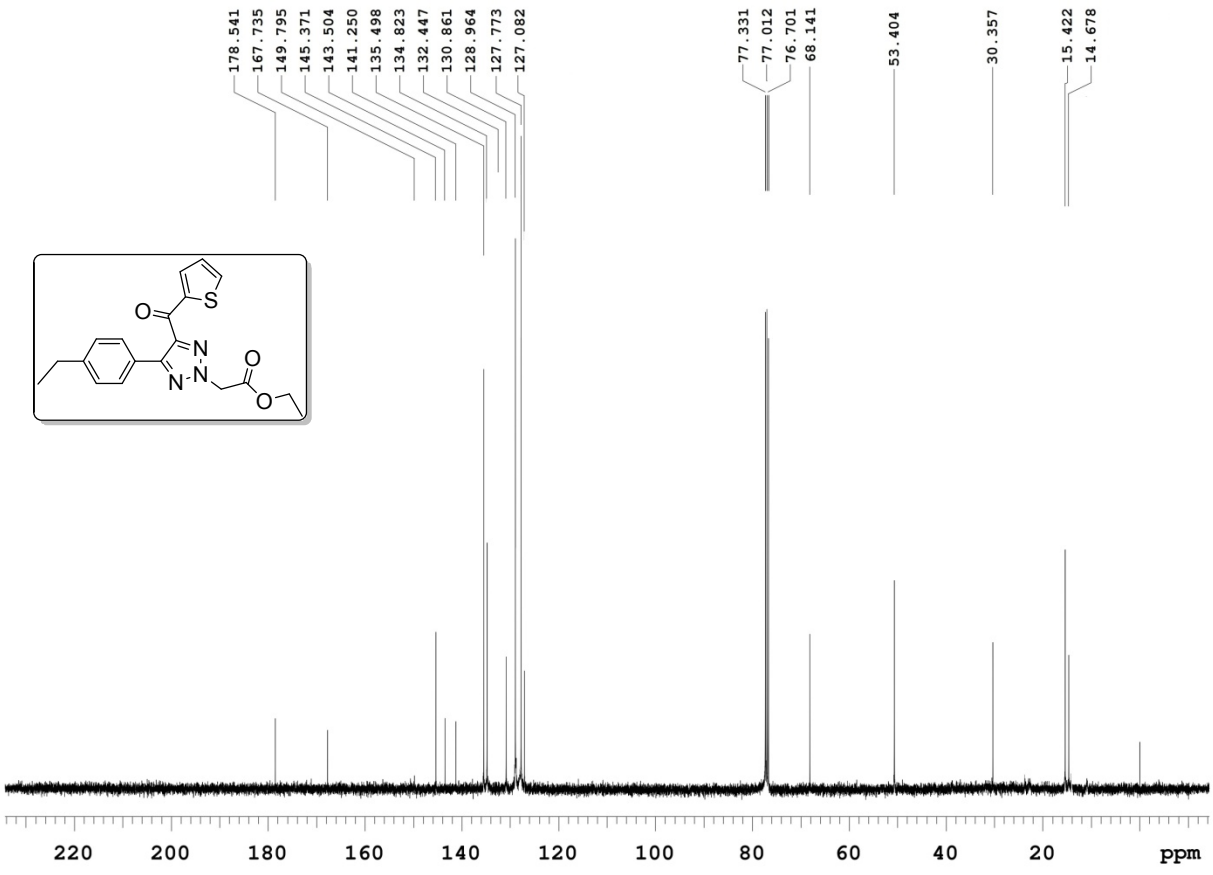

8.247
8.245
8.238
8.236
7.927
7.921
7.914
7.911
7.905
7.897
7.891
7.744
7.741
7.733
7.730
7.267
7.199
7.189
7.187
7.178
7.147
7.141
7.126
7.120
7.109
7.103
O
S
N
N
N
F
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
ppm
1.00
2.19
1.10
1.14
2.35



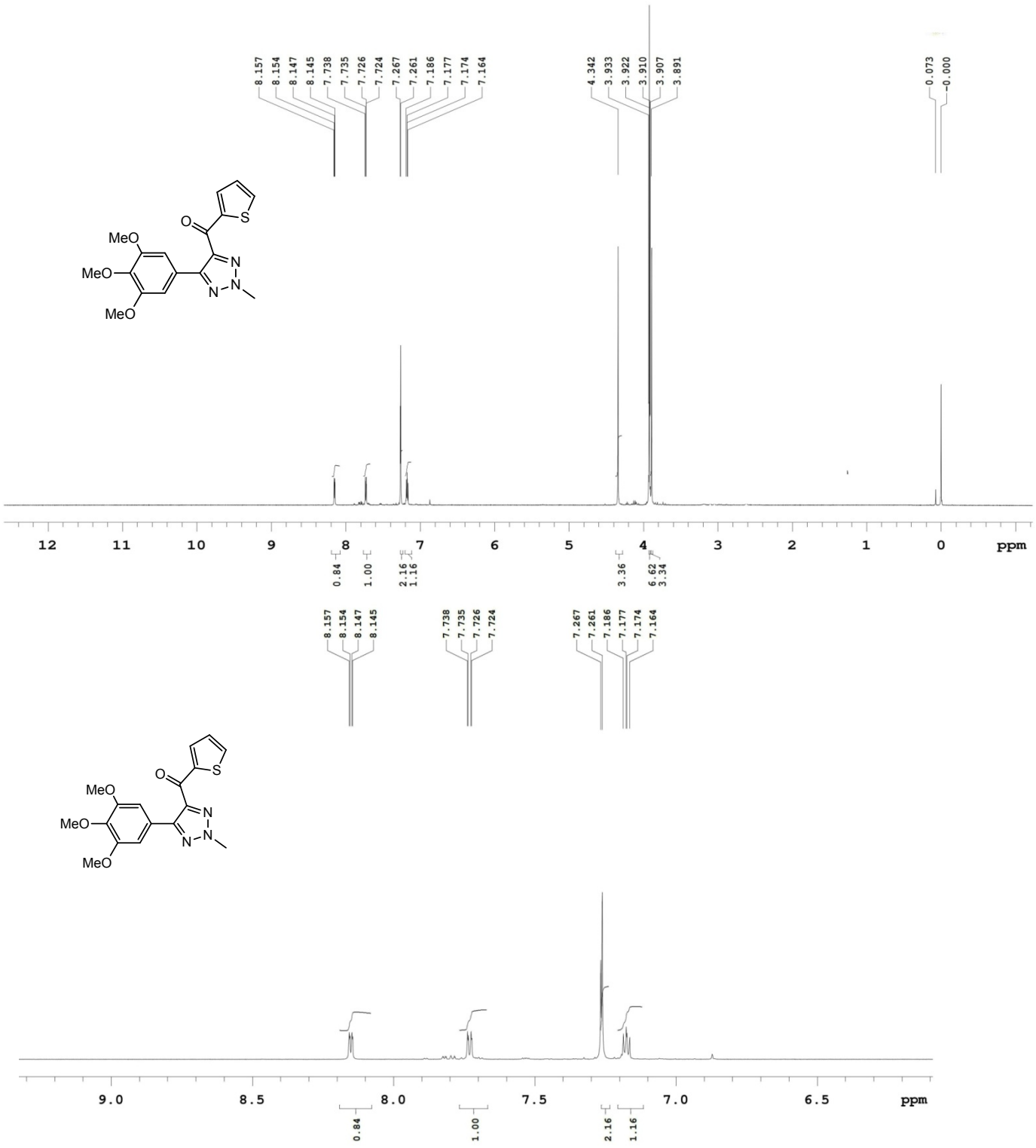
^{1}H and ^{13}C NMR Spectra of Compound (5-(4-fluorophenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl) (thiophen-2-yl) methanone **(2g)**

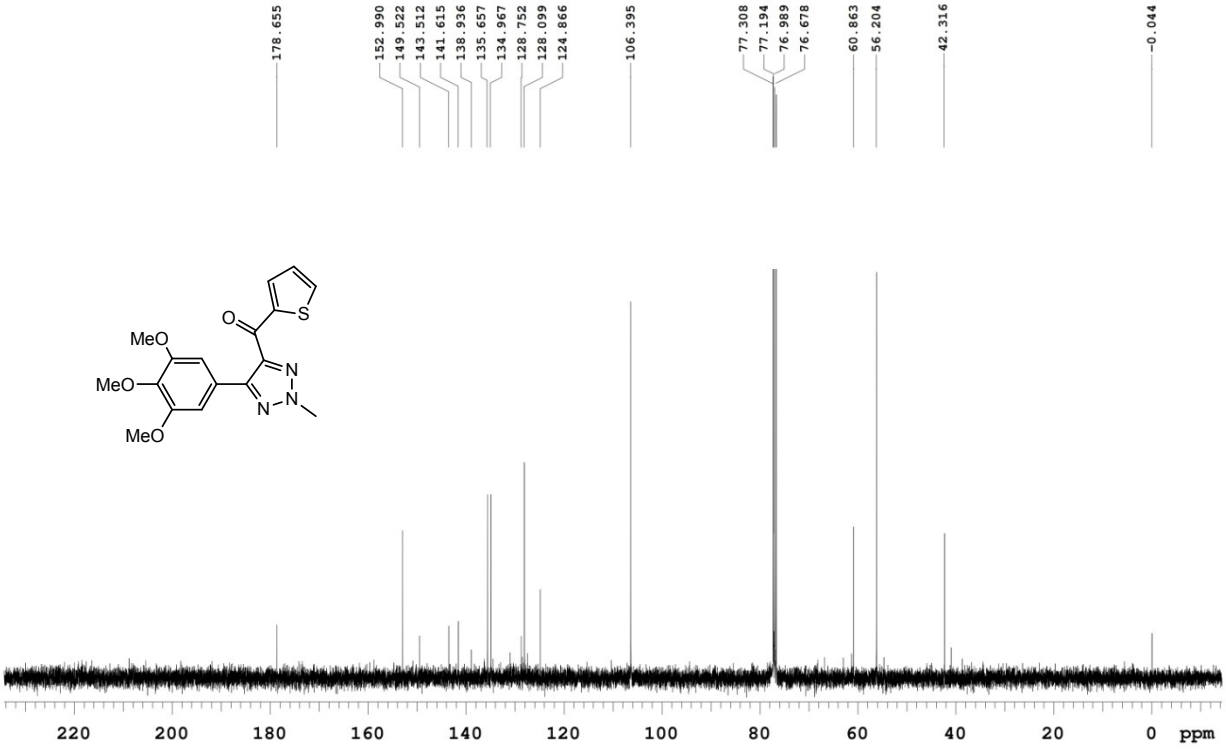

8.216
8.206
7.819
7.798
7.714
7.707
7.697
7.271
7.253
7.175
7.165
7.152
5.284
4.615
4.596
4.578
4.560
2.714
2.695
2.675
2.657
1.705
1.686
1.667
1.588
1.274
1.274
1.255
1.236
O
S
N
N
N
O
O
12
10
8
6
4
2
0
ppm
1.00
2.15
1.53
1.91
1.19
1.70
2.26
2.45
3.15
3.61


8.216
8.213
8.206
8.203
7.819
7.798
7.714
7.710
7.707
7.697
7.694
7.271
7.253
7.250
7.175
7.165
7.162
7.152
O
S
N
N
N
O
O
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
1.00
2.15
1.53
1.91
1.19

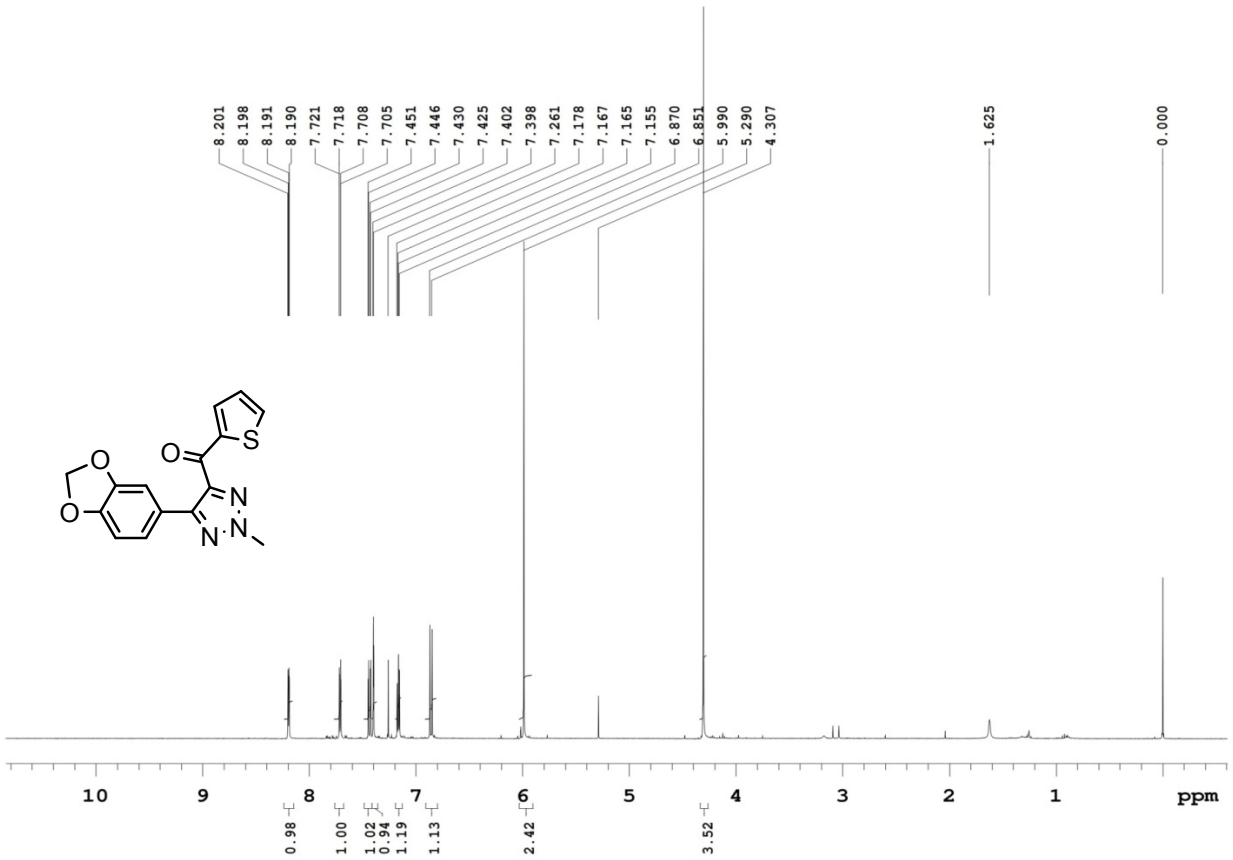


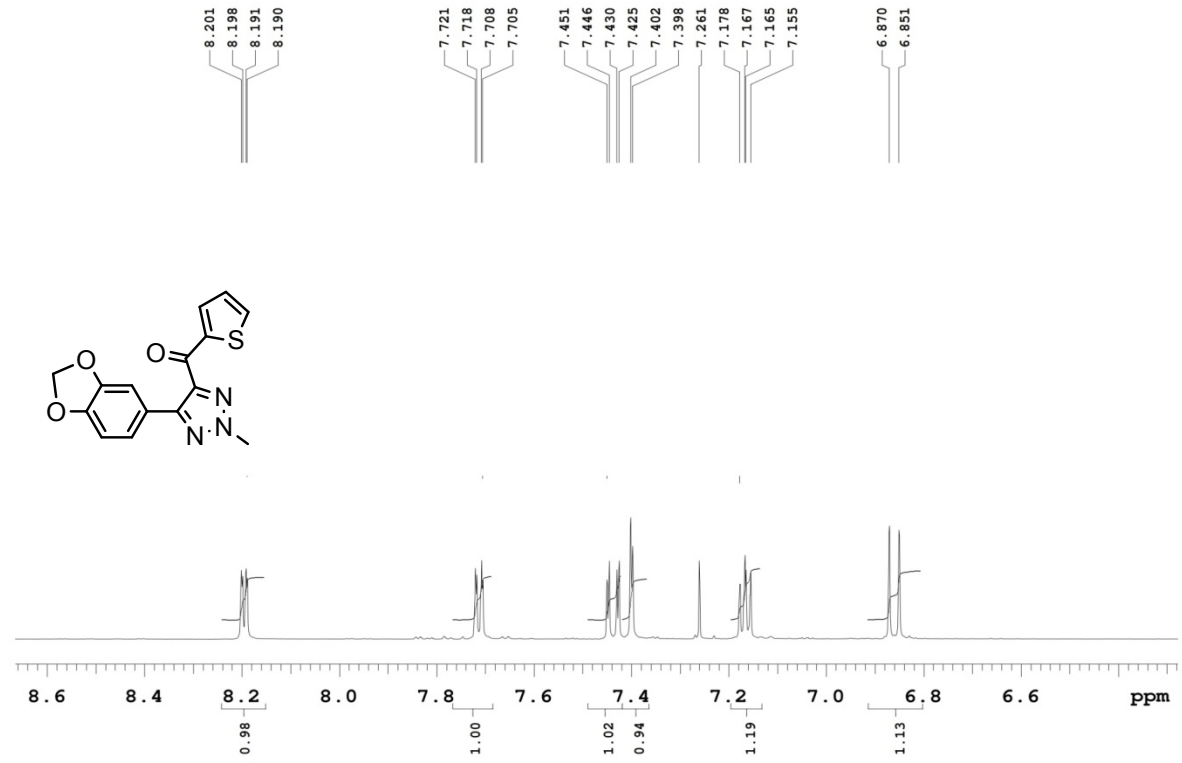
^{1}H and ^{13}C NMR Spectra of Compound Ethyl 2-(4-(4-ethylphenyl)-5-(thiophene-2-carbonyl)-2H-1, 2, 3-triazol-2-yl) acetate **(2h)**

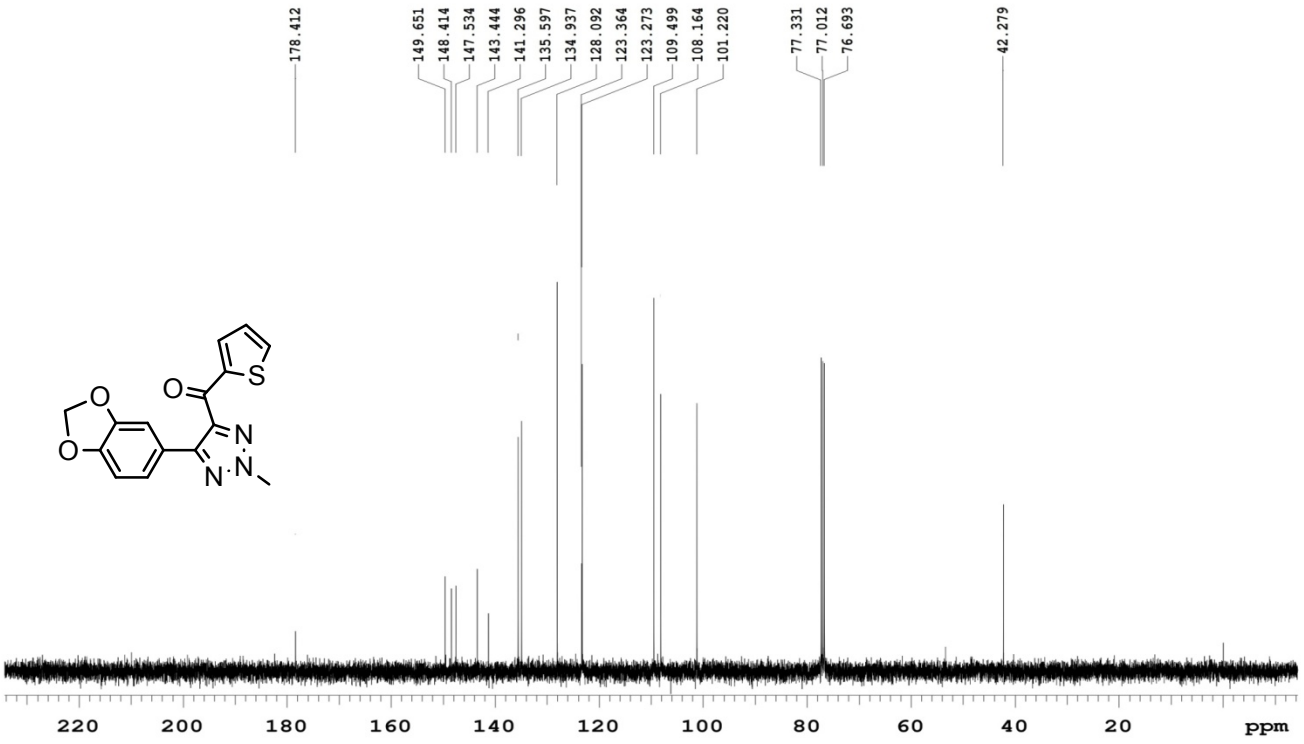

8.157
8.154
8.147
8.145
7.738
7.735
7.726
7.724
7.267
7.261
7.186
7.177
7.174
7.164
4.342
3.933
3.922
3.910
3.907
3.891
0.073
-0.000
MeO
MeO
MeO
O
S
N
N
N
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.84
1.00
2.16
1.16
3.36
6.62
3.34
9.0
8.5
8.0
7.5
7.0
6.5



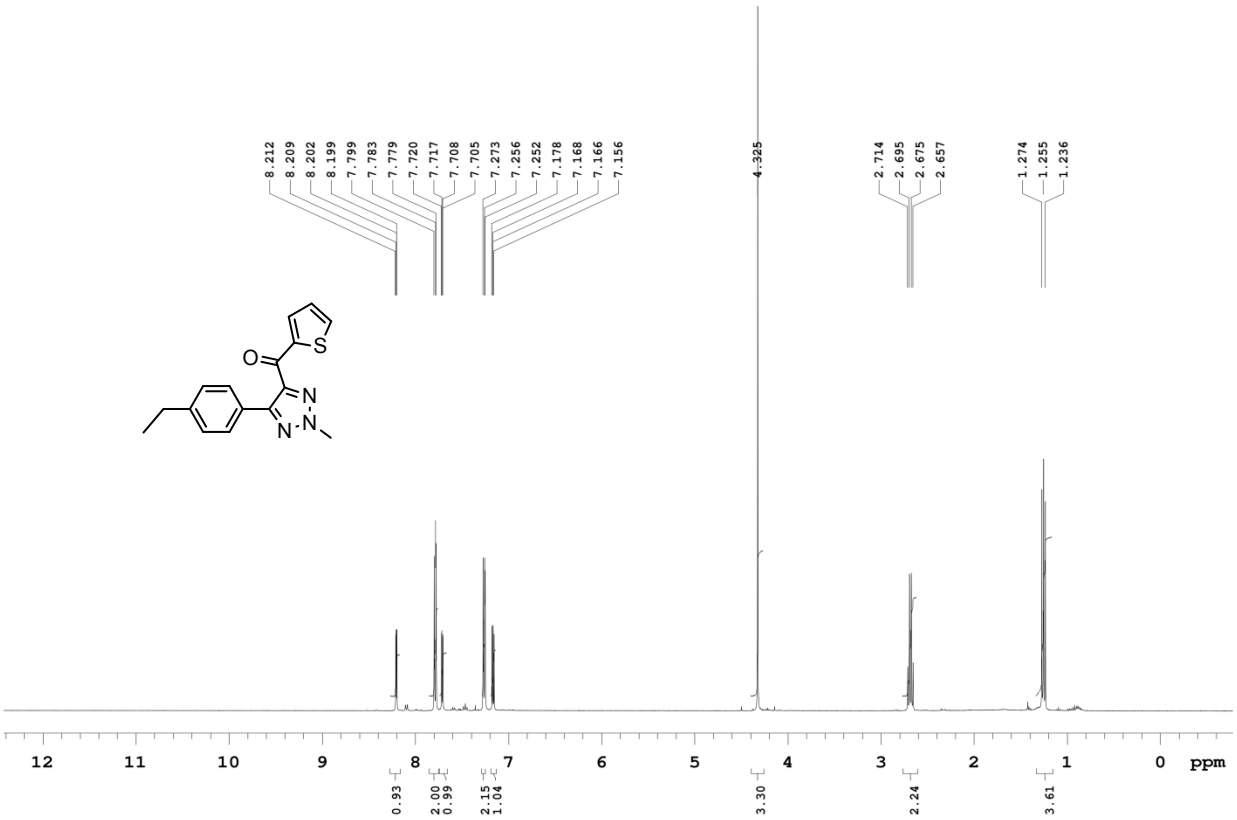
^{1}H and ^{13}C NMR Spectra of Compound (2-methyl-5-(3, 4, 5-trimethoxyphenyl)-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone **(2i)**

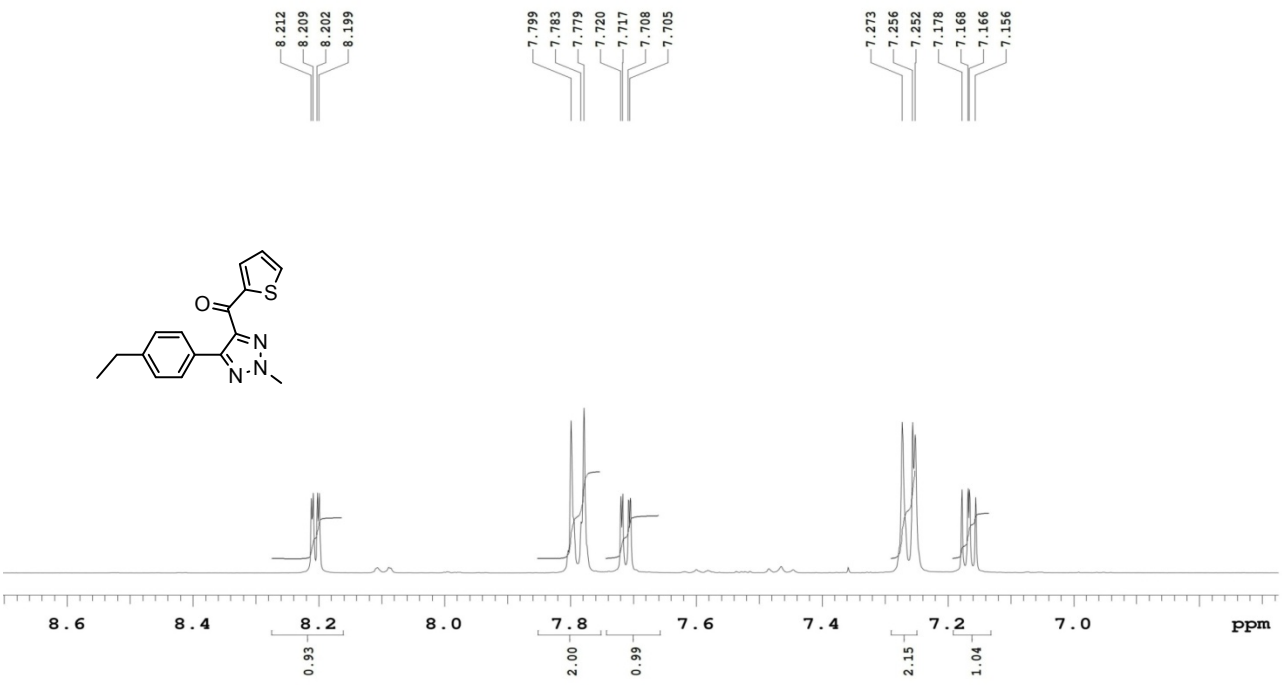

8.201
8.198
8.191
8.190
7.721
7.718
7.708
7.705
7.451
7.446
7.430
7.425
7.402
7.398
7.261
7.178
7.167
7.165
7.155
6.870
6.851
5.990
5.290
4.307
1.625
0.000
O
S
O
O
N
N·N
10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.00
1.02
0.94
1.19
1.13
2.42
3.52

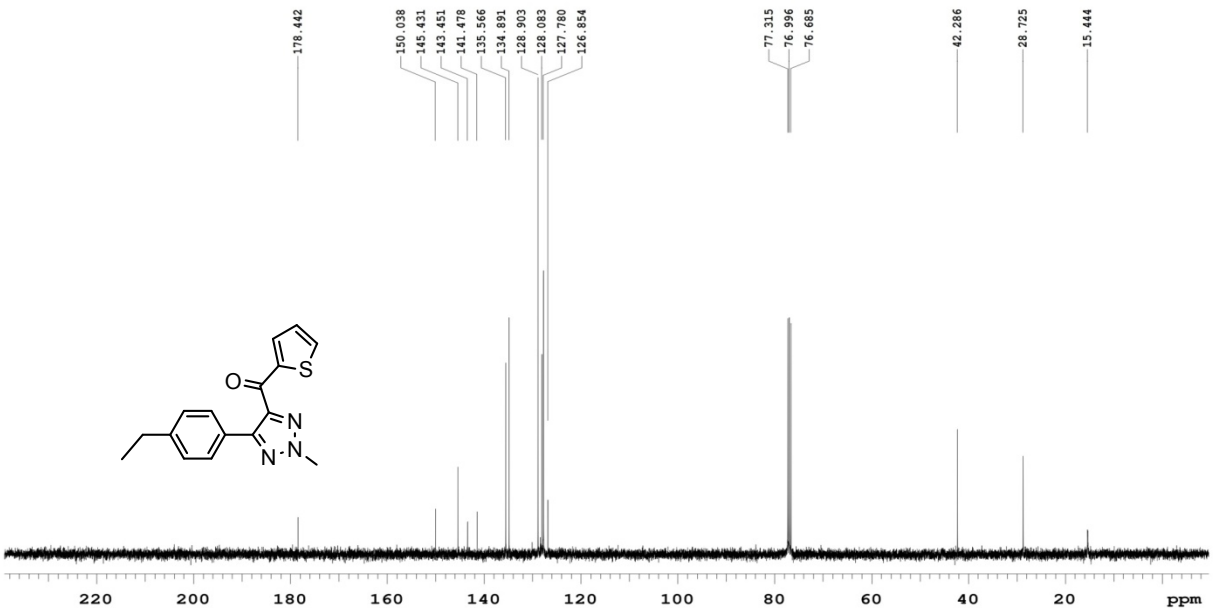

8.201
8.198
8.191
8.190
7.721
7.718
7.708
7.705
7.451
7.446
7.430
7.425
7.402
7.398
7.261
7.178
7.167
7.165
7.155
6.870
6.851
O
S
O
O
N
N·N
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
0.98
1.00
1.02
0.94
1.19
1.13



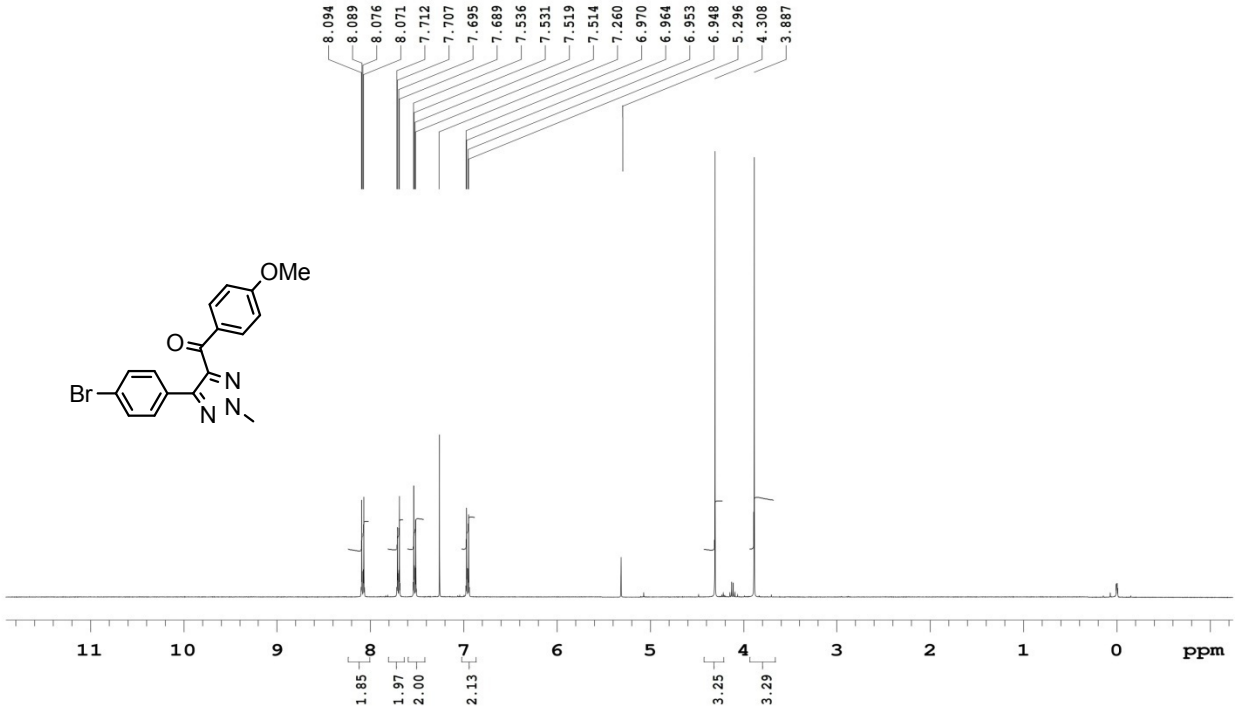
^{1}H and ^{13}C NMR Spectra of Compound (5-(benzo[d][1,3]dioxol-5-yl)-2-methyl-2H-1,2,3-triazol-4-yl)(thiophen-2-yl) methanone **(2j)**

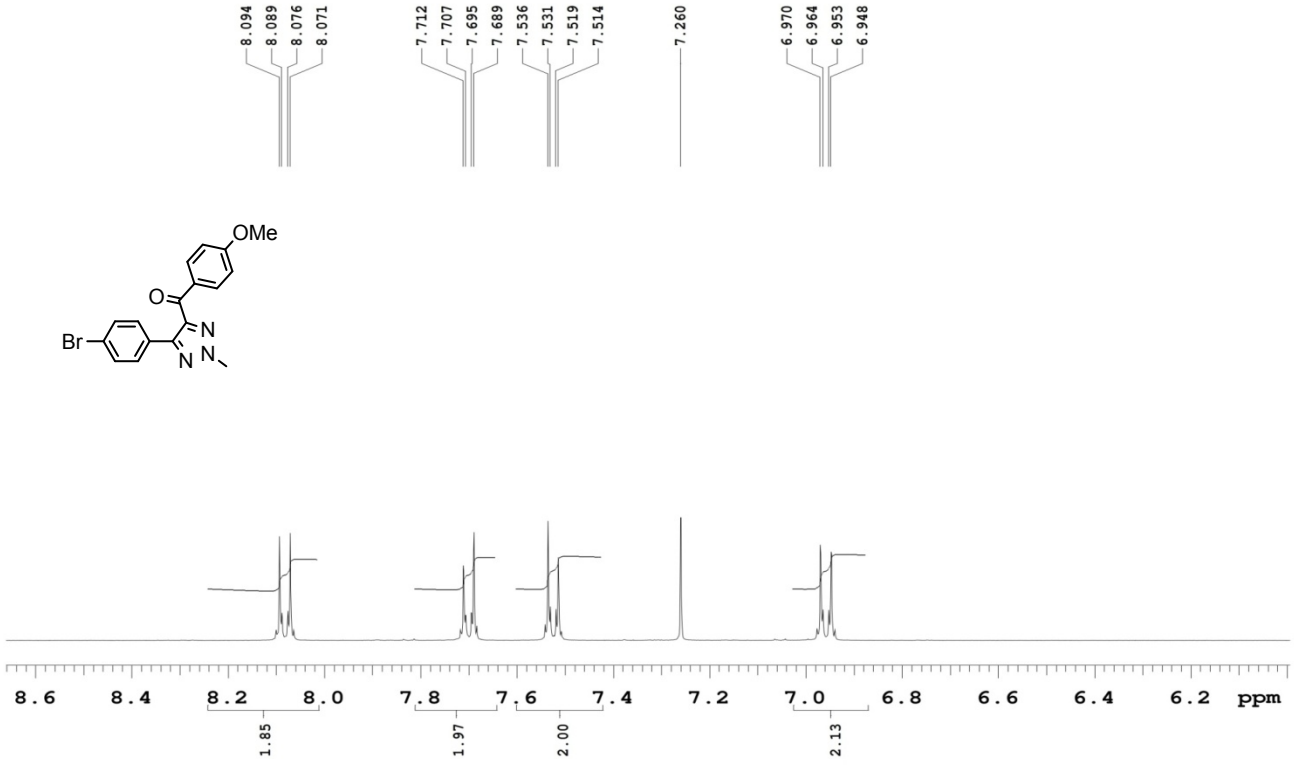

8.212
8.209
8.202
8.199
7.799
7.783
7.779
7.720
7.717
7.708
7.705
7.273
7.256
7.252
7.178
7.168
7.166
7.156
4.325
2.714
2.695
2.675
2.657
1.274
1.255
1.236
O
S
N
N
N
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.93
2.00
0.99
2.15
1.04
3.30
2.24
3.61

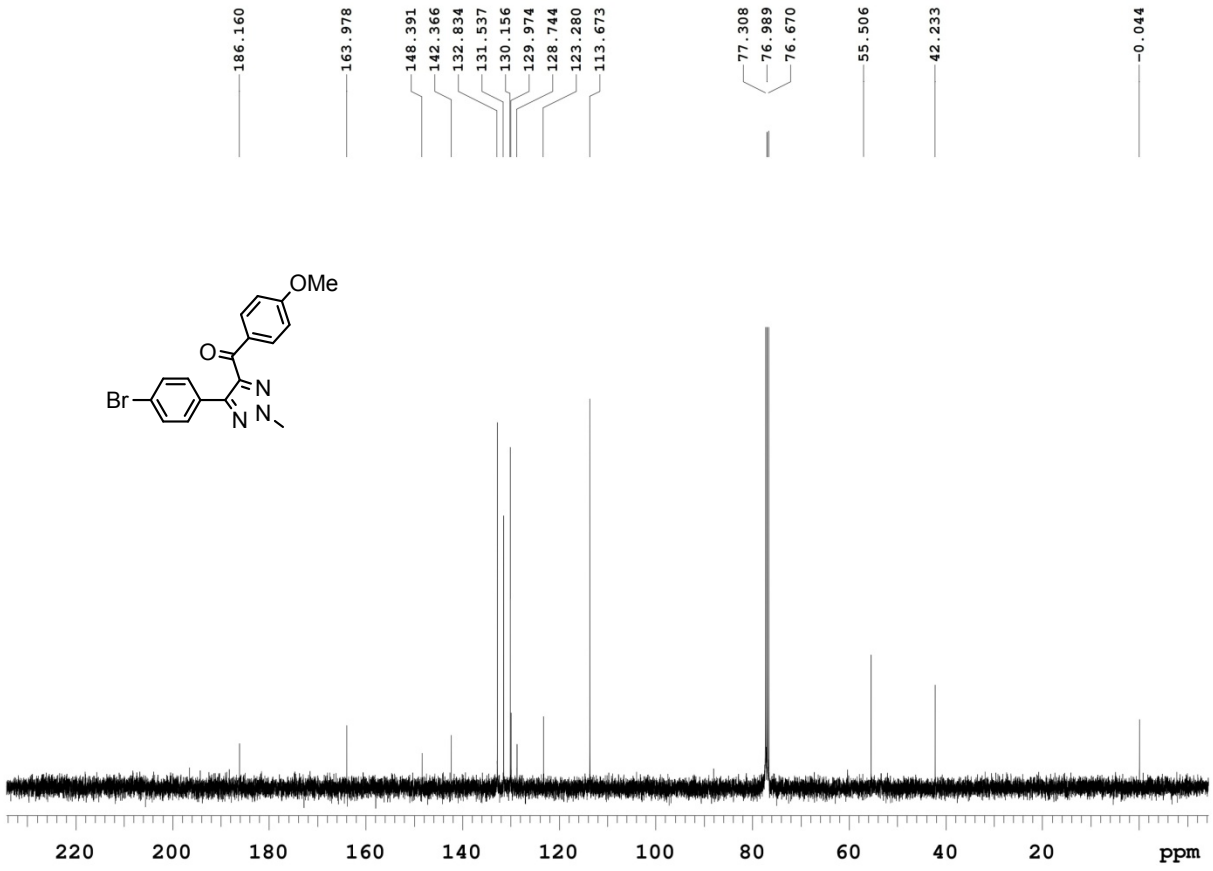

8.212
8.209
8.202
8.199
7.799
7.783
7.779
7.720
7.717
7.708
7.705
7.273
7.256
7.252
7.178
7.168
7.166
7.156
O
S
N
N
N
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
ppm
0.93
2.00
0.99
2.15
1.04



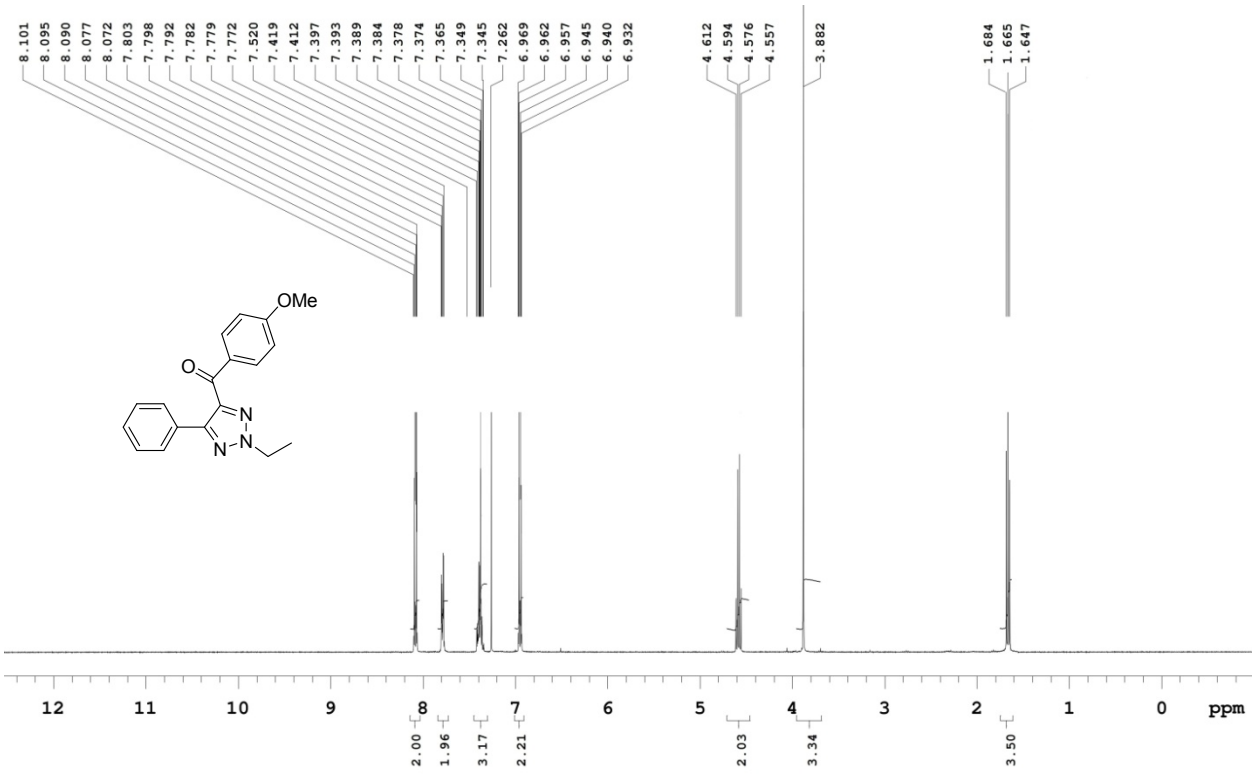
^{1}H and ^{13}C NMR Spectra of Compound (5-(4-ethylphenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone **(2k)**

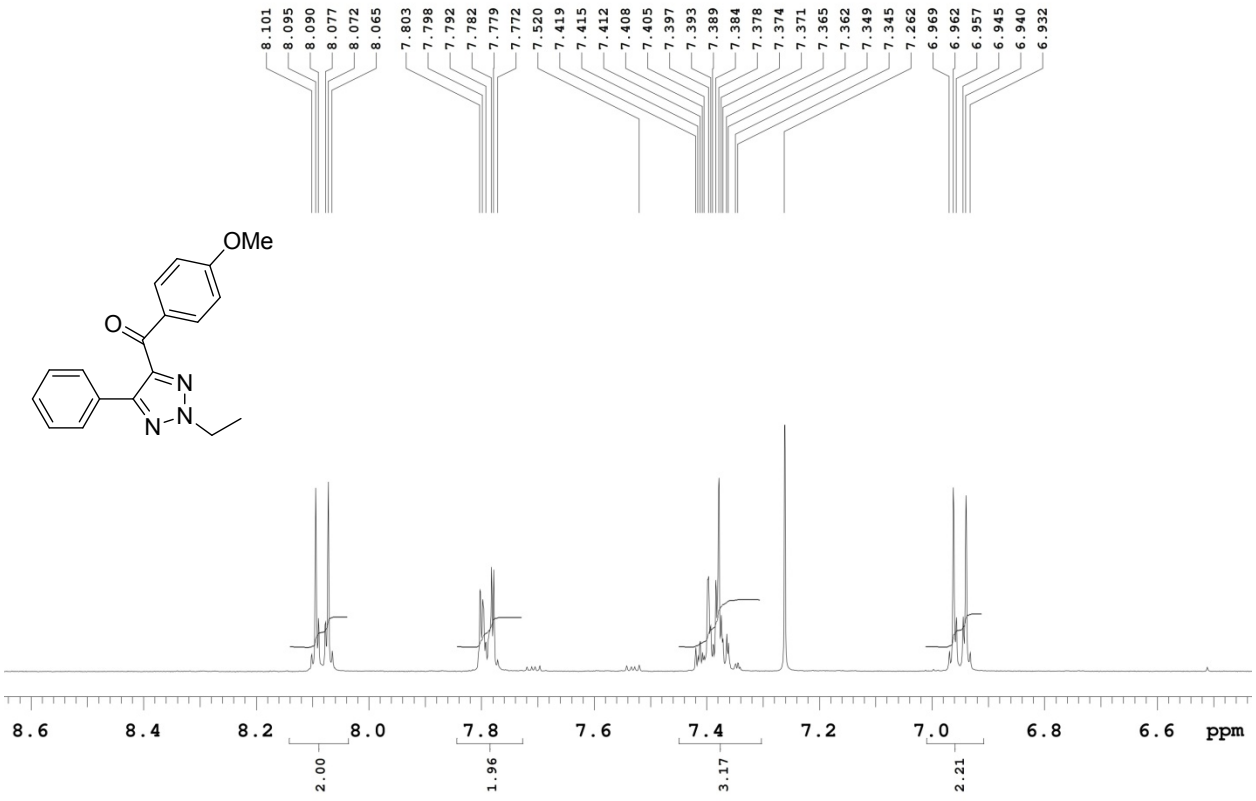

8.094
8.089
8.076
8.071
7.712
7.707
7.695
7.689
7.536
7.531
7.519
7.514
7.260
6.970
6.964
6.953
6.948
5.296
4.308
3.887
OMe
O
N
N
N
Br
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.85
1.97
2.00
2.13
3.25
3.29

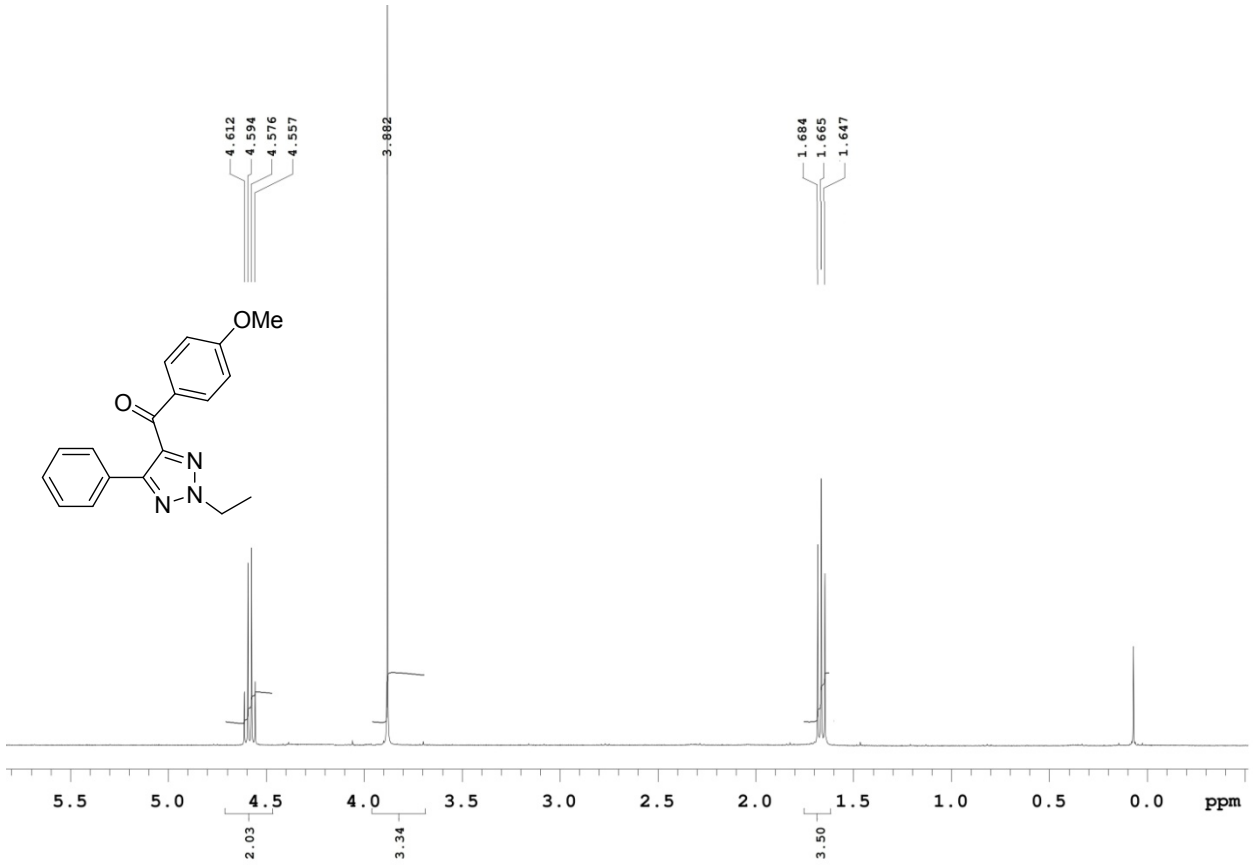

8.094
8.089
8.076
8.071
7.712
7.707
7.695
7.689
7.536
7.531
7.519
7.514
7.260
6.970
6.964
6.953
6.948
OMe
O
N
N
N
Br
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
ppm
1.85
1.97
2.00
2.13



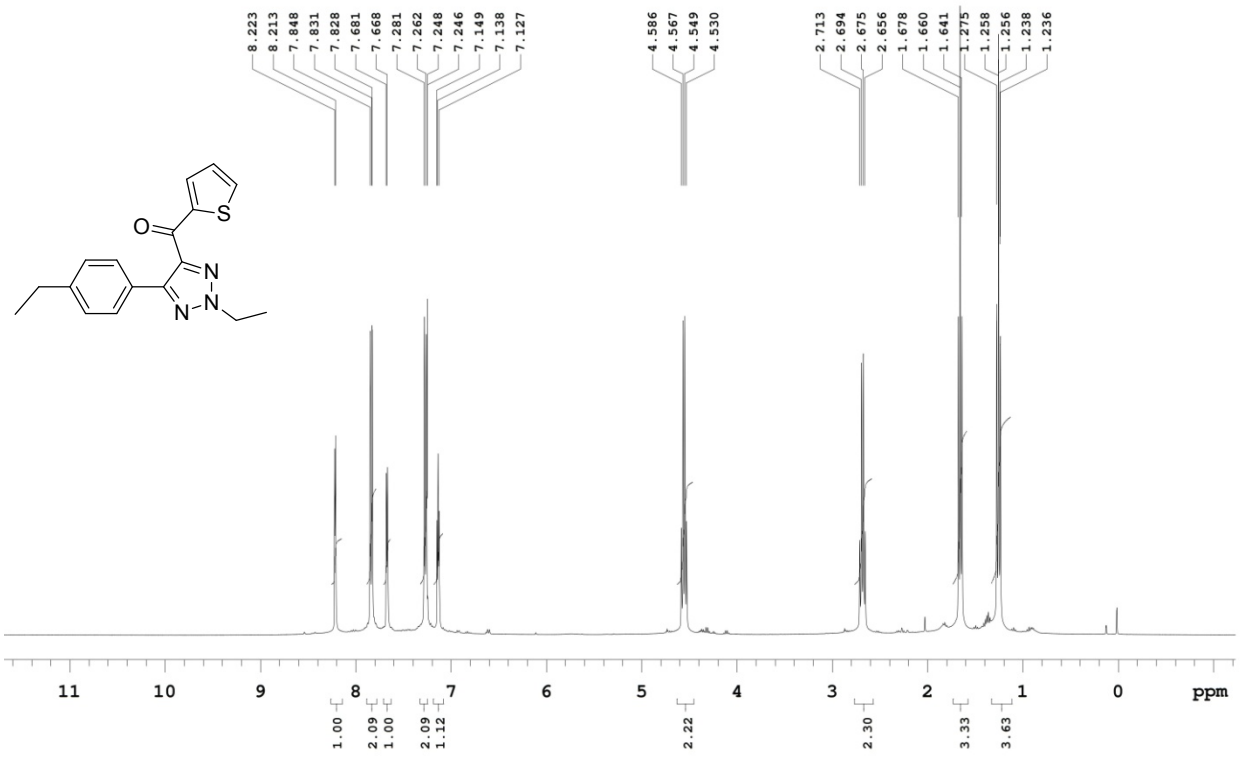
^{1}H and ^{13}C NMR Spectra of Compound (5-(4-bromophenyl)-2-methyl-2H-1, 2, 3-triazol-4-yl) (4-methoxyphenyl) methanone **(2l)**

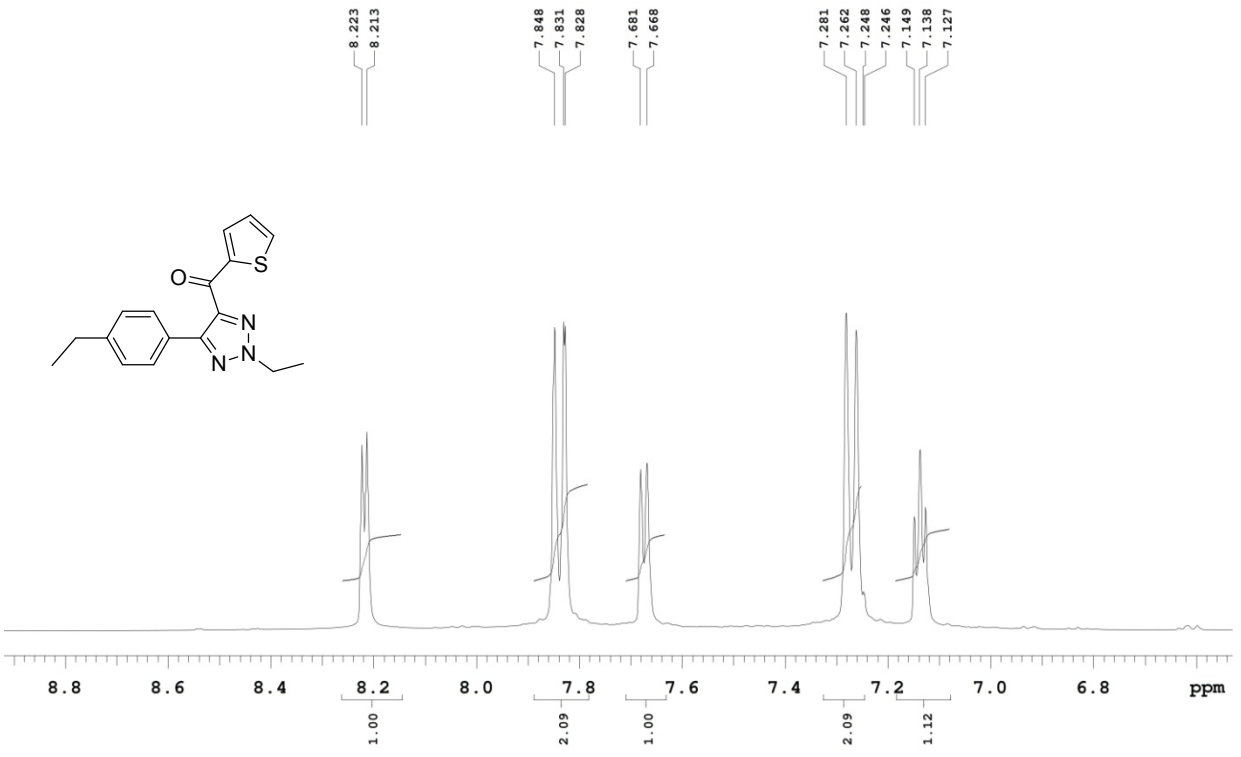

8.101
8.095
8.090
8.077
8.072
7.803
7.798
7.792
7.782
7.779
7.772
7.520
7.419
7.412
7.397
7.393
7.389
7.384
7.378
7.374
7.365
7.349
7.345
7.262
6.969
6.962
6.957
6.945
6.940
6.932
4.612
4.594
4.576
4.557
3.882
1.684
1.665
1.647
OMe
O
N
N
N
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.96
3.17
2.21
2.03
3.34
3.50

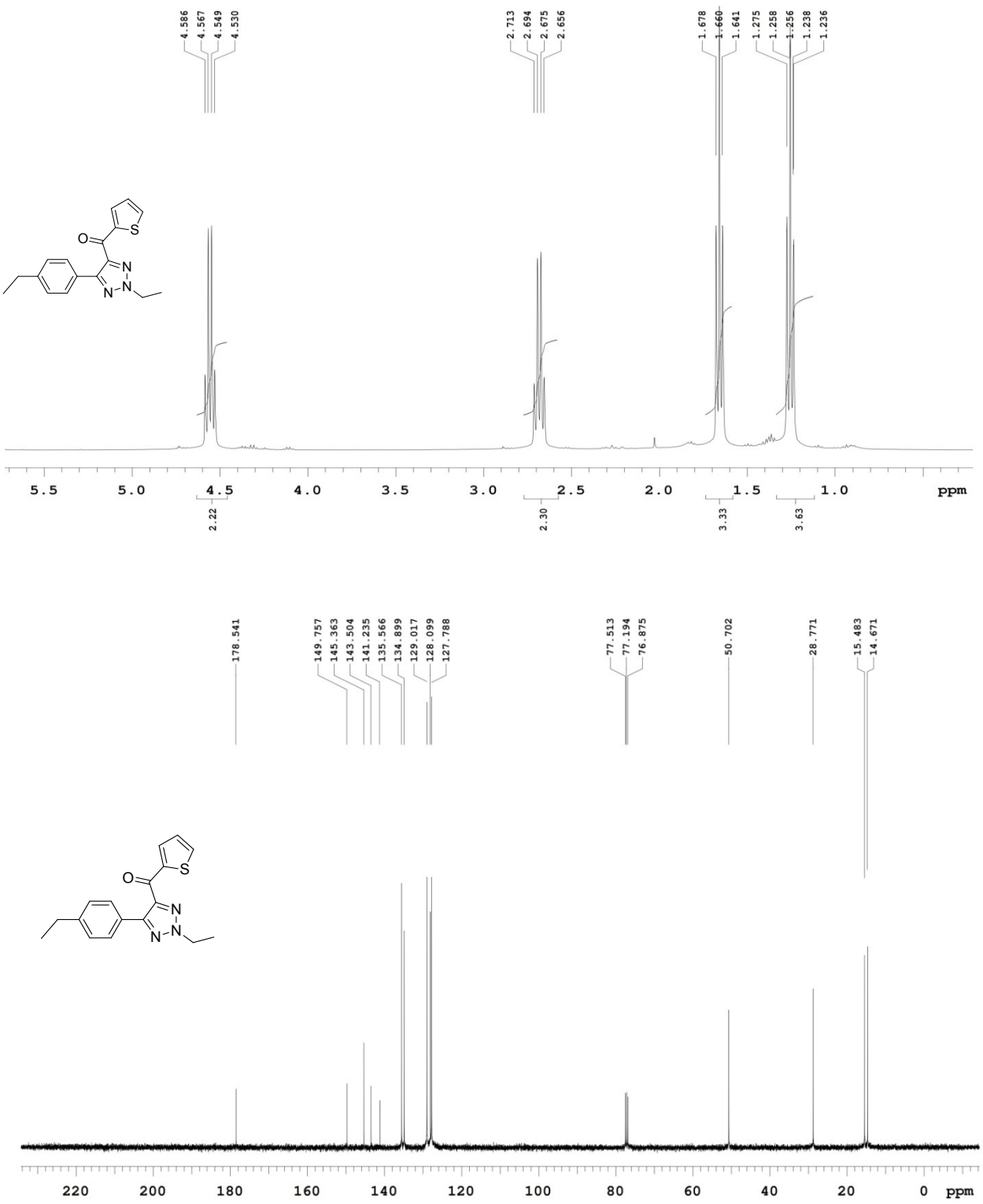

8.101
8.095
8.090
8.077
8.072
8.065
7.803
7.798
7.792
7.782
7.779
7.772
7.520
7.419
7.415
7.412
7.408
7.405
7.397
7.393
7.389
7.384
7.378
7.374
7.371
7.365
7.362
7.349
7.345
7.262
6.969
6.962
6.957
6.945
6.940
6.932
OMe
O
N
N
N
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
2.00
1.96
3.17
2.21



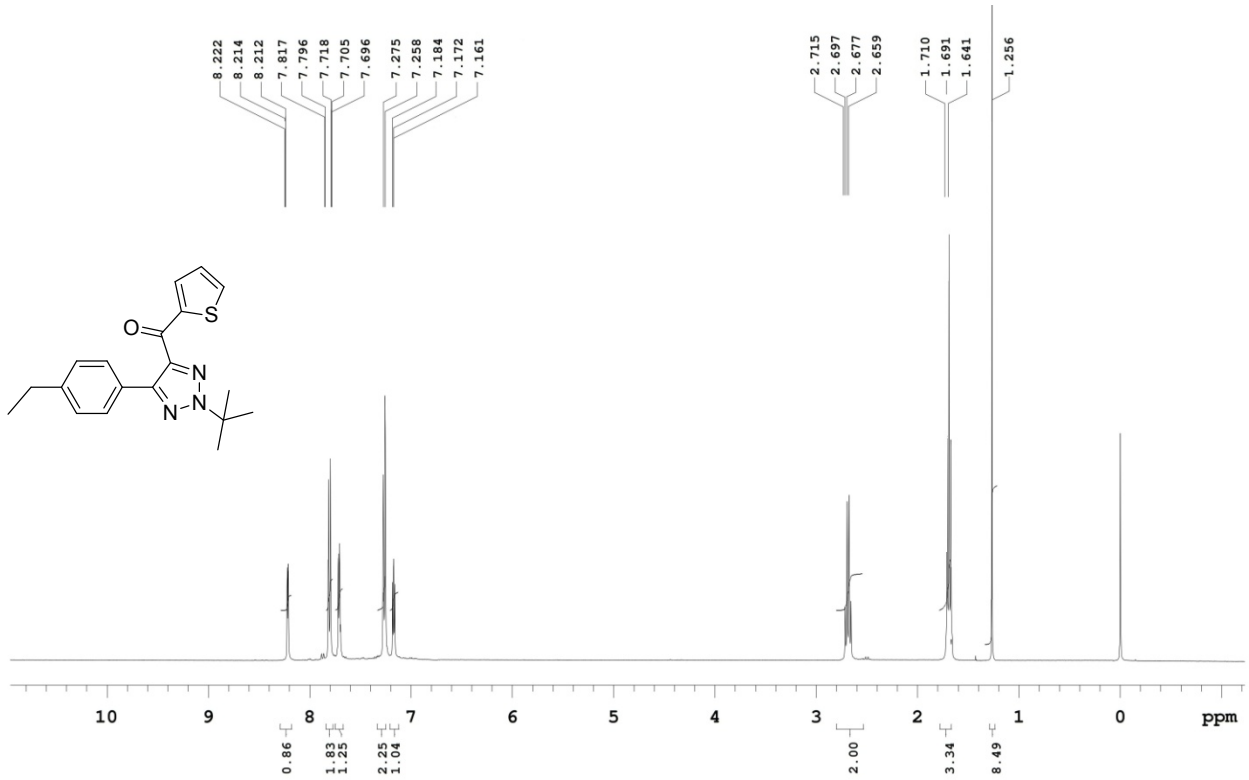
^{1}H NMR Spectra of Compound (4-methoxyphenyl)(2-methyl-5-phenyl-2H-1, 2, 3-triazol-4-yl) methanone **(2m)**

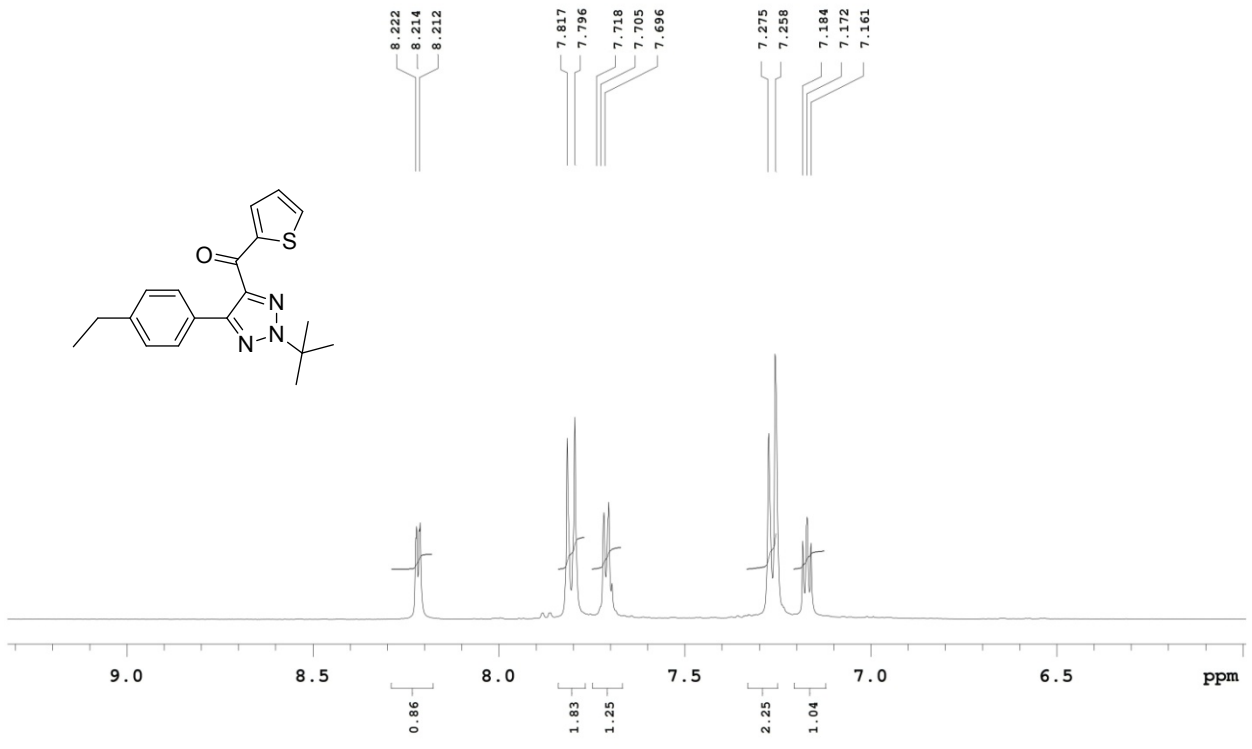

8.223
8.213
7.848
7.831
7.828
7.681
7.668
7.281
7.262
7.248
7.246
7.149
7.138
7.127
4.586
4.567
4.549
4.530
2.713
2.694
2.675
2.656
1.678
1.660
1.641
1.275
1.258
1.256
1.238
1.236
O
S
N
N
N
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.09
1.00
2.09
1.12
2.22
2.30
3.33
3.63

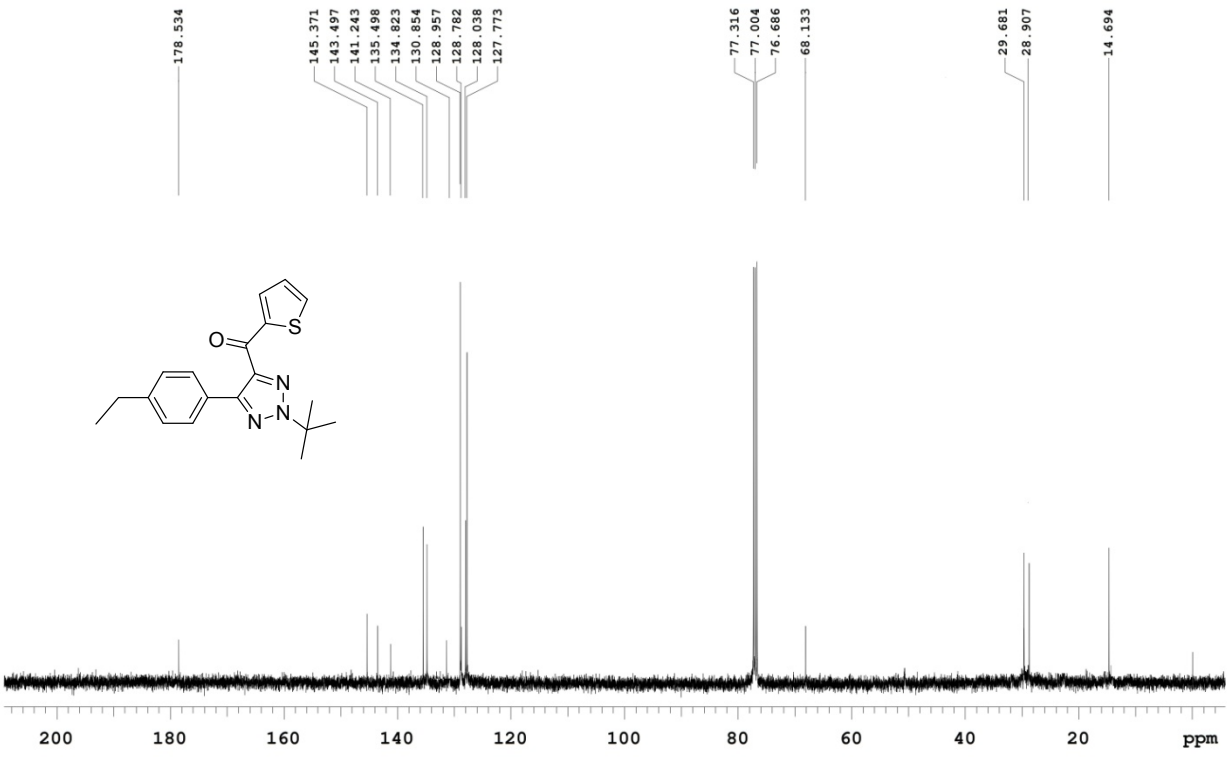

8.223
8.213
7.848
7.831
7.828
7.681
7.668
7.281
7.262
7.248
7.246
7.149
7.138
7.127
O
S
N
N
N
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
ppm
1.00
2.09
1.00
2.09
1.12



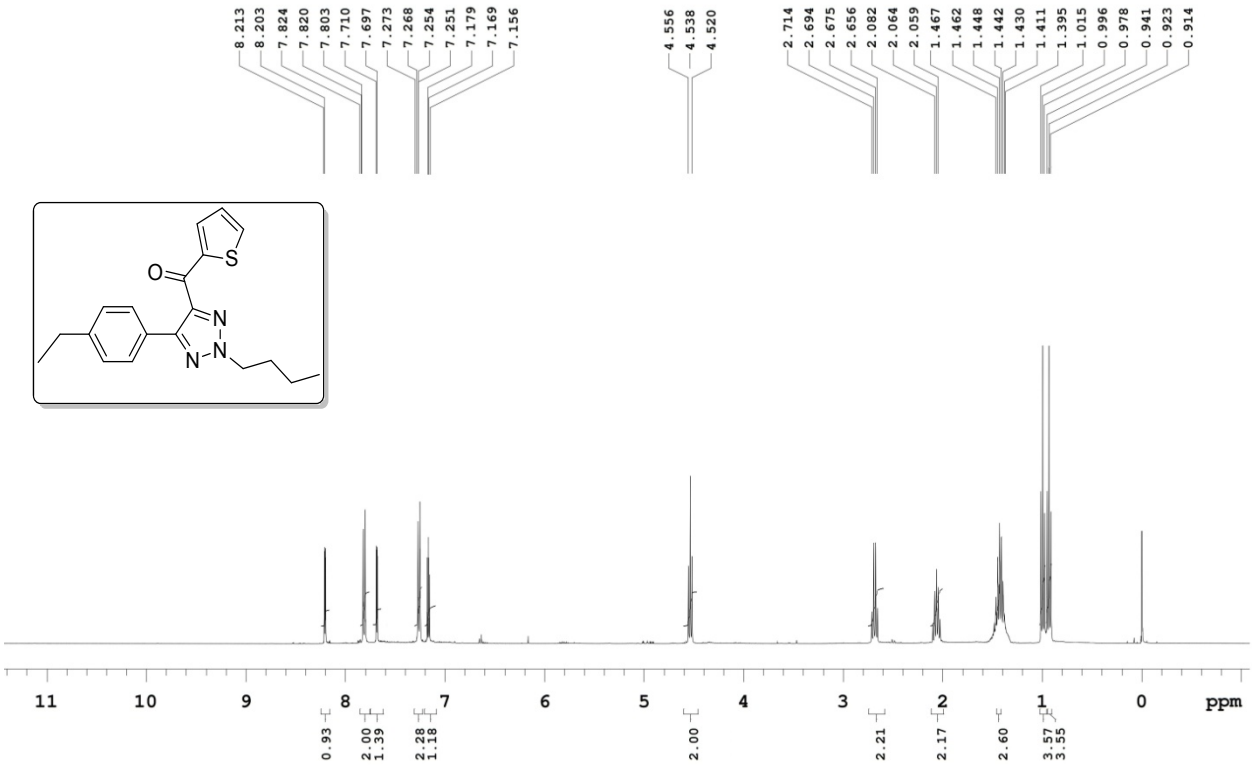
^{1}H and ^{13}C NMR Spectra of Compound (2-ethyl-5-(4-ethylphenyl)-2H-1, 2, 3-triazol-4-yl) (thiophen-2-yl) methanone **(2n)**


8.222
8.214
8.212
7.817
7.796
7.718
7.705
7.696
7.275
7.258
7.184
7.172
7.161
2.715
2.697
2.677
2.659
1.710
1.691
1.641
1.256
O
S
N
N
N
10
9
8
7
6
5
4
3
2
1
0
ppm
0.86
1.83
1.25
2.25
1.04
2.00
3.34
8.49


8.222
8.214
8.212
7.817
7.796
7.718
7.705
7.696
7.275
7.258
7.184
7.172
7.161
O
S
N
N
N
9.0
8.5
8.0
7.5
7.0
6.5
ppm
0.86
1.83
1.25
2.25
1.04



^{1}H and ^{13}C NMR Spectra of Compound (2-(tert-butyl)-5-(4-ethylphenyl)-2H-1, 2, 3-triazol-4-yl) (thiophen-2-yl) methanone **(2p)**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8.203
7.824
7.820
7.803
7.710
7.697
7.273
7.268
7.254
7.251
7.179
7.169
7.156
4.556
4.538
4.520
2.714
2.694
2.675
2.656
2.082
2.064
2.059
1.467
1.462
1.448
1.442
1.430
1.411
1.395
1.015
0.996
0.978
0.941
0.923
0.914
O
S
N
N
N
11
10
9
8
7
6
5
4
3
2
1
0
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1.18
2.00
2.21
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2.60
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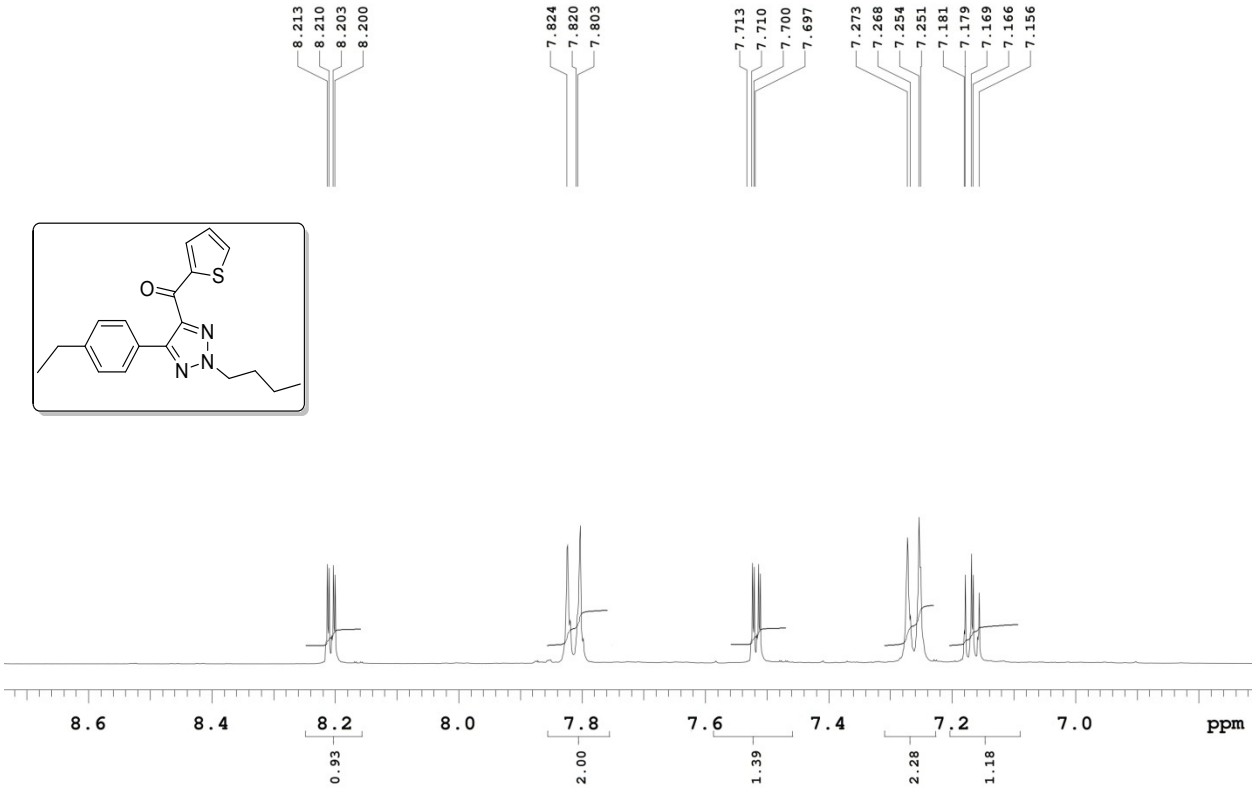
3.55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8.203
8.200
7.824
7.820
7.803
7.713
7.710
7.700
7.697
7.273
7.268
7.254
7.251
7.181
7.179
7.169
7.166
7.156
O
S
N
N
N
8.6
8.4
8.2
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7.4
7.2
7.0
ppm
0.93
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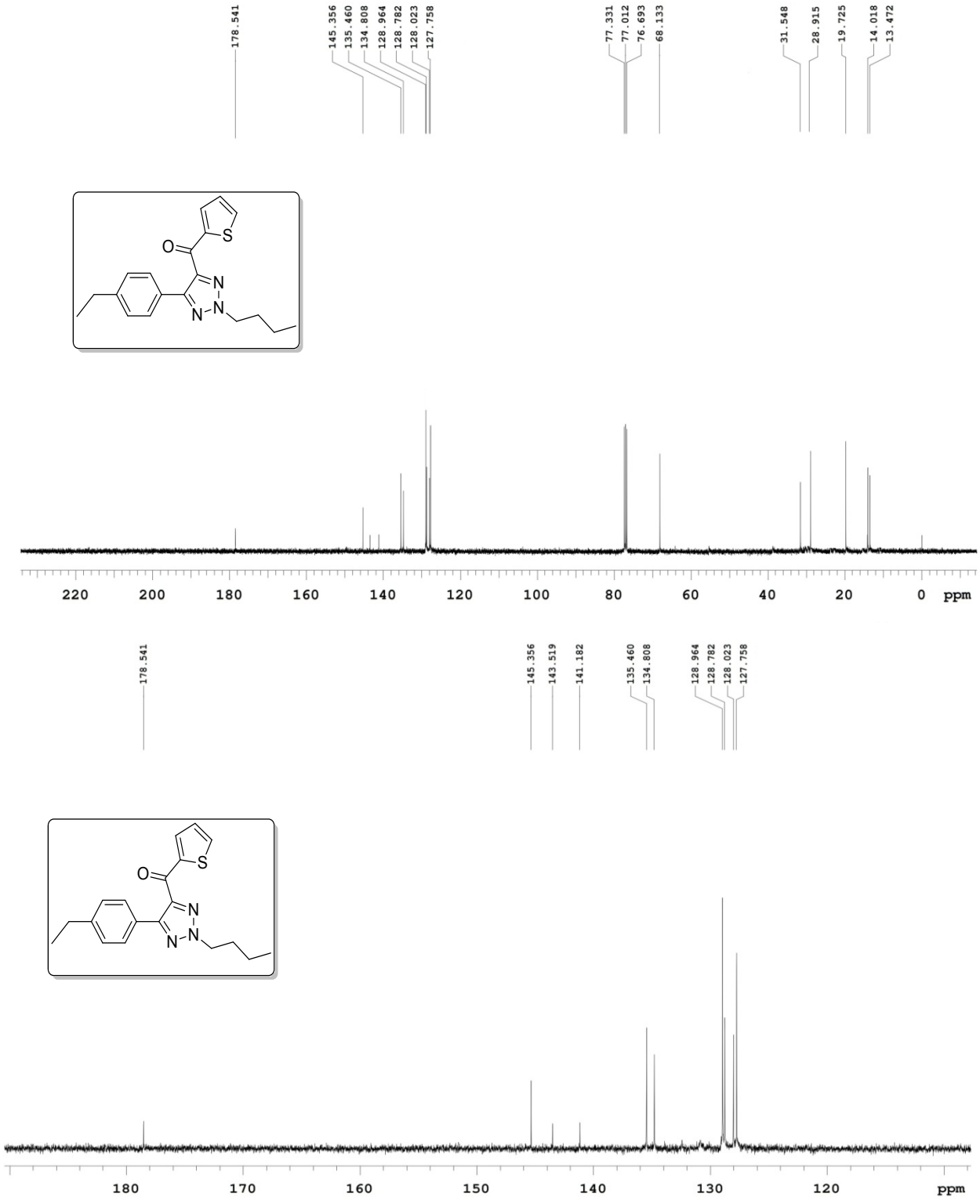
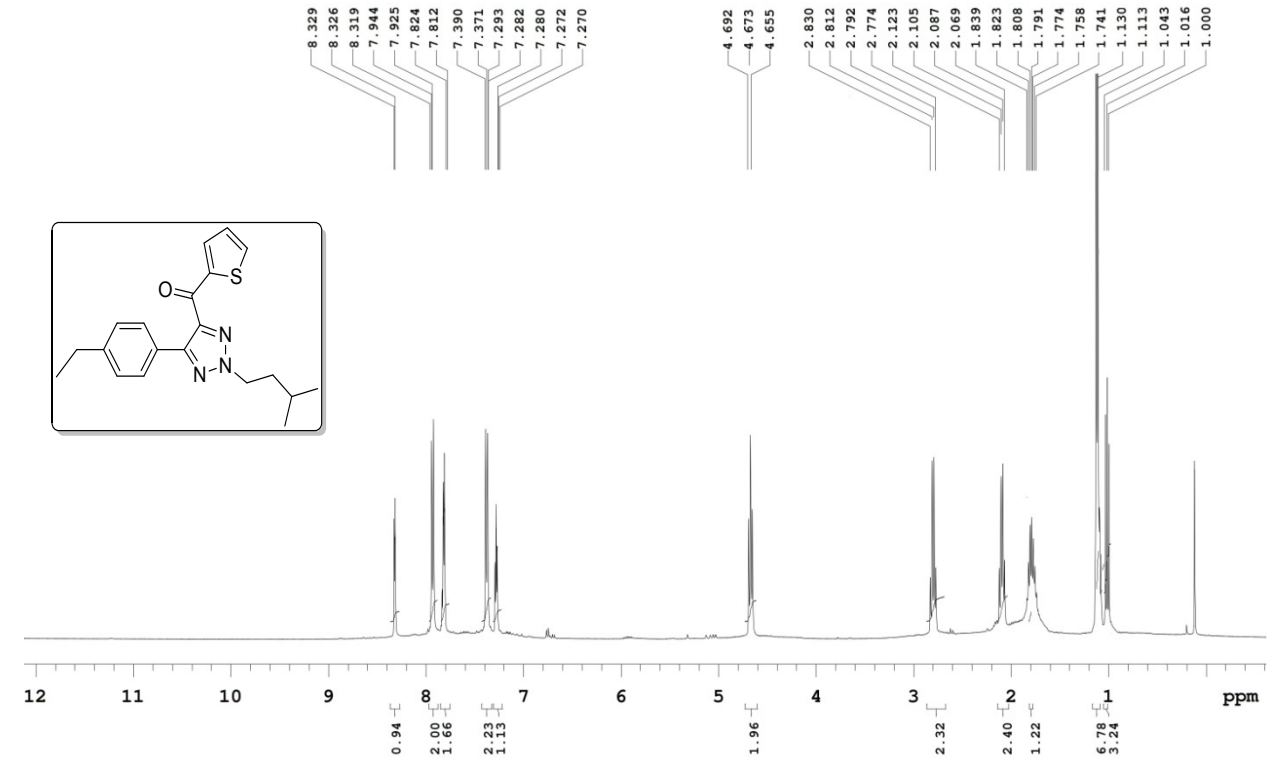
1.18



^{1}H and ^{13}C NMR Spectra of Compound (2-butyl-5-(4-ethylphenyl)-2H-1, 2, 3-triazol-4-yl)(thiophen-2-yl) methanone **(2q)**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8.319
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7.925
7.824
7.812
7.390
7.371
7.293
7.282
7.280
7.272
7.270
4.692
4.673
4.655
2.830
2.812
2.792
2.774
2.123
2.105
2.087
2.069
1.839
1.823
1.808
1.791
1.774
1.758
1.741
1.130
1.113
1.043
1.016
1.000
O
S
N
N
N
12
11
10
9
8
7
6
5
4
3
2
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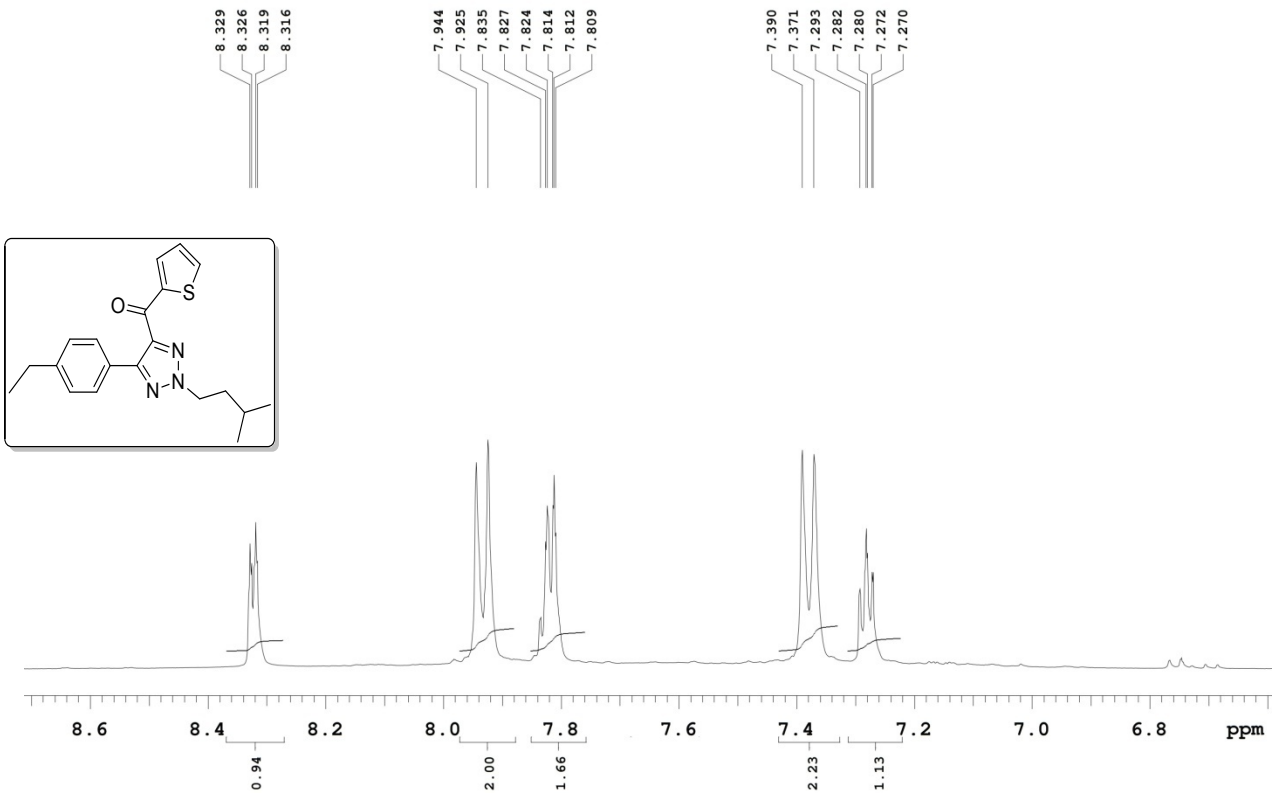
3.24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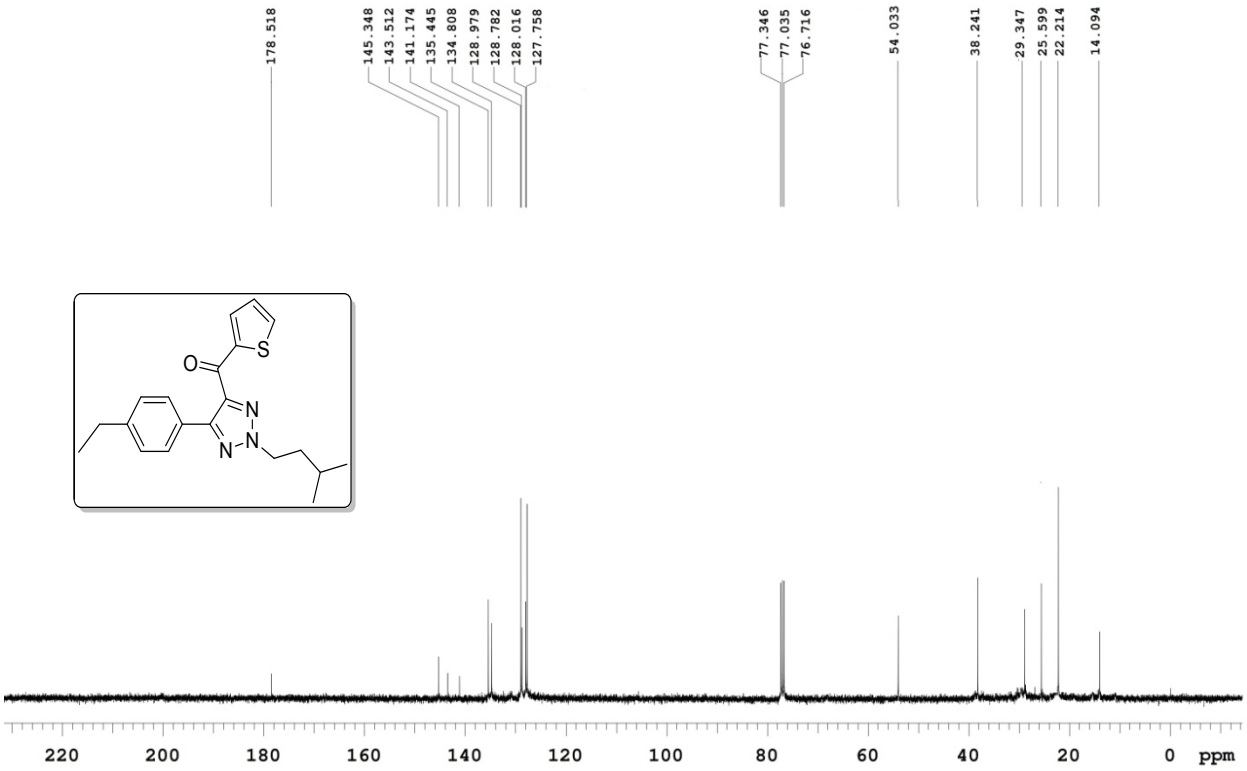
8.326
8.319
8.316
7.944
7.925
7.835
7.827
7.824
7.814
7.812
7.809
7.390
7.371
7.293
7.282
7.280
7.272
7.270
O
S
N
N
N
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
ppm
0.94
2.00
1.66
2.23
1.13



^{1}H and ^{13}C NMR Spectra of Compound (5-(4-ethylphenyl)-2-isopentyl-2H-1, 2, 3-triazol-4-yl) (thiophen-2-yl) methanone **(2s)**